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PREFACE

More than 2,100 papers were submitted by the nations, the specialized agencies, and the International Atomic Energy Agency, which participated in the Second United Nations International Conference on the Peaceful Uses of Atomic Energy. The number of papers was thus about twice that involved in the First Conference. Provision was therefore made to hold five concurrent technical sessions in comparison with the three that were held in 1955. Even so, the percentage of orally presented papers was less in 1958 than in 1955.

In arranging the programme, the Conference Secretariat aimed at achieving a balance, allowing adequate time for presentation of as many papers as possible and, nevertheless, leaving time for discussion of the data presented. Three afternoons were left free of programme activities so that informal meetings and discussions among smaller groups could be arranged. No records of these informal meetings were made.

A scientific editorial team assembled by the United Nations checked and edited all of the material included in these volumes. This team consisted of: Mr. John H. Martens, Miss L. Ourom, Dr. Walter M. Barss, Dr. Lewis G. Bassett, Mr. K. R. E. Smith, Martha Gerrard, Mr. F. Hudswell, Betty Guttman, Dr. John H. Pomeroy, Mr. W. B. Woollen, Dr. K. S. Singwi, Mr. T. E. F. Carr, Dr. A. C. Kolb, Dr. A. H. S. Matterson, Mr. S. Peter Welgos, Dr. I. D. Rojanski, Dr. David Finkelstein, Dr. Cavid Erginsoy (Dr. Erginsoy's services were furnished through the courtesy of the International Atomic Energy Agency), Dr. Vera J. Peterson. Dr. Hywell Jones, Dr. Paul S. Henshaw, Dr. Alvin Glassner and Mr. J. W. Greenwood.

The speedy publication of such a vast bulk of literature obviously presents considerable problems. The efforts of the editors have therefore been primarily directed towards scientific accuracy. Editing for style has of necessity been kept to a minimum, and this should be noted particularly in connection with the English translations of certain papers from French, Russian and Spanish.

The Governments of the Union of Soviet Socialist Republics and of Czechoslovakia provided English translations of the papers submitted by them. Similarly, the Government of Canada provided French-language versions of the Canadian papers selected for the French edition. Such assistance from Governments has helped greatly to speed publication.

The task of printing this very large collection of scientific information has been shared by printers in Canada, France, Switzerland, the United Kingdom and the United States of America.

The complete Proceedings of the Second United Nations International Conference on the Peaceful Uses of Atomic Energy are published in a 33-volume English-language edition as follows:

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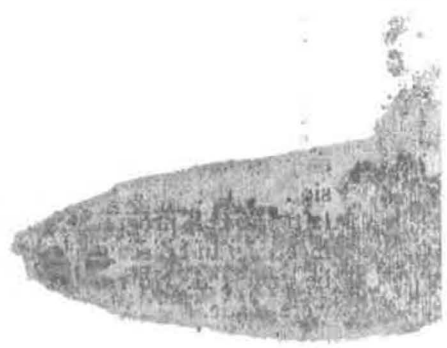

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Use of Radioactive Isotopes in Medicine

UN Survey

By Richard H. Chamberlain*

The variety and the extent of the employment of radioisotopes in medicine, both clinical and investigational, continues to increase. A very good indication of this is afforded by the large number of excellent papers which have been submitted for this section of the Second United Nations Conference on the Peaceful Uses of Atomic Energy. It is possible to present orally only a few outstanding papers, but a fuller appreciation of the scope and importance of these developments will be possible upon the publication of the entire group of scientific contributions.

Considerable emphasis is placed on the diagnostic applications of radioisotopes, for it is in investigational studies that they have become even more valuable than in therapeutic applications. Modern medicine has become increasingly dependent on diagnostic study techniques for the identification of disease entities and for intelligent evaluation of the course of events after the administration of treatment. These diagnostic procedures appear to become increasingly complex and some of the most involved ones employ radioisotopes, yet each adds new dimensions to the knowledge of the intricacies of the human body. Practically all organ systems and parts of the body are now accessible to study in dynamic form through the medium of radioisotopes. Frequently the information is unique, irreplaceable by any other means. Most often, one or more of the following principles are involved:

(1) Specific identification of a "tagged" dose, distinguishable within the body or after excretion or withdrawal from the body.

(2) Extreme detection sensitivity which allows very small amounts of administered material to be used and generally avoids disturbance of the metabolic process under observation (although the critical accuracy of this assumption is challenged in the work of V. P. Godin and S. I. Gorschkov on such phenomena as reflex time reactions).

(3) Opportunity for study of physiologic and metabolic processes *in vivo* without mechanical intrusion into the part under study.

It is important to remember that the development of clinical test procedures is not quick or easy. In addition to the original ingenuity and inspiration in the concept of a new test method, appropriate radioisotopes must be available for the purpose and it is necessary to have instruments with the required characteristics such as sensitivity, appropriate energy response, etc. There must then ensue a lengthy period of refinement in technical methodology and the accumulation of data on both normal and abnormal subjects. Finally, there must be a period of critical appraisal and interpretation of the value of the results. Often suitable human subjects are not readily available when studying the rarer diseases. Each time that a human subject is given radioactive material, the factors of potential radiation hazard must be considered in relation to the benefit which can be derived from the medical information obtained. It is not, therefore, surprising that many years of work may be devoted to the refinement of a single diagnostic test. To the contrary, it is amazing that so much has been accomplished in the relatively few years during which the radioactive tools and the instruments for their detection have been developing. It is appropriate that the presentations in this conference be viewed in the light of progress reports in an expanding field which is yet undergoing many major changes both in shape and direction.

DIAGNOSTIC PROCEDURES

The thyroid gland has been more intensively explored with radioisotope techniques than any other portion of the body. The extraordinary concentrating ability of this tissue for iodine and the ready availability of the iodine-131 isotope has made it possible to investigate the uptake patterns, the retention and release of the isotope from the gland, and the protein-bound fractions in the circulating blood. In spite of nearly 20 years of study, however, the metabolic pathways are still incompletely understood. At least twelve papers in this section deal with different aspects of such investigations of thyroid function by means of radioiodine. These papers emphasize the dynamics of thyroid function with respect to time relationships, to the production and proportions of the protein-bound fractions, and to the influence of pharmacological agents on these parameters. The refinement of interpretation of these values and their applicability to different disease states is likely to continue for some time. Among the contributions of special interest is one by

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K. E. Halnan and E. E. Pochin who have had a broad experience with the use of the iodine-132 isotope for diagnostic studies. This radioisotope, with its short half-life (2.3 hours), permits frequent repetition of studies in the same patient and with greatly reduced radiation dosage accompanying the procedures. It is obtained by distillation from a tellurium-132 source (half-life of 77 hours) which can be practically used for up to three weeks. By this means they have studied the day-to-day function of the gland and the influence of stimulating and depressing agents. Other contributors discuss the usefulness of triiodothyronine in conjunction with iodine-131 to sharpen the distinction of normal and abnormal thyroid function, the relationship between iodine-127 and iodine-131 ratios in functional evaluation of the thyroid, and the characteristics of the "capture" curve in various thyroid dysfunctions. Yet others deal with the significance of protein-bound iodine and its labelling in the study of thyrotoxicosis and the relative lack of interference by exogenous stable iodine in the radioiodine studies of thyrotoxic patients. Papers from as widely separated areas as the Soviet Union, Venezuela, Taiwan and Egypt describe the usefulness of radioiodine studies in regions of endemic goiter. Yet others are interested in the scintillation mapping of the gland and in instrumental techniques which will reduce the amount of radioactive material necessary, particularly in the study of infants and in the changes of function during progressive age periods in the same subjects. The analysis of the chromatographic fractions of the protein-bound iodine is reported to be useful in the evaluation of various dysfunctions and in following their post-therapeutic course.

The heart, circulatory system and lungs have been subjected to investigation by radioisotopes with special intensity during recent years. Methods have been developed for computing and estimating stroke volume, residual volume and cardiac output. Some use peripheral injection, others have been elaborated through selective injection *via* catheters in the circulatory system or by inhalation of radioactive gases. The gas methods, using krypton-85 and methylradioiodide by inhalation, are reported with special emphasis on the information obtained concerning the left side of the heart and circulatory shunts. Another method for investigation of the coronary blood flow employs rubidium-86. An interesting new technique for the study of pulmonary function is described by Dyson and co-workers, employing oxygen-15, a cyclotron-produced positron emittor which has a half-life of 2.2 minutes. In the studies of pulmonary abnormalities, external counting by single, paired, and coincidence-scintillation detectors has been used. The value of such cardiac and pulmonary studies is largely in special problems, but seems likely to increase in importance.

The liver has been the subject of increasing interest with procedures directed toward the evaluation of liver function and scintillation mapping of the configuration of the organ. As developed by Taplin and others, Rose Bengal labelled with iodine-131 is considered to give accurate information in the study of polygonal cell activity. The demonstration of tumor masses in the liver as well as abnormal configurations from other diseases is accomplished by scintillation mapping following the injection of colloidal radiogold, radioiodine-labelled human serum albumin or radioiodine-labelled Rose Bengal. The medical value of functional liver tests is reported in the differentiation of medical and surgical jaundice and in the study of patients with bilharziasis.

The cellular components of the blood offer good opportunities for radioisotope techniques in a variety of diseases affecting the circulation. Chromium-51 methods for red blood cell study are now widely used and have become standard methods in blood volume determinations. A new method for the study of white blood cells and platelets *in vivo* is now reported by M. Pollycove. This technique, employing phosphorus-32-diisopropylfluorophosphonate (DFP^{32}), has produced new values for life span studies of these cellular components and now seems suitable for clinical use. Another technique employing cerium-144 is not yet suitable for use with human beings.

Other specific parts of the body subjected to radioisotope investigation are reported in a variety of papers. The accuracy of brain tumor localization and the assessment of the potentialities and limitations of the isotope technique are discussed by Shamov and co-workers. Cassen and Crandall have studied the kinetics of cerebral blood flow by external counting after injection of labelled human serum albumin into the carotid artery. Metabolic studies of bone by means of radiocalcium, radiogallium, and other isotopes are described. Yet another paper deals with the study of the gastrointestinal system with labelled proteins and fats with special emphasis on postoperative states and the management of the patient in that period.

In addition to specific organ systems, attention is directed to general body metabolism, particularly with respect to exchangeable electrolytes. The disturbances of sodium, potassium, chlorine, calcium and magnesium in a variety of disease states and in postsurgical conditions are attracting increasing interest. An interesting special technique for analysis of body arsenic by activation method has special application to the toxicology and occupational health aspects of arsenic poisoning. It is possible to measure quantities of this element as small as 10^{-10} g.

RADIATION HAZARDS IN DIAGNOSTIC PROCEDURES

Attention has been focused on the potential radiation hazards associated with the medical uses of radiation. Diagnostic radioisotope studies are not yet so frequent as to account for a significant proportion of the radiation exposure of the reproductively, and hence genetically, significant segment of the world population. Yet appropriate consideration should be given to this aspect of their use, particularly below the ages of 30–40 and more particularly in children and pregnant women. In the balance of medical judgment,

however, it is equally important that undue fear or exaggeration of radiation hazards not be allowed to prevent proper action. The hazard of not doing a procedure which can contribute to effective action for the benefit of the patient may be much greater than the radiation hazard. The physician must have a high sense of responsibility in this decision. He alone can make the final decision for the specific patient, though he should have full assistance from all relevant fields of science in making it. In appropriate evaluation of safety aspects two points must not be neglected, namely, that a more serious medical situation may justify the use of a greater radiation exposure with increased potential hazard relative to less urgent situations and that it is frequently impossible to assess the importance of a procedure in an individual patient until it has already been performed.

APPARATUS AND METHODS

Notable advances, applicable to clinical purposes, have been made in scintillation detectors and their associated electronic apparatus, particularly in pulse height discrimination and selection methods. Very large scintillation crystals and appropriate shields have so greatly increased the sensitivity of some systems that the doses of administered radioisotopes can be greatly reduced or very small amounts of naturally occurring ones can be detected. There have been numerous adaptations of multiple scintillation counters to special uses. It is now possible to measure the internal deposition and distribution of radiophosphorus by means of its bremsstrahlung. Scintillation scanning has been vastly improved by the incorporation of these principles as well as by mechanical improvements, electronic techniques for contrast control, background suppression, and presentation of the information in the form of images on photographic films or on cathode ray tubes. K. H. Lauterjung and W. Gruhle describe an interesting device in which the area of interest for isotope distribution is covered with a closed layer of G-M tubes and the information is translated to a recording oscilloscope which maps position by time differentials in the spreading discharge. The microscopic study of radioisotope distribution in tissues by autoradiography continues to be of value in many investigational studies and further refinements have been made in its technical aspects. The adaptation of radioisotopes to diagnostic purposes by transmission radiography is the subject of other contributions. The most recent studies have explored the potentialities of europium-155 and promethium-147 for this application.

THERAPEUTIC USES OF RADIOISOTOPES

The three lines of application of radioisotopes in treatment have quite different potentialities and have had comparably different courses of development. Most intriguing in principle, but least rewarding clinically, has been the concept of metabolic, dynamic localization of the radioactive source in the tissue of interest. More success has been achieved in the techniques where radioisotopes are mechanically introduced into the body tissues and cavities. Yet more highly developed, but less basically original, is the employment of radioisotopes at short or long distances, utilizing the beam of emitted radiations.

Metabolic Localization

In this conference, there are few contributions dealing with therapy by means of radioisotopes administered orally or intravenously for their therapeutic effect through metabolic localization. The treatment of thyrotoxicosis with radioiodine remains the outstanding achievement accomplished with this principle and is widely used around the world, though with many workers feeling that cases should be selected to avoid the increased potential radiation hazard in young people, pregnancy, etc. An interesting method of estimation of thyroid gland size by the use of air injection with tomography is described by W. Clode and co-workers. This is felt to contribute appreciably to the accuracy of dose estimation. Suppression of the normal thyroid by radioiodine continues to be useful in the management of severe cardiac and pulmonary disease. The proportion of cases of thyroid carcinoma in which radioiodine is important therapeutically is small. It has not been specifically reported in the contributions to this conference, but remains of considerable research interest and of some practical value. The convenience and efficacy of radiophosphorus in the management of polycythemia vera and some leukemias are well recognized, but nothing essentially new is included in these presentations.

Two reports deal with the concept of neutron capture therapy. This fascinating principle has so far given discouraging clinical results in the few patients in whom it has been attempted, but explorations are being pursued toward finding more appropriate forms of boron compounds and methods of injecting them into specific tumor circulation; into the potentialities of using other nuclides, particularly a group of elements with epithermal neutron capture peaks; and into the theoretical considerations of dosage distribution attainable. With continued research and the construction of more suitable nuclear reactor sources for medical purposes now under way, we must await future reports on these concepts.

Interstitial and Intracavitary Therapy

The use of radiocolloids in the peritoneal and pleural cavities for the suppression of malignant ascites and pleural effusions has been widely adopted since it was first proposed by J. H. Muller. He now presents a report on five-year results of such therapy and evidence of increased salvage of ovarian cancer patients in early stages who have received colloidal radioactive gold as well as surgery. This report is accompanied by studies of the distribution of the radiocolloid on the serous surfaces in human cases and estimations of the ranges of radiation dosage delivered. Another paper deals with the distribution of radiocolloids of gold, yttrium and

phosphorus after intraperitoneal injection in experimental animals. With the interstitial injection of radiocolloid into the larynx, other workers have explored the interstitial planes of that structure, their relationship to the spread of malignant tumors in the area, and the feasibility of therapy by this technique. Another report deals with a new method of preparation of high specific-activity colloidal chromic phosphate.

The interstitial use of larger particulate radioactive sources has received considerable attention. The potentialities of two electron-capture decay isotopes, caesium-131 and palladium-103, for interstitial use are described by P. V. Harper and co-workers. Of especial interest is the promise of reduced radiation hazard to the operator, lack of tissue reaction, and suitable dose patterns achieved by their employment.

Two reports deal with interstitial implantation of radioisotopes into the pituitary for destruction of the gland by radiation rather than by surgical means. Moseley and co-workers report on the use of ytrrium-90 pellets, inserted through the trans-sphenoidal approach with image-amplified fluoroscopic control. Ellis has employed gold-198, also trans-sphenoidally, but with stereotaxic control. Some palliation in advanced breast cancer, susceptible to hormonal action, is reported. The stereotaxic placement of radioisotopes into the globus pallidus of the brains of animals and man has been studied by Campbell and co-workers with a view to employing the technique for the treatment of human Parkinsonism. Interstitial cobalt-60 sources, inserted into the brain at the time of operation for glioblastoma, supplemented by external therapy, is proposed by A. Jentzer, and a similar application is described by J. Becker and K. E. Scheer. The use of a variety of isotopic applicators in accessible body cavities is exemplified by reports on the use of strontium-90 in the uterine cavity for the treatment of cystic glandular hyperplasia (less ovarian dose), gold encased cobalt-60 sources in beads and plastic masses, and macrosuspensions to fill balloons within cavities.

External Therapy

In terms of extent of use and investment, the most developed therapeutic application of radioisotopes has been in the form of teletherapy units. Most of these have contained cobalt-60 sources, but caesium-137 is now in the developmental stage and will undoubtedly receive more attention because of its advantageous longer half-life and reduced radiation protection requirements. The apparatus for teletherapy is now well developed with full attention paid to beam collimation, optimal source size, shielding of source and emergent beam, and mechanical features. Over 300 teletherapy cobalt-60 sources have been distributed from the United States and Canada alone to over 30 countries. At the same time, no advantage in the form of increased cure of cancer has been demonstrated and almost certainly should not be expected. The key to this interest in teletherapy lies rather in adjuvant benefits of which the most important are increase in depth dose with so-called "sparing" of the superficial layers of the skin. A theoretical advantage, not practically demonstrated, exists in the relatively decreased mass absorption coefficient of bone. All of these can be comparably achieved with megavoltage therapy of other types (Van der Graaff, linear accelerator, betatron, etc.) and indeed most of them are not greatly advanced over what can be obtained with highly filtered, constant potential, 250 kvp therapy, employing rotation techniques or precision multiple portals. Dependability is an outstanding feature of cobalt-60 units, but is somewhat counteracted by the necessity for source renewal. Under optimal circumstances, the dose–volume relationships seem better with megavoltage therapy and may well give less "radiation sickness," but this is not easily evaluated in clinical terms.

Many of the specific features of the teletherapy and megavoltage therapy situation are dealt with comprehensively in the presentations of M. Brucer and N. Simon and E. R. Paterson. Paterson has analyzed not only the physical features, but also makes an important contribution to the radiobiological problems of this form of therapy. In a variety of biological media, the relative biological efficiency of megavoltage seems appreciably less than with the 300 kvp range, with an average clinical estimated factor of 0.87–0.82:1.00. This 15% difference must be taken into account in comparing the real merit of dosages which can and will be delivered to tumor areas.

The accessory advantages of high-energy therapy must be given full and appreciative consideration, but another factor must be included, which is also stressed by Paterson. This has to do with the physical planning of therapy, including the optimal arrangement of portals, beam shaping with wedge filters, and other critical considerations relating to dosage pattern. In the expenditure of funds, the greatest return may well be achieved by the utilization of competent radiological physics consultation with less expensive conventional therapeutic apparatus rather than by teletherapy or other megavoltage without such expert treatment planning. Of course, all advantages should be exploited whenever possible, but a fully realistic perspective should be maintained in deciding on the best arrangements for patient care in each individual situation and the "glamour" of radioisotopes and atomic energy should not confuse this choice. Furthermore, the lack of superficial reactions in the skin may well mislead the relatively inexperienced therapist into overly optimistic dosage and unfortunate results.

An interesting paper from J. Baarli describes the design and characteristics of a short-distance caesium-137 unit, designed for such relatively superficial uses as treatment of supraclavicular lymph nodes. The use of caesium-137 in superficial applicators and intracavitary sources is reported by F. Gauwerky. I. A. Mohamed and co-workers report the successful use of strontium-90 applicators in the treatment of trachoma.

The possibilities of external beam therapy methods are not limited to high-energy X rays and the gamma and beta emissions of radioisotopes. The contributions of L. Skaggs and others and J. L. Born and others de-

scribe the uses of high-energy electrons and heavier particles respectively. Skaggs, Lanzl and Avery employ a 5- to 50-Mev linear accelerator with a device which scans the field with the high-energy electron beam. The combination takes full advantage of the depth-dose properties of the electron beam, is flexible in beam direction, field size and shape, and affords good protection of the patient from stray radiation. Born and co-workers have investigated the characteristics of protons, deuterons, alpha particles and ions of carbon, nitrogen, oxygen and neon. The linear energy transfer of the heavier ions has extended our information on relative biological efficiency in a variety of biological systems. The precise collimation attainable with protons, deuterons and alpha particles affords a tool which can be used for accurate local destructive effect in such tissues as the brain and pituitary. At the clinical level, proton and helium ion radiation has been used for hypophysectomy in patients with advanced breast cancer. The former is reported to produce some encouraging palliative response, the latter has not been sufficiently investigated.

In summary, there is a widely varied and extensive application of radioisotopes to both diagnostic and therapeutic problems in clinical medicine. The development of these uses must proceed with caution and with the long term evaluation which is required in the testing of human reactions. Due attention must be given to factors of radiation safety and protection, weighed against the medical benefits which are to be derived. The value of each procedure must stand on its own merits apart from the considerations of prestige or of novelty. Within this framework, we can be proud of these peaceful applications of atomic energy as being one of the brightest and most exciting developments in modern science.

Thyroid Uptake of I^{131} in Humans after Administration of Triiodothyronine

By J. A. Henry,* G. Derome,* P. Dor* and J. Mahaux†

The high uptake of radioactive iodine in hyperthyroid cases has become a classic diagnostic method. Following administration of I^{131}, the evolution of this uptake shows, in general, an early maximum toward the second hour followed by a more or less rapid drop. This drop corresponds to the liberation by the hyperactive gland of protein iodine into the blood stream. But there are certain cases of hyperthyroidism in which fixation of the iodine by the thyroid gland is less rapid and is maintained for a longer period at high levels. In these cases the uptake curve then takes the form of a domed curve, with a maximum uptake higher than 40 per cent of the ingested dose, occurring about 24 hours following the administration of radioactive iodine.

In certain clinically euthyroid patients, iodine concentration by the thyroid is sometimes very high. These subjects show an uptake curve, in the shape of a dome, in all respects comparable to those described in certain cases of hyperthyroidism. Such curves may be observed especially in persons coming from regions where goiter is endemic or in persons with more or less significant thyroid hyperplasia which seems to be linked to certain familial factors. In these cases it may be very difficult to determine whether the thyroid function is normal by using the classic test method of radioactive iodine uptake. We have sought to determine, following Greer[1] and Werner,[2] whether the administration of l-triiodothyronine (TIT) would not bring about modifications in iodine uptake which would make it possible to determine whether thyroid activity is normal or pathologic.

MATERIALS AND METHODS

The test consists of measuring the uptake of radioactive iodine by the thyroid before and after administration of TIT—chosen because of its rapid action. In general, TIT was administered orally in doses of 100 to 200 micrograms per day for 10 to 12 days. In a certain number of cases, administration of TIT was stopped before the second series of measurements; the other patients continued to take it for the entire duration of the test. This, however, did not modify the general picture of the results obtained. No patient showed any disorders attributable to this medication.

The measurements of thyroid uptake were carried out by means of a scintillation directional counter 2 hours, 6 hours and 24 hours after administration of a tracer dose of 75 microcuries of carrier-free I^{131}. Tables 1 and 2 show the values obtained after 2 hours and after 24 hours; the measurements after 6 hours did not add any particular diagnostic information.

The patients were divided into the following two groups: The first group consisted of 45 euthyroid subjects of which there were 34 cases of euthyroid goiters probably resulting from a lack of iodine in the diet, 4 cases of euthyroid goiter whose origin could not be determined, 6 cases of juvenile goiter and one case of goiter induced by a prolonged diet of cabbage. Twenty nine of the patients in this group took TIT for the entire duration of the test. The second group consisted of 19 clinically hyperthyroid patients. Seventeen had never been treated and 2 manifested hyperthyroidism which had proven refractory to treatment with radioiodine. Nine patients in this group took TIT for the entire duration of the test.

Before administration of TIT, all the clinically euthyroid patients showed an I^{131} uptake of over 40 per cent of the dose ingested after 24 hours. The clinically hyperthyroid subjects also had either an uptake of over 40 per cent of the tracer dose after 24 hours or an uptake curve with an early, high maximum.

RESULTS

Tables 1 and 2 give all the individual measurements carried out on each patient. The difference between I^{131} uptake by the thyroid before and after administration of TIT is shown in absolute values in the last two columns of these tables.

For all of the 45 clinically euthyroid patients, the average value of the drop in uptake of radioactive iodine after 24 hours was 32.2 per cent of the dose ingested. The decrease was greater than 20 per cent in 37 patients, and in 28 of these the decrease was higher than 30 per cent. The decrease was between 10 and 20 per cent in 6 cases, and was insignificant in 2 cases. Examination of the relationship between the differences in uptake 24 hours before and after administration of TIT and the value at the time of the first test reveals that the uptake capacity of the thyroid had

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decreased—the decrease falling between the extreme values of 35.3 per cent and 88.7 per cent in 39 of 45 cases. In the 6 other cases, the variation was less than 25 per cent. This was due to an over-all decrease of the thyroid's capacity to take up radioiodine. In fact, even though TIT decreased the rate of I^{131} uptake less in absolute values after 2 hours—lower concentrations were observed after this lapse of time. Nevertheless, the uptake ability of the thyroid was decreased on the average by 53 per cent of the initial value; this held equally for measurements made after 2 hours and for those carried out 24 hours after ingestion of the tracer dose of I^{131}. It should be noted that similar results are shown by the 29 patients who continued to take TIT during the measurements of the second test and by those who ceased taking TIT on the eve of the "tracer."

For all the 19 patients with clinical hyperthyroidism, the decrease in thyroid uptake after administration of TIT had an absolute average value of 3.6 per cent, which was less than the limits of precision of the measurements. Two patients (cases 3 and 13) showed an aberrant decrease in their thyroid uptake 24 hours after TIT of 54.7 per cent and 15 per cent, respectively, but for one of these the variation was relatively small. In 3 other patients (cases 4, 14 and 15), a rather marked decrease in I^{131} uptake after 24 hours was observed, being 21.1 per cent, 14.2 per cent and 13.5 per cent, respectively. However, in these three cases the measurements taken after 2 hours gave higher values

Table 1. I^{131} Uptake by the Thyroid in 45 Euthyroid Patients before and after Administration of l-Triiodothyronine

Case	*Uptake before TIT % dose ingested after*		*TIT administered*		*Uptake after TIT % dose ingested after*		*Difference in uptake % dose ingested after*	
	2 hr	*24 hr*	*Dose, γ*	*Days*	*2 hr*	*24 hr*	*2 hr*	*24 hr*
1	37.2	75.3	150	12	8.8	10	−28.4	−65.3
2	49	81.6	150	12	10.4	20.5	−38.6	−61.1
3	27.3	67.6	100	12	15.4	14.6	−11.9	−53
4	30.9	69.4	100	12	8.2	21.1	−22.7	−48.3
5	38	73.3	150	10	7.1	26.9	−30.9	−46.4
6	31.4	62.1	100	10	13.4	16.3	−18	−45.8
7	27.6	54.5	100	12	6.8	8.9	−20.8	−45.6
8	56.4	69.5	100	10	22.3	24.1	−44.1	−45.4
9	21.4	54.3	150	12	9	11.1	−12.4	−43.2
10	46.9	73.8	150	12	17.7	31.1	−29.2	−42.7
11	73.2	82.8	100	3	40.3	40.2	−32.9	−42.6
12	19.3	47.4	100	12	9.4	5.6	− 9.9	−41.8
13	23.1	50.7	100	12	6.6	9.3	−16.5	−41.4
14	61.3	87.6	150	12	21.4	47.2	−39.9	−40.4
15	25.8	58.9	100	12	12.9	19.3	−12.9	−39.6
16	20.9	58.1	100	10	7.5	18.8	−13.4	−39.3
17	22.8	61	50	20	16.1	21.8	− 6.7	−39.2
18	21.2	58.6	100	12	12.3	20.5	− 8.9	−38.1
19	16.5	51.6	100	7	8.9	14.7	− 7.6	−36.9
20	22	45.4	100	12	8.7	8.7	−13.3	−36.7
21	33.3	75.5	150	12	16.4	39.3	−16.9	−36.2
22	27.8	51.6	50	30	10.7	17.3	−17.1	−34.3
23	40.5	64.5	100	12	25.2	31.3	−15.3	−33.2
24	22.7	44.9	100	10	8.1	12	−14.6	−32.9
25	52.5	74	150	12	18.7	41.3	−33.8	−32.7
26	19.7	45.7	100	12	11.5	13.6	− 8.2	−32.1
27	21	53.3	150	12	8.2	21.3	−12.8	−32
28	29.7	55.5	100	10	18.4	24.4	−11.3	−31.1
29	35.5	68.8	100	12	18.3	39	−17.2	−29.8
30		56	100	10		26.6		−29.4
31	23.4	42	100	10	11.2	13.2	−12.2	−28.8
32	21.5	49.8	150	12	13.5	22.4	− 8	−27.4
33	29.7	64.7	100	10	21.2	39.8	− 8.5	−24.9
34	28.8	53.4	100	10	12	28.8	−16.8	−24.6
35	18.3	51.3	100	12	15.5	27.2	− 2.8	−24.1
36	41.7	50.9	50	25	34	29.9	− 7.7	−21
37		44.9	150	10		24.6		−20.3
38	23.7	51.5	100	12	14.2	33.3	− 9.5	−18.2
39	23.3	48.2	75	20	14.6	30.3	− 8.7	−17.9
40	29.3	63.2	100	12	14.6	47.9	−14.7	−15.3
41		70.6	100	10		56.4		−14.2
42	38.8	63.2	150	12	28	50.3	−10.8	−12.9
43		66.9	100	12		55.8		−11.1
44		61	100	10		54		− 7
			200	10		68.1		+ 7.1
45		61.6	100	10	24.7	58.1		− 3.5

Table 2. I^{131} Uptake by the Thyroid in 19 Hyperthyroid Patients before and after Administration of l-Triiodothyronine

Case	*Uptake before TIT % dose ingested after*		*TIT administered*		*Uptake after TIT % dose ingested after*		*Difference in uptake % dose ingested after*	
	2 hr	*24 hr*	*Dose, γ*	*Days*	*2 hr*	*24 hr*	*2 hr*	*24 hr*
1[a]	64.8	47.1	150	10	84.7	36.2	+19.9	−10.9
	52.7	60.3	100	12	45.1	64.9	− 7.6	+ 4.6
2[a]	68.1	57.4	100	10	59.8	47.8	− 8.3	− 9.6
3	38.5	80.8	75	12	11.7	26.1	−26.8	−54.7
4	66.5	71.4	100	12	73.2	50.3	+ 6.7	−21.1
5	36.5	70.5	100	12	32.7	61.3	− 3.8	−10.2
6		41.9	100	10		39.1		− 2.8
7	24.3	49.8	100	12	14.5	47.6	− 9.8	− 2.2
8	75.1	33.7	100	10	74.9	33.3	− 0.2	− 0.4
9	52.9	28.5	100	10	61.8	28.1	+ 8.9	− 0.4
10	24.4	45	100	10	20.5	45.7	− 3.9	+ 0.7
	24.4	45	200	10	28.5	55.3	+ 4.1	+15.3
11	17.1	43.8	100	10	19.1	51.8	+ 2	+ 8
12	27.3	41.4	100	12	17.8	52.9	− 9.5	+11.5
	27.3	41.4	200	12	17.6	52.4	− 9.7	+11
13	34.1	72.6	150	12	26.6	57.6	− 7.5	−15
14	36.7	52.2	150	12	39.9	38	+ 3.2	−14.2
15	52.4	36.1	150	10	56.2	22.6	+ 3.8	−13.5
16	42.4	80.9	150	12	54.4	76.4	+12	− 4.5
17	56.6	29.5	150	10	51	31.4	− 5.6	+ 1.9
18	47	48.9	150	6	52.7	53.7	+ 5.7	+ 4.8
19	47.4	20.1	175	10	42.1	12.4	− 5.3	− 7.7

[a] Hyperthyroid patient resistant to treatment with I^{131}.

after the administration of TIT, the uptake rates increasing from 66.5 to 73.2 per cent, from 36.7 to 39.9 per cent and from 52.4 to 56.2 per cent, respectively.

DISCUSSION

Our observations confirm the fact that administration of l-triiodothyronine significantly decreases the capacity for iodine uptake by the thyroid gland in the majority of the euthyroid subjects studied.[3] It is probable that this action is due to a decrease in the secretion of hypophysial thyroid stimulating hormone. In 4 cases we could determine the amount of thyroid stimulating hormone (TSH) in the plasma before and after administration of TIT. The drop in TSH value in these cases was very marked and paralleled the decrease in the capacity of the thyroid to take up radioiodine.

In hyperthyroid subjects, there is in general no decrease in I^{131} uptake by the thyroid 24 hours after the administration of TIT. Moreover, it may be said that when the uptake rate remains high during the first hours following the administration of I^{131}, a decrease after 24 hours cannot be interpreted as the consequence of a decrease in thyroid activity. Unfortunately, the quantitative determination of TSH in hyperthyroid patients before and after administration of TIT is not yet available. Research is being carried out.

CONCLUSION

Administration of l-triiodothyronine in a dose of 100 micrograms per day for 10 to 12 days provides a most useful diagnostic tool for separating the different types of goiters which have a high uptake of I^{131} after 24 hours. In a great majority of cases, this test makes possible the separation of cases of hyperthyroidism from goiters due to an iodine deficiency and from juvenile goiters. TIT strongly depresses the amount of thyroid stimulating hormone in the plasma of euthyroid subjects who have goiters with a strong radioiodine uptake. Its effect on the TSH of hyperthyroid cases is in process of investigation.

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Methods for the Determination of Thyroid Function and Differentiation of Different Pathophysiologic Types

By Nelson Carvalho, Lieselotte J. Genter and Eliseario F. Vasconcellos*

During the period October 1954 to March 1958, 1300 tests for the determination of thyroid function using radioactive iodine were performed at the Radioisotope Laboratory of the Clinical Hospital, Faculty of Medicine, University of São Paulo. Of these, 1096 were made by the standardized method of Horst, and they comprise the basis of the present investigation.

The method developed by Horst takes into account the recent knowledge about thyroid physiology and its relation to iodine metabolism. The endogenous iodine cycle comprises two phases:

1. The *inorganic phase*, which includes absorption of inorganic iodine by the gastrointestinal tract, its transport by the blood vessels, its absorption by the thyroid, and renal excretion of unfixed iodine.

2. The *organic phase*, which starts with transformation of the inorganic iodine into thyroid hormone, which includes hormone secretion by the thyroid together with hormone transport to peripheral tissues where it is utilized, and which ends with the transformation of organic iodine into iodide. This iodide again enters the inorganic phase, thus completing the cycle.

It is indispensable that the functional analysis of the thyroid gland by means of radioactive iodine should deal with both phases of the iodine cycle.

METHODS OF EXAMINATION

Test procedure for dealing with the inorganic and organic phases according to the technique of Horst:

(*a*) Forty microcuries of I^{131} are administered while the patient is in the fasting state.

(*b*) After two hours, measurement of radioactivity is made over the thyroid. This determination, in relation to the 24-hour test, shows the avidity of the thyroid for iodine—that is, the uptake velocity of inorganic iodine.

(*c*) After 24 hours, another measurement of radioactivity is made over the thyroid. After this period of fixation, the storage and excretion by thyroid tissue has attained an equilibrium, the level of which is indicated by the number of impulses counted over the thyroid (thyroid activity: T.A.).

(*d*) After 48 hours, a venous blood sample is obtained for determination of total plasma activity (P.A.). This total activity is an index of the quantity of thyroid hormone produced. For control purposes, the protein bound iodine (P.B.I.) is also determined. The amount of iodine precipitated by trichloroacetic acid corresponds closely to the plasma activity.

(*e*) The iodine not absorbed by the thyroid or by the extrathyroid locations of hormone production, is excreted by the kidneys. For determination of this radioactivity, urine was collected during 24 hours, excluding the first miction after the iodine intake. Measurements of urine activity (U.A.) were made on the 24-hour sample.

(*f*) Salivary glands play a role in the iodine cycle, inasmuch as they not only concentrate the iodine ion but also thyroxin, perhaps influencing its deiodination. The thyroxin iodinase which is responsible for iodination of thyroxin in the thyroid, is also present in the submaxillary and parotid glands. They therefore are regarded as having a role in thyroxin degradation and in recycling of iodine to the thyroid gland. Since there is a relationship between thyroid and salivary gland function, it is reasonable to expect that measurement of radioactivity of the saliva (S.A.) would be useful as a means of supplementing conventional thyroid tests.

MEASUREMENT TECHNIQUES

Measurements over the thyroid were made with a G10Pb type Geiger-Mueller counter (20th Century Electronics).

Secondary radiation was reduced to less than 10% or entirely eliminated by means of a 2 mm lead filter. We also used longitudinal counters of great volume with lead cathode which were placed at 30 cm from the neck. The radioactivity measured was calculated as the percentage of thyroid activity in relation to a standard containing the same amount of radioiodine as administered to the patient but which was measured in a plastic phantom.

Radioactivity of the plasma was measured with M6H liquid counters (20th Century Electronics) at-

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Table 1. Normals

Number of cases	*T.A.* ↑←→↓	*U.A.* ↑←→↓	*V.U.R.* ↑←→↓	*S.A.* ↑←→↓	*P.A.* ↑←→↓	*P.B.I.* ↑←→↓	*C.R.* ↑←→↓	*U.R.* ↑←→↓	*B.M.R.* ↑←→↓
61.....	2–56–3	3–56–2	2–57–2	5–55–1					
13.....	2– 8–3	3– 8–2	2– 9–2	5– 7–1	0–13–0	0–13–0	0–13–0	0–13–0	3–10–0

tached to a Philips type PW4032 scaler. By using the results obtained by measurement of the standard, the percentage per liter of plasma was calculated.

Urinary measurements were made by a method similar to that for plasma, giving the utilization ratio.

RESULTS

In 61 patients without metabolic disturbances the following normal values for particular features were determined:

Thyroid uptake after 2 hours..		10–25%
Thyroid uptake after 24 hours.	(T.A.)	30–50%
Urinary excretion in 24 hours..	(U.A.)	30–60%
Velocity of uptake ratio.....	(V.U.R.)	30–50%
Salivary secretion after 24 hours.....	(S.A.)	0.01–0.1%
Total plasma activity after 48 hours.....	(P.A.)	0–0.30% per liter
Protein bound iodine after 48 hours.....	(P.B.I.)	0–0.25% per liter
Conversion ratio.....	(C.R.)	15–45% per liter
Utilization ratio.....	(U.R.)	0.5% per liter

The value of the thyroid function test with I^{131} in different groups of patients has been explored further by study of the 1096 cases.

It is difficult to evaluate diagnostic accuracy of the method, especially when borderline cases are numerous. With respect to the cases studied, it should be said that positive therapeutic results still give the best diagnostic confirmation. The degree of variation with respect to the different measurements is shown in Table 1 where the middle figure in each instance shows the number of cases within the range regarded as normal, where the left figure shows the number giving a value above this range, and where the figure at the right gives the number below. In these 61 cases, radioactive measurements were made over the thyroid, and for urine and saliva, and in 13 of them plasma iodine and protein bound iodine measurements were also made. While in the first group, abnormal results were found in 8% of the cases, the second group showed normal measurements in the organic phase, thus indicating the necessity of always making measurements on the two phases of iodine metabolism.

In 298 patients with thyroid hyperfunction, confirmed by positive therapeutic results, the radioactivity measurements showed error in the form of deviation from the normal range as follows: thyroid activity 13%, urinary activity 13%, velocity of uptake ratio 10%, salivary activity 15%, and plasma iodine activity, protein bound iodine, conversion ratio and utilization ratio 17%. In only 4% of these cases, however, no measurements of hyperfunction were observed, thus showing the importance of making measurements on the whole group. Whichever method is used for determination of iodine uptake for diagnostic purposes, there apparently will always exist on the borderline between the normal and the abnormal, a fairly great overlapping. For the overlapping cases, the results may be improved only by combination of the different methods and analysis of the results from different standpoints. The data for thyroid hyperfunction are shown in Table 2.

Among the cases with thyroid hyperfunction, which show high plasma levels, two different types may be observed: first, there is the group which shows high values for the two-hour measurements, but shows somewhat low values for the 48-hour measurements, as observed in cases of severe thyrotoxicosis resulting from highly accelerated iodine metabolism; and second, the group which shows decidedly high levels at two hours and still higher levels at 48 hours. Such are cases of hyperthyroidism of intermediate severity.

By comparing plasma iodine concentrations of normal and hyperthyroid individuals, one notices that at 48 hours after intake of iodine in hyperthyroid pa-

Table 2. Hyperfunction Confirmed by Therapy

Number of cases	*T.A.* ↑←→↓	*U.A.* ↑←→↓	*V.U.R.* ↑←→↓	*S.A.* ↑←→↓	*P.A.* ↑←→↓	*P.B.I.* ↑←→↓	*C.R.* ↑←→↓	*U.R.* ↑←→↓	*B.M.R.* ↑←→↓
298.....	259–39–0	1–39–258	267–29–1	1–44–253					
58.....	54– 4–0	0– 6– 52	55– 3–0	0– 6– 52	48–9–1	48–9–1	48–9–1	48–9–1	51–7–0

Table 3. Disguised Hyperfunction

Number of cases	*A.T.* ↑←→↓	*U.A.* ↑←→↓	*V.U.R.* ↑←→↓	*S.A.* ↑←→↓	*P.A.* ↑←→↓	*P.B.I.* ↑←→↓	*C.R.* ↑←→↓	*U.R.* ↑←→↓	*B.M.R.* ↑←→↓
23.....	20–3–0	0–3–20	19–4–0	0–5–18					
8.....	6–2–0	0–2– 6	8–0–0	0–1– 7	8–0–0	8–0–0	8–0–0	8–0–0	0–23–0

Table 4. Neurovegetative Dystonia

Number of cases	T.A. ↑←→↓	U.A. ↑←→↓	V.U.R. ↑←→↓	S.A. ↑←→↓	P.A. ↑←→↓	P.B.I. ↑←→↓	C.R. ↑←→↓	U.R. ↑←→↓	B.M.R. ↑←→↓
28.....	8–18–2	2–17–9	7–20–1	1–25–2					15–10–3
10.....	3– 7–0	0– 8–2	3– 7–0	0– 8–2	1–8–1	1–8–1	1–8–1	1–8–1	

Table 5. Nodular Goiter

Number of cases	T.A. ↑←→↓	U.A. ↑←→↓	V.U.R. ↑←→↓	S.A. ↑←→↓	P.B.I. ↑←→↓	C.R. ↑←→↓	U.R. ↑←→↓	B.M.R. ↑←→↓	P.A. ↑←→↓
135.....	71–50–14	16–50–69	77–50–8	9–49–77				35–72–28	
16.....	6– 9– 1	0–10– 6	12– 4–0	1– 6– 9	7–8–1	7–8–1	7–8–1		7–8–1

tients, the iodine is almost completely incorporated into proteins in a proportion 10 to 15 times that found in normal patients. The increased plasma protein activity in these cases appears to occur for the following reasons: since the thyroid of patients with hyperfunction is depleted of iodine, the specific activity of the hormone deposit is increased in relation to the normal thyroid, causing the daily hormone turnover to be increased 10 or more times. The result is an increase in the intrathyroid metabolism which is reflected in the utilization ratio. Accordingly, the metabolic turnover rate of intrathyroid iodine is expressed by the maximum quantity of iodine captured by the thyroid in relation to the I^{131} bound to the plasma proteins.

Twenty-three cases showed a normal basal metabolic rate with atypical symptomatology or disguised hyperfunction (Table 3). Measurements showed error as follows: thyroid activity 13%, urinary activity 13%, salivary activity 21%, plasma activity, protein bound iodine, conversion ratio and utilization ratio 0%. In these cases, radioactivity measurements of the organic phase had meaning and tended to clarify the diagnosis.

Table 4 shows results obtained for neurovegetative dystonia cases. The characteristic aspect of this group was the great percentage of positivity for excess uptake (28%) and the normal results for the hormonal phase. It is not possible in these cases to exclude recognition of thyroid participation nor, on the other hand, the possibility of altered peripheral tissue reactions with respect to the thyroid hormone. In these cases high levels were found frequently in the 2-hour measurements after radioiodine intake, whereas at 24 and 48 hours, the thyroid and blood values were normal.

Among the 135 cases with nodular goiter (Table 5), the following results were obtained: 69 cases with confirmed hyperfunction, 49 normal cases, 9 cases with confirmed hypofunction, and 7 doubtful cases, giving a 6% error. In this group it was sometimes very difficult clinically to make a differential diagnosis. In the inorganic phase, the toxic and nontoxic forms may be superimposed but in the organic phase the certainty of diagnosis is elevated.

With respect to the 106 cases with hypothyroidism (Table 6), findings were as follows: 81 cases of confirmed hypofunction, 22 cases with doubtful diagnosis, and 3 cases with unconfirmed diagnosis of hyperfunction, representing 23% error. Thyroid hypofunction obviously is characterized by subnormal uptake values in both phases, the low index of measurements at 2 and 24 hours after the test doses being the main symptoms. In the majority of cases, there is also a marked delay in intrathyroid iodine metabolism with resulting low output of thyroid hormone. The blood hormone level may be so low in these cases that it cannot be measured by present methods. Urinary excretion is greatly increased.

Table 6. Hypothyroidism

Number of cases	T.A. ↑←→↓	U.A. ↑←→↓	V.U.R. ↑←→↓	S.A. ↑←→↓	P.B.I. ↑←→↓	C.R. ↑←→↓	U.R. ↑←→↓	P.A. ↑←→↓	B.M.R. ↑←→↓
106...	3–18–85	79–24–3	5–20–81	80–24–2					11–57–38
22...	0– 3–19	18– 4–0	0– 2–20	19– 3–0	1–1–20	1–1–20	1–1–20	1–1–20	

Table 7. Treated Thyrotoxicosis

Number of cases	T.A. ↑←→↓	U.A. ↑←→↓	V.U.R. ↑←→↓	S.A. ↑←→↓	P.A. ↑←→↓	P.B.I. ↑←→↓	C.R. ↑←→↓	U.R. ↑←→↓	B.M.R. ↑←→↓
92.....	0–34–58	57–35–0	0–38–54	55–36–1					9–59–24
13.....	0– 3–10	9– 4–0	0–12– 1	10– 3–0	0–4–9	0–4–9	0–4–9	0–4–9	

Table 8. Extrathyroid Diseases

Number of cases	*T.A.* ↑←→↓	*U.A.* ↑←→↓	*V.U.R.* ↑←→↓	*S.A.* ↑←→↓	*P.A.* ↑←→↓	*P.B.I.* ↑←→↓	*C.R.* ↑←→↓	*U.R.* ↑←→↓	*B.M.R.* ↑←→↓
87	5–69–11	8–72–7	6–81–0	10–77–0					
10	0– 9– 1	2– 8–0	0–10–0	1– 9–0	2–8–0	2–8–0	2–8–0	2–8–0	0–0–87
56	0–55– 1	3–53–0	1–54–1	1–55–0					
5	0– 5– 0	0– 5–0	0– 5–0	0– 5–0	0–5–0	0–5–0	0–5–0	0–5–0	56–0– 0

Table 9. Without a Clinical Diagnosis

Number of cases	*T.A.* ↑←→↑	*U.A.* ↑←→↑	*V.U.R.* ↑←→↑	*S.A.* ↑←→↑	*P.A.* ↑←→↑	*P.B.I.* ↑←→↑	*C.R.* ↑←→↑	*U.R.* ↑←→↑	*B.M.R.* ↑←→↑
206	71–113–22	23–116–67	84–97–25	21–111–74					
21	6– 12– 3	1– 17– 3	6–10– 5	2– 16– 3	10–9–2	10–9–2	10–9–2	10–9–2	10–189–7

In the group of 92 cases with thyrotoxicosis treated either clinically or by surgery (Table 7), 35 were functionally normal, and 57 were hypofunctional. In all of these cases, the I^{131} test was performed because of continuing clinical symptoms of limited thyroid hyperfunction. In these cases the uptake values were normal or only slightly elevated, but the protein bound plasma iodine values were high. Even after strong stimulation of the thyroid by the hormone, no increase in uptake was detectable.

Table 8 shows results relative to extrathyroid diseases. In the first group of 87 patients with a low basal metabolic rate due to hypogenitalism, hyposomatism, Addison's disease, central affections, etc., and in the second group of 56 patients with an increased basal metabolic rate due to diabetes, leukemias, circulatory diseases, etc., the tests of the two phases analysed together permitted a diagnosis, showing a normal thyroid function. In thyroid dysfunctions due to other endocrine diseases participation of the thyroid is secondary. Diagnosis is difficult to make in these types of cases because of the compensatory functional equilibrium existent in the endocrine system. Due to the narrow correlation between the pituitary and the thy-

Table 10. Summary

U.A. 24 h 30-60%	T.A. 2 h 10-25%	T.A. 24 h 20-50%	I.V.C. 30-50%	S.A. 24 h 0.01-0.09%/1	P.A. 48 h 0.30%/1 0.30%/	P.B.I. 48 h 0.25%/1	C.R. 15-40%	U.R. 0,5%/1	B.M.R. +10	B.M.R. −10	Diagnosis / Normal values	Cases No.	Cases error (%)	Remarks
↔	↔	↔	↔	↔	↔	↔	↔	↔	↔		Normal	61	8%	In the organic phase 0% error
↓	↑	↑	↑	↓	↑	↑	↑	↑	↑		Thyrotoxicosis	298	4%	Taking both phases together
↕	↕	↕	↑	↓	↑	↑	↑	↑	↕		"Hot" adenoma	135	6%	In both phases
↓	↑	↑	↑	↓	↑	↑	↑	↑	↔		Disguised hyperfunction	23	13% in the iodine phase	0% in the hormonal phase
↑	↓	↓	↓	↑	↓	↓	↓	↓	↕		Hypo-thyroidism	106	23%	1.4% error in both phases
↕	↕	↕	↕	↔	↔	↔	↔	↔	↕		Neuro-vegetative dystonias	28	28% in the iodine phase	Normal in the hormonal phase
↔	↕	↔	↕	↔	↔	↔	↔	↔	↓	↑	Extra thyroid diseases	87	0%	In both phases
↕	↕	↕	↕	↕	↔	↔	↔	↔	↕		Treated thyro-toxicosis	92	0%	In both phases

roid, it is difficult to determine the origin of diseases of this group, especially in the presence of hyperfunction. In these cases, the measurement values for the 2-hour and the 24-hour tests are more or less high.

In a group of 206 patients without a definite clinical diagnosis (Table 9), the following results were obtained: 62 with hyperfunction, 96 normal, 21 with hypofunction, and 25 in which it was not possible to make a definite diagnosis due to the discrepancies of results, giving an error of 12%. The majority of these patients had received previous treatment either for hypo- or hyperfunction of the thyroid without a definite diagnosis. Part of the exogenous dysfunctions was due to fatigue of the thyroid caused by iodine deficiency. As a result of such deficiency, the thyroid stores are depleted and the hormone can be produced only from the minute amounts of iodine brought in by food. The iodine given for tests in these cases is taken up very rapidly and hormone production and excretion by the thyroid are immediate. The results therefore are equivalent to those obtained from cases of thyrotoxicosis; but, the high values obtained are opposed by the plasmatic iodine indexes which are either normal or only slightly increased. This difference between the thyroid and blood values is the only possible means of a differential diagnosis between thyrotoxicosis and abnormal thyroid functions due to chronic lack of iodine. The excess of iodine intake produces also a thyroid fatigue, however temporary, which shows all the signs of a primary thyroid hypofunction. In such cases the only possibility of clarifying the diagnosis is to use thyrotropic hormone and repeat the test which then will not be distorted.

SUMMARY

Above are some of the considerations we found of interest in attempts to clarify certain cases of thyroid diseases by means of functional diagnosis with radioiodine.

We believe that possibilities of the method may be increased by adding to the tests already described the test of pituitary–thyroid correlation.

Finally, we show Table 10 summarizing our experience with the different methods that were used and that together comprise the group of tests of the two phases of iodine metabolism which we feel are required to make a diagnosis of thyroid function.

Radioactive Iodine Studies in Normals and in Various Thyroid Disorders Among Filipinos

By Paulo C. Campos, Augusto D. Litonjua, Emilio G. Horrilleno, Irineo Lawas, Visitacion Manipol and Benjamin Baltasar*

Measurement of radioactive iodine uptake and urinary excretion has become a standard aid in the evaluation of thyroid function.[1–8,10–13,15–17] Much work has been done on this subject abroad. Measurements of 1st,[10] 2nd, 6th,[14] 24th,[14,21] and 48th[21] hour uptake have been undertaken and their comparative usefulness carefully evaluated. Previous workers have arrived at the conclusion that for routine diagnostic work the 24th hour uptake is the most reliable and practical.[14–18,20,21] The values obtained have ranged from 15 to 50% in 24 hours. This is the first extensive study of the sort undertaken in this country, and because of that we have decided to repeat the 1st, 2nd, 6th, 24th, and 48th hour uptake studies made among our subjects.

In addition to radioactive iodine and urinary excretion measurements, an investigation of the protein-bound iodine-131 conversion ratio and total accountable iodine-131 was done similarly on many of the subjects investigated.

As a complement to these studies, an investigation of the total iodine intake in the food and water per 24 hours was made among some of the subjects.

The average diet of the Filipino was found to have an iodine content of from 70–100 gamma per 24 hours. A representative diet is illustrated below:

Breakfast: Sardines, rice, sweet potato (boiled), burnt rice water, brown sugar.

Lunch: Broiled fish with squash and malunggay, bagong and kalamansi, rice and banana.

Supper: Broiled fish with mongo and camote leaves, bagong and tomatoes, rice and banana.

Broiled fish, it should be noted, was classified as sardines. Fresh water fish like mudfish and catfish are commonly used in inland towns. Bagong alamang was classified as shrimp. Table 1 gives a very rough estimate of the iodine in Filipino food.

It is only now that serious study has been undertaken to determine the iodine content of the sources of drinking water in the various communities of the country, especially where goiter is endemic. The iodine content of drinking water in Manila and its environs is around 50 to 100 gamma per liter. It will be noted therefore that there is a correspondingly sufficient intake of iodide per 24 hours for the average Manila inhabitant on the basis of an average iodine requirement of 114 gamma per day such as has been quoted for the New York city area. In as much as the majority of our subjects are from Manila, it is apparent that there is no demonstrable iodine deficiency in the normal subjects we studied. With this background, our findings are interesting. Our normal PBI, for instance, is from 4 to 8.5 gamma per cent which is slightly higher than the figures obtained by Barker *et al.* Equally interesting are the results obtained in our radioactive iodine investigations which differ slightly from the results obtained by investigators in the United States, as will be seen subsequently.

MATERIALS AND METHODS

The subjects in this study were taken from the wards, the thyroid clinic, the private and out patient groups, medical students and the staff of the Philippine General Hospital. Care was taken to insure that no antithyroid drugs, iodide containing preparations, or hormones had been administered to any of the subjects for at least one month prior to the investigation. Pregnancy, liver[19] and kidney[9] diseases were scrupulously ruled out. Basal metabolism studies and protein bound iodine studies using the procedure of Barker, Humphrey and Soley were done on these patients and soon after they were subjected to radioactive iodine uptake investigation. The patients received an average of from 10 to 12 μc. A few in whom scintigraphic examination was simultaneously done were given from 40 to 50 μc. Uptake in the thyroid was measured during the 1st, 2nd, 6th, 24th, and 48th hours. Measurements were done with a DS-1 directional scintillation detector having a removable directional shield and an aperture of one inch. The detector was placed 12 inches away from the thigh and the thyroid gland. Two one-minute counts were always made on both the thyroid and the thigh. A Model 183 Nuclear Count-O-Matic scaler was employed in all these investigations.

Each patient was provided with bottles containing thymol preservatives for collection of urine during 2 succeeding 24 hour periods immediately following

* Radioisotope Laboratory, U.P.-P.G.H. Medical Center, Manila. This work was aided by a grant from the National Research Council. The biostatistical computations in this paper were done by Dr. Victor Valenzuela, Dr. Arturo Librea and Mr. Idelfonso T. Cruz of the Institute of Hygiene, University of the Philippines.

administration of the tracer dose. If the resulting volume of a 24-hour period was less than one liter, the sample was subsequently diluted to one liter with ordinary non-radioactive tap water. On the other hand, if the volume of the 24-hour period exceeded one liter, that volume was measured off after thorough mixing of the sample and the total volume was noted down. In either case, 3 one cc aliquot portions were measured off from the one liter samples, and their radioactivity measured by the well-counter type of scintillation detector (Type DS-3). The excretion ratio (expressed as a percentage) was then obtained by dividing the mean net counting rate (corrected by subtracting the background rate) for 3 sample aliquots by the mean net counting rate for 3 standard aliquots which had previously been prepared by dissolving the administered dose of radioactive iodine (RAI) in one liter of tap water. If the volume of the original 24-hour sample was below one liter, the per cent excretion calculated from the above formula was taken as representing the total RAI excretion for that 24-hour period. On the other hand, if the volume of the 24-hour sample exceeded one liter, the per cent excretion as calculated above, multiplied by the total volume of the urine sample, gave the total per cent excretion of RAI for that 24-hour period.

Twenty four hours after administration of the tracer dose, a 5 cc sample of heparinized blood was taken. A count was then made on the supernatant plasma which was subsequently passed through an ion exchange column using the procedure described by Lahr and Tabern; protein bound iodine-131 subsequently was measured in a well counter. The conversion ratio, CR (expressed as a percentage) was then given by

$$\frac{\text{counts/min in effluent from column}}{\text{counts/min in original plasma sample}}$$

An attempt was likewise made to measure total accountable radioiodine at the end of 24 hours using the 24-hour uptake and the total 24-hour urinary excretion.

Table 1. Filipino Diet

	I_2/kg (gamma)	Amount used (g)	I_2 (gamma)
Banana	9.0	150	1.35
Rice	20.3	300 (raw)	6.09
Sweet potato	4.5	100	0.45
Sardines	479.0	120	57.48
Squash	9.8	100	0.98
Malunggay	17.5	40	0.7
Camote leaves (Ikomea reptans)	27.0	40	1.08
Mongo	33.8	50	0.169
Tomatoes	5.7	50	0.285
Kalamansi	5.1	10	0.051
Salt	180.0	3	0.54
Bagong alamang (shrimp)	1121.0	20	22.42
Tap water	0.45	1500	0.0068
		Total	91.6018

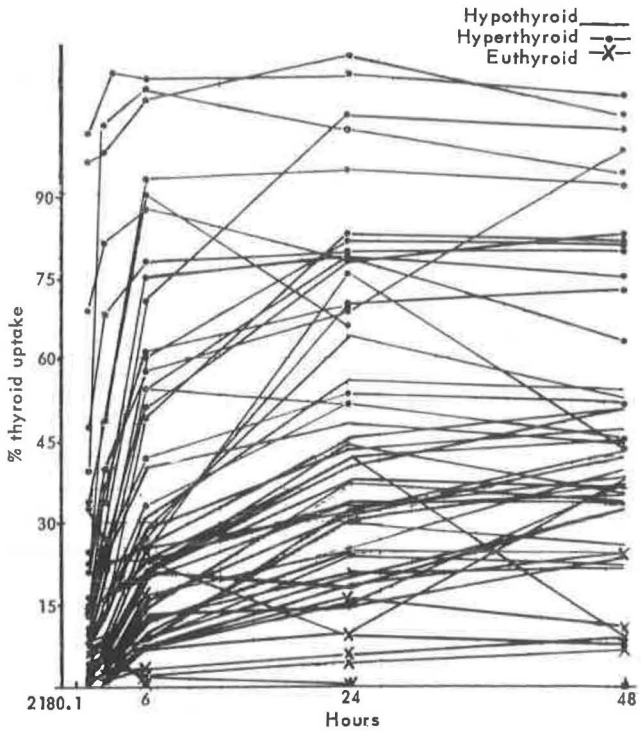


Figure 1. RAI uptake in euthyroid, hyperthyroid, and hypothyroid subjects

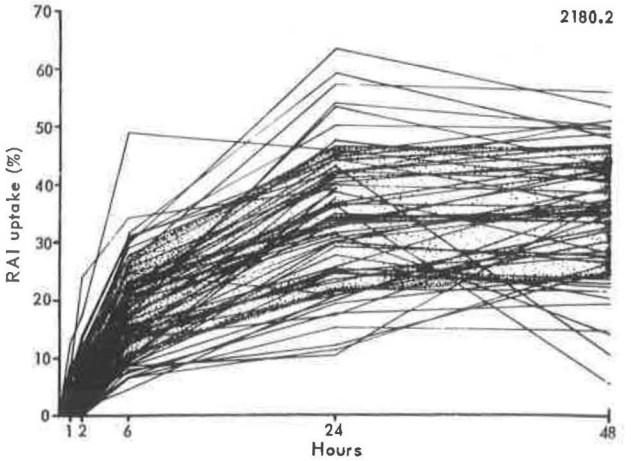


Figure 2. RAI uptake in normal subjects, the shaded area indicating the range of variability regarded as normal

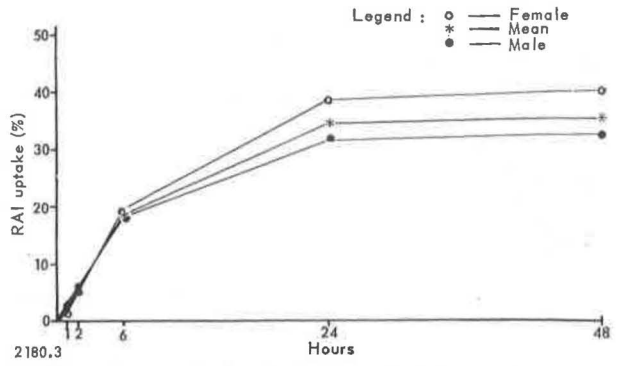


Figure 3. RAI uptake by sex

Decay factors for the tracer doses as employed in this study were also taken into consideration. The final diagnosis of euthyroidism, hyperthyroidism and hypothyroidism was made in each instance only after a careful evaluation of their BMR's, PBI's, RAI's and clinical pictures. They were separated into five categories clinically as follows:

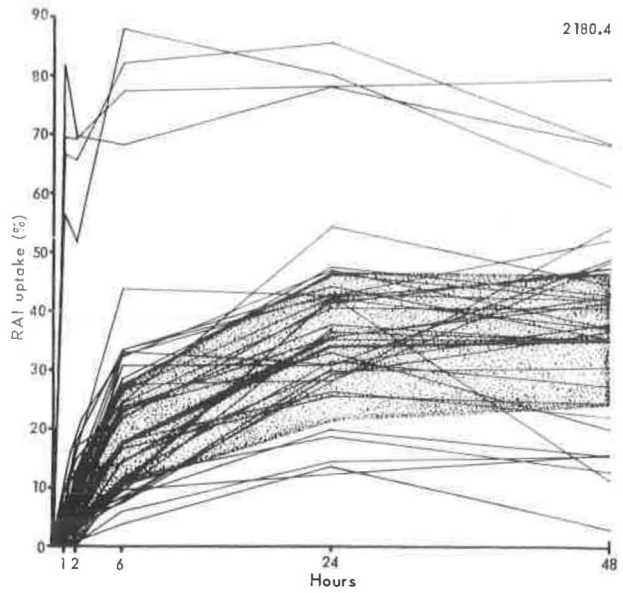


Figure 4. RAI uptake in euthyroid subjects with goiter; the shaded area is the same as that shown in Fig. 2 for normal subjects

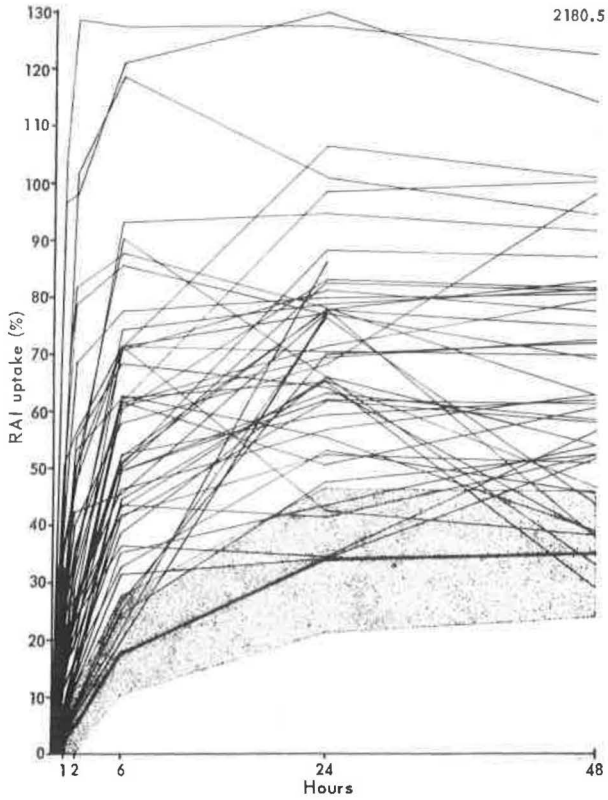


Figure 5. RAI uptake in hyperthyroid subjects; the shaded area is the same as that shown in Fig. 2 for normal subjects

1. *Euthyroid controls:* these were normal healthy adults with no evident complaints referable to any of the various systems and whose thyroids were normal on inspection and palpation.

2. *Goitrous euthyroids:* these were clinically euthyroid patients whose only complaint was their thyroid enlargement. In all instances PBI was normal and BMR almost always within normal range.

3. *Hyperthyroid group:* patients with clinical manifestations of increased thyroid activity whose PBI's and BMR's were invariably above normal values.

4. *Hypothyroid group:* patients with clinical manifestations of hypothyroidism and whose PBI's and BMR's were invariably below normal.

5. *Other diseases:* this was a loose category of patients sick with various diseases.

PART I. UPTAKE STUDIES

Results

A total of 177 patients (Table 2) were studied carefully. Of this number, 60 were normal clinically and did not present any gross abnormality of the thyroid gland on physical examination. About 41 showed an abnormal thyroid gland but were clinically euthyroid. Forty eight patients were definitely hyperthyroid clinically and their thyroid glands varied from slight to moderate enlargement. Eight were definitely hypothyroid clinically. There were 20 other cases of various etiologies. The data are being presented here because they present interesting aspects of thyroid function study.

The normals were mostly medical students, members of the staff and a few individuals who came for check-up. Their PBI's ranged from 3.9 to 8.5 gamma per cent with a mean of 7.26 gamma per cent. Their BMR's ranged from -12% to $+44\%$, and their ages ranged from 12 to 62. Results of the radioactive iodine uptake studies are shown in Tables 3 through 9.

Discussion

Figure 1 is a composite graph of radioactive iodine uptake in all the subjects studied, including normals and abnormals. Figure 2 shows the results of uptake studies in normals. Figure 3 presents the slight differ-

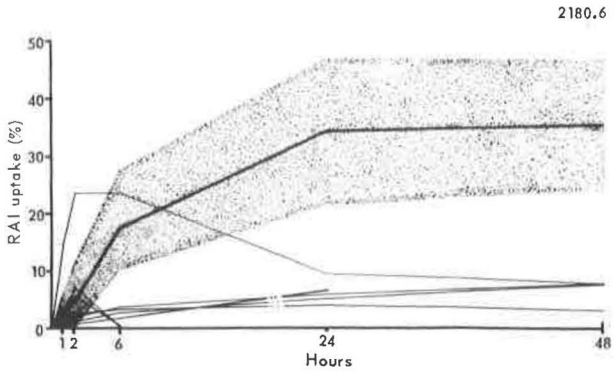


Figure 6. RAI uptake in hypothyroid subjects; the shaded area is the same as that shown in Fig. 2 for normal subjects

Table 2. Number of Patients

	Male	*Female*	*Total*
Normals	38	22	60
Euthyroids with goiter	6	35	41
Hyperthyroids	7	41	48
Hypothyroids	1	7	8
Other Diseases	11	9	20
Grand total	63	114	177

ence between males and females. This difference has been found to be statistically significant. Figure 4 shows the results in patients with goiter but who were clinically euthyroid. What is significant is the marked difference in the values between normals (euthyroids) and hyperthyroids, and between normals (euthyroids) and hypothyroids (Figs. 5 and 6). There is, however, some overlapping of the values between hyperthyroids and euthyroids, and between euthyroids and hypothyroids. In other words, the upper limits of normals overlap to a considerable degree with the lower limits of hyperthyroids and the lower limits of normals overlap to a similar extent the upper limits of hypothyroids. There is, however, a gap between the lowest hyperthyroid values and the highest hypothyroid values. As we look over the graphs, it is apparent that the most reliable single uptake reading is the 24-hour reading. Accordingly, even if the highest normal reading recorded was 63.5% during the 24th hour and the lowest 10.2%, the lowest hyperthyroid reading recorded was 34.1% during the 24th hour and the highest hyperthyroid reading was 130.7%. It may be noticed that the highest hypothyroid reading during the 24th hour was 9.4% while the lowest reading recorded was 0 (Fig. 7). One of the most important reasons for this big overlap is the fact that while the instrument we have is acknowledged to be one of the best for the pur-

Table 3. RAI Uptake

	1st hr	*2nd hr*	*6th hr*	*24th hr*	*48th hr*
Normal					
Males					
Mean	3.02	5.76	18.61	31.52	32.92
Standard deviation	2.99	4.40	9.01	11.39	11.26
Females					
Mean	1.95	5.65	19.66	38.40	40.01
Standard deviation	2.56	5.33	7.91	13.81	9.74
Males and females					
Mean	2.64	5.72	18.97	34.14	35.33
Standard deviation	2.90	5.33	8.67	12.70	11.28
Euthyroids with goiter					
Males					
Mean	4.1	8.4	20.1	32.8	33.13
Standard deviation	2.42	4.21	8.22	8.36	10.29
Females					
Mean	12.2	15.6	29.1	41.5	38.8
Standard deviation	22.14	19.49	21.75	17.46	11.57
Males and females					
Mean	10.9	14.45	27.6	40.15	37.86
Standard deviation	20.51	18.10	20.40	16.61	11.72
Hyperthyroids					
Males					
Mean	19.55	34.85	51.6	62.65	60.0
Standard deviation	12.1	20.09	25.94	21.97	29.22
Females					
Mean	22.9	35.31	60.24	71.82	67.47
Standard deviation	23.0	28.15	24.65	21.63	22.22
Males and females					
Mean	22.39	25.24	58.94	70.48	66.58
Standard deviation	21.82	36.54	21.63	22.05	23.45
Hypothyroids					
Males and females					
Mean	4.12	7.05	5.82	4.69	4.40
Standard deviation	5.28	7.61	7.95	3.06	3.52
Other diseases					
Males					
Mean	1.73	4.95	14.41	21.73	25.56
Standard deviation	1.91	7.47	12.93	15.31	15.93
Females					
Mean	4.83	9.43	18.39	24.91	27.73
Standard deviation	4.15	6.28	12.77	16.40	17.19
Males and females					
Mean	3.47	7.47	16.65	23.16	26.78
Standard deviation	3.69	7.18	12.99	15.89	16.67

Table 4. Normals

Patient	*Age*	*Sex*	*RAI uptake*					*RAI excreted*		*PBI*	*BMR*	*Total Ac'tbl I^{131}*
			1st hr	*2nd hr*	*6th hr*	*24th hr*	*48th hr*	*24th hr*	*48th hr*			
1. P.C.	36	M	2.1	3.5	15.3	25.7	39.9	51.3	6.0	5.0	+ 8	77.0
2. B.S.	24	M	—	6.7	19.3	30.7	37.5	43.0	—	8.5	+10	73.7
3. I.L.	39	M	4.6	11.9	29.0	44.3	47.1	—	—	6.1	+12	—
4. J.P.	24	M	3.7	6.1	—	19.9	37.4	46.3	3.3	6.5	—	—
5. A.L.	27	M	5.6	7.2	16.7	30.1	36.3	52.2	2.6	7.5	—	82.3
6. C.C.	24	M	6.5	12.0	23.1	33.9	33.6	—	—	9.7	—	—
7. E.C.	28	M	0	0	9.4	30.0	26.7	53.7	8.9	7.7	—	83.7
8. R.D.	24	M	8.2	9.4	30.4	50.9	50.0	37.1	—	7	—	88.0
9. A.G.	40	M	1.7	5.0	12.7	25.4	24.9	76.5	6.9	4.6	+12	101.9
10. F.F.	24	M	5.8	9.2	20.1	34.1	35.0	96.2	3.9	10.4	—	130.3
11. U.L.	22	M	0	1.9	9.9	24.8	22.3	36.1	—	8.3	—	60.9
12. J.B.	22	M	4.6	10.4	24.9	—	43.1	47.8	4.6	9.4	—	—
13. B.A.	22	M	2.3	5.0	15.3	23.7	27.9	40.3	—	9.6	—	64.0
14. R.O.	36	M	6.4	13.6	31.0	42.2	41.1	35.9	1.7	6.3	+15	78.1
15. E.A.	21	M	3.1	5.5	23.0	31.8	36.7	11.8	4.3	5.4	—	43.6
16. M.C.	25	M	2.4	2.7	20.4	31.5	14.3	—	—	5.2	—	—
17. D.C.	25	M	3.3	8.7	25.5	40.4	44.5	51.4	4.5	7.0	—	91.8
18. R.E.	22	M	0	4.6	7.3	17.5	19.5	40.4	12.6	—	—	57.9
19. M.E.	24	M	0.3	5.3	13.3	27.8	21.4	47.9	3.8	—	—	75.7
20. R.B.	23	M	12.4	17.2	49.0	46.0	40.5	44.0	1.5	8.9	—	90.0
21. R.P.	12	M	8.7	11.4	25.9	20.9	30.2	—	—	7.4	−12	—
22. F.G.	22	M	—	1.5	6.9	15.2	14.9	95.2	7.6	6.0	—	110.4
23. E.M.	23	M	3.1	5.8	13.9	24.9	24.0	86.4	2.9	7.8	—	111.3
24. R.V.	22	M	0	1.5	4.7	21.0	—	41.4	3.5	8.8	—	62.4
25. Q.U.	23	M	2.4	6.3	15.6	—	32.8	9.1	2.0	7.4	—	—
26. J.F.	33	M	1.5	2.6	21.9	36.4	5.7	56.2	3.2	7.2	—	92.6
27. D.N.	25	M	5.4	7.7	13.6	25.0	28.5	57.9	4.8	6.6	+ 6	82.9
28. A.C.	29	M	0	0	6.6	11.3	26.6	72.4	4.6	3.9	—	83.7
29. B.I.	22	M	0	2.5	26.4	45.3	51.3	54.6	4.2	8.2	—	99.9
30. L.G.	24	M	4.3	7.0	22.4	43.2	10.8	38.6	2.7	8.3	—	81.8
31. T.G.	22	M	1.0	6.0	19.8	36.2	42.6	65.4	3.5	6.0	—	101.6
32. O.R.	17	M	6.5	10.7	—	53.6	43.4	—	2.6	4.9	− 1	—
33. R.C.	23	M	0.7	0.1	13.6	42.3	47.7	51.5	5.1	8.5	—	93.8
34. A.F.	22	M	0	0	8.0	12.1	25.3	67.1	4.9	6.0	—	79.2
35. C.G.	22	M	0	0.7	8.9	29.1	27.9	48.7	5.0	4.4	—	77.8
36. D.F.	25	M	0	1.6	13.2	30.0	39.4	50.2	2.2	7.4	—	80.2
37. F.F.	22	M	0.5	2.4	21.2	41.1	43.6	53.8	1.6	5.4	—	94.9
38. G.L.	22	M	4.5	5.5	21.9	36.7	43.9	38.3	2.8	5.6	+ 7	75.0
1. V.M.	30	F	4.4	3.5	13.9	20.7	32.2	50.4	—	5.0	—	71.1
2. L.B.	22	F	0	2.7	13.9	36.6	36.2	50.3	—	5.9	—	86.9
3. E.C.	21	F	2.8	8.2	22.0	44.3	36.2	—	—	8.4	—	—
4. B.B.	22	F	0	0	6.7	19.3	24.5	33.3	13.6	4.7	—	52.6
5. H.C.	20	F	0	2.7	10.9	21.9	21.6	—	—	7.5	—	—
6. M.A.	23	F	4.4	9.0	—	54.2	50.3	—	—	6.7	—	—
7. A.U.	13	F	0	2.3	23.0	40.0	38.9	45.3	3.0	6.2	+ 2	85.3
8. J.T.	37	F	2.3	5.3	18.5	41.7	51.4	—	—	7.5	+44	—
9. C.F.	32	F	5.2	4.3	13.4	17.3	32.0	—	—	8.2	—	—
10. P.R.	21	F	4.0	4.7	31.6	59.4	47.5	50.0	2.8	7.2	+ 2	109.4
11. P.M.	24	F	0	2.0	16.9	38.9	28.2	44.2	7.2	5.5	+ 9	83.1
12. M.L.	24	F	0	3.8	8.6	10.2	37.6	33.2	—	8.5	—	43.4
13. N.I.	22	F	0.5	6.1	29.9	63.6	53.9	50.6	2.2	6.0	—	114.2
14. Z.C.	22	F	0	0	14.3	33.1	42.2	62.2	2.1	4.9	—	95.3
15. L.B.	23	F	0	1.8	21.4	42.2	45.9	61.7	3.5	6.9	—	103.9
16. R.S.	24	F	0	3.2	26.6	57.4	56.3	54.1	3.2	5.4	—	111.5
17. F.T.	48	F	3.5	7.3	14.9	35.0	33.1	56.0	3.3	9.5	+10	91.0
18. P.C.	22	F	6.9	13.9	30.8	45.0	49.1	24.1	0 9	4 4	+ 8	69.1
19. E.R.	32	F	0.8	8.3	22.1	47.9	42.7	36.9	1.4	—	—	84.8
20. F.M.	25	F	8.3	24.0	34.2	39.3	—	28.5	—	—	—	67.8
21. M.C.	25	F	—	—	—	37.7	—	—	—	—	—12	—
22. T.A.	65	F	—	—	—	39.2	—	—	—	5.9	+16	—

pose of uptake studies (we are using a DS-1 directional scintillation counter with a shield), still the incidence of scattered radiation is considerable. This is best attested by the observation that the highest value in the hyperthyroid group during the 24th hour is as high as 130.7% which means that scattered radiation alone can alter the true reading by as much as 30%. On the whole, however, we can with confidence say that the 24th hour uptake reading of between 15 and 45% are well within normal limits. Moreover, females show higher uptake for the 6th, 24th, and 48th hours than males, although the 1st hour uptake was higher in the males than in the females (Fig. 3).

In four of the patients it was observed that there was an early and marked increase in uptake attaining the maximum at the 6th hour, and the 24th hour uptake being within normal limits. Investigation of these patients showed that they were rendered euthyroid with Tapazole.

In the data for hyperthyroid females, there is a significant correlation between the 24th hour RAI uptake and PBI (Table 10), in the positive direction, that is, with increase of RAI uptake (24th hr), there was increase of PBI. Changes or variations of PBI did not fully parallel the RAI 24th hour uptakes. Only about 13.3% of the total showed significant positive correlation. For the males in this group there is correlation, 7.7% of the variation of PBI values being accompanied by a commensurate increase in RAI uptake. However, the sample studied was small and further study is suggested.

For the hypothyroids there is negative correlation; 6.4% of the variation of PBI could be explained by changes in RAI uptake.

Table 5. Euthyroids with Goiter

Patient	*Age*	*Sex*	*RAI uptake*					*RAI excreted*		*PBI*	*BMR*	*Total Ac'tbl I^{131}*
			1st hr	*2nd hr*	*6th hr*	*24th hr*	*48th hr*	*24th hr*	*48th hr*			
1. T.C.	21	F	0.30	0.35	6.0	14.4	15.7	28.7	3.4	7.4	+24	43.1
2. E.A.	45	F	1.6	2.7	14.6	29.9	30.6	39.4	8.4	6.0	−11	69.3
3. L.O.	13	F	9.2	15.5	43.7	42.6	52.3	27.3	0.7	7.5	−20	69.9
4. A.C.	31	F	1.9	6.5	23.0	37.9	35.0	48.5	5.6	6.6	+ 5	86.4
5. A.B.	37	F	1.6	3.2	10.2	42.5	47.7	40.2	4.0	4.8	+ 8	82.7
6. E.L.	38	F	15.5	21.9	32.1	47.1	37.2	8.9	0.5	3.8	+16	56.0
7. O.E.	21	F	3.6	7.9	17.5	35.2	35.2	30.4	1.9	5.2	− 9	65.6
8. A.G.	56	F	9.5	12.2	33.5	44.3	35.5	22.0	0.6	4.7	+ 4	66.3
9. L.T.	57	F	9.6	14.9	24.5	54.5	44.7	27.3	1.1	4.7	+ 2	81.8
10. D.P.	49	F	1.4	3.3	11.1	18.9	13	62.0	2.2	—	—	80.9
11. F.F.	43	F	6.2	17.8	33.4	42.9	11.5	39.8	1.3	6.6	—	82.7
12. E.A.	22	F	0	0.7	3.9	13.6	3.2	38.5	3.4	6.6	+39	52.1
13. V.M.	32	F	3.4	3.7	11.9	31.5	27.4	24.9	1.7	5.2	+23	56.4
14. L.G.	34	F	2.2	8.6	30.8	30.9	49.0	40.9	2.0	—	−25	71.8
15. R.E.	38	F	3.5	12.1	27.1	47.7	43.0	37.4	1.2	4.7	+ 4	85.1
16. E.M.	23	F	3.2	10.2	32.4	43.0	42.1	19.2	1.3	6.5	+ 8	62.2
17. R.F.	28	F	3.5	12.1	28.4	46.5	42.1	38.2	1.8	6.6	+ 2	84.4
18. G.R.	26	F	4.1	17.0	21.5	—	—	—	—	4.6	− 9	—
19. P.L.	28	F	2.6	6.8	27.6	28.2	48.6	12.8	0.4	6.2	+ 1	41.0
20. S.M.	26	F	2.7	8.1	23.7	35.9	39.7	55.3	1.7	—	+13	91.2
21. I.C.	52	F	0.9	0.2	17.8	36.7	42.6	25.6	5.4	4.6	+71	62.3
22. L.D.	21	F	3.1	4.1	—	—	54.2	40.2	1.6	6.6	− 5	—
23. T.O.	19	F	3.9	3.7	17.8	26.4	22.5	33.0	1.9	6.1	+19	59.4
24. C.F.	25	F	2.1	5.0	9.7	—	16.0	50.5	9.0	5.2	+ 4	—
25. P.T.	8	F	66.7	65.6	82.1	85.9	68.6	4.4	2.4	3.0	+11	90.3
26. P.T.	8	F	69.4	69.2	77.4	78.4	79.6	0.2	2.3	1.6	+30	78.6
27. A.T.	9	F	81.8	69.7	68.2	78.2	68.3	—	—	3.0	−12	—
28. N.I.	37	F	5.5	10.0	23.5	33.0	20.1	40.6	1.3	8.6	+16	73.6
29. C.T.	33	F	56.1	51.6	88.0	80.2	61.2	12.2	0.3	5.4	+ 3	92.4
30. A.C.	21	F	2.7	4.7	7.4	29.2	36.9	53.2	3.2	5.7	−13	82.4
31. L.R.	37	F	0.8	8.7	24.4	40.7	40.8	27.0	1.4	5.8	+19	67.7
32. M.V.	30	F	—	—	—	30.2	—	—	—	5.8	+13	—
33. T.B.	40	F	—	—	—	42.9	—	—	—	7.4	−28	—
34. R.G.	39	F	—	—	—	37.1	—	—	—	6.4	−10	—
35. S.S.	16	F	—	—	—	42.2	—	—	—	6.3	—	—
1. M.P.	58	M	3.5	12.9	14.4	36.3	35.4	58.1	5.0	6.0	+ 7	94.4
2. S.G.	42	M	7.3	10.0	29	41.5	47.4	46.0	2.4	5.6	−18	87.5
3. S.M.	42	M	2.9	5.9	8.4	20.0	15.8	60.6	6.0	—	—	80.6
4. A.U.	54	M	5.7	12.7	26.5	42.4	37.4	4.2	1.5	4.1	−12	46.6
5. T.D.	62	M	0	1.2	33.1	31.1	38.0	—	—	6.4	+53	—
6. T.C.	5	M	5.5	8.2	16.6	25.8	24.8	13.7	7.2	11.0	+ 7	39.5

Among euthyroids with goiter, for both sexes, there is significant negative correlation, and with increase of RAI 24th hour uptake there was decrease of PBI. Among the females, 48.4% of total variations and for males 80.4%, the PBI values were commensurate with changes in RAI uptake (24th hour).

Among the normals, correlation of RAI and PBI is low and not significant. For RAI 24th hour uptake and BMR (Table 10), correlation is not significant. For euthyroids with goiter (both sexes) and hyperthyroid males, there is negative correlation.

PART II. URINARY EXCRETION STUDIES

Results

Results of the study of the different groups of subjects are shown in Table 11.

Two ranges of values are given for the euthyroid controls, one using the mean excretion ±1 (Standard Deviation); and the other employing the mean excretion ±2 (SD). It is seen that use of the latter range causes a considerable overlap of excretion values for the different groups, invalidating any diagnostic

Table 6. Hyperthyroids

Patient	*Age*	*Sex*	*RAI uptake*					*RAI excreted*		*PBI*	*BMR*	*Total Ac'tbl I^{131}*
			1st hr	*2nd hr*	*6th hr*	*24th hr*	*48th hr*	*24th hr*	*48th hr*			
1. E.V.	63	F	10.3	33.1	74.5	79.2	82.1	15.9	0.9	12.2	+27	91.1
2. V.T.	51	F	16.6	25.6	42.0	52.8	51.3	23.5	0.6	7.4	+52	76.3
3. E.V.	45	F	96.8	98.0	121.3	130.7	115.3	4.5	1.4	13.7	+40	135.2
4. E.A.	33	F	14.4	21.5	52.5	58.8	62.8	16.7	0.3	4.7	+ 4	75.5
5. E.P.	33	F	103.9	128.7	127.8	128.2	123.9	6.5	1.0	10.7	+58	134.7
6. L.T.	26	F	32.8	26.7	71.2	107.0	102.0	11.4	0.1	4.9	+26	118.4
7. A.D.	19	F	7.5	14.4	50.0	83.0	82.0	41.6	2.3	5.5	0	124.6
8. S.P.	34	F	39.6	101.6	118.9	109.4	95.4	4.4	1.1	11.6	+85	113.8
9. Z.B.	38	F	3.9	8.8	26.6	70.3	72.9	42.7	4.7	—	−16	113.0
10. S.E.	42	F	13.2	26.9	52.2	78.1	75.7	39.2	—	7.4	− 3	117.3
11. L.S.	22	F	7.0	16.2	38.9	66.4	54.7	28.3	2.3	5.8	−30	94.7
12. L.S.	26	F	0	7.4	25.0	76.9	44.2	54.9	2.2	6.2	−19	131.8
13. S.T.	37	F	22.1	36.5	61.0	69.9	73.3	28.8	0.5	5.9	−10	98.7
14. S.M.	14	F	33.4	—	93.1	95.1	92.8	1.1	0.2	4.1	+13	96.2
15. E.G.	29	F	14.4	23.9	60.4	83.5	82.6	4.3	0.2	5.4	+14	87.8
16. N.C.	21	F	69.1	81.7	87.9	78.5	63.5	0.8	0.9	9.8	−16	79.3
17. E.G.	24	F	15.5	35.4	70.9	81.7	78.2	21.9	0.6	—	—	103.6
18. D.C.	39	F	15.1	27.1	46.2	57.0	63.5	15.7	1.0	5.4	+10	72.7
19. I.V.	34	F	0.9	16.7	49.7	63.5	59.1	23.5	1.3	4.9	+ 9	87.0
20. M.D.	37	F	17.6	23.2	43.1	66.2	33.4	30.6	0.9	3.7	+26	96.8
21. L.B.	38	F	19.3	53.0	62.5	65.4	29.3	1.4	1.7	9.4	+40	66.8
22. P.P.	25	F	37.2	47.2	71.7	70.9	70.5	18.3	0.3	6.7	− 8	89.2
23. R.S.	21	F	11.3	15.7	49.5	62.3	62.0	34.6	1.1	3.4	− 5	96.9
24. M.D.	36	F	50.7	56.1	71.6	77.7	69.9	2.2	1.1	11.0	+48	79.9
25. C.R.	15	F	16.8	30.1	62.9	55.7	39.5	21.9	0.7	4.6	−16	77.6
26. A.M.	17	F	5.2	12.5	35.2	43.8	54.5	18.0	1.0	—	—	61.8
27. T.V.	15	F	16.5	18.7	43.6	41.6	52.9	3.6	0.5	5.8	0	45.2
28. E.C.	15	F	5.3	11.3	31.3	43	52.3	15.4	0.6	5.8	− 9	59
29. P.V.	32	F	21.7	32.0	61.7	51.0	61.1	0.4	0.2	—	—	51.4
30. D.S.	27	F	5.9	13.8	44.8	65.6	47.1	33.5	1.0	5.6	+12	99.1
31. A.C.	20	F	6.4	16.1	41.7	62.3	58.7	30.0	1.7	4.6	+ 8	92.3
32. M.W.	42	F	27.2	55.3	68.3	64.5	38.9	2.7	0.9	11.8	—	67.2
33. P.A.	38	F	22.6	23.5	36.4	34.8	57.1	42.7	1.3	10.4	+22	77.5
34. P.G.	29	F	17.2	50.2	71.5	42.7	38.7	4.1	2.5	3.5	+25	46.8
35. C.A.	28	F	14.2	24.7	50.6	88.8	88	—	—	—	—	—
36. E.M.	10	F	17.7	23.4	61.7	99.0	101.2	32.6	0.9	4.8	+13	131.6
37. A.D.	22	F	1.6	7.1	24.3	47.9	52.0	25.7	4.5	4.1	−12	73.6
38. A.A.	14	F	16.7	19.2	61.4	72.0	81.5	25.4	0.5	6.8	+ 4	97.4
39. Y.L.	19	F	45.6	78.7	85.7	77.3	—	—	—	11.6	+49	—
40. L.A.	34	F	—	—	—	71.7	—	—	—	15.5	+77	—
41. S.H.	70	F	—	—	—	86.6	—	—	—	13.2	+80	—
1. P.D.	47	M	41.1	68.5	77.8	80.1	81.3	12.0	0	10.6	+21	92.1
2. C.C.	46	M	7.6	15.3	32.9	53.4	46.0	34.5	1.6	9.8	+35	87.9
3. M.C.	44	M	9.9	23.8	51.1	78.3	83.9	35.5	0.5	7.6	−23	113.8
4. F.R.	65	M	21.0	40.0	58.0	68.6	99.2	18.9	3.6	11.4	+47	87.5
5. D.C.	30	M	24.7	49.1	90.2	66.1	—	8.5	—	10.1	+21	74.6
6. M.W.	45	M	27.7	42.2	45.4	78.4	38.4	10.8	1.4	13.7	+27	89.2
7. P.S.	28	M	—	—	—	77.3	—	—	—	15.0	+41	—

Table 7. Hypothyroids

Patient	Age	Sex	RAI uptake					RAI excreted		PBI	BMR	Total Ac'tbl I^{131}
			1st hr	2nd hr	6th hr	24th hr	48th hr	24th hr	48th hr			
1. M.R.	3	F	14.6	23.4	23.4	9.4	7.9	—	—	—	—	—
2. P.F.	31	F	1.4	1.2	2.8	5.1	7.6	64.5	16.9	7.0	+17	69.6
3. R.G.	28	F	0.3	1.9	3.9	5.9	7.8	88.1	11.7	5.0	− 1	94.0
4. R.G.	43	F	0	7.2	0.2	0	0	72.7	13.0	5.4	+10	72.7
5. M.C.	38	F	—	—	—	6.6	—	51.8	2.7	6.0	+24	58.4
6. M.A.	44	F	—	—	—	6.5	—	—	—	2.1	+20	—
7. L.N.	24	F	2.0	2.8	3.3	4.0	3.1	27.4	6.9	6.8	+ 7	31.4
8. P.S.	32	F	2.3	5.8	1.3	0	0	64.3	11.2	—	—	64.3

Table 8. Other Diseases

Patient	Diagnosis	Age	Sex	RAI uptake					RAI excreted		PBI	BMR	Total Ac'tbl I^{131}
				1st hr	2nd hr	6th hr	24th hr	48th hr	24th hr	48th hr			
1. E.H.	Hypopituitarism (?)	41	F	1.5	4.5	6.2	16.0	11.9	36.0	0.5	5.3	+ 5	52.0
2. E.C.	N C A	33	F	0.3	0.6	1.2	3.1	3.6	53.9	10.5	7.0	+ 14	57.0
3. L.B.	Adrenal cortex adenoma	18	F	14.2	15.1	26.9	48.6	30.3	42.8	2.3	4.0	+ 8	91.4
4. P.D.	Hashimoto's (S. lymphomatosa) Chronic thyroiditis	78	F	2.4	4.1	4.7	3.1	4.1	30.3	11.1	6.6	—	33.4
5. M.L.	Carcinoma thyroid	42	F	7.7	16.7	35.2	46.7	30.0	25.3	0.3	7.2	+155	72.0
6. L.S.	Post thyroidectomy goiter	43	F	5.8	17.0	19.7	18.8	41.0	56.4	3.1	8.4	+ 18	75.2
7. T.J.	N C A	29	F	4.4	12.8	29.9	41.5	46.7	41.8	1.8	5.5	− 5	88.2
8. T.L.	N C A	32	F	6.5	12.5	33.8	27.4	50.5	31.9	2.7	5.2	− 5	59.3
9. T.M.	Abdominal lymphoma	39	F	0.7	1.6	7.9	19.0	27.0	22.6	1.8	4.8	+ 25	41.6
1. R.A.	Para hypopituitarism (?) Simmond's disease (?)	26	M	0	1.8	8.5	31.8	38.3	44.7	10.5	7.6	− 29	76.5
2. J.V.	Rh. H.D. inactive	16	M	0.1	0.7	23.0	23.6	29.0	29.2	4.8	5.6	− 21	52.8
3. I.S.	Gouty arthritis	69	M	1.9	2.3	4.3	7.9	11.5	27.3	16.7	5.6	− 30	37.0
4. L.S.	Chronic blastomycosis	62	M	1.1	0.9	4.9	13.1	13.5	42.8	—	—	+ 25	55.9
5. P.V.	Thyroiditis, chronic	45	M	0	0.1	0.4	0	0.5	37.4	1.3	6.0	+ 32	37.4
6. W.D.	N C A	30	M	5.3	22.7	39.7	48.4	46.3	29.0	6.1	6.5	− 3	77.4
7. O.S.	Duodenal ulcer	30	M	3.7	6.1	20.1	14.3	39.8	33.2	2.7	5.9	− 21	47.5
8. A.S.	N C A	52	M	—	—	—	6.1	—	—	—	6.7	− 31	—
9. R.A.	Cushing's syndrome	45	M	—	—	—	18.7	—	—	—	3.8	+ 2	—
10. E.A.	Genital infantilism	21	M	—	—	—	49.7	—	—	—	7.2	− 33	—
11. L.C.	Malignant exophthalmos	48	M	—	—	—	23.9	—	—	—	5.7	− 13	—

Table 9. Status of Thyroid Function in 139 Subjects for RAI Studies

	1st 24-hour samples	*2nd 24-hour samples*
Euthyroid controls	60	52[a]
Goitrous euthyroids	32	32
Hyperthyroids	41	40
Hypothyroids	6	6

[a] Although the same patients were used for both 24-hour determinations, some of the subjects failed to collect their 2nd 24-hour urine sample, hence the discrepancy in the number of samples.

conclusion for the method as a test for thyroid function. This overlap is strikingly demonstrated for the 48-hour excretion ranges of the hyperthyroid patients where all subjects belonging to the hyperthyroid group had RAI excretion values falling within the euthyroid range.

Table 11 is translated diagrammatically in Figs. 8 and 9 with the zones of overlap for the different groups demonstrated both for the ± 1 (SD) and ± 2 (SD) range of values. In general, when one uses the range of values as calculated from ± 1 (SD), we find that the classification of thyroid states by means of the determination of the 24-hour excretion of RAI in the urine becomes fairly accurate. Hyperthyroid patients generally excrete RAI below the normal euthyroid range, while hypothyroid patients yield RAI excretion values above the euthyroid range. Goitrous euthyroids excrete RAI within the normal range of values. The findings are less definite for the 2nd 24-hour period, except for the hypothyroid group of patients.

Discussion (a)

From Fig. 8, we believe that use of the mean excretion ± 1 (SD) is a more feasible euthyroid range of excretion, and makes for a fairly accurate diagnosis of thyroid status based on the urinary output of radioiodine. With this range of 23.4–60.0% excretion of RAI per 24 hours, eight subjects or 13% of our euthyroid controls had excretion values above 60%, while three subjects or 5% of our normals excreted RAI below 23.4%; that is, a total of 11 subjects or 18% of our euthyroid controls had RAI excretion values out of the range of normality. Similarly; with the use of this range of values, some hyperthyroids and hypothyroid patients are included in the normal range. This is to be expected since there is no clear cut dividing line between normality and the mild disease states.

The basic considerations in using radioactive iodine in the study of thyroid function in general, are, firstly, that in hyperthyroid states, the thyroid gland collects more of the administered dose, so the kidneys excrete less than in the normal patient. Secondly, and conversely, in hypothyroid states the kidneys excrete more RAI than in the normal subject because the thyroid gland collects less of the RAI. However, there are limitations to this statement because it is not always correct to assume that in a hypothyroid state we will always get a high RAI excretion. Basic facts about iodine

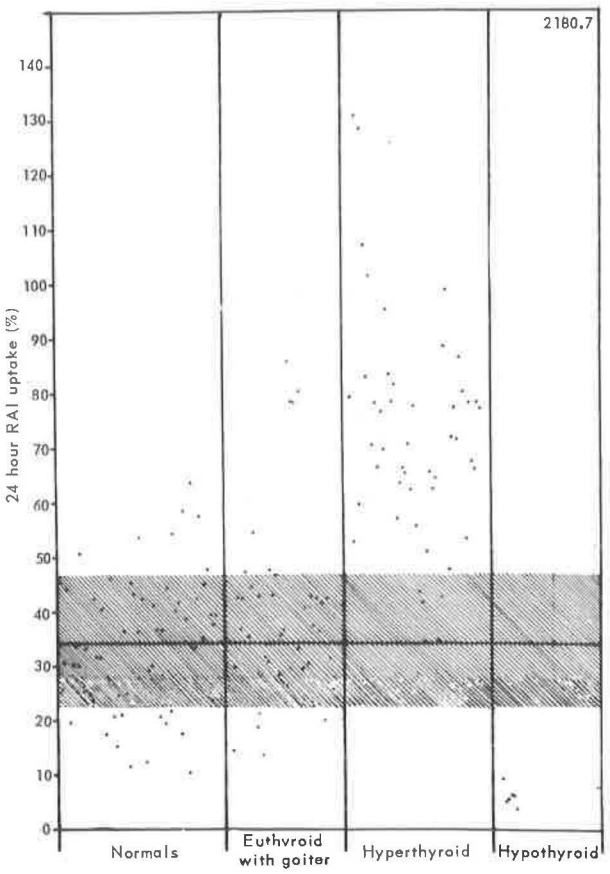


Figure 7. RAI uptake for subjects with different thyroid conditions; the shaded area indicates the range of variability regarded as normal

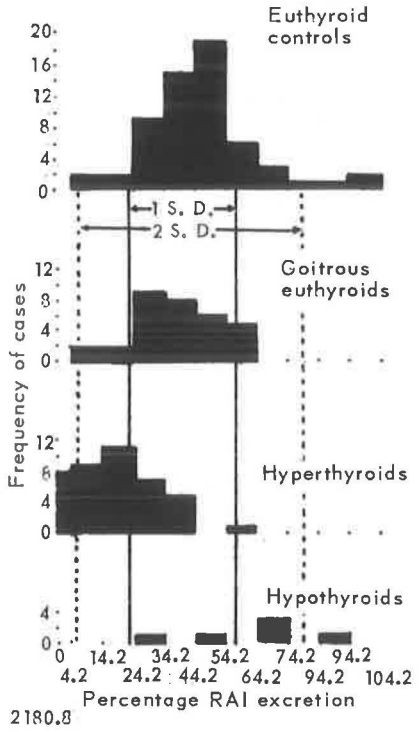


Figure 8. Frequency distribution graphs for subjects with regard to the first 24-hour urinary excretion. The 1(SD) and 2(SD) ranges of values of the euthyroid control group are shown together with the resulting zones of overlap for the other groups

Table 10. Correlation of RAI with PBI and BMR

24th hour RAI uptake and PBI		*r*	*R*	r^2	$t_{.05}$	*for n.d.f.*
Normals	Females	0.116	0.66	0.014	2.042	32
	Males	0.161	0.11	0.025	2.110	17
Euthyroids w/goiter	Females	−0.696	−5.04	0.484	2.052	27
	Males	−0.896	−3.50	0.804	3.182	3
Hyperthyroids	Females	0.365	2.29	0.133	2.042	34
	Males	0.27	1.44	0.077	2.571	5
Hypothyroids		−0.252	−0.52	0.064	2.776	4
24th hour RAI uptake and BMR		*r*	*R*	r^2	$t_{.05}$	*for n.d.f.*
Normals	Females	0.068	0.231	0.470	2.447	6
	Males	0.214	0.581	0.045	2.365	7
Euthyroids w/goiter	Females	−0.107	−0.56	0.011	2.052	27
	Males	−0.655	−1.50	0.429	3.182	3
Hyperthyroids	Females	0.274	1.66	0.075	2.042	34
	Males	−0.399	−0.97	0.159	2.571	5
Hypothyroids		0.318	0.67	0.101	2.776	4

metabolism should not be forgotten. We know, for example, that thyroid hormone synthesis occurs in sequential steps. If the pathologic defect of a low thyroid hormone output, hypothyroidism, resides in the oxidation of iodide, or in the subsequent "organification" of this oxidized iodine, we should expect in this particular instance that the iodide uptake by the gland would not be impaired. Consequently, the urinary excretion would still be within the normal range of values. Furthermore, knowledge of the existence of certain iodide trapping structures in the body aside from the thyroid gland would help in rationalizing a diagnosis of hypothyroidism in instances of low or normal iodide excretion values. These and certain other basic facts of thyroid physiology emphasize the importance of taking the composite picture of several thyroid function tests as a basis of diagnosis, rather than a single RAI urinary excretion, or RAI uptake or PBI determination alone. It should also be borne in mind, that the determination of RAI in the urine, as in all tests which require urine collection, requires full cooperation of the patient for completeness of collection. One fractional

Table 11. Comparison of Results of RAI Excretion Studies in 60 Euthyroid Controls with the Results in Patients Who Had Goiters without Hyperthyroidism, Patients with Hyperthyroidism, and Patients with Hypothyroidism

	1st 24-hour determination	*2nd 24-hour determination*
Control euthyroids		
No. of samples	60	52
Mean excretion	41.7	4.35
±1 (SD) range	23.4–60.0	1.35– 7.35
±2 (SD) range	5.1–78.3	0.0 –10.35
Goitrous euthyroids		
No. of samples	32	32
Mean excretion	43.9	3.56
% of Subjects in normal ranges		
1 (SD)	81.0	71.0
2 (SD)	96.0	96.0
Observed range	4.2–62.0	0.0 –10.5
Hyperthyroids		
No. of samples	41	40
Mean excretion	20.9	1.15
% of Subjects in normal ranges		
1 (SD)	39.0	30.0
2 (SD)	73.0	100.0
Observed range	0.4–54.9	0.0 – 4.7
Hypothyroids		
No. of samples	6	6
Mean excretion	69.2	11.0
% of Subjects in normal ranges		
1 (SD)	33.0	16.0
2 (SD)	83.0	16.0
Observed range	31.3–88.1	2.7 –16.9

voiding which is left uncollected will vitiate reliance on the examination.

From this study, it is apparent that the determination of RAI in urine is most accurate for the diagnosis of euthyroidism with thyroid enlargement. The decision as to whether a nodular goiter is hyperthyroid or not can be made with some sense of security on the basis of RAI excretion determination. The test seems to be least accurate with the hyperthyroid group. The underlying pathology in some hyperthyroid states may not actually reside in the greater avidity of the gland for iodide, such states being a result rather of the abnormally rapid proteolytic process which pours out into the circulation an undue amount of hormone. In such instances, we might expect that the radioiodine uptake of the gland would not necessarily be elevated, and hence that excretion of the RAI would also be within the normal range. This could explain in part the great overlap of values for our hyperthyroid and euthyroid subjects.

Determination of the 2nd 24-hour RAI excretion is inconclusive except for the hypothyroid group. Irrespective of how sensitive the detection equipment employed in radioiodine tracer tests is, the detection of a minute fraction of a dose is attended by poor results. This is especially so for us who must depend on a distant source of isotopes. Apparently, the classification of a hypothyroid state can still be made fairly accurate on the basis of a 2nd 24-hour urinary determination of RAI, but the very small number of our hypothyroid subjects precludes any satisfactory conclusion.

There was no attempt in this study to correlate the amount of RAI excretion with severity of the disease.

Correlation of RAI Uptake with Urinary Excretion

Correlations of radioactive iodine excretion at both 24 and 48 hours with RAI uptake and PBI for normal euthyroid and hyperthyroid were made and the results are shown in Table 12.

Figure 10 shows scatter diagrams which represent an attempt to correlate the RAI uptake and excretion in all the groups of subjects for the two 24-hour periods immediately following administration of the tracer dose. It is obvious that there is no correlation between the uptake and excretion. Whatever significance there is in the euthyroid controls' 48-hour RAI values is obviated by the fact that the figures we are dealing with and which represent the 2nd 24-hour excretion values are very small. Accordingly, the "significance" figures in Table 12 have no real meaning.

Figure 11 presents the scatter diagrams which correlate the 1st 24-hour RAI excretion and the serum PBI values. Of the four groups of patients, only the hyperthyroid group shows any significant amount of correlation, although the amount of variance in the variables correlated (r^2 in Table 12) does not approach the minimum 50% so as to have a real meaning.

Figure 12 shows the scatter diagrams of different groups of patients correlating the RAI excretion

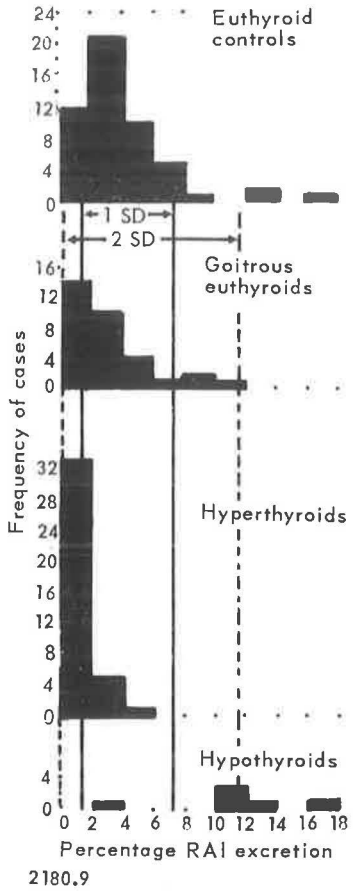


Figure 9. Frequency distribution graphs of subjects with different thyroid conditions as regards their second 24-hour urinary excretion of radioiodine; the 1(SD) and 2(SD) are shown

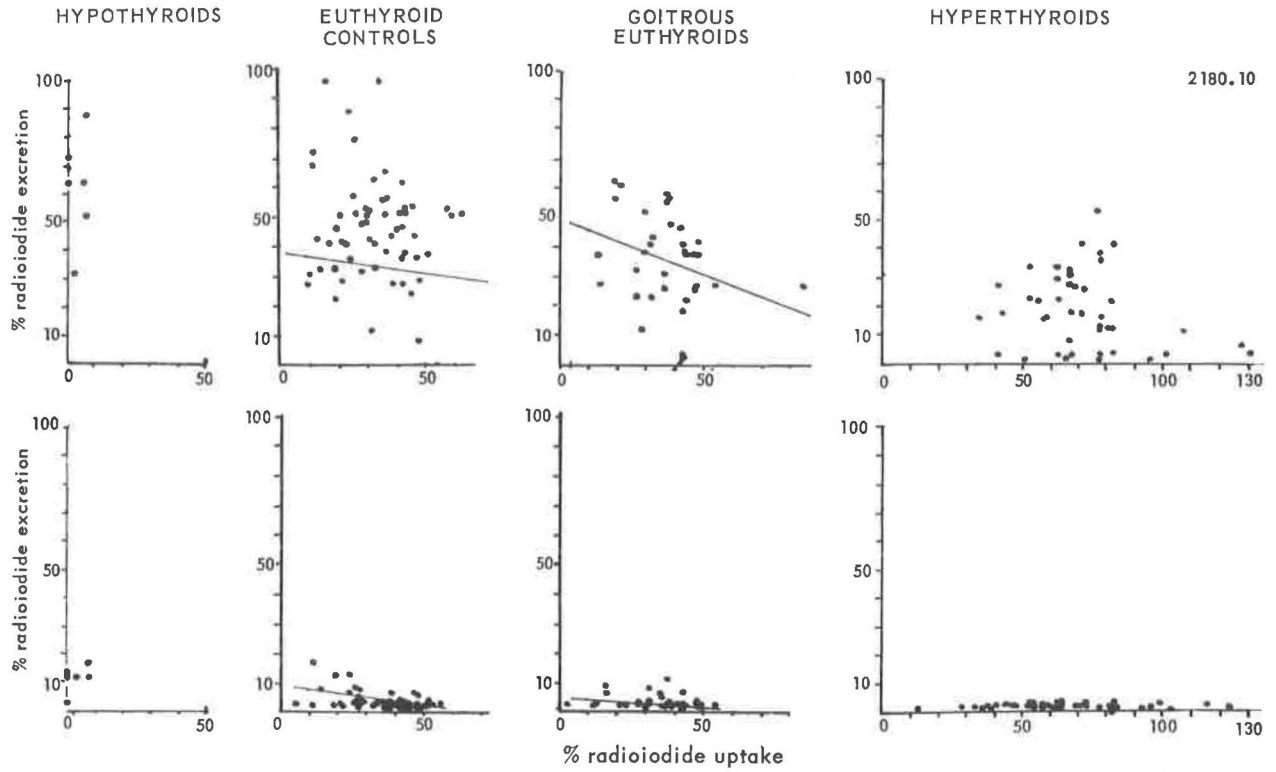
values with BMR levels. As in Fig. 11, only our hyperthyroid group of patients show significant correlation between the two variables.

The hypothyroid groups were not correlated, but only because the number of patients involved was small. However, the scatter diagrams of this group are included for optical correlation.

Discussion (b)

The general principle of urinary RAI determination tests runs thus: the greater the amount of excretion, the lesser is uptake of the gland as regards the administered RAI; hence, in such a case, the thyroid is less active and vice versa. While all the groups of subjects included have followed this general trend (except for the 48th hour period in the hyperthyroid group which shows a positive correlation), the resulting correlation is not significant. This means that it is not always true that the uptake of the gland determines the amount of RAI excreted.

Figure 10 shows that the correlates tend to be diffusely scattered over a given area of the graphs. If one attempts to draw a linear correlation in this case, he gets a more or less parallel slope with the abscissa, which would necessarily be insignificant if interpreted in mathematical terms.



Figures 10. Scatter diagrams of the different groups of subjects correlating excretion with uptake of radioiodine. Diagrams above are for the first 24-hour period and those below are for the second 24-hour period

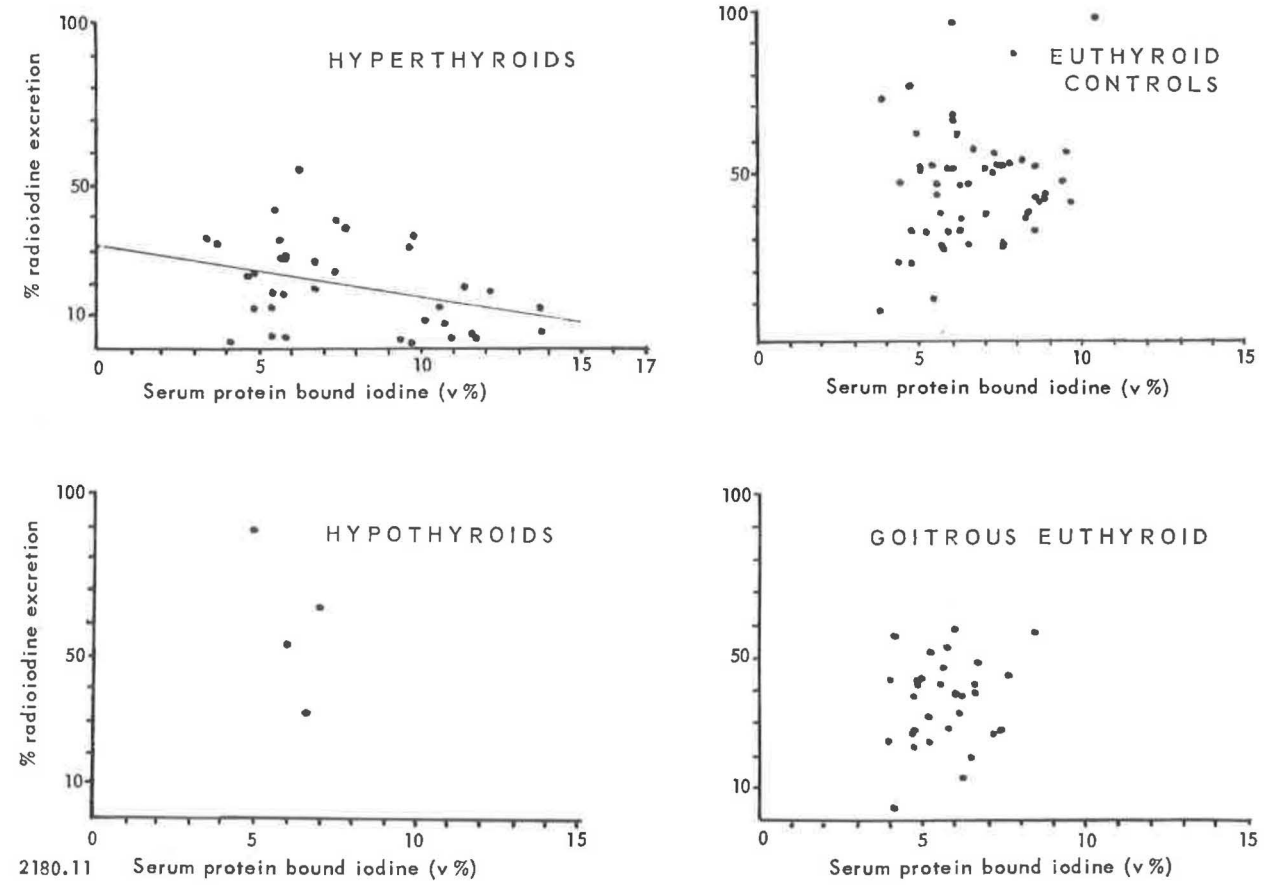


Figure 11. Scatter diagrams showing the correlation between the first 24-hour excretion of iodine with the levels of PBI in the different groups of subjects

Table 12. Summary of Correlation Studies

Group	*y*	*x*	*Correlation coefficient (r)*	*Number of subjects (n)*	*Degrees of freedom (n − 2)*	$(1 - r^2)$	$t = \frac{r\sqrt{n-2}}{\sqrt{1-r^2}}$
Normals	24 hr RAI excre.	24 hr RAI uptake	−0.204	46	44	0.958384	1.382
	48 hr RAI excre.	48 hr RAI uptake	−0.444	40	38	0.802864	3.053[a]
	24 hr RAI excre.	PBI	0.024	44	42	0.999424	0.155
Euthyroids with goiter	24 hr RAI excre.	24 hr RAI uptake	−0.557	32	30	0.689751	3.673[a]
	48 hr RAI excre.	48 hr RAI uptake	−0.343	34	32	0.882351	2.065[a]
	24 hr RAI excre.	PBI	0.329	30	28	0.891759	1.843
	24 hr RAI excre.	BMR	−0.212	31	29	0.955056	1.168
Hyperthyroid	24 hr RAI excre.	24 hr RAI uptake	−0.188	43	41	0.964656	1.225
	48 hr RAI excre.	48 hr RAI uptake	−0.123	41	39	0.984871	0.774
	24 hr RAI excre.	PBI	−0.335	39	37	0.887775	2.162[a]
	24 hr RAI excre.	BMR	−0.526	39	37	0.723324	3.762[a]

[a] Significant.

It should be remembered that the remainder of the thyroid uptake does not of necessity follow a mathematical exactitude of excretion; when the gland takes up 30% of the administered RAI, it does not mean that the kidneys will excrete 70% of it. The excretion might be of the same amount as the uptake, since we know that the extracellular iodide is routed only in part through the kidneys. A great portion of the iodide which is not taken up by the thyroid gland might be stored in the so-called "iodide pool of the body" or collected by the serous salivary glands and certain other body structures endowed with a similar iodide trapping mechanism as the thyroid gland. In such a case, it would not be difficult to explain the "insignificance" of our negative correlation.

At least we expected in this study that the negative correlation would be significant for our hyperthyroid group, since the uptake values seemed to be very much different from the excretion values from a cursory glance at the data. However, as with the euthyroid group of patients, our negative linear correlation was found to be insignificant. It seems that there is a rapid turnover of iodine in the gland, as well as a rapid utilization and deiodination in the target tissues. If this were the case, it would be amiss to say that the iodide liberated from such processes would find its way into the kidneys, nullifying the expected low excretion values. Indeed, a glance at Fig. 10 gives the impression that excretion values of the euthyroids and the hyperthyroids do not differ greatly when plotted. This, together with the fact that our hyperthyroid group did not show a marked elevation of their uptake values, would produce again a more or less parallel slope.

We look at the serum protein bound iodine level as a measure of the amount of circulating thyroid hormones. Translated in terms of RAI, it is that fraction of the administered dose which has been bound with tyrosine and thrown out by the gland into the circulation. In general, we should expect that when the amount of RAI excreted in the urine is high, the serum PBI level would be low, and vice versa. The correlation then takes on again a negative nature. Our study shows that the euthyroid controls and hyperthyroids followed the same trend, with the euthyroid goitrous subjects deviating from the negative linear correlation. Referring to Table 12, it is seen that only the hyperthyroid patients demonstrated a significant negative linear correlation.

It should be noted that there is a great overlap of serum PBI values for different thyroid states. A value of 4.5% (r) for example, might mean either a state of euthyroidism, hypothyroidism, or hyperthyroidism. In other words there is no exclusive middle range of values which can be taken as that belonging to the euthyroid

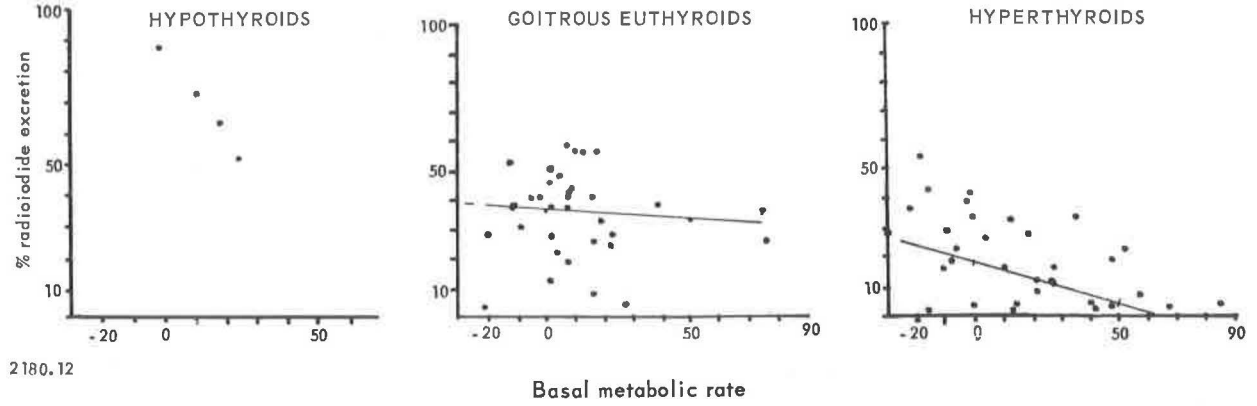


Figure 12. Scatter diagrams correlating the first 24-hour period of RAI excretion with BMR

Table 13. Total Accountable RAI[131]

	No.	Mean	Standard deviation
Normals	46	83.95	18.39
Males	31	83.63	17.34
Females	15	84.62	20.29
Euthyroids with goiter	32	71.39	49.58
Males	5	69.72	22.33
Females	27	71.70	14.09
Hyperthyroids	43	90.75	23.17
Males	6	90.85	11.61
Females	37	90.73	24.0
Hypothyroids	6	65.06	18.70

group, nor a low or high range as meaning a hypothyroid or hyperthyroid state. This tends to disperse our correlates in a diffuse fashion without a tendency to become distributed along a particular slope, hence accounting for the insignificance of the resulting correlation.

However, since the PBI values of our hyperthyroid group show a marked elevation on the average, the resulting correlation becomes significant. It would seem, therefore, that the PBI values alone, or the RAI excretion alone, can be taken to indicate rather accurately a hyperthyroid state.

It has been the general viewpoint that basal metabolic rate is the most accurate of all thyroid function tests if properly carried out.

As regards the RAI excretion-BMR correlation portion of this study, it was carried out only with the goitrous euthyroids and hyperthyroids because of the extreme technical difficulties in our clinic which did not permit BMR determination to be accomplished in most of our subjects, especially the euthyroid controls. Our study shows that there is a significant correlation which is of a negative nature with our hyperthyroid group. This is so because the elevations of the BMR and the RAI excretion values are materially different from the normal ranges to make a more significant slope of the linear correlate.

PART III. TWENTY-FOUR-HOUR TOTAL ACCOUNTABLE RAI[131]

An investigation was likewise done on the total accountable RAI[131] on the various subjects studied, utilizing the values previously obtained on the 24-hour uptake and excretion of tracer doses of I^{131} (Table 13).

Results

A total of 127 subjects, classified in the same manner as in the previous parts of this report were studied. The results are given in Tables 14 through 17.

It will be seen that the group having the lowest total accountable I^{131} was the hypothyroid group, and that the group having the greatest total accountable I^{131} was the hyperthyroid group. The euthyroid subjects,

Table 14. Normals

Patient	RAI uptake 24th hr	PBI[131] conversion ratio	RAI excreted 24th hr	BMR	PBI	Total Ac'ibl I^{131}
Females						
1. C.S.	48.89	22.8	—	+19	6.8	—
2. D.R.	45.45	41.47	—	—	3.8	—
3. M.V.	46.76	51.48	—	—	5.0	—
4. L.T.	59.89	15.90	46.31	+10	4.6	106.2
5. M.R.	15.16	5.78	74.87	—	6.8	90.03
6. L.A.	17.59	26.11	41.41	− 8	3.4	59.0
7. M.V.	33.67	18.21	39.18	+11.3	6.8	72.85
8. A.C.	43.60	17.39	47.47	+ 2	4.0	91.07
9. E.A.	37.22	28.49	23.31	− 5	5.0	60.53
10. A.L.	38.01	10.83	43.91	—	3.8	81.92
11. A.G.	48.00	47.7	37.6	− 4	3.4	85.6
12. L.M.	49.65	23.61	44.13	—	5.6	93.78
13. N.S.	35.97	7.33	49.74	—	4.9	85.71
14. E.S.	44.02	12.0	48.48	—	4.8	92.5
15. A.H.	35.95	8.97	48.94	—	6.6	84.89
16. T.H.	53.63	33.25	55.64	− 4	6.2	109.27
17. M.S.	52.15	31.17	59.51	—	6.2	111.66
18. J.S.	35.31	20.72	62.12	—	6.6	97.43
19. A.Z.	30.84	11.61	59.84	—	6.9	90.68
20. R.G.	4.01	6.75	73.34	+14	7.2	77.35
21. T.G.	41.99	40.15	46.55	− 8	5.4	88.54
22. C.R.	28.31	7.24	44.94	—	5.4	73.25
23. E.C.	16.99	13.27	18.58	+51	6.0	35.57
Males						
1. I.C.	30.89	11.84	—	+11	8.4	—
2. C.P.	35.51	42.54	46.47	—	6.4	81.98
3. C.A.	50.33	20.54	46.42	− 1	5.7	96.76
4. G.M.	37.13	19.70	56.13	−29	5.5	93.26
5. P.V.	32.85	11.49	26.14	+34	6.2	58.99
6. A.Q.	34.62	7.13	52.0	—	4.9	86.62

both normal and those with goiters, fall as intermediate, the euthyroids with goiter having the lower value. Within a group, the difference between male and female subjects is not appreciable. The overlap in values between the four groups is large.

Discussion

Determination of the 24-hour total accountable I^{131} sets off the hypothyroids as a group. From our previous discussion on the urinary excretion of RAI, we have said that the general principle underlying urinary excretion studies makes use of two tracer disposal sites—the thyroid and the kidneys. The total accountable I^{131} determination brings to the fore, a third important site of RAI^{131} disposal: the extrathyroidal-extraurinary, or ETEU tissues. It appears that the turnover from ETEU tissues in hypothyroidism is very slow, paralleling the likewise slow renal clearance rate and making for the greatest unaccountable radioiodine fraction in this group. A hyperthyroid state on the other hand, is responsible for a small unaccountable radioiodine fraction, perhaps because of the greater avidity of the thyroid for iodine or a greater specific activity of the thyroid hormone on the ETEU tissues, hence a more rapid ETEU tissue clearance rate.

The determination of the 24-hour total accountable RAI^{131} and hence of the unaccountable radioiodine fraction bids to be a sensitive index of thyroid function, especially for states of hypothyroidism.

Correlation

We correlated the 24th hour RAI uptake with the total accountable RAI^{131}. In all the groups, we found a significant correlation (see Table 18 B). In all the

Table 15. Hyperthyroids

Patient	*RAI uptake 24th hr*	*PBI^{131} conversion ratio*	*RAI excreted 24th hr*	*BMR*	*PBI*	*Total Ac'tbl I^{131}*
Females						
1. N.E.	79.10	82.9	—	+ 25	11	—
2. F.G.	79.91	86.65	—	+ 58	12.6	—
3. O.M.	85.4	84.40	—	+ 71	14.4	—
4. K.T.	72.80	86.37	30.4	+ 9	11.1	103.20
5. M.V.	85.66	79.79	15.71	—	20.0	101.37
6. F.G.	33.20	63.72	32.41	+ 19	5.6	65.61
7. P.B.	69.97	83.0	8.6	+ 74	9.6	78.51
8. H.M.	94.51	78.63	7.6	+ 33	10.6	102.11
9. Am. M.	85.24	84.16	5.29	+100	10.2	90.53
10. V.M.	62.5	61.9	34.0	+ 4	5.4	96.5
11. B.P.	79.36	79.13	7.86	+ 74	2.0	87.22
12. V.L.	66.80	56.21	30.12	—	7.4	96.92
13. C.V.	74.61	78.99	21.30	—	10.3	95.91
14. L.S.	56.55	88.47	1.61	+ 27	7.9	58.16
Males						
1. N.E.	87.10	66.19	—	—	10.2	—
2. P.D.	66.83	33.11	—	+ 30	9.8	—
3. M.C.	58.31	88.67	11.79	+ 52	11.3	80.10
4. E.P.	89.30	61.78	3.57	+ 73	15.7	92.87
5. D.S.	70.19	73.83	34.77	—	7.3	74.96
6. N.E.	33.84	79.12	25.48	− 6	3.0	59.32
7. M.M.W.	39.66	76.43	39.06	—	5.2	78.72

Table 16. Euthyroids with Goiter

Patient	*RAI uptake 24th hr*	*PBI^{131} conversion ratio*	*RAI excreted 24th hr*	*BMR*	*PBI*	*Total Ac'tbl I^{131}*
Females						
1. R.P.	57.68	31.31	—	−10	5.0	—
2. C.B.	55.69	51.9	—	—	4.5	—
3. J.P.	60.19	68.5	28.40	−16	6.9	88.59
4. C.M.	50.44	44.95	15.06	+34	4.2	65.50
5. J.L.	13.93	7.56	77.08	+ 2	4.7	90.01
6. M.D.	28.65	49.44	28.48	+31	3.6	57.13
7. S.K.	44.82	32.84	—	+48	7.1	—
Males						
1. M.C.	50.20	43.6	55.75	−13	5.1	105.95
2. R.G.	47.17	28.03	36.87	− 3	4.4	84.04
3. J.R.	35.56	38.13	3.05	—	6.2	38.61
4. M.P.	67.38	65.90	47.33	+ 6	6.2	114.71

groups, except the hypothyroid, the correlation was of a positive nature, that is, as the thyroid takes in more of the tracer dose, the total accountable radioiodine also increases. In the hypothyroid group, however, the correlation was of a negative nature. The seeming discrepancy of the latter group as compared with the others is due to the fact that in the hypothyroids the ETEU tissues are a major site of temporary radioiodine disposal.

PART IV. PBI^{131} CONVERSION RATIO

As a supplement to the preceding studies on thyroid function, we determined the protein bound iodine conversion ratio. For this we employed the methods described by Lahr and Tabern of Chicago using ion exchange columns.

Results

The results of our studies on 68 patients are shown in Tables 14 through 19. It will be noted that the differences which exist between the four groups are significant—more significant, in fact, than the results obtained with ordinary uptake studies.

Within groups, male and female subjects did not differ significantly, except in the case of the hypothyroid group, wherein the mean value for the five female subjects was twice that for the two male subjects studied.

As with the other portions of this report, we found our overlaps to be quite extensive for the four groups.

Discussion

In many thyroid states, it becomes necessary to know the rate at which the gland converts the acquired iodine into thyroid hormone. This should be a more accurate measure of the gland's activity, because, after all, what finally determines a hypo-, hyper- or euthyroid state is the amount of hormone released by the gland, that is, if we disregard the body cells' individual sensitivity to the hormone. However, any effort to determine the conversion ratio should take into account two features; firstly, that the gland does not pour out into the circulation all at once its hormone (and there is no way of determining the stored protein iodine), and secondly, that we do not know as yet the rate at which the circulating thyroid hormone is metabolized in the different body tissues. However, determination of the PBI conversion rate is a very useful adjunct in the diagnosis of thyroid function.

As expected, our hyperthyroid subjects showed the greatest conversion ratio and our hypothyroid subjects gave the lowest conversion value. In general, our Filipino patients follow the conversion values reported for American subjects, i.e., conversion ratios of below 10% which generally are considered as indicative of hypothyroidism, those between 13% and 42% as euthyroid and those above this level as hyperthyroid.

Correlation

We correlated the 24th hour uptake of RAI by the gland with the conversion ratio, and in all groups we found the positive correlation to be significant (Table 18 B). This would mean that the greater uptake of RAI results in a greater output of the hormone.

SUMMARY

Part I

1. The results of radioactive iodine studies on 177 subjects have been presented. Of this number 60 were normal, 41 presented goiter but were clinically euthyroid, 48 were hyperthyroid, 8 were hypothyroid and 20 were suffering from other diseases.

2. It was observed that for practical and routine diagnostic tests, the 24th hour uptake is enough and sufficiently reliable.

3. The normal 24th hour uptake was found to be 34.14% with a standard deviation of 12.70%.

4. Euthyroid subjects with goiter presented a mean of 40.15% and a standard deviation of 16.61% for the 24th hour uptake.

5. Hyperthyroid subjects gave a mean of 70.48% and a standard deviation of 22.05% for the 24th hour uptake.

6. Hypothyroid patients gave a mean of 4.69% and a standard deviation of 3.06% for the 24th hour uptake.

7. There is some significant difference in the uptake between males and females. Normal females presented a mean of 38.40% with a standard deviation of 13.81%, while males presented a mean of 31.52% and a standard deviation of 11.39%. Female euthyroids with goiter presented a mean of 41.5% with a standard deviation of 17.46% as contrasted with males whose mean is 32.8% and a standard deviation of 8.36%. Hyperthyroid females gave a mean of 71.82% with a standard deviation of 21.63% as compared with males who presented a mean of 62.65% and a standard deviation of 21.97%. Values are on the basis of the 24th hour uptake.

8. It is obvious that there is a big overlap in values but it is also obvious that radioactive iodine uptake is informative in evaluating thyroid function.

9. Significant correlation is demonstrated between PBI values and 24-hour RAI uptake, especially in euthyroids with goiter and hyperthyroids.

10. No significant correlation, however, could be shown between BMR values and 24-hour RAI uptake. However, in spite of the fact that correlation is not significant, there is a definite tendency for BMR and RAI uptake values to be elevated in hyperthyroids and depressed in hypothyroids.

Part II

1. The results of studies on 136 subjects in various thyroid states have been given.

2. The normal range of RAI excretion for the first 24 hours after administration of the tracer dose is set at 23.4–60%. The 2nd 24-hour determination shows a euthyroid range of 0–10.4% of the administered dose. The latter method, however, is believed to be a very poor diagnostic aid in classifying thyroid states.

3. The method of RAI excretion determination as

Table 17. Hypothyroids

Patient	*RAI uptake 24th hr*	*PBI^{131} conversion ratio*	*RAI excreted 24th hr*	*BMR*	*PBI*	*Total Ac'tbl I^{131}*
Females						
1. A.G.	9.75	26.14	42.37	−6	1.0	52.12
2. M.C.	11.10	6.68	67.38	—	5.8	78.48
3. F.F.	9.94	7.50	59.49	−5	0.6	69.43
4. L.R.	5.93	3.48	72.98	—	4.0	78.90
5. F.B.	12.52	0.75	4.15	—	3.8	16.67
Males						
1. C.A.	8.18	1.82	51.39	—	2.0	59.57
2. F.A.	7.92	7.82	63.01	—	3.4	70.93

Table 18. Correlation of RAI Uptake with BMR, PBI, Urinary RAI Excretion, PBI^{131} Conversion Ratio and Total Accountable RAI^{131}

	r	*r²*	*R*	*nt .05*
A. *Normals*				
6th hr uptake & 24 hr uptake	0.665	0.443	6.38	2.02
6th hr uptake and PBI	0.895	0.803	14.12	2.01
6th hr uptake and BMR	−0.204	0.0417	0.722	2.17
Euthyroids with goiter				
6th hr uptake & 24 hr uptake	0.909	0.953	25.45	2.042
6th hr uptake and PBI	−0.463	0.215	2.86	2.042
6th hr uptake and BMR	0.072	0.0052	0.403	2.042
Hyperthyroids				
6th hr uptake & 24 hr uptake	0.715	0.511	6.7	2.021
6th hr uptake and PBI	0.473	0.224	3.31	2.021
6th hr uptake and BMR	0.639	0.41	5.14	2.021
Hypothyroids				
6th hr uptake and 24 hr uptake	0.874	0.765	3.61	2.776
6th hr uptake and PBI	0.7311	0.535	1.516	4.303
6th hr uptake and BMR	−0.2913	0.085	0.431	4.303
Other diseases				
6th hr uptake & 24 hr uptake	0.747	0.558	4.2	2.145
6th hr uptake and BMR	0.215	0.046	0.796	2.16
6th hr uptake and PBI	0.075	0.0057	0.274	2.16
B. *Normals*				
RAI and Conversion ratio	0.468	0.219	2.75	2.06
RAI and Urinary excretion	−0.146	0.021	0.709	2.069
RAI and BMR	−0.260	0.068	0.936	2.179
RAI and PBI	−0.295	0.087	1.606	2.06
RAI and Total Ac'tbl I^{131}	0.647	0.419	4.075	2.069
Euthyroids with goiter				
RAI and Conversion ratio	0.705	0.498	2.99	2.262
RAI and Urinary excretion	−0.249	0.062	0.631	2.447
RAI and BMR	−0.1314	0.0172	0.351	2.365
RAI and PBI	0.1426	0.0203	0.433	2.262
RAI and Total Ac'tbl I^{131}	0.4633	0.2148	1.281	2.447
Hyperthyroids				
RAI and Conversion ratio	0.101	0.0103	0.426	2.093
RAI and Urinary excretion	−0.556	0.31	2.31	2.145
RAI and BMR	0.608	0.37	2.76	2.16
RAI and PBI	0.629	0.396	3.53	2.093
RAI and Total Ac'tbl I^{131}	0.745	0.555	4.175	2.145
Hypothyroids				
RAI and Conversion ratio	0.0407	0.0016	0.0911	2.571
RAI and Urinary excretion	−0.960	0.922	7.68	2.571
RAI and PBI	0.098	0.0097	0.222	2.571
RAI and Total Ac'tbl I^{131}	−0.6379	0.407	1.85	2.571

a test for thyroid function is relatively easy and fairly accurate.

4. Limitations in the interpretation of the results of the test are given.

5. The results of correlation of RAI excretion values and those of several other thyroid function tests are given.

6. In these urinary excretion studies, only the hyperthyroid subjects showed a significant negative correlation as regards their first 24-hour RAI excretion values and PBI and BMR values.

Part III

1. The results of the determination of the 24-hour total accountable RAI^{131} in 127 subjects have been set forth.

2. The 24th hour uptake and 24-hour excretion were utilized for the 24-hour total accountable RAI^{131}.

3. The 24-hour total accountable RAI^{131} determination is useful in the diagnosis of thyroid states, and sets off especially the hypothyroids as the group having the greatest extrathyroidal extraurinary site of RAI disposal.

4. Within a group, there was no appreciable difference in the values for female and male subjects.

5. In all the four groups studied, with the exception of the hypothyroid group, the correlation between the 24th hour RAI uptake and 24-hour total accountable RAI^{131} was of a positive nature. In all the groups, this correlation was significant.

Table 19. Protein Bound Iodine-131 Conversion Ratio

	No.	*Mean*	*Standard deviation*
Normals	29	21.25	13.07
Females	23	21.87	13.33
Males	6	18.87	11.57
Euthyroids with goiter	11	42.01	16.61
Females	7	40.92	17.91
Males	4	43.91	13.88
Hyperthyroids	21	74.92	52.3
Females	14	78.16	9.77
Males	7	68.44	16.56
Hypothyroids	7	7.74	7.97
Females	5	8.91	8.9
Males	2	4.82	4.8

Part IV

1. The results of the determination of PBI^{131} conversion ratio in 68 patients have been presented.

2. The PBI^{131} conversion ratio is a useful adjunct in the diagnosis of the different thyroid states.

3. Correlation between the 24th hour RAI uptake and the PBI^{131} conversion ratio is of a positive nature and has been significant in all the groups studied.

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Uptake of I^{127} as a Measure of Thyroid Function

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Evaluation of thyroid function by means of radioiodine-131 as developed and practiced by us at the Isotope Service of the Beaujon Hospital involves two distinct stages:

(i) Determination of the rate of uptake of radioactive iodine by the thyroid;

(ii) Determination of the level of labeled hormonal iodine in the blood, representing thyroidal synthesis.

The "hormonal index" in particular, i.e., the plasma concentration of radioactive hormonal iodine after 48 hours (expressed as per cent of the tracer dose given per liter) which is calculated from the plasma and globulin activities,[1] has proved to be a precise and reliable test that differentiates between untreated hyperthyroid patients and euthyroids. Included in the latter category are the "simple, iodine-deficient goiters" where the quantity of radioactive iodine taken up by the thyroid gland is comparable to that taken up by hyperthyroids.

Figures 1 and 2 illustrate a case of untreated hyperthyroidism and a case of simple, iodine-deficient goiter, respectively. The latter is very clearly differentiated from the former by following the plasma concentration of labeled hormonal iodine secreted by the thyroid gland.

Our experience[2] in treating hyperthyroidism with I^{131} indicates that very frequently the results of therapy show a disparity on one hand between a clinical picture of euthyroidism with return to normal of the basal metabolic rate, of protein-bound iodine and of total blood cholesterol, and on the other hand, the results of radioiodine uptake studies.

Thus in three-fourths of our cases of hyperthyroidism treated with I^{131} and brought to a euthyroid state, the hormonal index remains markedly elevated. Furthermore, in nearly half of these patients, this hormonal index is higher than before treatment. The same is true for the thyroid uptake of I^{131}, which remains elevated in half the subjects treated and brought to a euthyroid state. In about one-fourth of these patients, a characteristic "angle of leakage" also occurred or became more pronounced.

These discrepancies have led us to undertake a study of these phenomena and to evaluate the quantitative variations in the avidity of the thyroid for circulating iodine by applying the simple ratio,

$$\text{Thyroid } I^{131}/\text{Urinary } I^{131} = \text{Thyroid } I^{127}/\text{Urinary } I^{127} \quad (1)$$

This ratio was proposed by us in a collaborative study on thyroidal uptake of radioactive iodine which has previously been reported.[3]

This report presents a preliminary study dealing with an analysis of about 50 cases studied between October 1957 and March 1958.

PRINCIPLES AND METHODS

Our method for measuring the avidity of the thyroid for circulating compounds of iodine involves three steps:

(i) Determination of the thyroid uptake of radioiodine two hours after injection of the tracer,

(ii) Determination of the radioactivity in the urine excreted during the same interval of time, and

(iii) Determination of excreted I^{127} which is essentially the determination of inorganic iodine.

Our apparatus for measuring thyroid uptake of radioiodine has been described previously.[3] In that report we emphasized the necessity for standardizing the tracer dose with maximum accuracy (the dose is given intravenously) and for assuring a pattern with maximum reproducibility which eliminates secondary radiations that may come from other portions of the patient's body.

Urinary output of I^{131} is determined on urine samples in a well-type scintillation counter, suitable correction being made for the quantitative reciprocal comparison of results obtained with two different systems of measurement. An important precaution is to ensure that the patient drinks enough water both before and during the test in order to obtain a controlled and adequate diuresis.

The chemical determination of I^{127} in urine samples involves a modification of the method of Barker, which we shall briefly review noting the principal steps involved in the determination of blood protein iodine:

(i) Precipitation of plasma proteins by zinc sulfate and sodium hydroxide, and washing of the precipitate;

(ii) After the addition of sodium carbonate, the precipitate is dried at 100°C for 24 hours with the test tube in an inclined position. The dried residue is then muffled in an electric furnace at 600°C for 1½ hours;

(iii) The ash is redissolved in sulfuric acid; the solution is clarified by filtration and treated with arsenious

Original language: French.

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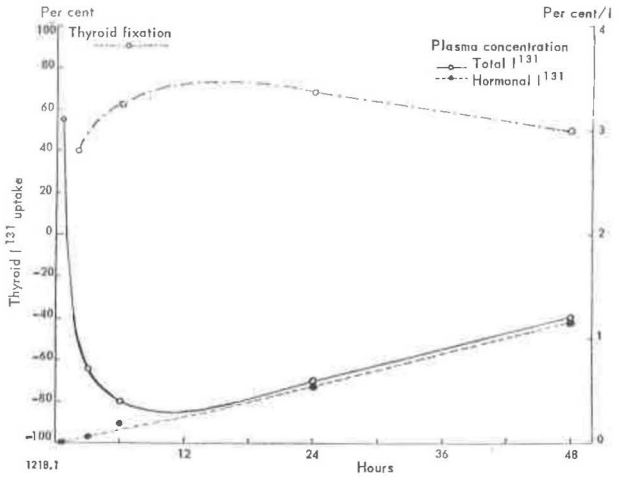


Figure 1. Thyroid concentration of I^{131}, total plasma radioactivity and hormonal activity in a case of untreated hyperthyroidism. Neck tissue, 200; BMR, +31%; plasma protein-bound I^{127}, 16 γ/100 ml; hormonal index, 1.15%/liter

acid and ceric sulfate. It is placed in a water bath at 37°C and the optical density is measured 20 minutes after the addition of the ceric sulfate.

Inorganic iodine in the urine was first determined with the aid of a carefully preserved serum sample of known iodine content (Versatol Warner-Chilcott). This serum sample was treated as outlined above. Before drying (step (ii), above) a known quantity of urine was added. The urinary iodine content was then obtained by subtracting from the total value the iodine content of the serum sample. Inasmuch as the urinary iodine concentration varies widely, a volume of urine between 0.25 and 2.0 ml is required to obtain a reading on the scale used.

The iodine content of the urine was then determined without making use of a serum sample; only the usual reagents were employed and the sample of urine was added before the drying step.

This was the procedure finally adopted for our work. The levels of iodine measured by this procedure varied between 0 and 15 μg-%, with a precision of the order of 1 μg-% and a sensitivity limit of 1 μg-%.

Factors in Thyroid I^{127} Uptake

The equivalence of the figures resulting from the application of ratio (1) for determining the quantity of I^{127} taken up by the thyroid gland in two hours is subject to certain reservations concerning the validity of the assumptions made in setting up this ratio.[3] These four assumptions are restated:

(1) *The values of K and R (plasma clearance of thyroid uptake and urinary excretion of inorganic iodine, respectively) do not vary significantly during the two hours of the test.* This assumption is probably valid if one takes into account the limited duration of the test and the regulatory action of the diuresis which we attempt to get by administering water during the course of the test. A series of systematic measurements —independent of the dispersion of results due to the collection of urine samples over short intervals of time (e.g., 30 minutes)—are planned to establish the statistical validity of this assumption.

(2) *Right after the injection of radioiodine the plasma becomes marked with I^{127}.* Mixing curves obtained when substances as different as Evans blue, radioactive sodium chloride and erythrocytes labeled with Cr^{51} enter the circulatory stream, confirm the statement that in large blood vessels like those supplying the thyroid gland and the kidneys the injected tracer becomes homogeneously distributed in less than 40 seconds. Even if one had to take into account the time required for the tracer to enter the capillary circulation—which may be as long as 5 minutes—the time intervals involved are small compared with the duration of the test. Consequently this second assumption is undoubtedly justified.

(3) *The I^{127} eliminated by the kidneys is inorganic in origin and only an inappreciable quantity is derived from iodine that originally circulated in a hormonal form.* This postulate is qualitatively confirmed by numerous previous experiments, particularly those which show the fading of the renal clearance and of the ratio "urinary radioactivity/plasma radioactivity" as soon as the major portion of the circulating I^{131} becomes incorporated in the hormone (*cf.* Fig. 9 in Ref. 3).

But because we are dealing here with a fundamental assumption, particularly as the plasma concentration of I^{127} in hormonal form is far higher than its concentration in the inorganic form, a series of systematic determinations have been undertaken with the aim of establishing the magnitude of the error involved if a significant proportion of the iodine eliminated in the urine came from protein I^{127}.

The subjects chosen for this study were patients with frank hyperthyroidism. Plasma concentrations of hormonal and inorganic I^{131} were determined as precisely as possible, as was the radioactivity in the urine

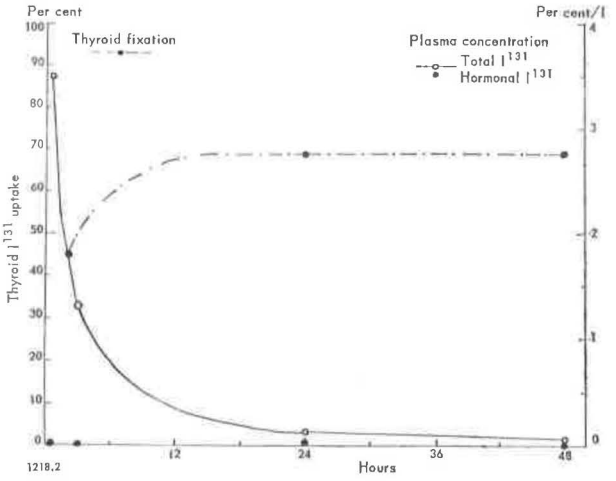


Figure 2. Thyroid concentration of I^{131}, total plasma radioactivity in a case of a simple, iodine-deficient goiter. The plasma concentration of the hormonal I^{131} did not exceed 0.05% per liter during the course of the first 48 hours following administration of the tracer. Neck tissue, 55; BMR, −1%; plasma protein-bound I^{127}, 8 γ/100 ml; hormonal index, 0

between the third and fifth days following the administration of the tracer dose, the period in which the plasma concentration of I^{131} is elevated and principally due to the hormonal iodine.

As this program is still in the beginning stage, precise quantitative results are still unavailable. However, the results obtained to date are not incompatible, within analytical error, with assumption (3). It should be added that subjects with significant proteinuria are not good subjects for testing this assumption.

(4) *Radioactivity levels measured in the neck region after two hours represent thyroidal uptake of injected radioiodine.* Both in hyperthyroid patients and in cases of simple goiter with high iodine uptake this assumption is valid, the validity increasing the higher the uptake at the end of two hours. The validity of this assumption is less certain, however, in euthyroids and particularly less so in cases of hypothyroidism.

Thyroid uptake of I^{127}, as calculated by this method without correction, is overestimated, the error being greater the lower the measured uptake after 2 hours.

We are at present planning a program which would quantitatively establish for our method of measuring the role of the extrathyroidal I^{131}, and particularly of the intrathyroidal I^{131} in equilibrium with that in the plasma. We plan to do this by means of detailed functional tests which would involve analysis of thyroid uptake curves and of the release of I^{131} into the circulation in the first hours following administration of a tracer dose. Examples of these calculations have already been presented in our previous communication.[3]

It is our hope that these studies will then permit us to apply a valid correction factor to the various thyroid uptake values measured at the end of two hours.

First results indicate that the correction factor is in the neighborhood of 15 to 20 per cent when uptake ranges from 10 to 15 per cent. This correction does not apply, of course, to the exceptional case where the intrathyroidal concentration in exchange equilibrium with the plasma predominates.

Inasmuch as we have not completed the studies designed to evaluate the various points raised in the preceding considerations, this communication will restrict itself to the uncorrected results which have been obtained with the use of the proportionality ratio (1).

RESULTS

Results obtained so far on approximately 50 patients will be described briefly and illustrated by typical examples.

Figure 3 illustrates results obtained on three normal subjects. Plotted on it and on all succeeding figures is thyroid uptake of I^{127}, expressed as micrograms elementary iodine taken up in two hours, as well as:

(i) Thyroid uptake of I^{131} after two and after 48 hours, expressed as per cent of injected dose;

(ii) The hormonal index, or plasma concentration of hormonal I^{131} after 48 hours, expressed as per cent of dose injected per liter of plasma;

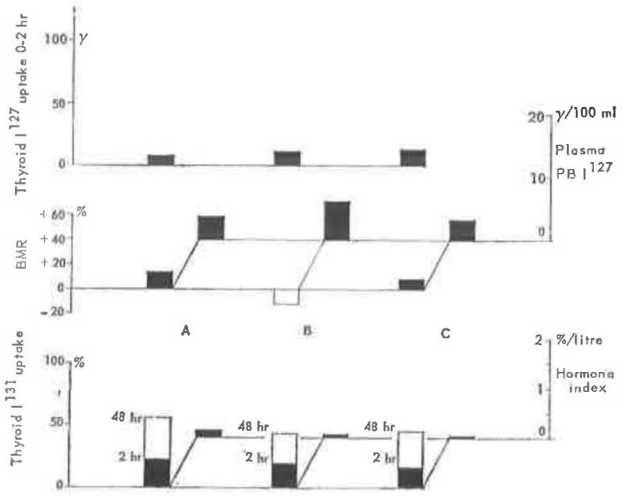
(iii) The basal metabolic rate; and

(iv) The circulating protein-bound iodine, expressed as micrograms elementary iodine per liter of plasma.

The mean uptake of I^{127} in nine normal subjects was 7.5 μg in two hours. The magnitude of these figures compares well with that of figures recently published by Shipley and Buchwald[4] who, with the exception of minor details, used a method for measuring absolute rates of thyroid uptake which was similar to ours.

Figure 4 shows results for a hyperthyroid patient following treatment (A) and of two cases of simple, iodine-deficient goiter (B and C), all three of which evinced a high rate of thyroid uptake of I^{131}.

It can be seen that even though the hormonal index quite clearly differentiates between these two categories of disease, the rate of thyroid uptake of I^{127}



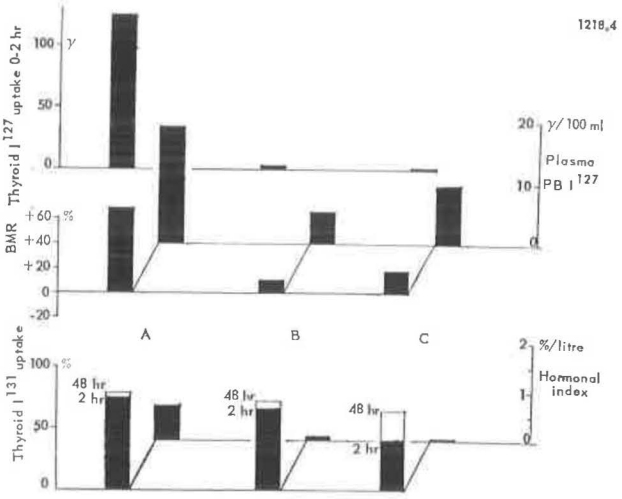


Figure 3 (left). Evaluation of thyroid function in three normal subjects: A, B, C. In Fig. 3, as in all succeeding ones, the scales on the left ordinate, reading from bottom up, represent: I^{131} concentration in the thyroid, BMR, thyroid uptake I^{127} (expressed as micrograms of elementary iodine fixed in two hours, uncorrected result). The scales on the right ordinate represent, in the same order: the hormonal index (plasma concentration of hormonal I^{131} measured 48 hours after injection of the tracer), plasma concentration of protein-bound I^{127}. Figure 4 (right). Evaluation of thyroid function: A, case of untreated hyperthyroidism. B and C, patients with simple, iodine-deficient goiters

affords an even better differentiation (125 μg in the case of the patient with hyperthyroidism as compared with less than 5 μg in two hours for the two cases of simple, iodine-deficient goiter).

In the five cases of simple, iodine-deficient goiter which we studied, uptake by the thyroid gland of I^{127} was in the neighborhood of normal, whereas in the six cases of untreated hyperthyroidism the mean uptake of I^{127} amounted to 150 μg in two hours.

However, as we stated at the beginning of this paper, the principal practical interest in thyroidal uptake of I^{127} is in using this parameter for the study of hyperthyroid patients who had been treated with radioiodine.

Quantitative information on thyroid uptake of I^{127} will allow us to interpret better the discrepancy, so frequently observed in hyperthyroid patients after treatment, between clinical observations which are confirmed by certain biological tests, such as the BMR and protein-bound I^{127} on the one hand, and the results obtained with radioiodine studies (i.e., thyroid uptake, hormonal index) on the other.

Furthermore, knowledge of thyroid uptake of I^{127} can give valuable information on which to base subsequent therapeutic doses of I^{131} without the risk of overdosage which may occur through an erroneous interpretation of the biological changes seen after the initial dose of I^{131}. Such overdosage may lead to a permanent post-therapeutic hypothyroid state that is a major problem in this type of treatment.

Figure 5 illustrates this point. It summarizes the results of thyroid function studies in a patient with hyperthyroidism before treatment and three months following the administration of a therapeutic dose of 10 mc I^{131}. The results of this study indicate a change in function induced by the radiation, in that the quantity of hyperfunctional tissue has been reduced considerably; and this in turn indicates that considerable

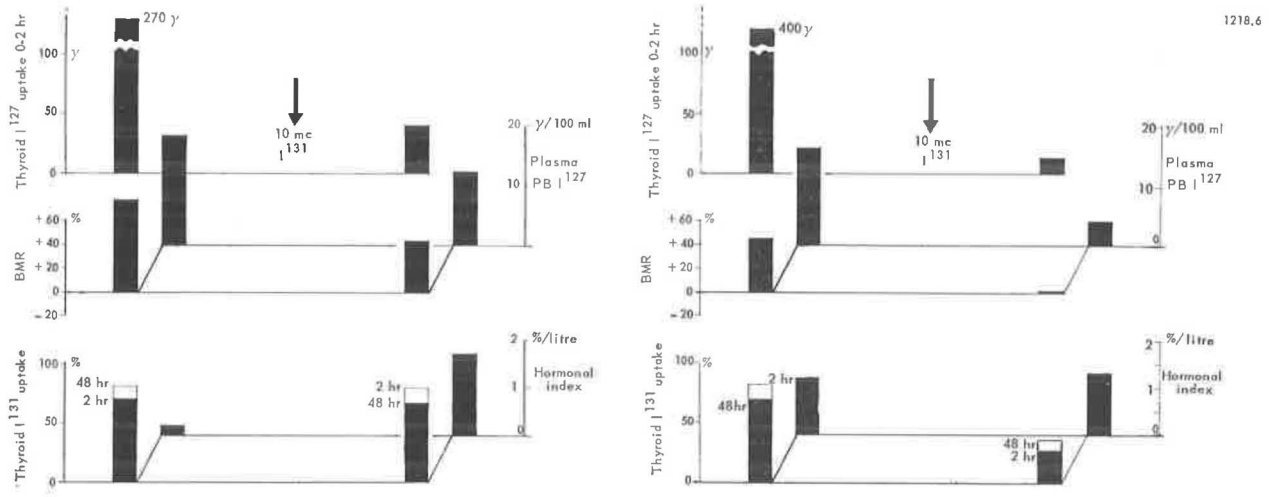


Figure 5 (left). Evaluation of thyroid function in a case of hyperthyroidism. Left, before treatment. Right, three months after administration of a therapeutic dose of 10 mc I^{131}. Figure 6 (right). Evaluation of thyroid function in a case of hyperthyroidism. Left, before treatment. Right, three months after treatment with a therapeutic dose of 10 mc I^{131}

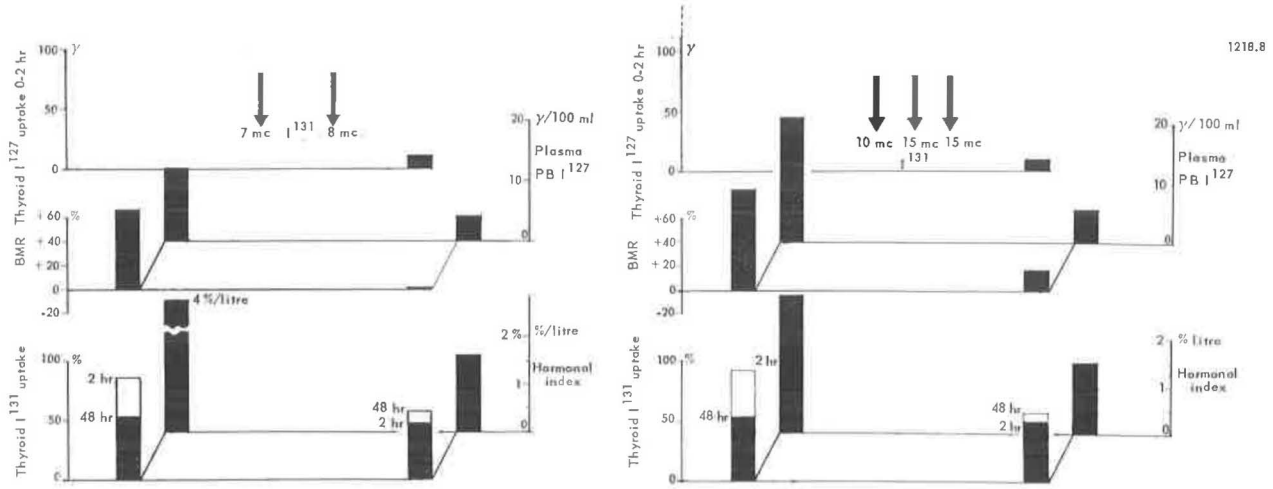


Figure 7 (left). Time–course study of thyroid function in a case of hyperthyroidism treated with I^{131}. Left, before treatment. Right, eight months after administration at intervals of four months of two doses of 7 and 8 mc I^{131}, each. Figure 8 (right). Time–course study of thyroid function in a case of hyperthyroidism treated with I^{131}. Left, before treatment. Right, 13 months later, after treatment at intervals of 5 and 3 months with three doses of 10, 15 and 15 mc I^{131}

caution should be exercised in determining a second therapeutic dose.

The preceding considerations are in complete accord with the marked decrease in the rate of I^{127} uptake (from 270 to 40 μg in two hours), contrasted with the persistence of an elevated uptake of radioiodine, the persistence of a considerably increased hormonal index, associated with the occurrence of an "angle of leakage," seen in this patient. On the other hand, the decreased uptake in I^{127} is in accord with the appreciable drop in BMR and in the quantity of protein-bound I^{127}.

Figure 6 shows results obtained on another patient with hyperthyroidism, studied before and three months after administration of a therapeutic dose of 10 mc I^{131}. Here, all parameters except the hormonal index have tended to return to normal, coinciding with a drop in thyroid uptake of I^{127} from 400 to 14 μg in two hours; the hormonal index, however, increased.

Figures 7 and 8 show results obtained with two other cases of hyperthyroidism, seen before treatment with two or three therapeutic doses of I^{131}, and seen 8 and 13 months later, respectively, when they had returned to a euthyroid state. Nevertheless both patients retained a higher than normal rate of uptake of radioiodine and very high hormonal indices. However, I^{127} thyroid uptake studies—this had not been done before treatment—of these patients showed that the gland had returned to a normal state of uptake for circulating iodine compounds (in both cases, uptake was 10 μg elementary iodine in two hours).

In 14 cases of hyperthyroidism treated with I^{131}, the mean thyroid uptake in two hours was 40 μg. A similar result was obtained in five cases of hyperthyroidism treated medically (their average uptake amounted to 50 μg in two hours).

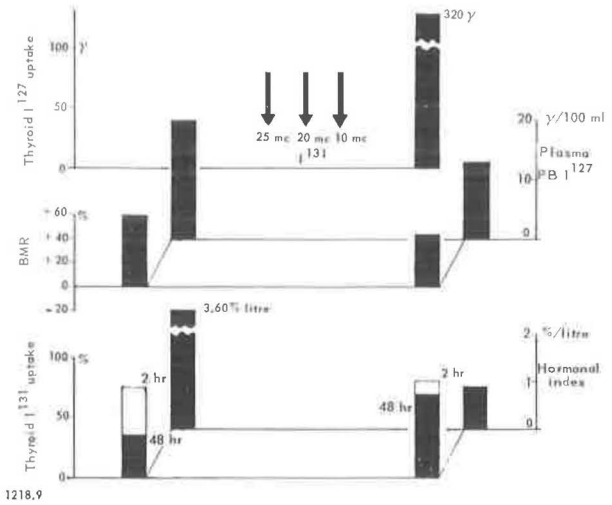


Figure 9. Evaluation of thyroid function in a case of Basedow's disease treated with I^{131}. Left, before treatment. Right, during treatment, nine months later

Figure 9 deals with a case of Basedow's disease, studied in all respects except I^{127} uptake, before and nine months after treatment with a total of 55 mc I^{131}. This dose proved insufficient, a finding also confirmed by the very elevated thyroid uptake of elementary iodine (320 μg) in two hours.

Although our results are as yet incomplete and fragmentary, we feel encouraged by the results in these cases in which thyroid function was evaluated by means of the I^{127} uptake test. Furthermore, these studies have a theoretical interest; they tend to explain, because they represent measurements of the specific activity of I^{131}, the apparent discrepancies of the tracer technique especially during treatment. They also have a practical value because they make possible a more precise determination of the size of successive therapeutic doses to be given.

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The Use of Iodine-131 in Thyroid Diseases

Edited by Takehiko Tsuchiya* et al.

The diagnosis and the therapy of thyroid diseases with iodine-131 have been studied by a number of investigators in Japan. The diagnostic uses of iodine-131 were demonstrated by studies of the iodine uptake of the thyroid, of the urinary excretion of iodine-131, of thyroidal I^{131} clearance, of the conversion ratio of PBI^{131} in blood, and of the scintigram and other tests. I^{131} was found to be therapeutically effective in cases of hyperthyroidism and thyroid cancer. Four recent studies on the use of I^{131} are reported in this paper.

USE OF I^{131} FOR DIAGNOSIS

Nonbackground Scintigram

By T. Miyakawa, H. Etō and T. Tsuchiya*

Etō and Tsuchiya[1] reported previously on the universal type scintiscanner with a recording system based on the neon-lamp film method. Hundreds of patients have been measured with this instrument, but the background recorded on the scintigram with this scanner often made diagnosis difficult because of the indistinctness of the image produced. We have attempted, in collaboration with Oda *et al.*, to develop a nonbackground-scintigram recording instrument.

Principle of the Nonbackground Scanner

In the conventional system, the pulses from the scaling circuit pass directly to the lamp as signals. In the new system, we use the photographic recording method shown in Fig. 1, in which a new device is inserted between the scaling and recording circuits so that signals coming from the background can be clipped off. In the new device, input pulses are distributed into ten channels by a beam-switching tube circuit (BST 6700) and each pulse duration is enlarged by a monostable multivibrator (univibrator) and a superposed circuit. These pulses are converted into DC signals; the level of the signals is low when the number of counts is small (e.g. background), and it is higher as the number of counts increases. When these signals are clipped off at no less than background value, the DC signals over the clipping level are carried to the lamp in the recording system; the clipped signals, however, are not recorded in the scintigram. Thus, a nonbackground scintigram can be obtained.

Principles and Application of the Method

Two phantoms, 0.5 cm deep and respectively 3 and 1.5 cm in diameter, were filled with iodine-131 solution, and arranged at a distance of 2 cm from each other. Under identical conditions, scintigrams were obtained by the conventional method and the method described above. The scintigrams produced by each method are shown in Figs. 2 and 3. In the conventional scintigram, the image must be distinguished from the background and isolation of the image from the background depends on personal judgment. However, in the scintigram taken by the new method there

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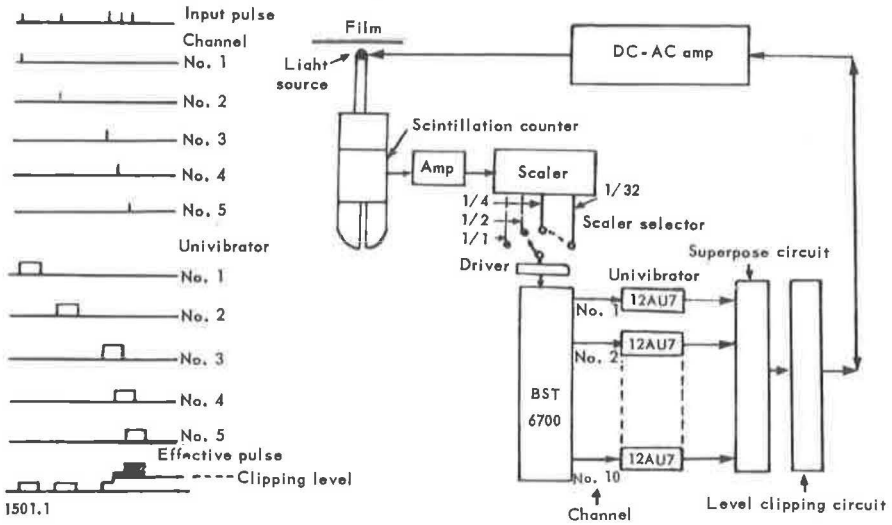

Figure 1. Diagram of nonbackground scintiscanner

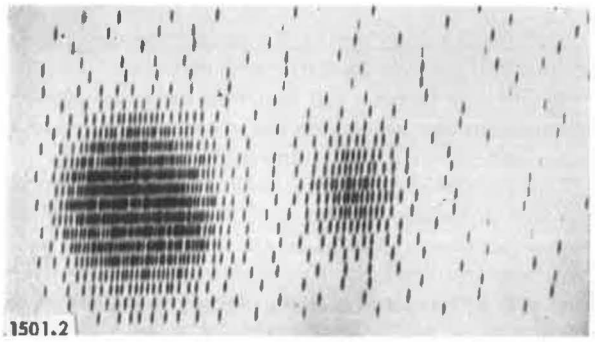

Figure 2. Scintigram using conventional apparatus shows background activity

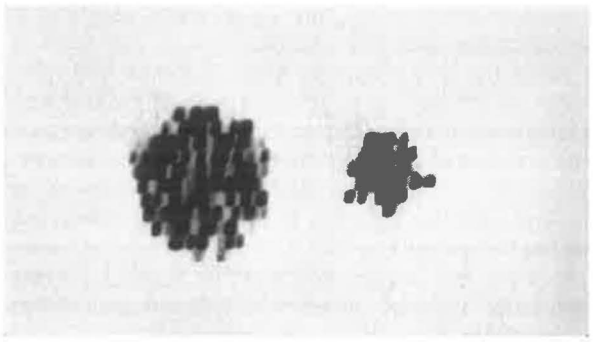

Figure 3. Scintigram taken with nonbackground scanner shows image alone

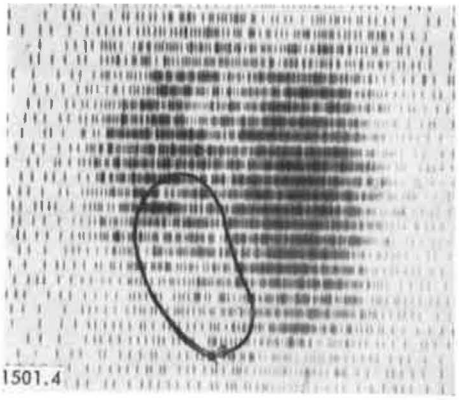

Figure 4. Diagrammatic representation of a thyroid tumor by the conventional scintigram method

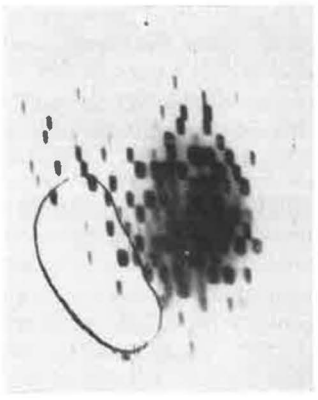

Figure 5. Thyroid clearly revealed by new scintigram method

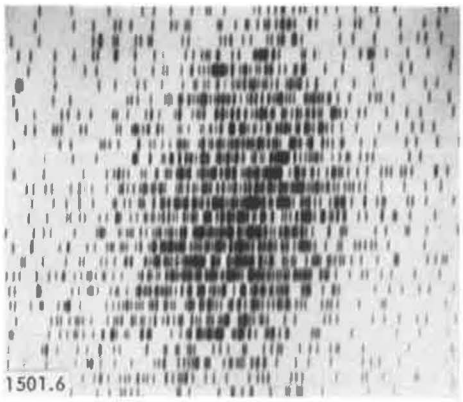

Figure 6. Right hemithyroidectomy. Visualization of thyroid by the conventional scintigram method is poor

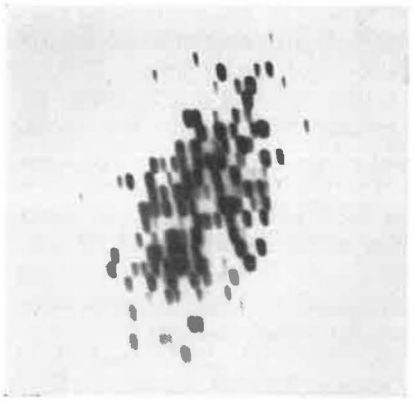

Figure 7. Scintigram by new method taken after right hemithyroidectomy shows left lobe of thyroid distinctly; no evidence of thyroid tissue on right side

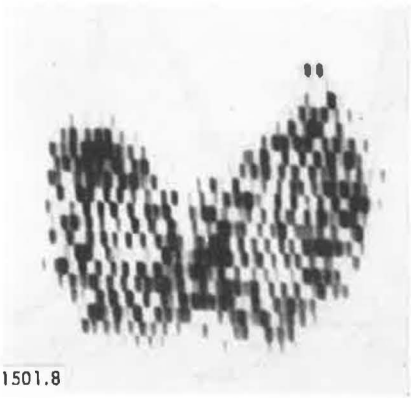

Figure 8. Scintigrams of case of hyperthyroidism, new method

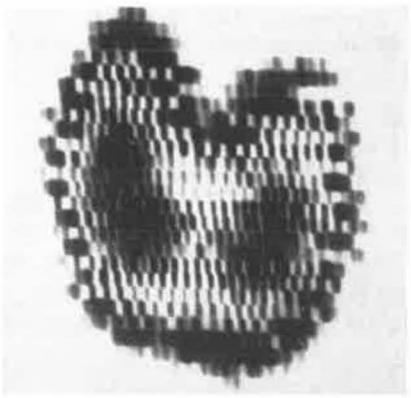

Figure 9. Scintigrams of case of hyperthyroidism, new method

is no background and only the size and shape of the phantom are seen (see Fig. 3).

After the oral administration of 150 to 300 microcuries of iodine-131 to patients with thyroid disease, scintigrams are obtained at 24 hours by both methods. The position of a thyroid tumor is shown diagrammatically in Fig. 4, a scintigram taken by the conventional method. The background in the tumor prevents clear delineation of the thyroid. The new scintigram method eliminates the background and the thyroid is clearly seen (Fig. 5); it is, therefore, a valuable contribution to diagnosis. Figure 6 is a scintigram of the thyroid by the conventional method after removal of the right lobe (hemithyroidectomy) in which the shape of the gland is poorly visualized. Figure 7 is a scintigram of the same thyroid under the same conditions by the new method and in this figure the left lobe of the thyroid shows up very distinctly; there is no evidence of a right lobe. Figures 8 and 9 are scintigrams of cases of hyperthyroidism.

For calculating the weight of the thyroid by Allen-Goodwin's equation, the dimensions of the thyroid should be measured from the scintigram. On the conventional scintigram, experience is required to determine these dimensions. We have demonstrated that sharpness of the image's shape by the new method permits objective and exact measurements to be made.

Discussion

A disadvantage of the method, as can be seen in Figs. 8 and 9, is the appearance of low density areas in some parts of the scintigrams. This is due to the fact that as the counting rate increases and the pulse intervals become smaller there is a univibrator dead time during which each channel circuit becomes nonoperative. Despite this disadvantage, the new method is effective for clinical use since an exact and clear image can nevertheless be obtained. This disadvantage will be eliminated in the near future and nonbackground scintigrams will be a useful tool for the clinical application of the radioisotopes.

Radioiodine Uptake Measurement

By Hirotake Kakehi†

Radioiodine uptake measurements have been used relatively widely in Japan in recent years as one of the thyroid function tests. The results of these measurements show considerable variation.

The author carried out some research work on these problems‡ and found that the following factors influence thyroid uptake measurements: (*a*) changes of gamma-ray spectra through absorption and scattering, (*b*) phantoms for the measurement of the standard sources, (*c*) formula used for calculating the per cent uptake, (*d*) the size and shape of the 100% total dose standards, (*e*) the filter for cutting off scattered rays, and the thyroid eclipsing shield, (*f*) isoresponse lines "seen" by the detectors of the measuring devices, (*g*) collimation, and (*h*) measurement distance.

Of all these factors, the first four have the greatest influence on the results of the measurement, and of these four, (*a*) and (*b*) are the most important.

The changes of spectra by absorption and scattering and the difference of the spectra with and without A-filter are shown in Figs. 10 and 11; a neck-size water phantom was used for the experimental study. The A-filter is a thin piece of lead, placed very close to the detector to cut off the scattered rays. A thyroid-shaped mock-iodine source was moved in water 0 to 9 cm from the front surface of the phantom. The dotted lines (see Figs. 10 and 11) indicate the spectra with the source in air for comparison.

The means of obtaining more accurate measurements are summarized in the following points:

(*a*) If the spectrum seen by the detector could be controlled to a sufficiently high degree, about three-quarters of the errors could be improved.

(*b*) A phantom designed to give a spectrum similar to that of the patient's neck should be used. The misuse of phantoms and the use of improperly designed phantoms account for about one-quarter of the potential errors in those laboratories where spectrometers are used for thyroid uptake studies.

(*c*) The effects of the other factors in thyroid uptake measurements without spectrometer control must be considered. These are shown in Fig. 12. A scintillation counter was used to measure two different manikins. One was a high-thyroid, low body-background manikin, and the other was a low-thyroid, high body-background manikin. In the measurement of thyroid uptake four standard formulas were used: (i) the O formula (without any filtration), (ii) the A formula (with an "A"-filter only), (iii) the B formula (with a thyroid eclipsing shield only), and (iv) the AB formula. Three different kinds of phantoms were used. One was the shallowest possible kind of phantom, that

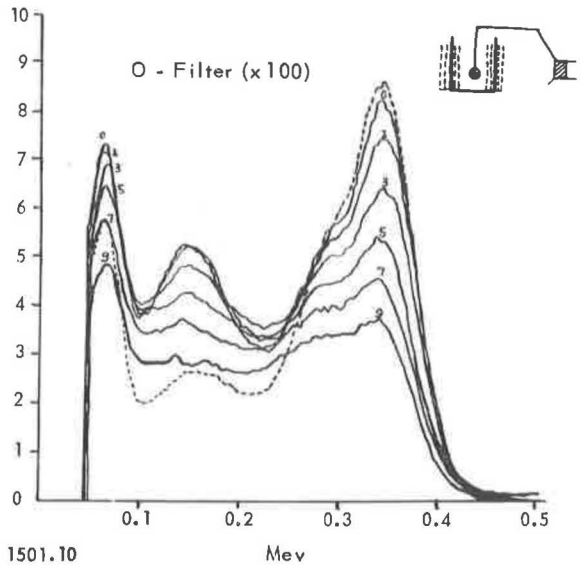

Figure 10. Thyroid I^{131} uptake measurement without the use of filter

† Chiba University Hospital, Chiba, Japan.
‡ At ORINS Medical Division, Oak Ridge, Tennessee, USA.

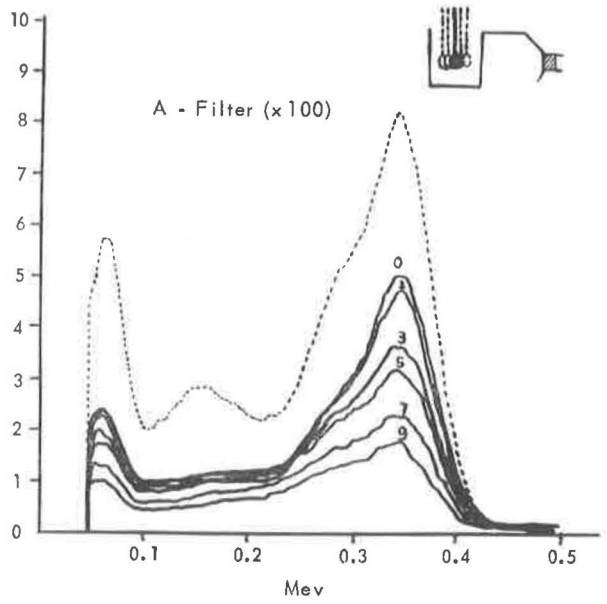

Figure 11. Thyroid I^{131} uptake measurement with the use of A-filter

is, the source was in the air; the second was a lucite phantom in which the source was placed very deeply within the phantom; and the third, the standard phantom, was one in which the spectrum of emission from the source matched the spectrum of emission from the patient's neck. The measurements were made at five different distances. It can be seen (Fig. 12) that when a very shallow phantom is used, there is a tendency for a wide range of results. When the very deep phantom is used in the high-thyroid type of patient, all the measurements are too high. When a standard phantom is used, except where there is no filtration, a reasonably good result is usually obtained.

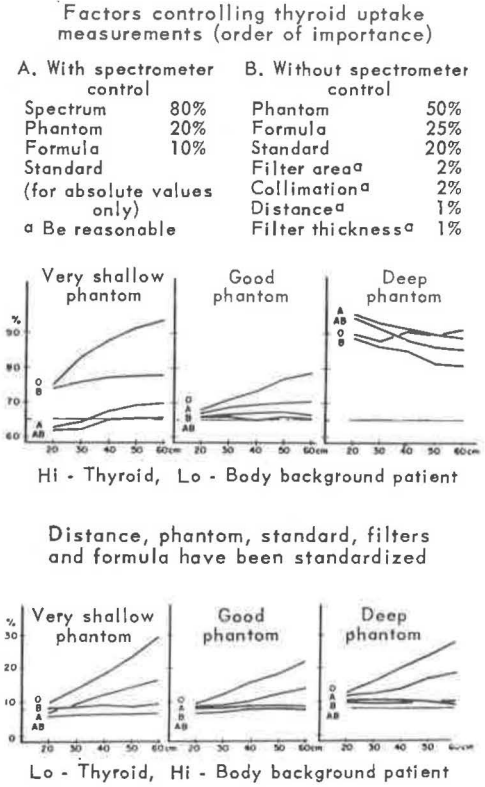

Figure 12. Other factors that influence thyroid I^{131} uptake measurements

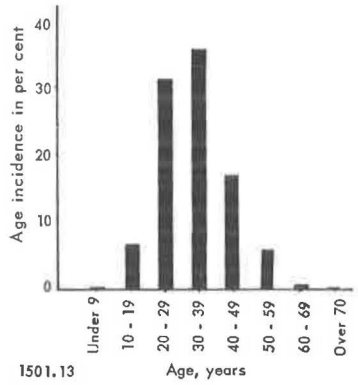

Figure 13. Age incidence of hyperthyroidism

The results in the low-thyroid, high body-background patient illustrate the value of the thyroid eclipsing shield or B-filter. Even where the phantom is improperly designed, if a thyroid eclipsing shield is used, the results are acceptable. The AB formula gave the best measurements under all conditions.

THERAPEUTIC USE OF I^{131}

Treatment of Hyperthyroidism with I^{131}

By Hisao Yamashita, Junichi Fujita, Masatoshi Masuko and Hiroji Tottori§

Five hundred cases of hyperthyroidism, 430 females (86%) and 70 males (14%), were treated in the Second National Hospital during a period of about 5 years from January 1952 to June 1957. The observation periods were over 6 months. Age incidence is shown

§ The Second National Hospital, Tokyo, Japan.

Table 1. Dose I^{131} calculated from the Thyroidal Uptake Rate of Iodine-131 and from the Weight of the Thyroid Gland

Weight of gland, g	*I^{131} doses in μc with I^{131} uptake rates of:*		
	40–50 %	*60–79 %*	*over 80 %*
Over 60	10–15	8–12	7–10
59–35	6–12	5–10	4– 8
Under 34	4– 7	3– 6	2– 5

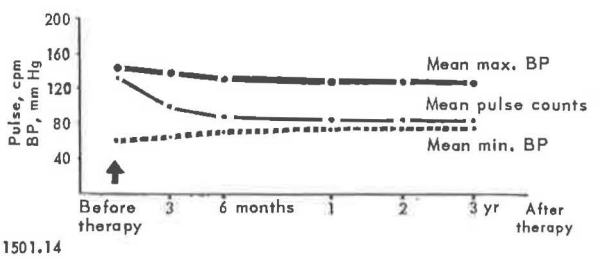

Figure 14. Changes of pulse counts and blood pressure during I^{131} treatment of hyperthyroidism

Table 2. Initial Oral Doses I^{131} given to 500 Cases

Dose, μc	*No. cases*	*Dose, μc*	*No. cases*	*Dose, μc*	*No. cases*	*Dose, μc*	*No. cases*
2	5	5	71	8	80	11	0
3	23	6	102	9	4	12	2
4	73	7	130	10	10	13	

Table 3. Effect of I^{131} Treatment on Symptoms

Symptoms	*Cases*		*Results*					
			Disappeared		*Improved*		*No change*	
	No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
Struma	489	98	470	96	20	4	0	
Tachycardia	440	88	417	95	23	5	0	
Tremor								
(Fingers)	405	81	392	97	13	3	0	
(Eyelid)	325	65	305	94	20	6	0	
Loss in body weight	375	75	368	98	7	2	0	
Hyperhidrosis	410	82	390	95	20	5	0	
Exophthalmos	270	53	41	15	60	22	169	63
Staring eyes	335	67	251	75	84	25	0	
Nervous symptoms	360	72	320	89	40	11	0	

in Fig. 13. In carrying out iodine-131 therapy, age was considered in every case and doses were reduced for younger individuals and increased for older people. Iodine-131 was given only by mouth and the dose was determined according to size of the thyroid gland, basal metabolic rate and uptake rate of I^{131} by the gland. A dose of 100 microcuries iodine-131 per gram of the gland was taken as a standard, as shown roughly in Table 1. The doses administered to the 500 cases ranged from 2 to 12 μc (average 5–8 μc) per individual dose with an interval of 2 to 3 months between administration (see Table 2). The side-effects after administration of I^{131} were almost negligible; only very slight symptoms, such as fever, tachycardia, diarrhea, etc., were observed in 50 cases (10%).

The results of I^{131} treatment are summarized in Table 3. Thyrotoxic symptoms were clinically improved in 2 to 3 weeks after the beginning of treatment. Pulse counts were gradually reduced and tachycardia improved (see Fig. 14). Changes of blood pressure after treatment are shown in Fig. 14; maximal blood pressure tended to fall and minimal blood pressure to rise. The reduction of abnormal pulse pressure is one of the significant signs of cure.

Table 4. Reduction in Size of Struma after I^{131} Treatment

Weight of struma, g	*No. cases*	*Size reduced in:*	
		No.	*%*
Over 60	97	77	79
59–35	259	238	92
Under 34	133	133	100
Total	489[a]	448 (436)	92

[a] In the other 11 cases the thyroid gland was impalpable.

About 90% of the cases treated had diffusely enlarged thyroid glands and the other 10% had nodular goiters. Struma began to decrease gradually in size after 3 to 4 weeks of treatment; better responses were seen in the diffusely enlarged goiter than in the nodular goiter (Table 4). Loss of body weight is one of the chief symptoms of hyperthyroidism and gain of body weight after beginning treatment is a good indication of improvement. Tremor and other nervous symptoms also improved. Habitual piercing stare of the eye was seen in 355 cases (67%); it disappeared after treatment in 251 cases (75%) and was reduced in another 84 cases (25%). Exophthalmos was seen in only 53% of all the cases (270 patients) and disappeared in 41 cases (15%) or decreased in 60 cases (22%). However, increase of exophthalmos after treatment occurred in 9 cases. Exophthalmometry and the measurement of eyeball pressure were carried out in 67 cases. There were many more cases showing recession of exophthalmos by ex-

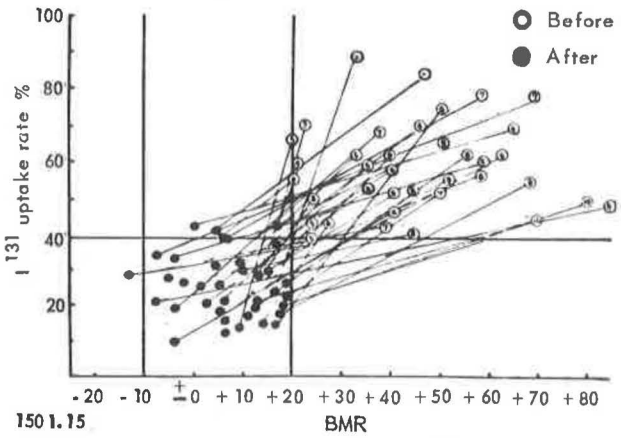

Figure 15. Relationship between BMR and I^{131} uptake rate

Table 5. Changes in Eyeball Pressure after I^{131} Treatment

Exophthalmos in mm	*Before treatment*			*After treatment*		
	Y[a] *100*	*Y 200*	*Y 300*	*Y 100*	*Y 200*	*Y 300*
Over 15	2.8	4.7	5.8	3.3	5.3	6.6
Under 15	2.2	4.1	4.9	2.5	4.2	5.4
Normal	3.2	4.7	5.8			

[a] Y, value in g.

Table 6. Results of Exophthalmometry and Measurement of Eyeball Pressure (showing Effect of I^{131} Treatment on Exophthalmos)

Exophthalmometry			*Measurement of eyeball pressure*		
Result	*No. cases*	*%*	*Result*	*No. cases*	*%*
Disappeared	8	11.9	Normal value	8	11.9
Improved	13	19.4	Improved	30	44.8
Unchanged	37	55.2	Unchanged	20	29.8
Increased	9	13.4	Increased	9	13.4
Total	67	100.0	Total	67	100.0

Table 7. Electrocardiographic Studies of Hyperthyroid Cases after I^{131} Treatment

Findings	*No. cases examined*	*No. positive before treatment*	*Findings after treatment, No.:*			
			Unchanged	*Disappeared*	*Appearing first time*	*Total*
Myocardial failure	19	14	8	6	5	13
Sinus tachycardia	31	23	5	18	1	6
Sinus bradycardia	0	0	0	0	3	3
Respiratory arrhythmia	1	1	1	0	0	1
Ventricular extrasystole	2	2	1	1	0	1
Auricular extrasystole	3	3	0	3	0	0
Auricular fibrillation	2	2	2	0	0	2
Atrioventricular block	3	3	0	3	0	0
Auricular block	1	1	0	1	1	1
WPW	1	1	0	1	1	1
Pulmonary P	2	2	1	1	0	1
Mitral P	3	2	1	1	0	1
Dextrocardia	4	3	1	2	0	1
Sinistrocardia	3	3	0	3	0	0

Table 8. Results of I^{131} Treatment of 500 Cases of Hyperthyroidism

Results	*6 mo*		*1 yr*		*2 yr*		*3 yr*	
	No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
Cured	400	80	325	84.5	132	88	60	95
Improved	88	17.5	37	10	9	6	2	3
Unimproved	2	0.5	2	0.5	0		0	
Recurrence	0		0		1	1	1	2
Hypothyroidism	10	2	8	2	0		0	
No follow-up	0		11	3	8	5	0	
Total	500	100	383	100	150	100	63	100

ophthalmometry than by inspection, and measurement of eyeball pressure (Tables 5 and 6) gave a much better indication of the response of the orbital condition to I^{131} treatment.

The accelerated basal metabolic rate gradually declined and the high I^{131} uptake rate of the thyroid gland began to fall and almost paralleled the BMR, as shown in Fig. 15. The only change appearing in the blood picture was in the leucocyte count; changes during treatment with I^{131} are shown in Fig. 16.

Electrocardiographic examinations were carried out in 109 cases and many pathological states were ob-

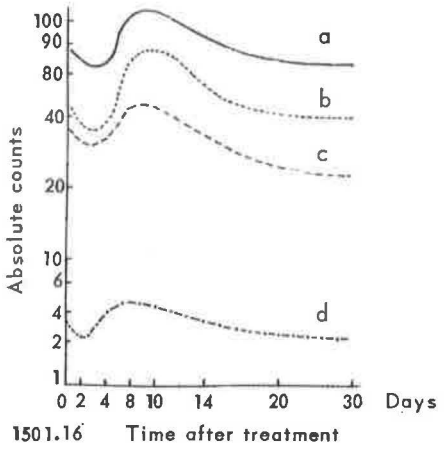

Figure 16. Changes in the leucocytes during I^{131} treatment: a, total leucocyte count; b, neutrophilic leucocytes; c, lymphocytes; d, eosinophilic leucocytes

served (see Table 7). These abnormal signs disappeared or improved after treatment in some cases; in others they became worse or appeared for the first time after therapy (Fig. 17).

Table 8 summarizes the results of iodine-131 treatment of the 500 cases of hyperthyroidism. Four hundred cases (80%) were cured after 6 months, 85% after one year and 95% after 3 years. The occurrence of post-therapeutic hypothyroidism was seen in 10 cases (2%), but these were only temporary and all disappeared after one year. Even in younger patients poor results were never seen.

From these results we can conclude that radioactive iodine, I^{131}, is the most dependable agent available for the treatment of hyperthyroidism.

The Effect of I^{131} Treatment of Hyperthyroidism on the Histology and Function of the Thyroid Gland

By Yoshikatsu Saito, Akinori Ishida, Kozo Sanada and Akihisa Takede‖

The relationship between histological changes in the thyroid and the function of the gland was studied in

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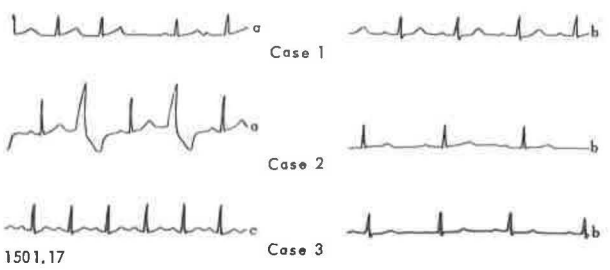

Figure 17. Electrocardiographic changes in some cases of hyperthyroidism before and after treatment. Case 1, a–incomplete block of Wenckebach's cycle; b–complete cure. Case 2, a–ventricular extrasystoles and auricular block; b–disappearance extrasystoles and appearance slight myocardial failure. Case 3, a–sinus tachycardia; b–disappearance tachycardia and onset of myocardial failure

the I^{131} treated hyperthyroid patients. Specimens were obtained by excision or by needle biopsy of the gland from 62 cases, 10 to 108 hours and again 3½ to 33 months after the administration of radioiodine. The specimens were prepared by hematoxylin–eosin staining. The histological picture in the thyroid 10 to 108 hours after I^{131} administration showed changes in the nuclei of the follicular epithelium, with irregular enlargement of the nuclei. These changes were observed in 68.8% of the cases. In specimens obtained 3½ to 33 months after I^{131} administration these changes were observed in 89.2% of the patients. During this period there was no increase in fibrous thickening in the gland. The characteristic findings in these I^{131}-treated hyperthyroid glands are a reduction and even disappearance of the papillary projection of the follicular epithelium with a decrease in the height of the epithelium and a decrease in the number of vacuoles in the follicles.

From these findings we can conclude that cure in cases of hyperthyroidism treated with I^{131} occurs without producing inflammation, necrosis or any marked fibrous thickening.

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Applications of I^{132} to Measurements of Day-to-Day Changes in Human Thyroid Function

By K. E. Halnan*† and E. Eric Pochin*

Radioiodine-131 has been very widely used in the study of thyroid function and is of outstanding value for many clinical investigations. In two important respects, however, an iodine isotope with a much shorter half-life, such as radioiodine-132, offers considerable advantages. Since March, 1955, we have carried out over 2000 tests of thyroid function using I^{132} and wish to describe some applications of this isotope to the study of human thyroid activity.

The greatest advantage in the use of I^{132} as compared with I^{131} lies in the very much smaller radiation doses delivered to thyroid per microcurie administered, a given oral dose of I^{132} delivering from $\frac{1}{40}$th to $\frac{1}{100}$th the thyroid radiation received from an equal amount of I^{131}. This considerable reduction in dosage is due not only to the short half-period of I^{132} (of 2.3 hours, which is less than $\frac{1}{80}$th that of I^{131}), but also to the relatively slow course of radioiodine uptake into the gland from the circulation. In a normal thyroid gland iodine uptake will only be half completed in about 6 hours, and by this time 85% of the administered I^{132}, but only 2% of I^{131}, will have undergone decay.

The radiation dose received by the thyroid, in rads per microcurie of radioiodine administered, will depend upon the time course of uptake and discharge, as well as upon the mass of the gland and the proportion of the dose which becomes concentrated there. Estimates of this dose[1] are given in Table 1 for I^{132} and I^{131}, and for adults and children of normal or increased thyroid activity. It will be seen that the thyroid radiation per microcurie of I^{132} administered is usually between 1% and 2% that for I^{131}.

The much smaller radiation doses received by the gonads per microcurie of I^{131} are given in Table 2, which shows that these also are reduced by the substitution of I^{132}. It is clear, therefore, that any estimate of thyroid activity which is completed within a few hours of administering a radioiodine dose may be made with only trivial tissue radiation, even to the thyroid, by the use of I^{132}. Moreover the greater number of gamma rays emitted per disintegration and the higher mean gamma radiation energy of I^{132} as compared with I^{131} (Table 3) imply that for most counting systems, fewer microcuries of I^{132} are required at the time of counting to cause a given counting rate. For counts made two hours after administration, the greater efficiency in counting I^{132} will about offset the loss of activity due to decay during this period, so that equal initial quantities in microcuries of I^{131} and I^{132} will give equal counting rates two hours later, and the full reductions in dosage shown in Tables 1 and 2 can be realised in practice.

Despite its short half-life, the supply of I^{132} can be arranged very conveniently by distillation from a source of tellurium-132.[2] This latter isotope is available as a fission product of uranium-235 and decays with the conveniently long half-period of 3.2 days to form iodine-132. The iodine is held in solution as iodate until needed, then distilled off after conversion to free iodine, and converted to iodide in the distillate. The distillation and preparation of doses, which requires about 20 minutes, can be repeated several times daily if necessary, since an equilibrium amount of I^{132} is rapidly reformed from tellurium decay (see Fig. 1).

We have used a test of thyroid activity depending upon the administration of up to 6 microcuries of I^{132} and the determination of radioactivity in the neck and the thigh two hours later. It is clear that the greater the thyroid radioiodine uptake during this period, the greater will be the counting rate at the neck and the smaller will be that at the thigh, so that the ratio of the neck to the thigh counting rates will give a simple estimate of thyroid activity in this respect. The dose is usually given orally in solution as iodide at 10 A.M. to a subject who has not eaten since a small breakfast before 7:30 A.M. so that uptake of the radioiodine from the alimentary tract is not delayed by gastric contents. Two hours later the subject returns for measurements involving from 1 to 5 minutes of counting. The neck and thigh radioactivities are measured simultaneously, the former by a square of four shielded Geiger Muller counters grouped round the thyroid position in the neck, and the latter by a single large-cathode counter placed between the thighs and so shielded that negligible radiation only reaches it from the bladder. The position of the subject and of the counters can be measured and is, therefore, reproducible if repeated determinations are being made on the same subject. The counting is stopped electronically at the next whole minute after sufficient counts above the background rate have been recorded

* Work undertaken on behalf of the Medical Research Council, Dept. of Clinical Research, University College Hospital Medical School, London.

† Now at the Christie Hospital and Holt Radium Institute, Manchester.

Table 1. Thyroid Radiation (rads) per Microcurie of Radioiodine Administered Orally

	Normal adult	*Thyro-toxic adult*	*Pregnant adult*	*Foetus*[a]	*Breast-fed infant*[a]	*Infant*	*Child*	*Thyro-toxic child*
				Values assumed				
Mass, g	25	50	30	0.08%/g	2	2	5	10
Uptake, %	30	70	50	−4.8%/g	45	45	45	90
Half-period of uptake, hr	6	1	6	3	3	3	3	1
				Radiation dose estimated (rads)				
Per μc I^{131} β	1.3	1.6	1.8	0.089–5.3	2.9	25	10	10
γ	0.09	0.13	0.14					
Total	1.4	1.7	1.9	0.089–5.3	2.9	25	10	10
Per μc I^{132} β	0.011	0.032	0.016	0.0011–0.069	0.012	0.32	0.14	0.21
γ	0.0017	0.006	0.0025			0.02	0.01	0.02
Total	0.013	0.038	0.019	0.0011–0.069	0.012	0.34	0.15	0.23
Dose ratio, I^{131}/I^{132}	110	45	100	79	240	74	67	44

[a] From radioiodine administered to the mother.

Table 2. Gonad Radiation

	Adult (and foetus)	*Infant*
Rads per μc I^{131} β	0.00037	0.0074
γ	0.00016	0.0012
Total	0.00053	0.0086
Rads per μc I^{132} β	0.000073	0.0015
γ	0.00011	0.00081
Total	0.00018	0.0023
Dose ratio I^{131}/I^{132}	3	4

Table 3. Physical Properties of Iodine-131 and -132

	I^{131}	I^{132}
Half-life	8.0 days	2.3 hours
Average β energy	0.19	0.49 Mev/disintegration
Average γ energy	0.40	2.0 Mev/disintegration
β dose rate	0.41	1.0 rads/hr/μc/g
Total β dose	110	3.5 rads/μcd
K-factor (γ dose rate)	2.1	11 rads/hr/mc at 1 cm

to ensure that the standard error with which the ratio is determined is less than 5% of the value of the ratio. The value of the ratio is registered on the dial of a computer which combines the counting rates being recorded for neck and thigh with corrections for background rates and for dead time (see Fig. 2).

This method has advantages of speed and convenience—the total time spent being about 10 minutes for each subject—producing a result which becomes available during a clinic at which the patient is first seen. A possible defect is that it gives a result expressed in empirical units which depend upon the geometrical arrangement and sensitivity of the counters, although such results can, if necessary, be correlated with absolute values derived from other tests. Or the same equipment may be used to measure the thyroid uptake as a percentage of the dose given. In comparing different patients, the position of neck and thigh counters and the size of neck and thigh have some influence on the result obtained, although successive readings on the same subject may be made strictly comparable by measurement and standardisation of position. Delays in intestinal absorption of the radioiodine could influence the result, but average values of 2-hour ratios after intravenous doses and oral doses to subjects who have fasted for 2½ hours agree well. The method is free from technical sources of error due to contamination of glassware and loss of urine specimens, it does not involve the collection of blood samples, and, since its result depends upon a ratio of simultaneous counting rates, the size of dose given does not enter the calculation and need not be measured exactly. For many physiological and clinical studies, moreover, it is valuable to be able to repeat the test daily, and the rapid decay of I^{132}, to less than 0.1% in 24 hours, and the very low tissue doses delivered, allow this to be done safely and easily.

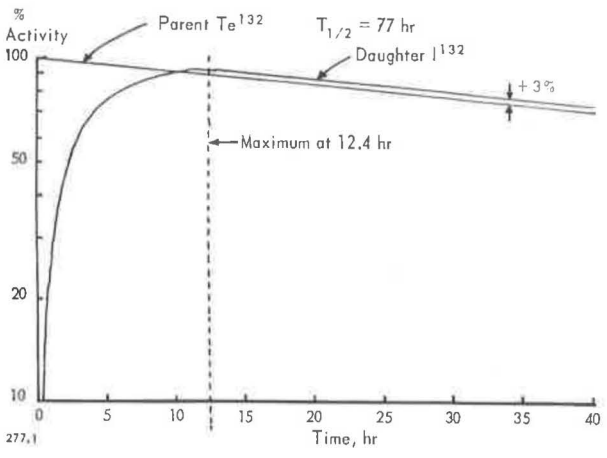

Figure 1. Formation of daughter I^{132} from parent Te^{132}, showing the rapid build-up to transient equilibrium

Figure 2. Measurement of ratio of radioactivity in neck and thigh two hours after administration of I^{132} by mouth

When the activity of the normal thyroid is examined in this way, it is found to vary substantially in activity from day to day. Multiple determinations have been made in 25 normal subjects and have shown that, for any individual, determinations made on different days have varied round the mean value for that individual with a standard deviation of 20% of the mean (Fig. 3). The response of the human thyroid to physiological and other stimuli can thus only be studied accurately by this means if several measurements are made before the stimulus is applied.

The effect and speed of action of various stimuli have been investigated in order to examine the factors controlling the iodine uptake of the human thyroid. It is known that, in many mammals, a rise in hormonal iodine concentration in the blood causes decreased release of thyrotropic hormone from the pituitary and a reduced uptake of radioiodine and formation of hormone by the thyroid. However it was not clear how rapidly this mechanism operated in man to maintain a normal hormonal concentration in the blood, nor whether an increased daily iodine intake caused a reduction in the proportion of this iodine concentrated by the thyroid directly, or whether it had this effect only when an increased uptake of iodine by the gland had started to cause a rise in blood hormonal iodine content. Therefore iodine was added to the diet of a group of normal subjects in amounts such that the total intake was approximately trebled, and the thyroid radioiodine uptake was followed during the ensuing weeks. The uptake was found to fall progressively but slowly to a reduced level that was reached several weeks after increasing the iodine uptake, the uptake then remaining depressed while increased iodine was being given.

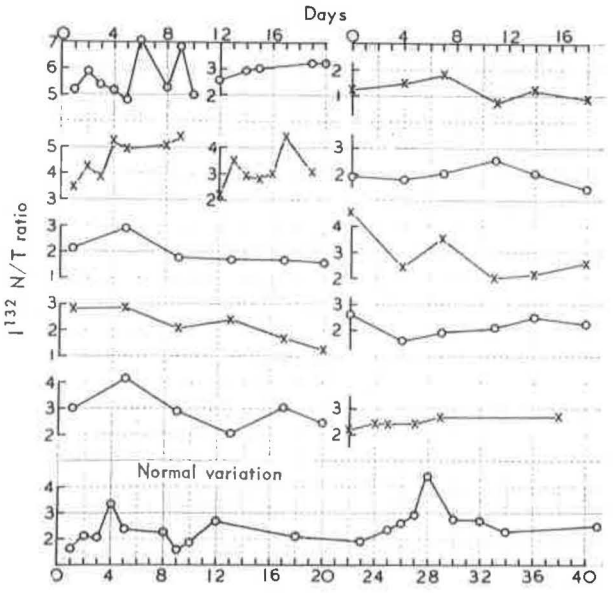

Figure 3. Variation of the neck-thigh ratio in thirteen euthyroid subjects measured repeatedly over periods of ten to forty days, showing normal variation in thyroid function

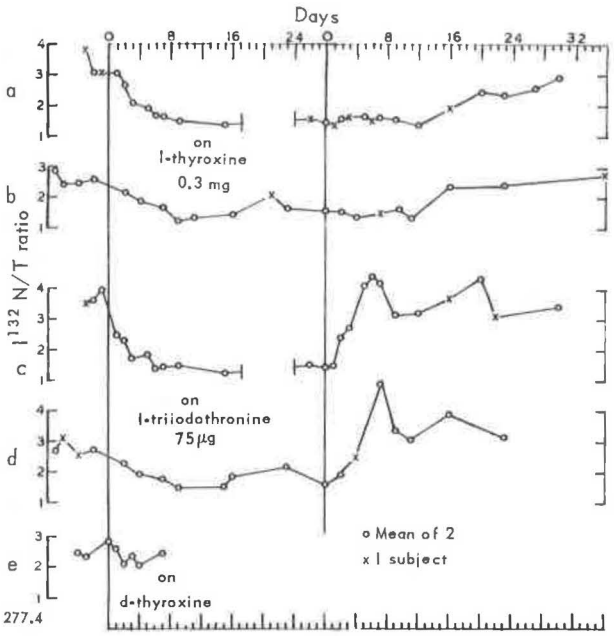

Figure 4. Change in "neck-thigh ratio" before, during and after administration of thyroid hormone as follows:
(a) 0.3 mg sodium-l-thyroxine daily for 3 weeks to 2 euthyroid subjects.
(b) 0.3 mg sodium-l-thyroxine daily for 4 weeks to 2 euthyroid subjects.
(c) 75 μg sodium-l-triiodothyronine daily for 3 weeks to 2 euthyroid subjects.
(d) 75 μg sodium-l-triidothyronine daily for 4 weeks to 2 euthyroid subjects.
(e) 0.3 mg sodium-d-thyroxine daily for 8 days to 3 euthyroid subjects.
In each case a circle represents the mean of measurements on 2 subjects and a cross a single measurement only, except that in (e) a circle represents the mean of measurements on each of 3 subjects

This result was compared with that following the administration of l-thyroxine in amounts approximately equal to the normal daily output of the hormone. In these circumstances, the radioiodine uptake fell progressively during the first week of thyroxine administration and then continued at a reduced level until thyroxine ceased to be given, after which the uptake slowly returned, reaching its normal value about 3 to 4 weeks after stopping thyroxine. Simultaneous measurements in control subjects showed no comparable systematic changes nor was there any

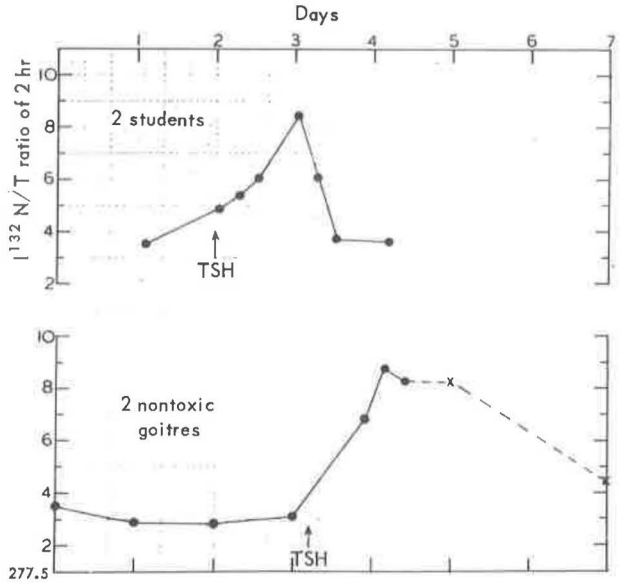

Figure 5. Variation of the neck-thigh ratio in two euthyroid subjects and two patients with nontoxic goitres, before and after injection of pituitary thyrotropic hormone (10 units USP Thyrotropar Armour). Circles represent the mean of measurements on each of two individuals, crosses measurements on one only

comparable change during administration of d-thyroxine (Fig. 4).

The figure shows, therefore, that the human thyroid uptake of iodine is not rapidly reduced when the hormonal iodine concentration of the blood rises. The latency of a week or longer before the full effect occurs might be due to one of several possibilities.

(i) The stimulus to the pituitary might not depend simply on a raised thyroxine concentration in the blood, but upon some effect of an increased activity due to this rise in concentration, and delayed by the time required for metabolism of some part of the administered thyroxine.

(ii) A time lag might occur between adequate stimulation of the pituitary and a reduction in its release of thyrotropin.

(iii) A similar time lag might intervene between a reduction of thyrotropin release and a fall in thyroid radioiodine uptake.

In an attempt to distinguish between these possibilities, the effect of triiodothyronine was compared with that of thyroxine in equivalent dosage (Fig. 4). It was found that the thyroid iodine uptake fell at a rate similar to that caused by giving thyroxine, but that after ceasing administration of triiodothyronine the return of thyroid uptake occurred with the suggestion of a "rebound" to higher than normal levels during the following week in all of the four subjects examined. This possible difference between the effects of triiodothyronine and of thyroxine might be due to the difference in their speeds of metabolism.

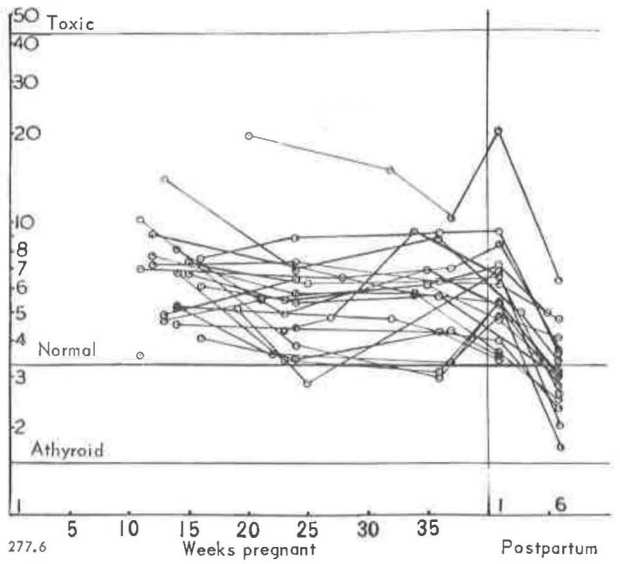

Figure 6. Variation of the neck-thigh ratio at 2 hours during and after pregnancy in 21 normal patients, compared with the mean ratios in groups of thyrotoxic, normal and athyroid subjects (see Figure 8). Each circle represents one measurement and the successive measurements on each individual are joined by a line

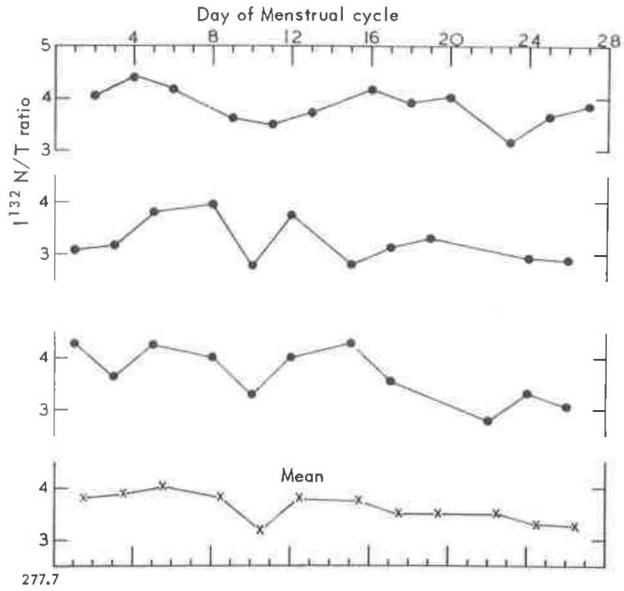

Figure 7. Variation of the neck-thigh ratio in three female subjects, showing no significant correlation with the menstrual cycle

An attempt was then made to estimate the speed with which the thyroid uptake responded to changes in thyrotropin stimulation, by giving a single dose of thyrotropin (10 units USP Thyrotropar Armour). The uptake was found to be maximally increased at about one day after the injection, and to return nearly to normal a day later (Fig. 5). If the thyroid responds equally rapidly to physiological changes in thyrotropin release, it is evident that the lag of a week in response to changes in thyroxine and triiodothyronine levels cannot be due to delay in thyroid response.

The lack of difference between the speed with which uptake is depressed by thyroxine and by triiodothyronine suggests that the delay is not due to the time required for metabolism of hormone, since that for triiodothyronine is very much shorter than that for thyroxine. It remains possible that the

release of thyrotropin is not immediately altered by appropriate and adequate stimulation of the pituitary in man.

The use of I^{132} has thus made possible an estimation of the speed with which thyroid function changes after administration of thyrotropic and thyroid hormones. The additional advantage of the very low tissue radiation dosages with this isotope appear to justify measurements, with greater freedom from radiation hazards, on pregnant women and children and other volunteer subjects—mostly medical students. Measurements have been made of the radioiodine uptake in the thyroid gland by this method in 21 women at 12, 24 and 36 weeks' pregnancy, and at 1 and 6 weeks after delivery. The uptake was very significantly raised at all these times, except at 6 weeks after delivery, when it was normal (Fig. 6). This rise in iodine uptake during pregnancy might perhaps be related to oestrogen

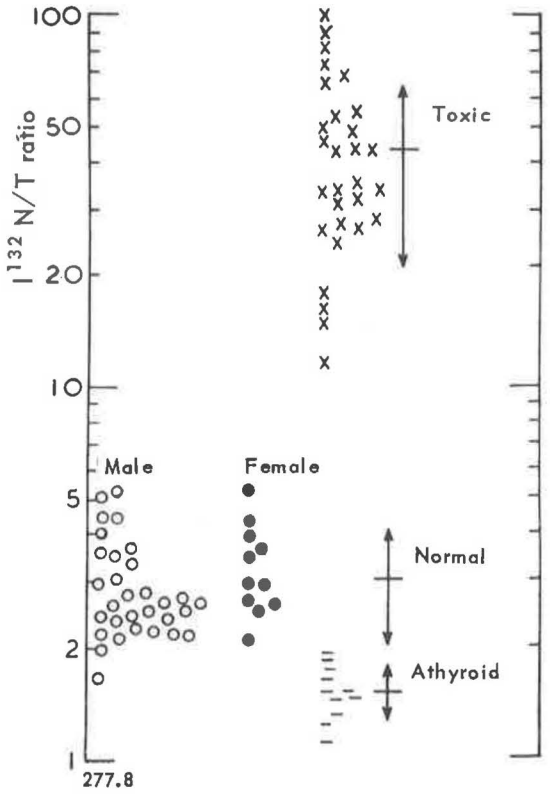

Figure 8. Neck-thigh ratios measured two hours after oral I^{132} in randomly selected patients with clinical thyrotoxicosis (crosses), in euthyroid male and female subjects (circles and dots), and in patients after complete thyroid ablation (horizontal lines). The mean ratio is shown for each group. Arrows represent twice the calculated standard deviation

metabolism. Measurements were therefore made in three female subjects throughout one menstrual cycle but no correlation was observed between iodine uptake and the time of menstruation (Fig. 7).

In the diagnosis of certain thyroid disorders, we have adopted the same procedure of determining the ratio of radioactivity in neck and thighs two hours after oral administration of about 6 μc of I^{132} to a fasting subject. In normal subjects this ratio has values which vary round a mean of 3.0, their distribution

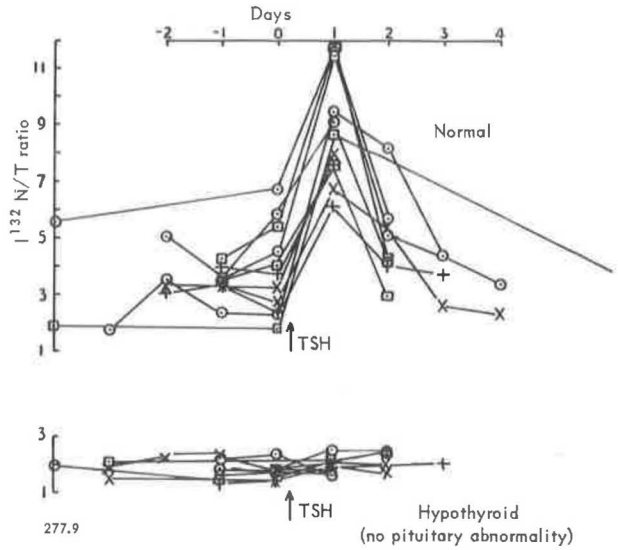

Figure 9. Day-to-day variation of the neck-thigh ratio before and after injection of thyrotropic hormone in ten euthyroid subjects and ten hypothyroid subjects without other signs of pituitary abnormality

being positively skewed but with a standard deviation of 0.6. The range of results in known hyper, hypo and euthyroid subjects, is shown in Fig. 8. It will be seen that the method is likely to be of much greater value in the diagnosis of hyperthyroidism than in that of hypothyroidism.

Repeated measurements of thyroid function following administration of thyrotropic[3] or thyroid hormone may be of value also in certain cases. Day-to-day tests

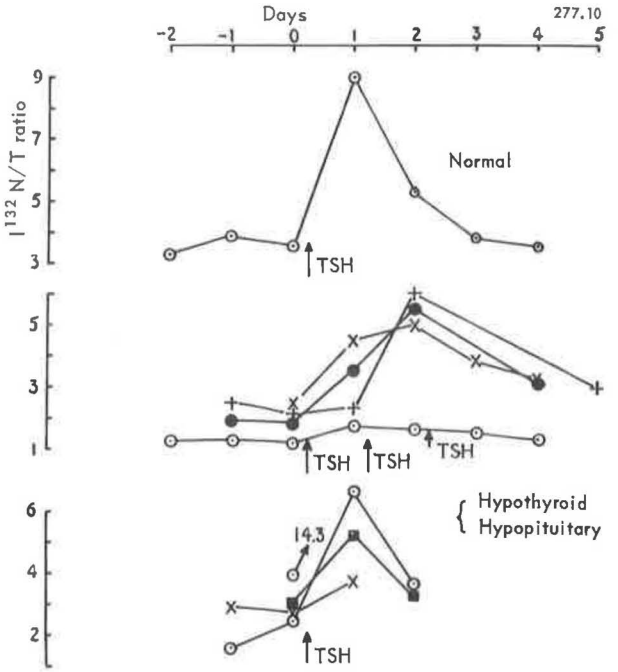

Figure 10. Day-to-day variation of the neck-thigh ratio in a typical euthyroid subject before and after injection of thyrotropic hormone compared with that in three hypopituitary patients who showed a partial response after two injections, in one hypopituitary patient who showed no response to three injections and in four hypopituitary patients who showed a response to one injection

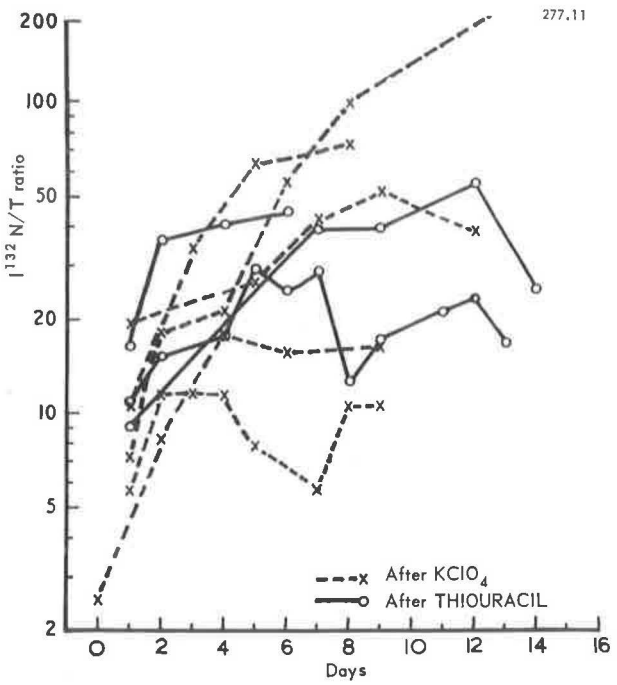

Figure 11. Thyrotoxicosis after ceasing antithyroid drugs. Change in the neck-thigh ratio after cessation of administration of antithyroid drugs (methyl thiouracil or potassium perchlorate) to thyrotoxic patients. Each line represents measurements on a single patient and commences on the day after the last dose of antithyroid drugs

with I^{132} will readily demonstrate an effect of a single injection of thyrotropic hormone on the normal thyroid or on the thyroid of most patients with hypofunction of the pituitary, but no effect will be demonstrable in patients with primary hypothyroidism (Figs. 9 and 10). In clinical use it will usually be

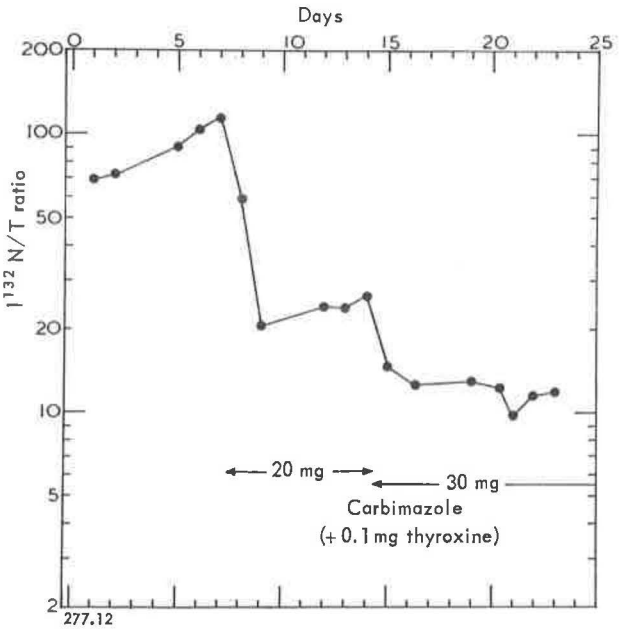

Figure 12. Variation in neck-thigh ratio of a patient with thyrotoxicosis with exophthalmos before and after treatment with carbimazole and sodium-l-thyroxine

sufficient to give an injection of thyrotropin immediately after the first I^{132} test and then to repeat the test at the same time a day later. When the diagnosis of thyrotoxicosis is in doubt, it may be valuable to administer thyroid hormone to the patient for one week and then to repeat the I^{132} test, since the normal fall in radioiodine uptake does not occur in the hyperfunctioning gland.[4,5]

In certain conditions it may be of special value to know how the iodine uptake of a patient's thyroid changes from day to day; for example in the case of a thyrotoxic patient controlled by antithyroid drugs (such as methyl thiouracil or potassium perchlorate) whom it is desired to treat with iodine-131. It is normally desirable to cease administration of the antithyroid drug for an interval before giving I^{131}, so that there may be sufficient uptake of this dose. However, it may often be clinically desirable for this interval to be as short as possible, so that symptoms of thyrotoxicity do not recur. In these circumstances we have

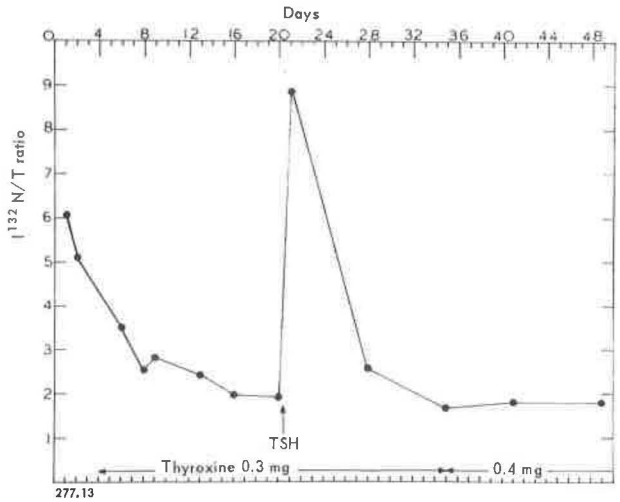

Figure 13. Variation in the neck-thigh ratio of a patient with widespread breast cancer before and after oral administration of thyroxine and injection of thyrotropic hormone

made repeated measurements with I^{132}, usually finding that iodine uptake rises to abnormal values within a few days of stopping the drug, although the level reached often varies widely from day to day (Fig. 11).

Two further examples may be mentioned. First, daily measurements were made on a thyrotoxic patient with severe exophthalmos who was initially untreated until it was clear that the eye condition was not progressing. He was then treated with progressively increasing doses of carbimazole (Fig. 12). In this case it can be seen that the iodine uptake of the overactive gland was increasing before treatment and that it was then brought progressively under control by the antithyroid drug. The second example formed part of an investigation into the thyroid function of patients with breast cancer. Figure 13 illustrates that the thyroid of a patient with widespread breast cancer may behave normally, its iodine uptake falling in the usual way when thyroxine was administered and show-

ing a normal response to thyrotropin during thyroxine administration.

It appears that the short half-life of iodine-132 gives it two substantial advantages over iodine-131 both in diagnostic and in research examination of human thyroid function: a reduced radiation dosage to the subject investigated and convenience when repeating tests at short intervals. We have not found its preparation from tellurium-132 to involve any difficulty or hazard sufficient to outweigh these advantages.

ACKNOWLEDGEMENTS

We wish to express our thanks to members of the staff of University College Hospital for help in these investigations; to the patients and other volunteer subjects, mostly medical students; to Mrs. R. Barnes, Miss M. Adams and Miss G. Adkins for their helpful technical assistance and to Mr. B. D. Corbett and Mr. A. Cronquist for their skill in the design and construction of the apparatus.

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Radioiodine Studies in Endemic Goiter in the Libyan Desert

By P. Ghaliounghi and K. Shawarby*

In previous publications we reported a focus of endemic goiter in Dakhla oases of the Libyan desert.[1–3] It was impossible at the time to perform any further experiments, but it was felt that a study of thyroid gland physiology would aid in elucidating causes of the endemicity, and also in shedding light on thyroid function. Since conditions in the oases preclude local application of experimental procedures, it was considered impractical to plan and execute a comprehensive series of investigations such as those performed in Argentina by Stanbury and associates.[4]

We had to content ourselves with determining the conversion ratio (C.R.) of one hundred persons living in the area after a rapid clinical examination (being the only study possible locally) and with carrying out experiments on seventeen selected patients transported by air from Dakhla for a one-week stay in the medical wards of the Ein-Shams University Hospital in Cairo.

MATERIAL AND METHODS

Local authorities were asked to designate 100 unselected persons from the different villages of the oases. Condition of the thyroid gland was noted carefully and then a dose of 50 μc of I^{131} was administered by mouth. Exactly 24 hours later, 10 cc of blood were withdrawn, stored in ice-cooled tubes and kept thus until analysed in Cairo. In addition, 17 selected patients were transported to Cairo. Air travel was insisted upon as it takes about 3 hours compared with 2–3 days by surface travel, also because it ensures a minimum change in dietary habits and, therefore, a more or less steady state of thyroid function.

The conversion ratio was determined by the following method: 3–5 cc of plasma were placed in a test tube and the radiation determined by means of a well-scintillation counter. Four or 5 drops of 3% NaI carrier were delivered into the plasma and 10 cc of 20% trichloracetic acid added to contents of the tube. This was centrifuged at 3000 rpm, and the supernatant fluid decanted and discarded. The precipitate so obtained was washed twice with 10% trichloracetic acid and counted.

$$\text{C.R.} = \frac{\text{corrected count/minute of precipitate}}{\text{corrected count/minute of plasma}} \times 100$$

The radioiodine thyroid uptake was measured twenty-four hours after a 20 μc dose of I^{131} by means of the scintillation counter.

RESULTS

Of the 92 cases collected at random and whose C.R. was examined, 47 had normal glands, 34 had palpably enlarged glands, and 11 had grossly enlarged glands. The range, mean, and mode for each group are shown in Table 1.

The detailed findings for each clinical group are shown in Table 2. The mean C.R. of all cases was 44.8. This value did not differ appreciably from those for normal, palpably enlarged, or grossly enlarged glands where it was 44.2, 45.4, and 46.1, respectively. The mode for all the cases occurred between 55 and 59 with a slightly higher figure for the third group.

The range was extremely wide; had the number of cases examined been larger, a more definite incidence pattern might possibly have been found. This wide variability, however, may be attributed in part to the random way in which the subjects were gathered. It is probable that the glands of these people were widely different functionally though they all appeared clinically euthyroid. This possibility was confirmed in the second series of cases by the greater variability found in glands that were grossly enlarged and presumed to be the seat of widely varying pathological changes. As they appear, the figures have too wide an index of variability to be statistically significant. However, 46 (i.e., half of the cases) lie above the level of 50% which is the upper limit of the accepted normal; another 10% lie in the range of 40–50% where normal and hyperthyroid values overlap.

Results for 17 patients hospitalized in the Ein-Shams University Hospital are shown in Table 3, which provides information regarding age, sex, clinical condition of the glands, the radioiodine uptake and the conversion ratio.

The iodine uptake was definitely high in our cases. In Egypt, the normal range from our experience lies between 15 and 55%. Figures for only three of our special study cases fell within this range (Case 5: 52.7; Case 9: 45.6; Case 14: 45.7), although nearer its higher limit. Figures for the remaining 14 ranged from 55.7 to 79.6%. It will be seen that all the cases but four lie above Skanse's value of 57.7%, which represents the

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Table 1

State of thyroid gland	No. of cases	Range	Mean	Mode[a]
Normal	47	3.6–96.6	44.2	55–59
Palpable	34	0.4–90	45.4	55–59
Grossly enlarged	11	5.9–86.6	46.1	60–65
Total	92	0.4–96.6	44.8	55–59

[a] To calculate the mode, the C.R. values were divided into groups 0–4 5–9, 10–14 . . .

mean plus twice the standard deviation for euthyroid subjects in Boston.[15] Of the eight with normal or slightly enlarged glands (mostly diffuse), seven showed conversion ratios above the limits of normal (average: 57.5). The range was 52.9 to 60% in all but one case: No. 9 (28.1%), who also had the lowest uptake of the two categories.

The five cases with nodular goiters had widely varying conversion ratios. The three largest glands exhibited the lowest values of the series (cases 15, 16, 17).

Graphic arrangement of the data shows the relation between uptake and conversion ratio in these cases. If we exclude the three patients with the largest goiters, a positive correlation is found between the I^{131} uptake and the C.R. (coefficient of correlation: 0.7). The grounds for this exclusion are based on the well known erratic behavior of nodular goiters with respect to radioiodine measurements. Keating and associates found in adenomatous goiters without hyperthyroidism that, although the mean for radioiodine uptake did not differ from normal, the range of values was nevertheless much wider than in the nonadenomatous group. He concluded that in these cases radioiodine tracer doses are of limited value at best no matter how measured.† Actually, the position of these three cases on the scatter diagram gives confirmation of this view, for the remainder show good correlation thus indicating that the more avid glands are also the more active.

DISCUSSION

The uptake of I^{131} is an index of the rate of thyroid hormone formation only if it bears a constant relation to hormone output. Physiologically, this is true except (*a*) in case of low iodide concentration in the plasma when the gland must increase the plasma iodide clearance rate in order to maintain a normal output of hormone, or (*b*), as seems possible from recent studies, in case iodine can leave the gland in a form other than thyroid hormone.

There appears to be agreement on the view that simple goiters are in a state of hyperfunction in an attempt to make up (*a*) for a deficient supply of available iodine, or (*b*) for a block in the synthesis of thyrotropin. Such goiters in the experience of many authors[4,8] take up abnormally large quantities of ingested iodine. In the case of nonendemic cretinism and goiter, the rapidly accumulated iodine is quickly liberated after KCNS and is not incorporated into hormonal iodine.[9] The defect in this case is one of enzymatic synthesis of freely available iodine into organic combination. On the contrary, when the defect is one of supply, the glands show a more rapid turnover of hormone when iodine becomes available. Simply measuring the absolute level of protein bound iodine is not of great value in determining the functional level in such cases. As Stanbury has shown in Mendoza,[4] the PBI may be within normal range but still show an inverse relationship to iodine uptake of the gland and to iodine in the food as measured by urinary iodine.

A better indication of thyroid function can be found in the conversion ratio suggested by Chaikoff on the basis of animal experiments,[10] and used by Clark[11] as a diagnostic test. Harsha[12] presented evidence that PBI measures thyroxin iodine and that rate of conversion parallels the degree of dysfunction. In cases from nonendemic areas the blood thyroxin and C.R. results were nearly identical for all classes of thyroid dysfunction. He showed that patients with ratios over 50% were hyperthyroid and those with less than 10% were hypothyroid and thinks that the ratio is the most useful single test of thyroid function. Sheline[13,14] considers the C.R. to be more or less directly related to the rate at which the thyroid gland utilizes circulating inorganic iodine of the plasma to form plasma PBI, and to be approximately equal to the value obtained by chemical determination of PBI. His findings are shown in Table 4. In 1954 Van Middlesworth[15] devised a simplified method for determining C.R. and confirmed that it correlated better with the ultimate diagnosis than any other single test and was more sensitive than iodine uptake measurement. He considered rates between 10 and 30% to be normal and above 50% to be indicative of hyperthyroidism. Thode[16] gives the figures shown in Table 5.

There seems, therefore, to be agreement among the various observers that any C.R. reading above 50% is abnormal and denotes hyperthyroidism. However, additional evidence indicates that the C.R. measures level of activity and not rate of output. In two cases of myxoedema following thyroidectomy, Blom[17] found high C.R. values in spite of very low BMR and PBI levels. It is now recognized that plasma studies after thyroidectomy are of limited value. In these cases, the glandular remnants probably remain hyperactive with very low storage capacity and the low PBI with high activity manifest, the rapid rate of synthesis and delivery of an amount of hormone (insufficient in Blom's cases to maintain health) or, in other cases, just adequate for euthyroidism.

In the case of endemic goiter also, a comparable discrepancy occurs. Costa and his collaborators,[8] studied 20 subjects from an endemic area where no iodine prophylaxis was practiced, and found rapid and high uptakes: 49.2% after one hour: 49.05% after 24 hours (normal: 18% and 30% respectively). The conversion ratios after 24 hours in three cretins were also found

† Eichhorn[7] is also of the opinion that radioiodine measurements in nodular goiter and in endemic cretinism cannot differentiate these conditions from hyperthyroidism.

Table 2

State of thyroid gland	Total No. of cases	Conversion ratios (C.R.)									
		0–9	10–19	20–29	30–39	40–49	50–59	60–69	70–79	80–89	90–100
Normal	47	3	5	3	7	7	10	4	5	2	1
Palpable	34	3	2	7	2	2	9	4	2	2	1
Grossly enlarged	11	1	1	2	1	0	1	3	1	1	0
Total	92	7	8	12	10	9	20	11	8	5	2
%	100	7.6	8.6	13	11	9.7	21.6	12	8.6	5.4	2.1

Table 3

Case No.	Age	Sex	Thyroid gland	Iodine uptake	Conversion ratio (C.R.)
1	18	M	Normal	77.7	58.9
2	50	M	Normal	59.8	—
3	50	M	Normal	60.0	57.7
4	40	M	Normal	55.7	52.9
5	14	M	Palpable	52.7	53.9
6	11	M	Palpable	79.6	—
7	12	M	Palpable	71.2	66.9
8	12	M	Palpable	60.9	—
9	18	M	Palpable	45.6	28.1
10	18	M	Palpable	75	60
11	10	M	Palpable	75	82
12	12	M	Diffuse enlargement	71.2	—
13	45	M	Nodular × 2	70	86.6
14	25	F	Nodular × 3	45.7	54.3
15	30	F	Nodular × 3	65	22.2
16	50	M	Nodular × 3	76.8	19.2
17	30	F	Nodular × 5	65.1	32.1

to be high: 77.6 and 43%. They concluded that the endemic cretin presents not only an increased uptake of iodine by the thyroid, but also a remarkable transformation of captive iodine into protein-bound compounds. Thus, these glands, in spite of the absence of hyperthyroidism, are actually highly active.

Our results are consistent with those of Stanbury and Costa.

Table 4

	Range	No. of cases
Euthyroid	4–34%	22
Hyperthyroid	33–100%	19
Hypothyroid	4–25%	4

Table 5

	Average	Range	No. of cases
Normal	17	11–23	7
Hyperthyroid	80	45–100	20
Hypothyroid	9–1	2.5–16	20
Thyroid function questionable	24	11–53	22

SUMMARY

1. The conversion ratio for 92 persons living in an area of endemic goiter was determined. The values obtained show a wide range of variability but half of them are above the normal range. The findings are consistent with the information available about rapid hormonal turnover of glands in areas with iodine deficiency.

2. In 17 cases of endemic goiter from the same area, high values were obtained for the iodine uptake. In 13 of these, the conversion ratio was estimated and found to be high in 9. This evidence suggests that goiter in Dakhla oases is due to a deficiency of dietary iodine.

ACKNOWLEDGEMENT

The authors are indebted to the Egyptian Atomic Energy Commission for valuable help and generous supply of radioisotopes and equipment. This work was carried out with help of the Egyptian Air Force which placed at our disposal a plane to carry the group and the patients across the desert to and from the oases. The Frontiers Service of the Egyptian Army provided indispensable help in collecting the patients, taking them back from Cairo and affording lodging and other facilities to our group.

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The Triiodothyronine Suppression Test in the Diagnosis of Toxic and Nontoxic Goiters

By S. Artunkal, T. Kapicioğlu and V. Seyahi*

It is now well known that the high uptake of I^{131} found in thyrotoxicosis indicates the increased rate of iodine metabolism in the thyroid gland. But a high radioiodine uptake may occasionally be seen in patients without clinical evidence of hyperthyroidism. Similar abnormalities in the test may arise from iodine deficiency due to any cause. Different procedures using radioiodine have been suggested to distinguish between thyrotoxicosis and other cases showing a high radioiodine uptake.

The administration of exogenous thyroid hormone, for example, desiccated thyroid, causes a decrease in the radioiodine uptake of euthyroid subjects.[1] McConahey and Owen found that the daily dosage required to achieve full suppression varies between 25 and 140 μg per day among normal subjects. There was no significant inhibition of the 24-hour radioiodine uptake in thyrotoxic patients to whom *l*-triiodothyronine was administered.[2–4] Werner and Spooner gave daily oral doses of 75–150 μg triiodothyronine for 8 days, to produce a sharp decrease in the 24-hour radioiodine uptake.

This procedure is called "the triiodothyronine suppression test" and is used to determine whether or not an unexpectedly high thyroid uptake is really due to thyrotoxicosis.[5] Similar results were obtained independently by Greer.[6]

We have used this suppression test in order to evaluate its reliability in differentiating the nodular and the diffuse goiters with high I^{131} uptake from true thyrotoxicosis.

MATERIALS AND METHOD

This investigation was carried out on 168 goiter cases with or without clinical evidence of thyrotoxicosis. Forty-six patients presented clinical signs of thyrotoxicosis and 4 of these had only early eye signs of Grave's disease.

The 122 cases that presented no clinical evidence of thyrotoxicosis were classified as follows:

Nontoxic diffuse goiter	95 cases
Nontoxic nodular goiter	22 cases
Surgically treated Grave's disease (in euthyroid state)	5 cases

All 168 patients were given 50 μc of I^{131} and their 24 hour uptake was measured by a Geiger-Müller counter. They were then given a daily dose of 100 μg triiodothyronine for 8 days, and the 24 hour iodine uptake test was repeated. Nine patients who did not respond were given triiodothyronine for another 8 days and tested again.

RESULTS

The results obtained are given in the Table 1.

DISCUSSION

The suppression of thyroid function by thyroid hormone is most satisfactorily explained by the pituitary–thyroid regulatory mechanism. The concentration of thyroid hormones in the blood determines the rate of TSH secretion. This secretion can be inhibited by the administration of an appropriate amount of thyroxine or triiodothyronine.

In hypophysectomised rats given TSH, the administration of thyroid hormones does not further decrease the iodine uptake of the gland.[7] This suggests that the hormones act through the pituitary by inhibiting TSH. McConahey and Owen have observed in euthyroid patients previously suppressed by triiodothyronine that injection of TSH was followed by an increase of I^{131} uptake.[2] This observation would also support the theory that thyroid hormones exert a thyroid suppressive action through the inhibition of TSH secretion.

The findings in experimental iodine deficiency in animals suggest that the excessive uptake of the iodine-deficient thyroid arises from similar pituitary stimulation. Higgins and Fraser suggest that a similar mechanism may explain the high thyroid uptake in nontoxic goiters.[8]

Study of our data reveals that the uptake of iodine was not suppressed by triiodothyronine in thyrotoxic patients. In patients with nontoxic goiters, whether nodular or diffuse, response to the triiodothyronine test was similar to that of euthyroid patients in 100 out of 117 cases. In the remaining 17 patients, the radioiodine uptake could not be suppressed by an 8-day administration of triiodothyronine. In 9 of these, the drug was continued for 8 more days and by the end of this time an additional 5 patients responded by a decrease in radioiodine uptake; the others showed no appreciable change in the uptake.

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Table 1. I^{131} 24-hour Uptake after the Use of Triiodothyronine as a Suppressive

Clinical diagnosis	*No. of cases*	*24-hr uptake I^{131} in %*			
		Before		*After*	
		Av	*Range*	*Av*	*Range*
Thyrotoxicosis	42	64	47–88	61	40–80
Early eye signs of Grave's disease, euthyroid	4	55	39–70	56	44–71
Thyroidectomy in Grave's disease, euthyroid	5	54	47–69	31	17–50
Nontoxic goiters[a]					
Diffuse	83	57	31–80	19	6–44
Nodular	17	55	23–63	17	6–29
Nontoxic goiters[b]					
Diffuse	12	60	43–87	48	39–80
Nodular	5	65	41–88	53	38–69

[a] Nontoxic goiters which responded to triiodothyronine.
[b] Nontoxic goiters which did not respond to triiodothyronine.

CONCLUSION

The triiodothyronine suppression test is able to be used to distinguish the high-uptake nontoxic goiters from thyrotoxicosis. However, a number of the nontoxic goiter patients do not respond satisfactorily to this test. The reason for this unsatisfactory response may be due to a lack of balance between the doses of triiodothyronine used and the degree of iodine depletion of the gland.

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The Significance of the Capture Curves in the Study of Thyroid Dysfunction

By Jorge A. Traibel* and Walter S. Hill†

In 1952, Pochin and the members of his group[1] presented a modification of the commonly used method whereby an external count is made of the gamma rays emitted by subjects to whom a tracer dose of I^{131} has been administered. Their modification consists of the following: instead of resorting to static collimation on a circular area, a strip parallel to the longitudinal axis of the patient is scanned by moving a G-M counter along this axis. This counter, which is of the tube type, mounted perpendicular to the patient's axis, is linearly collimated in such a manner that it collects the radiation from the full width of the strip.

Using this technique, Pochin and his group succeeded in determining the capture percentages for a certain number of transverse bands of the body. The graph obtained with these figures and referred to the patient's longitudinal axis makes up what these authors call the "capture curves" or "contours." Basically, the method was used for research purposes, in the presence of metastases from a cancer of the thyroid.

At some subsequent date, Pochin published a paper dealing with the results obtained in the conditions described above,[2] showing that shortly after the ingestion of the tracer dose, three activity peaks are observed as a rule, in the cervical, epigastric and hypogastric areas, corresponding, respectively, to the accumulation of radioiodine in the thyroid, stomach and urinary bladder. As days go by, other peaks appear, corresponding to the areas of the metastases. The author does not give any details about the variations noted in the contours, as related to the functional status of the thyroid.

In order to carry out similar investigations, we built a device in our own laboratory which was designed for the specific purpose of giving gamma-radiation contours automatically. We shall describe it in greater detail below.

A survey made with a first series of patients showed that there were some differences between the contours obtained early and those prepared two days after the administration of the tracer dose, in keeping with the condition of the thyroid function of the patient being examined. While the number of patients examined to date is small (22), we feel that the results obtained in these first experiments are of some significance and that, with subsequent adjustments in our technique, it will be possible to gain a better understanding of the patient's iodine metabolism, provided the radiation measurements be repeated at suitable time intervals, which is made simpler by the speed and ease of the operation.

MATERIALS AND METHODS

The equipment used consists of four main assemblies (Fig. 1):

(1) A gamma-scintillation counter, of the circular collimation type;

(2) A carriage which automatically travels along the longitudinal axis of the bed or stretcher. The gamma-ray detector is attached to this carriage. The speed of the carriage is uniform and predetermined. Similarly, the detector is free to move laterally and vertically, as desired. We used a carriage speed of some 28 cm/min;

(3) A scaler, with rate meter;

(4) An automatic count recorder (Esterline-Angus, 0–1 mA). The speed used for the recorder paper is about 75 mm/min.

In order to make a tracing, the patient is placed in dorsal decubitus and the carriage is run, along with the detector and at the desired height, from the patient's forehead to his legs, following a preset course. The frequency of the pulses generated in the detector will show the activity in terms of the location of the various areas of the body scanned by the device, as recorded on the paper strips. Activity tracings can be made along all such lines as may be deemed necessary, but in general three will prove adequate, one following the median line and two lateral, at the level of the anterior axillary lines, or else at the level of the mammae (see Figs. 2 and 7).

We have applied this technique, up until now, to 22 patients, made up of normal, hyper- and hypo-thyroid subjects, plus a few cases of depression of the rate of iodine capture by drugs such as iodine, dehydrated thyroid and antithyroid medications.

RESULTS

By drawing up the contours in the course of the first hour following administration (early contours) and others 48 hours after the administration of the tracer dose (late contours), we have been able to verify three facts, which are of interest.

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(1) There is a palpable difference, which can be of diagnostic significance, between the contours obtained with normal subjects, and with those which correspond to patients with some disturbance of thyroid function.

(2) There are also some differences in the late tracings made for hyperthyroid patients, making it possible to divide them into two main groups, a fact which may be of value when it comes to treating the affection with radioiodine.

(3) Under similar conditions of emptiness of the stomach, the rate of gastrointestinal absorption of I^{131} varies in direct proportion to the degree of thyroid function. It is most rapid in the hyperthyroid subject and, on the contrary, very much slowed down in all cases of endogenous or exogenous depression of the thyroid capture function.

SPECIFIC STUDY OF CASES

Normal Contours or Tracings

Early Contours. By making a series of tracings, for instance every 15 minutes starting from the ingestion of the dose until one hour has elapsed, the migration of I^{131} from the gastric cavity to the two areas to which it will be attracted—the thyroid and the kidney (urine), Figs. 3a and 3b—can be shown objectively and in a most graphic manner.

During the first few minutes, all that is observed is a high epigastric peak, which, in the subsequent tracings, will decrease while the cervical (thyroid) and hypogastric (urinary bladder) peaks become higher. After a period of 60 minutes, the three peaks are nearly equivalent.

Late Contours. The tracing obtained in a normal person after 48 hours shows only one peak, the cervical one, while no activity is detected at the level of the epigastrium or of the hypogastrium. The absence of the latter is in agreement with the lack of activity noted in the urine at the same time in the euthyroid subjects (Fig. 4).

Hyperthyroid Contours

Early Contours. In these cases, the main finding is that the epigastric peak decreases much more rapidly than it does in normal persons, in such a way as to disappear in no more than one hour. Since no hypogastric activity is observed at that time, the graph shows only one raised area, the cervical one, of a substantial height, unlike the three peak graph usually noted (Fig. 5) in early normal contour tracings.

Late Contours. The tracing made 48 hours after administration in the case of the hyperthyroid subject is also different at this time from that of the normal subject. As we already pointed out, the contour for the latter only shows a cervical peak and, on the other hand, the late tracing for the hyperthyroid subject gives two well-defined peaks, one cervical and the other in the thoracic and abdominal area.

As we shall see later, this is an expression of the activity which is present in the liver at that time (Figs. 6a and b).

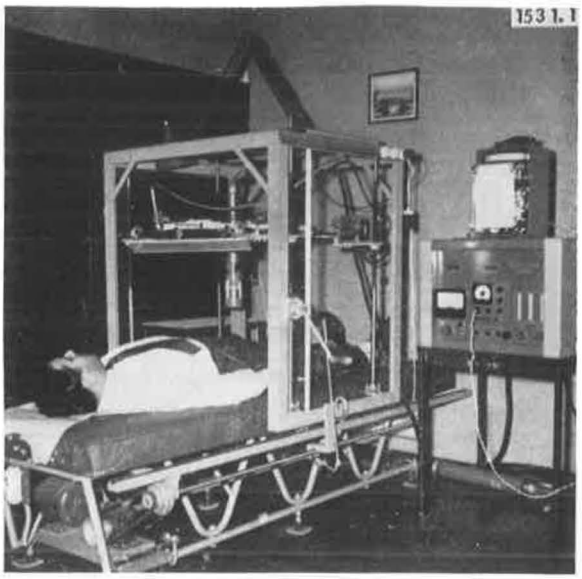

Figure 1. Gamma-radiation profilometer

In fact, while the significance of the cervical peak is obvious, we must clarify the thoracic and abdominal peak to some extent. Pochin[2] mentions the existence of this peak after 48 hours in his own paper, but he calls it epigastric and ascribes it to the "gastric secretion" of I^{131}. Nevertheless, it is clear from our observations that this increase in activity which is found in the hyperthyroid patient at the level of the thoracic and abdominal area, is nearly exclusively due to the accumulation of radioactive material at the level of the liver, as shown by the three contours on Fig. 7, which were obtained with the same patient 48 hours after the administration of the tracer dose.

It should at the same time be noted that the right lateral contour (see Fig. 7a) shows a much higher peak than those of the median and left lateral contours (see Figs. 7b and 7c).

We feel that this increase in activity in the right hypochondrium is, in the main, due to the activity of I^{131} from thyroxine, for the following reasons: (1) The existence of a peak in the right hypochondrium in hyperthyroid patients and the sharp increase in the PBI^{131}. (2) The height of the peak varies proportionally to the value of this PBI^{131}, as determined in the blood collected at the same time (Figs. 6a and 6b). (3) It is well known, on the other hand, that the liver concentrates thyroxine (and triiodothyronine) selectively, since it plays a part of the utmost importance in the metabolism of the thyroid hormone.

We must point out at the same time that this elevation of the tracing at the level of the right hypochondrium is not seen with the same clearness in every case of hyperthyroidism.

In general, the peak is marked in the cases which are fairly serious clinically, as well as in those in which a radioiodine metabolic study reveals a well-marked increase in the thyroid iodine turnover: unduly high initial rate of capture, thyroid activity after 48 hours less than after the first hour and very high PBI^{131}. Con-

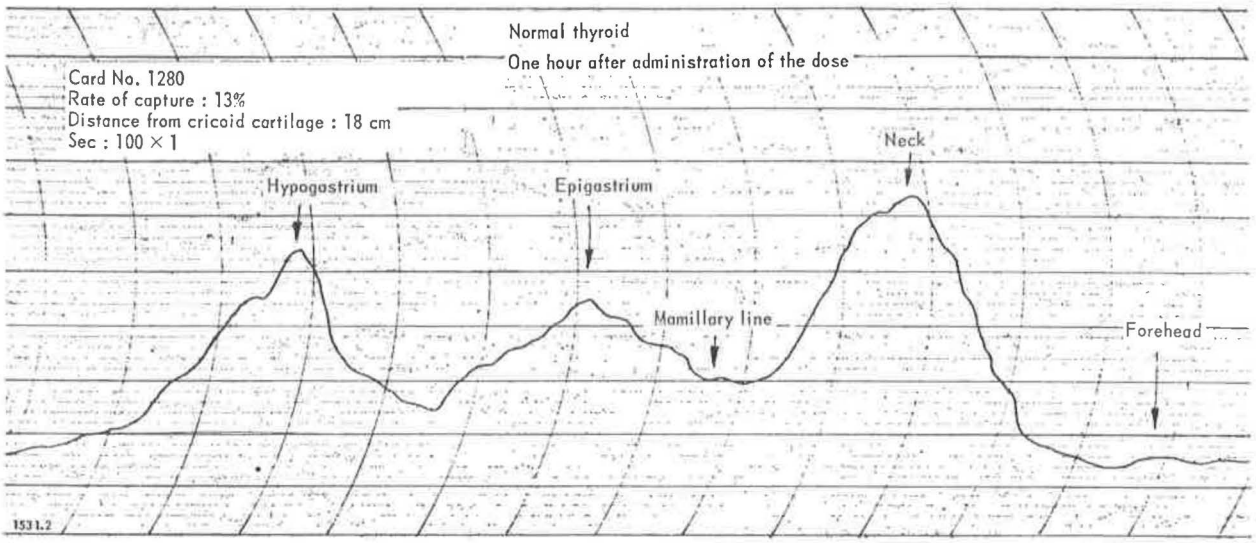

Figure 2. Typical appearance of normal tracing made one hour after the administration of the I^{131} tracer dose. Three characteristic centers will be noted: related to the neck (thyroid), epigastrium (stomach) and hypogastrium (urinary bladder). It will be noted that the emptying of the stomach is proceeding normally and that the I^{131} is being efficiently captured by the thyroid, while urinary excretion already is beginning

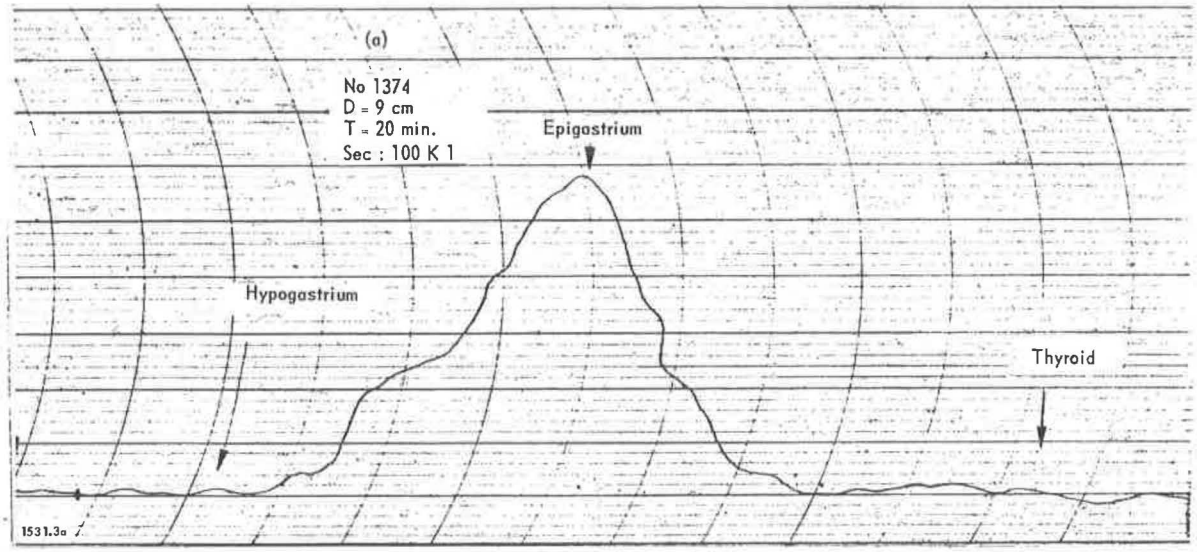

Figure 3a. Normal thyroid. A contour made 20 minutes after administration. Only on the level of the epigastrium can any activity be noted

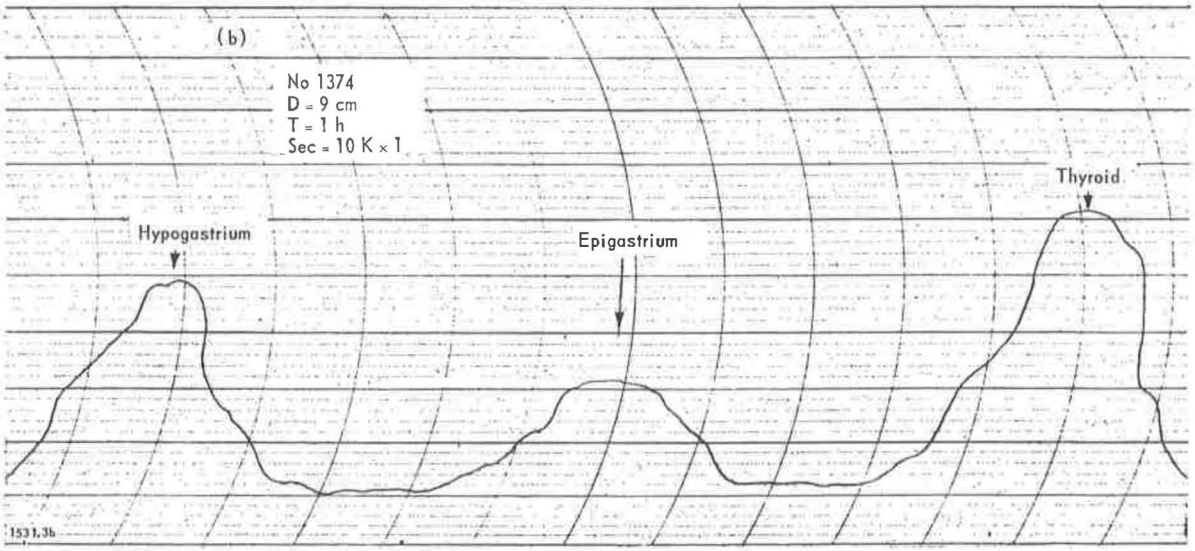

Figure 3b. Normal thyroid. A contour made after one hour in the same patient. It will be noted that epigastric activity is much reduced, while two new peaks have developed, related to the thyroid and the urinary bladder

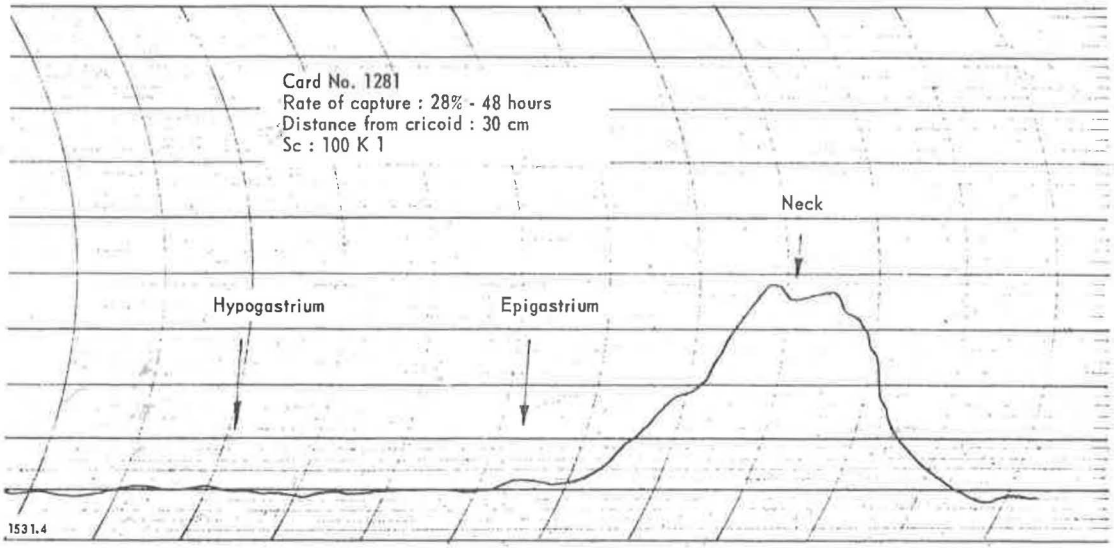

Figure 4. Contour for a normal subject after 48 hours. The only raised area is that which corresponds to thyroid activity itself

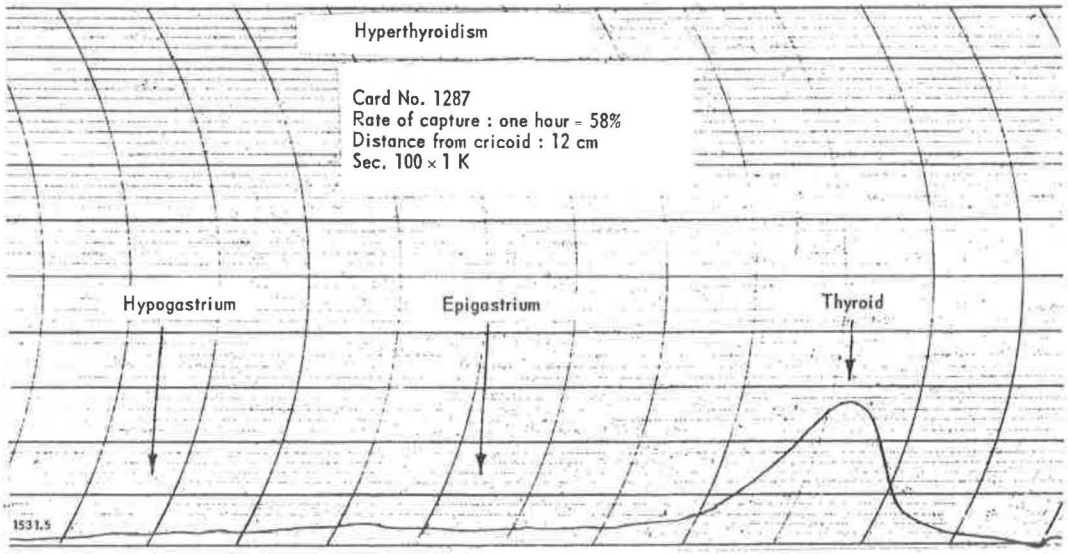

Figure 5. Tracing obtained one hour after administering I^{131} in a case of hyperthyroidism. Compare with figures 2 and 3b (normal) and observe that the stomach is nearly totally empty and that there is no activity in the urinary bladder. Only the raised part corresponding to the thyroid is to be seen

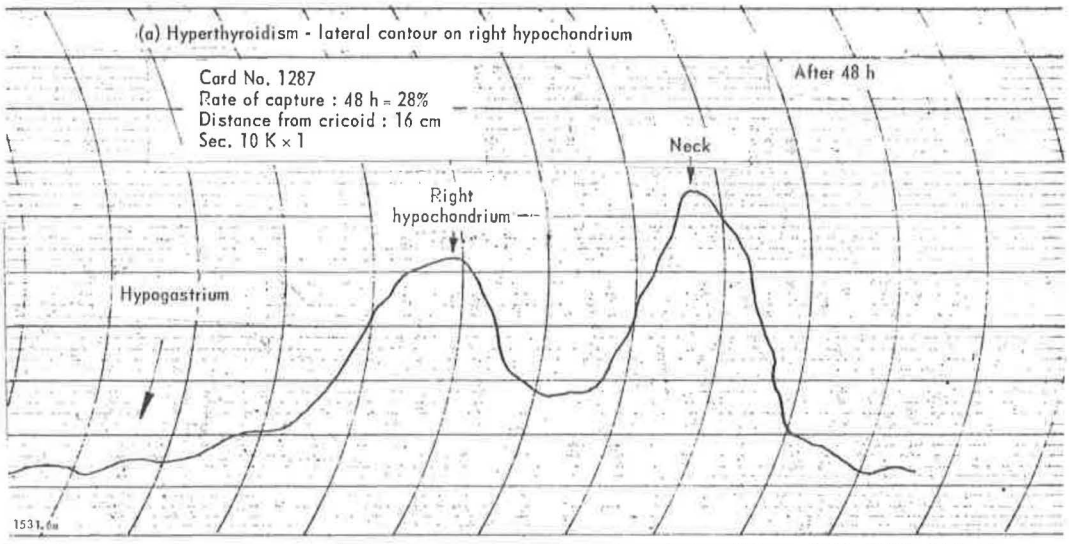

Figure 6a. Case of hyperthyroidism, with increased iodine turnover. Activity in the thyroid after 48 hours, 28%; PBI^{131}, 4.4%. Two zones of activity can be seen, one in the neck, the other in the right hypochondrium

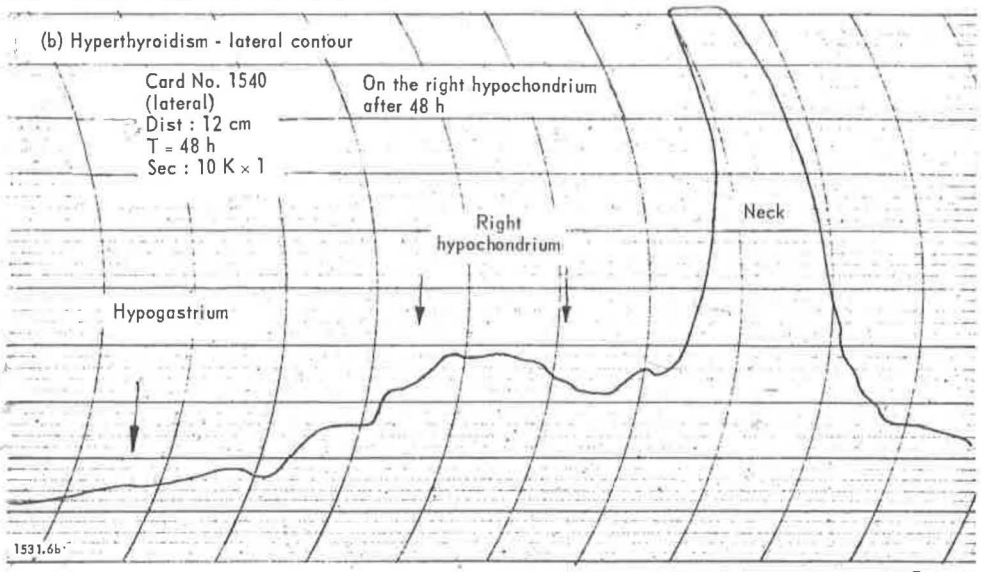

Figure 6b. Another case of hyperthyroidism. The gland retains iodine more efficiently: activity after 48 hours, 67%; PBI^{131} 0.53%. Comparing with (a) it will be seen that this graph shows a greater height of the thyroid peak and a lesser definition of the right hypochondrium elevation

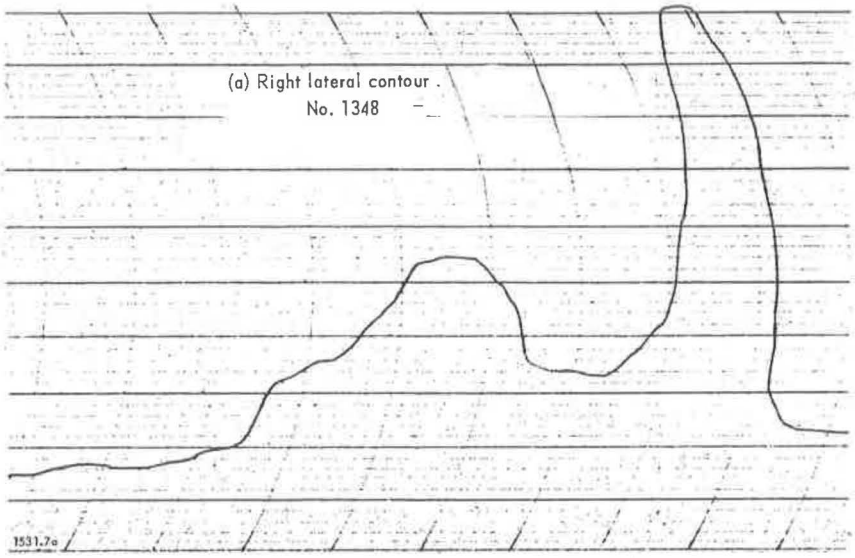

Figure 7a. Hyperthyroidism. Lateral contour on the right hypochondrium. Comparing with (b) and (c), it will be seen that the major activity appears in the latter, showing the influence of the liver

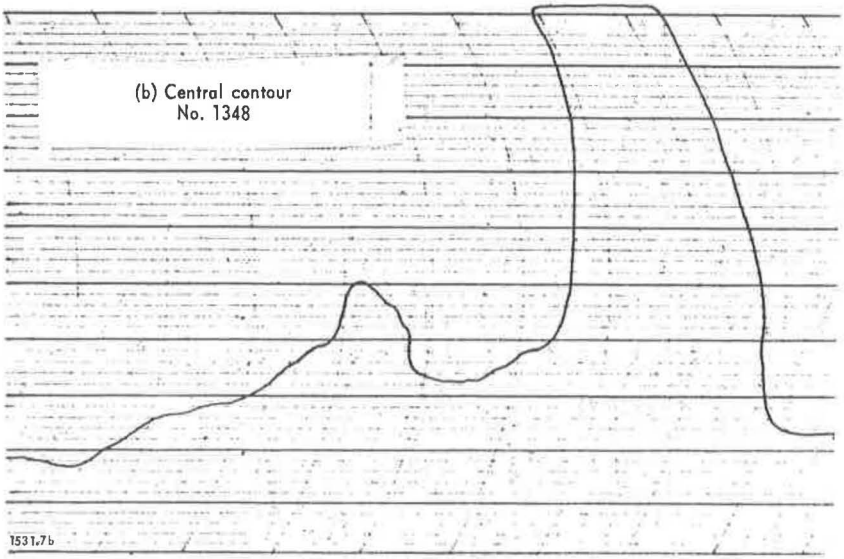

Figure 7b. Central contour (same case). Elevation could be ascribed to the epigastrium. Lateral profiles reveal this to be due to the liver

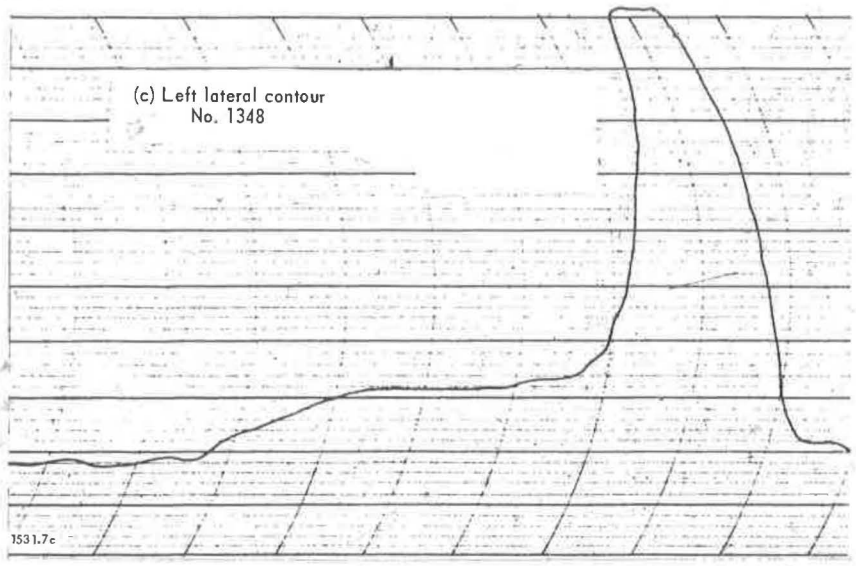

Figure 7c. Hyperthyroidism (same case). Left lateral contour. No activity at the level of the left hypochondrium

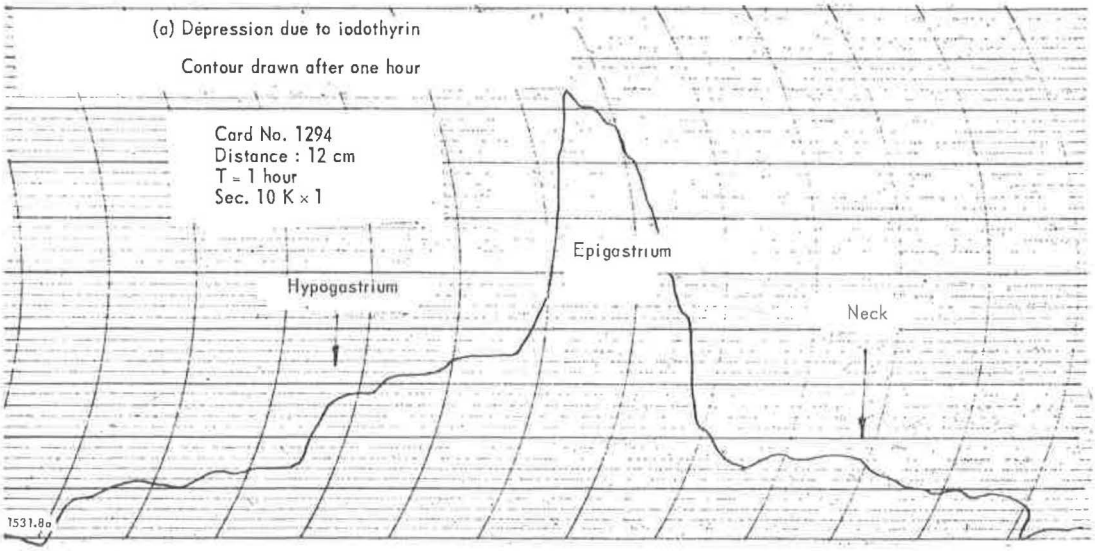

Figure 8a. Depression by iodothyrin—early contour (1 hour). Compare with Figs. 2 (normal) and 5 (hyperthyroidism)

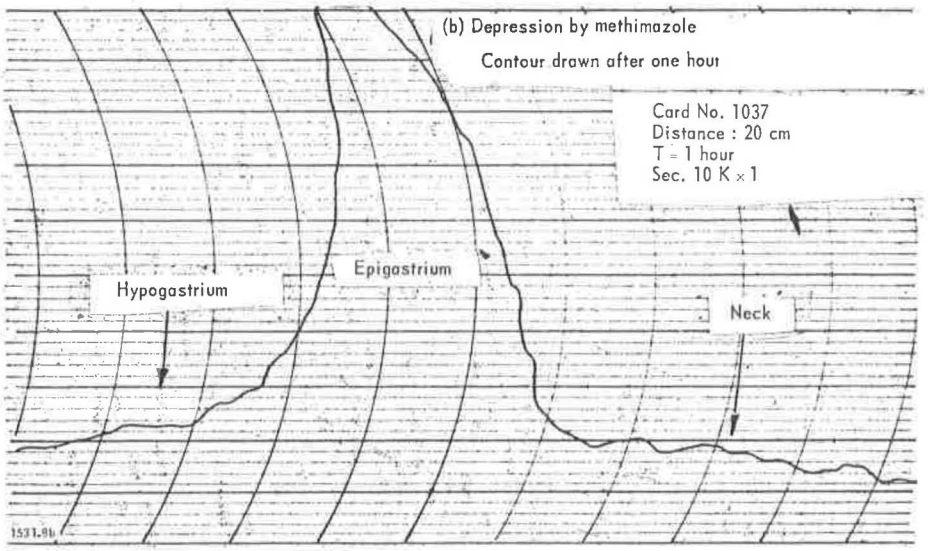

Figure 8b. Depression by methimazole—early tracing (1 hour). Compare with Figs. 2 (normal) and 5 (hyperthyroidism)

versely, the right hypochondrium peak is low in the hyperthyroid patients who, after 48 hours, still present a high glandular activity (over 60%), and whose PBI^{131} values are lower than 1% of the dose per liter of plasma.

Tracings where the Capture Function Is Depressed

In this paragraph, we do not only take in the hypothyroid patients, but also all those in whom there is some depression of the thyroid capture function due to drugs, since the same picture is found in all of them: single peak early contour (epigastric) figures, and complete lack of activity in the late contour (Fig. 8).

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Exogenous Iodine as a Factor of Interference in Radioiodine Thyroid Tests

By Jorge A. Traibel* and Walter S. Hill†

The previous administration of iodine, whether in the organic or inorganic form, constitutes the most common source of errors in tests which use radioiodine for the functional exploration of the thyroid. It is also felt that the administration of iodine prior to the treatment of hyperthyroidism with I^{131} is absolutely contraindicated. However, Kelsey and his group[1] feel that, while stable iodine (I^{127}) in doses smaller than 85 micrograms given by the oral route has no effect on the rate of capture, there is a 20% increase in urinary excretion when a dose of 1 mg is reached.

The period of time during which capture is depressed due to previously administered inorganic iodine compounds varies and is dependent on the amount administered and the time during which the iodine was taken. It is generally estimated that in normal persons this depression lasts from 4 to 6 weeks and that up to 3 months may elapse before the normal capture capacity is reached again.

In the hyperthyroid patient, Werner[2] indicates that, as a general rule, the inhibition of the capture, following suspension of the inorganic iodine compound course, will last as long as the course itself if the latter does not exceed one month. The action of the organic compounds (lipiodol, X-ray contrast media, etc.) lasts much longer than that of inorganic iodine. In the normal subject, the period of inhibition due to organic compounds lasts 6 months as a rule. It is less after pyelography and maximum after myelography or bronchography; the actual time will also depend on the substance used to achieve roentgenological contrast. While it is conceded that the duration of the period of depression in isotope capture as a result of the administration of both organic and inorganic compounds is longer in hyperthyroid than in euthyroid subjects[3] we have neither concrete nor statistical data on this point.

Upon studying the results obtained in a group of patients who had been inadvertently tested with radioiodine (since there had been exogenous administration of iodine before), we were surprised to note that, while capture inhibition persisted for the customarily accepted time in the euthyroid subject, this period was so delayed in the true hyperthyroid cases, that it no longer offered a problem for a possible subsequent course of I^{131} therapy. These first cases led us to a systematic study of the action of previous iodine administration in I^{131} thyroid function tests.

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EFFECT OF EXOGENOUS IODINE ON TRACER TEST

This paper reports the capture percentage observed at the level of the thyroid 48 hours after the administration of a 100 microcurie tracer dose.

Our study included 121 subjects of both sexes. All of them, at various times, had received stable iodine in one of its forms prior to the test: 99 had taken inorganic iodine as Lugol solution and cholecystography had been performed earlier on the other 22.

RESULTS

Inorganic Iodine

Of the 99 subjects who had taken Lugol solution, 58 were normal and 41 hyperthyroid. Figure 1 shows the results obtained.

The ordinates give the capture values as a percentage of the dose administered and the abscissae the time, in days, which had elapsed since the suspension of iodine administration. Two straight lines have been drawn, parallel to the abscissae, which show the limits of normal values for this test, as accepted in our laboratories.

As can be seen clearly from the graph, the mean capture rate among the hyperthyroids always remains above the normal maximum, whatever the time elapsed since the suspension of the iodine-containing drug course. In the euthyroid group, on the contrary, the capture figures are plainly below normal until 60 days after iodine suspension, when they begin increasing progressively.

Organic Iodine

Figure 2 shows the 48-hour capture percentages obtained from 11 normal subjects and 12 hyperthyroid patients, on all of whom a cholecystogram had been performed earlier. The arrangement of the graph is similar to that shown in Fig. 1, although for reasons which will readily be appreciated, the time coordinate is expressed in months. The graph shows that in hyperthyroid subjects, the influence of the cholecystogram on the capture rate is very small; among normal subjects on the other hand, there is a depression of this rate until about the eighth month.

DISCUSSION

We wanted to call attention to these facts because they are not clearly shown in the literature. We should like to point out, however, that the earlier graphs were based on mean values. It should be borne in mind that the duration of the depression depends on individual factors as well as on the duration of the course of previous iodine intake. In our case, this duration never was less than 15 days (inorganic iodine).

It should also be remembered that while we studied exclusively persons who had taken Lugol (in studying the influence of inorganic iodine), this was due to the frequency with which this drug is prescribed in our circles and to the desire of observing the influence of the same pharmaceutical for statistical uniformity. Nevertheless, we observed similar results in patients who had ingested the iodine in another and less apparent form. In this connection we might mention the case of two patients, one normal and the other hyperthyroid, who had been taking a multivitamin preparation containing 100 micrograms of iodine per capsule for about one month prior to the tests.

In the euthyroid patient, for whom the medication had been discontinued three days earlier, the 48-hour-capture rate did not reach 15%. In the hyperthyroid subject, on the contrary, who had taken his capsule on the day of the test, the capture rates were high (72%) and his PBI^{131} was 0.67%.

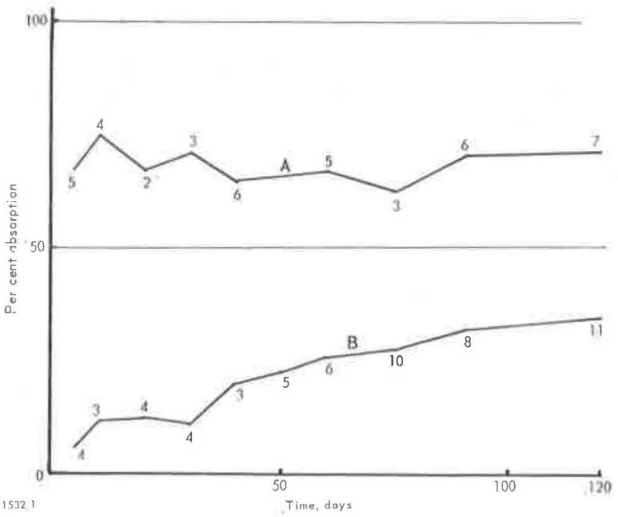

Figure 1. Capture rates after 48 hours by hyperthyroid (A, 41 cases) and euthyroid subjects (B, 58 cases) previously treated with inorganic iodine compounds (Lugol, etc.). Abscissa shows time elapsed between last ingestion of iodine and administration of I^{131}

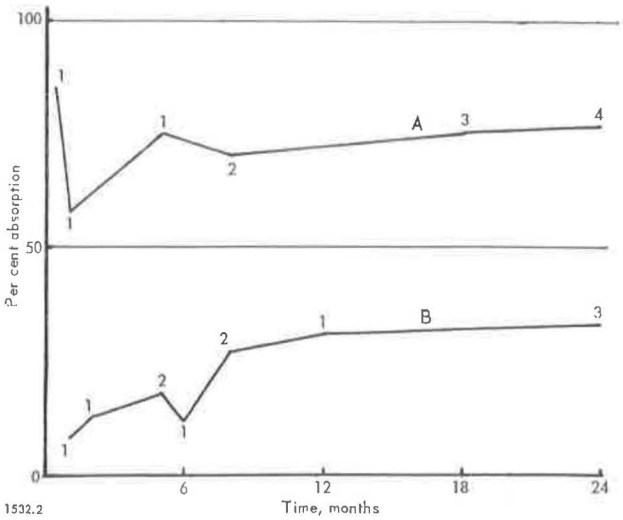

Figure 2. Capture rates after 48 hours in 12 hyperthyroid patients (A) and 11 euthyroid cases (B) previously having a cholecystogram. Abscissa shows the time elapsed between the cholecystogram and the administration of I^{131}

The reduced importance of an earlier course of iodine therapy in true cases of hyperthyroidism—the point we wish to stress in this work—obviously is due to the marked acceleration of iodine turnover in these cases. The therapeutic implication of this fact is clear, since radioiodine treatment of hyperthyroidism is frequently avoided in some centers only because the patient had earlier received stable iodine.

We feel that in such cases before rejecting this type of therapy a radioiodine survey should be made if the hyperthyroid picture is clear, even though there might have been a recent past course of iodine treatment. By following this procedure, it will often be noted with surprise that past iodine treatment has not greatly altered the high capture values commonly noted in such cases. Thus, the patient may receive I^{131} therapy if it is indicated in his case.

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Studies in Endemic Goiter with Radioactive Iodine

By F. de Venanzi, M. Roche and K. Gaede*

The studies of Stanbury *et al.*[1] in Argentina have shown that there is a marked avidity of the thyroid gland for radioactive iodine in endemic goiter. This finding has been repeatedly confirmed in different localities of Venezuela.[2–6]

This paper presents some of the results of our investigations in an attempt to clarify the role of iodine lack in the etiology of endemic goiter.

MATERIAL AND METHODS

The studies were carried out in four towns of Venezuela with a varying prevalence of endemic goiter: Bailadores and Tabay with a high prevalence, Manuare in the intermediate range and San Joaquín with the lowest prevalence. Thyroid uptake was measured using a scintillation detector placed 40 cm away from the thyroid notch 24 or 48 hours after a tracer dose of 50 μc of radioactive iodine had been administered. These measurements were corrected by multiplying by a factor 0.85 and by subtracting from the resulting values the "background" measured 40 cm away from the thigh. Results were expressed in terms of percentage of an equal dose measured in a 250 ml beaker at the same distance and the results were corrected for background. Urinary radioactivity was measured with a shielded or well-type scintillation detector.

Thyroid clearance was determined according to a previously described method[6] and by following the directions of Kretchmar[7] and of Berson *et al.*[8] The conversion ratio was determined by measuring the radioactivity of 3 cc of plasma in a well-type scintillation detector 24 hours after administration of the dose. Proteins were precipitated by trichloroacetic acid, washed with the same acid and then redissolved with sodium hydroxide and the radioactivity bound to the protein was measured.

This result, expressed in percentage of the total plasma radioactivity, is considered the "conversion ratio." Saliva was obtained without stimulation and the radioactivity of a 3 ml sample measured 24 hours after administration of the isotope; the results were expressed in counts per minute in the manner described by Thode *et al.*[9] A study of the two-hour uptake of triiodothyronine-I^{131} by erythrocytes using the technique of Hamolsky *et al.*[10] was also carried out.

RESULTS AND COMMENTS

The general results[2–6] show that in endemic goiter as in hyperthyroidism there is increased thyroid clearance; increased protein-bound I^{131}; increased conversion ratio; decreased saliva radioactivity and decreased I^{131} urinary excretion with normal renal clearance.

The only test in which the results differ from those found in hyperthyroidism was in the uptake of triiodothyronine-I^{131} by the erythrocytes. The results were significantly lower in endemic goiter than in normal thyroids, as opposed to the findings in hyperthyroidism in which a high uptake was found.[10]

The effect of potassium perchlorate administration on the uptake curve of I^{131} by the thyroid was studied in several groups of patients. It was shown that administration of the drug produced a flattening of the curve, especially when there is fast uptake.[2] This could be interpreted to be due to a lack of organic binding of iodine, analogous to that produced by certain goitrogenic substances, or it may be explained by the greatly accelerated turnover rate of iodine.

It was interesting to try to establish whether there is a difference of thyroidal I^{131} uptake between subjects with endemic goiter and subjects living under the same conditions but showing no thyroid enlargement. In an area of high prevalence, neither the thyroid uptake nor urinary excretion were significantly different.[2] In a town where endemic goiter was less prevalent, there was a significant difference between the thyroid uptake of the two groups[3] and this difference persisted in the region of least prevalence.[4] Changes in geometry may account for this finding since there was no statistically significant difference in the urinary excretion of I^{131} in the subjects tested in the three areas. If increased thyroid I^{131} uptake, and hence iodine lack, is present in both goitrous and nongoitrous subjects, then it cannot be said that iodine deficiency necessarily causes goiter.

However, a rough correlation between I^{131} thyroid uptake and goiter prevalence does seem to exist as shown in the following:

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Locality	*No. of subjects*	*Thyroid enlargement* %	*Av thyroid uptake* %
Bailadores	110	83	76
Manuare	38	65	67
San Joaquín	41	41	57

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I^{131} Thyroid Uptake Study of Endemic Goiter in Taiwan, China

By Tien-cheng Kao, Kuang-chu Wang, Sheh-fang Yang and Jui-san Chen*

The usefulness of radioactive isotopes in the medical field has led us to use these radioactive elements in clinical diagnosis as well as in therapy. A Radioisotope Laboratory was set up and equipped in the National Taiwan University Hospital in the summer of 1957. All radioactive isotopes have to be imported from abroad and at present only I^{131}, P^{32} and Co^{60} can be imported. It has only been since April of this year that a Co^{60} kilocurie unit has been set up.

A project was started for the study of endemic goiter on this island. There are some areas of intense endemic goiter which have been supplied with iodized salt. The present I^{131} thyroid uptake analysis was made in those areas where iodized salt had not been supplied. The first study was carried out in Hsinchu, about 40 miles south of Taipei in the northwestern part of Taiwan. One hundred cases on which clinical examination and I^{131} thyroid uptake had been made were selected for investigation. Protein-bound iodine in the blood (PBI) and urine output were not measured, but these investigations will be made later in selected cases. Most of these 100 cases had greatly enlarged thyroid glands and some of them measured hundreds of grams. The findings in the cases of adults and of school children are presented in Tables 1 and 2 respectively. In the adult group, there were more nodular types of goiter with hypothyroidism. There was no obvious hypothyroidism among the school children.

The measurements were taken with a scintillation counter using a ¾-inch NaI crystal with collimation. We used the so-called standard method as recommended by Brucer,† with A and B filters and a 10-inch distance from crystal center to the neck surface. The uptake measurement was made 24 hours after administration of 25 microcuries Radiocaps I^{131} (Abbott Lab., USA) and the ORINS standard neck-phantom was used for 100% standard measurement.

Uptake measurements were made on 88 of the 100 cases; the other cases did not return for counting.

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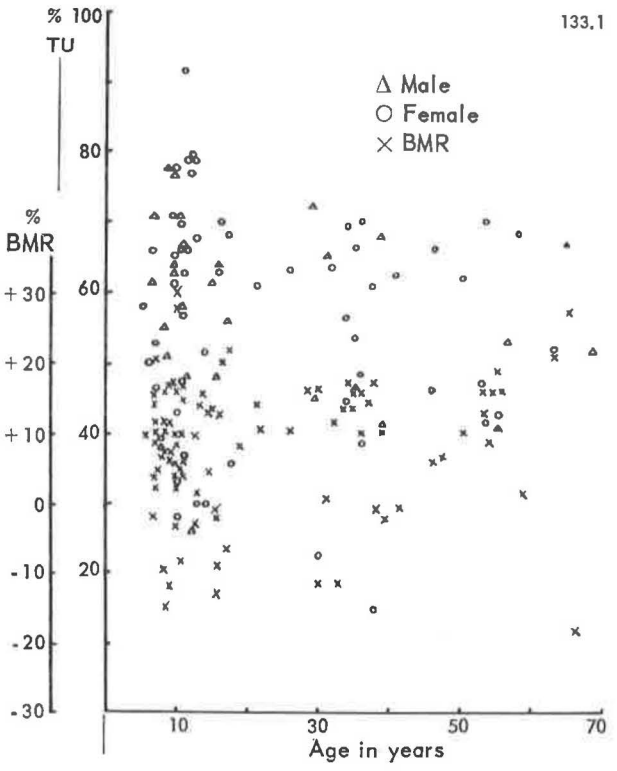

Figure 1. BMR and uptake (TU) relative to age

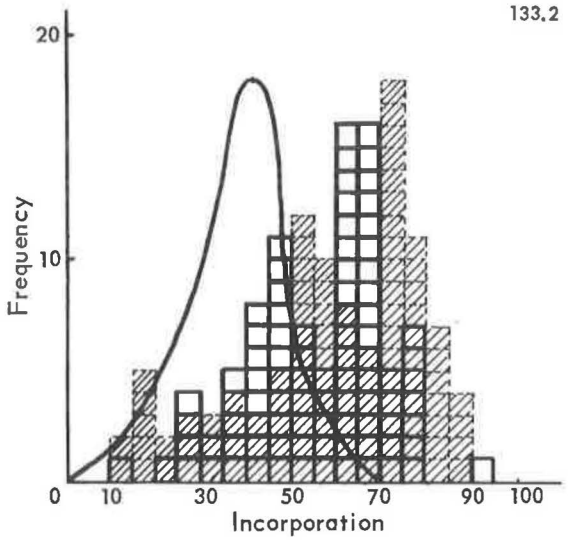

Figure 2. Histogram of the frequency of I^{131} thyroid uptake in Hsinchu endemic goiter area, Taiwan, compared with that of Mendoza area, Argentina (shaded area) and distribution curve for normal subjects in the area of Boston, Massachusetts, USA (curve)

Most of these patients were euthyroids with normal BMR showing a heavy concentration of I^{131} in the gland. Figure 1 shows the uptake of all patients with BMR in the normal range. The uptake by the thyroid was higher, especially in the younger group of patients.

A comparison is made between the distribution curve obtained by us and those drawn by Skanse and Nuñez and is shown in the histogram in Fig. 2.

This preliminary study appeared to show a higher uptake of I^{131} in the Hsinchu endemic goiter area and a still higher uptake in the younger age group. This would indicate that iodine hunger is more prominent in children than in adults but that hypothyroidism develops at later ages.

Table 1. Adults

Case	*Age*	*Goiter*	*Pulse*	*BP*	*Symptoms*	*Physical signs*	*BMR %*	*Uptake %*
Males								
1	15	II	112	110/90	+	−	+14	62
2	16	II	84	100/80	++	+	− 9	64
3	17	III	64	110/70	−	−	− 7	56
4	29	II SUN	60	100/70	+	−	+16	72
5	30	III	60	100/80	+	−	−11	45
6	31	III	68	100/70	−	−	+ 1	65
7	35	III	92	100/70	++	+		46
8	55	MUN	84	120/80	++	+	+17	41
9	57	IV	76	110/80	++	+	+17	53
10	65	Mul N	80	130/80	+	+	+27	67
11	68	LUN	92	120/80	+	+	−18	52
Females								
1	16	II SUN	88	100/70	−	+	− 2	63
2	16	III SUN	72	110/70	−	−	+13	70
3	17	III	88	110/70	−	−	+20	68
4	18	SUN	84	120/90	+	−	+22	36
5	19	SUN	84	110/90	−	−	+ 8	49
6	21	II	72	110/80	+	−	+14	61
7	22	MUN	76	110/70	+	−	+16	32
8	26	LUN	76	110/70	+	+	+11	64
9	30	III	72	110/70	+	+	−16	23
10	32	II	88	110/80	+	−	+12	63
11	33	III	72	110/80	+	+	+11	56
12	34	II	84	120/90	+	+	+16	68
13	34	IV SUN	80	146/80	+	+	+13	44
14	35	III	72	110/70	+	+	+13	66
15	35	II	76	100/70	+	+	+15	45
16	36	II	76	100/70	+	+	+15	70
17	36	IV	92	120/90	+	+	+10	48
18	36	III	84	120/80	+	+	+ 9	39
19	37	III	92	110/80	+	+	+14	61
20	38	IV	72	120/90	+	+	+17	15
21	38	III	80	100/70	+	+	− 1	53
22	39	III	88	120/90	+	+	+10	68
23	39	II	76	110/80	+	+	− 2	41
24	41	III	64	110/80	+	+	− 1	62
25	46	III	72	130/90	+	+	+ 6	46
26	47	II	84	120/80	+	+	+ 7	66
27	50	III	76	120/90	+	+	+10	62
28	53	IV SUN	112	140/90	−	+	+17	48
29	53	IV SUN	80	120/90	+	+	+13	42
30	54	II	68	110/80	+	+	+ 9	75
31	55	III	64	110/80	+	+	+19	43
32	58	IV SUN	100	120/80	+	+	+ 2	68
33	62	SUN	84	110/80	+	+	+21	52

Explanatory key for Tables 1 and 2:

o No goiter.
I Slight diffuse goiter.
II Moderate diffuse goiter.
III Markedly enlarged goiter.
IV Diffuse greatly enlarged goiter.
SUN Uninodular goiter of small size.
MUN Uninodular goiter of moderate size.
LUN Uninodular goiter of large size.
Mul N Multinodular goiter.
Symptoms Symptoms of hypothyroidism such as general weakness, dizziness, headache, fear of cold, lumbago and numbness of extremities.
Physical Signs Findings of hypothyroidism such as puffy face, dry skin, coarse skin and non-pitting edema.

\+ Present
− Absent

Table 2. School Children

Case	Age	Goiter	Symptoms	Physical signs	BMR %	Uptake %
Males						
1	7	I	–	–	+15	70.5
2	7	II	–	–	+14	62.4
3	7	I	–	–	+10	65.2
4	7	I	–	–	+ 2	37.8
5	7	II	–	–	+11	
6	7	I	–	–	+ 4	
7	7	I	–	–	+ 8	
8	7	I	–	–	+ 4	
9	7	II	–	–	+20	
10	8	I	–	–	−15	55.2
11	8	I	–	–	+ 9	62.7
12	9	I	–	–	+ 8	77.4
13	9	II	–	–	+ 9	71.1
14	9	I	–	–	−12	78.0
15	10	II	–	–	+ 4	71.3
16	10	II	–	–	+15	66.6
17	10	II	–	–	− 7	47.9
18	10	I	–	–	+17	66.8
19	11	SUN	–	–	+14	58.1
20	12	I	–	–	+ 4	26.9
21	15	SUN	–	–	−13	48.5
22	8	0	–	–	+17	28.2
23	9	0	–	–		51.0
24	10	0	–	–	+30	64.0
25	11	0	–	–		52.8
Females						
1	5	I	–	–	+10	57.7
2	6	II	–	–	− 3	50.3
3	7	II	–	–	+16	39.1
4	7	I	–	–	+12	52.9
5	7	I	–	–	+10	46.6
6	7	II	–	–	− 9	77.3
7	7	III	–	–	+ 3	66.1
8	8	III	–	–	+16	62.2
9	8	II	–	–	+11	
10	9	I	–	–	+18	43.3
11	9	II	–	–	+ 3	65.6
12	9	II	–	–	+27	70.3
13	10	SUN	–	–	− 1	77.8
14	10	II	–	–	+10	63.7
15	10	II	–	–	+ 5	36.5
16	10	SUN	–	–	+ 5	91.8
17	10	II	–	–		48.6
18	10	Mul N	–	–	+ 3	57.5
19	10	II	–	–	+ 9	67.8
20	10	II	–	–	+11	
21	12	II	–	–	+ 1	78.9
22	12	II	–	–	+ 9	78.9
23	12	II	–	–	− 2	78.8
24	13	MUN	–	–	+14	29.6
25	14	Mul N	–	–	0	51.6
26	8	0	–	–	+ 7	32.5
27	10	0	–		+ 6	68.4
28	12	0	–		+15	29.5

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P^{32} Uptake by the Thyroid, Adrenals and Testes after Administration of Epiphyseal Hormone

By I. Negoescu, A. Bojinescu, F. Cocu, C. Petrescu and A. Lupulescu*

Half a century's research has resulted in a better knowledge of epiphyseal function and its relation to endocrine physiology. Most authors today accept the idea of antagonism between the epiphysis, on the one hand, and the thyroid, adrenals and gonads, on the other. Results achieved in therapy with epiphyseal extracts confirm this antagonism, although some authors have not encountered it. The methods of investigation and experimental conditions used may account for these contradictory results. Morphological, physiological and, to some extent, biochemical facts testify to this antagonism. New research has recently been undertaken with the aid of radio-active isotopes, notably P^{32} (Borell, Simonnet, Parhon, etc.). The Romanian School of Endocrinology has made a special study of P^{32} uptake by the various endocrine glands after administration of epiphyseal hormone.

MATERIALS AND METHODS

Experiments were carried out with two groups of male albino rats, weighing between 100 and 120 g. One group of twenty animals received daily intraperitoneal doses of 2 cc of epiphyseal hormone per animal for ten days, which was followed by an injection of 30 μc of P^{32} per animal. The epiphyseal hormone doses were continued, 6, 12 and 18 hours after the P^{32} injections.

Ten animals were sacrificed 6 hours after the P^{32} injection, and the remainder 24 hours after the P^{32} injection.

The 20 control animals not treated were sacrificed 24 hours after a P^{32} injection. The epiphysis, hypophysis, thyroid, adrenals, testes and seminal vesicles were then removed. The radioactivity was measured by means of a beta-radiation counter.

RESULTS

There was no appreciable difference in gland weights between the two groups.

Microscopic examination confirmed inhibition of the thyroid, adrenals and testes after administration of epiphyseal hormone.

Radioactivity measurements showed slight P^{32} uptake by the glands examined after administration of epiphyseal hormone (Tables 1 and 2, and Fig. 1).

Phosphorus uptake by the thyroid was 64.1 ± 2.8 cpm after 6 hours, and 47.2 ± 2.1 after 24 hours. In the animals treated with epiphyseal hormone, phosphorus uptake was on the average lower: 55.3 ± 2.3 after 6 hours, and 39.2 ± 1.7 after 24 hours.

Similarly, uptake by the adrenals was lower in the animals treated with epiphyseal extract: 59.1 ± 1.3 after 6 hours, and 44.2 ± 2.0 after 24 hours, than in the controls: 77.2 ± 3.4 after 6 hours, and 64.3 ± 2.2 after 24 hours.

The same inhibition of phosphorus uptake was observed in the testes: 22.1 ± 1.0 after 6 hours, and 31.4 ± 1.4 after 24 hours, compared with the controls: 29.3 ± 1.3 and 41.2 ± 1.9.

The seminal vesicles also fixed smaller quantities of P^{32} after treatment with epiphyseal hormone: 44.3 ± 2.1 after 6 hours, and 52.2 ± 2.3 after 24 hours, compared with the controls: 60.2 ± 2.5 and 71.1 ± 3.1.

It is interesting to note that phosphorus uptake at the thyroid and adrenal levels, in both controls and treated animals, was found to be higher after 6 hours than after 24 hours, whereas phosphorus uptake by the testes and seminal vesicles appeared lower after 6 hours than after 24 hours.

This shows that the P^{32}, although fixed initially by the thyroid and adrenals, is subsequently transmitted to other tissues where phosphorus metabolism is more active: the testes and seminal vesicles.

DISCUSSION

If we accept phosphorus uptake as a means of evaluating the functional level of an endocrine gland, our experiments can be taken to show that epiphyseal hormone inhibits function of the thyroid, adrenals, testes and seminal vesicles.

Our results confirm the findings of other authors as to the antagonism between the epiphysis and the glands examined, arrived at by different methods (Kothman, C. I. Parhon *et al.*, S. M. Milcu *et al.*, I. Milcu *et al.*, Trautmann, Wislanski, H. Simonnet, Engel, L. Thiéblot and H. le Bars, etc.).

In a further series of studies, not yet published, we observed, after administering epiphyseal hormone, a decrease in phosphorus-32 uptake by the hypophysis, after intervals of 6 and 24 hours.

Original language: French.

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Table 1. Cpm/mg of Dry Tissue (mean values)

Hours after P^{32} injection	Thyroid		Adrenals	
	Controls	Treated	Controls	Treated
6	64.1 ± 2.8	55.3 ± 2.3	77.2 ± 3.4	59.1 ± 2.5
24	47.2 ± 2.1	39.2 ± 1.7	64.3 ± 2.2	44.2 ± 2.0

Least of all is known about the relation between the epiphysis and the seminal vesicles. By implanting human epiphysis in rats previously treated with gonadotrophine, Engel produced an inhibition in the testes and seminal vesicles.

The mechanism of the inhibition produced by epiphyseal hormone in the glands examined is not very clear. Judging by research completed so far, many authors are agreed that there is inhibition of the hypophyseal stimulants, which control the functioning of the various glands.

Table 2. Cpm/mg of Dry Tissue (mean values)

Hours after P^{32} injection	Testes		Seminal Vesicles	
	Controls	Treated	Controls	Treated
6	29.3 ± 1.3	22.1 ± 1.0	60.2 ± 2.5	44.3 ± 2.1
24	41.2 ± 1.9	31.4 ± 1.4	71.1 ± 3.1	52.2 ± 2.3

According to Engel, inhibition of the gonadotrophine does not take place at the level of the hypophysis, as the epiphyseal hormone acts only at the gonad level. Direct action by the epiphyseal hormone on those glands is not excluded; our results relating to the seminal vesicles confirm this hypothesis.

Our conclusion is that, after the administration of epiphyseal hormone, a decrease is observed in the phosphorus uptake of the thyroid, adrenals, testes and seminal vesicles. These results can be interpreted, therefore, as indicating that there is inhibition of the respective glands.

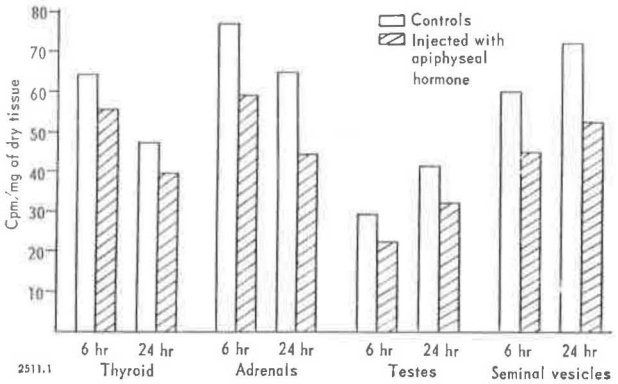

Figure 1. P^{32} fixation after administration of epiphyseal hormone

A Study with Radioactive Iodine of the Effect of Vitamins B_1 and B_{12}, Benzedrine and Phenobarbital on Thyroid Function

By A. Lupulescu, I. Negoescu, A. Pop and F. Cocu*

The relation between vitamins and hormones is of great importance in present-day endocrinology.

The isolation and synthesis of a large number of vitamins now widely used in the treatment of various endocrine diseases, and their effect on the endocrine glands, led to some discussion as to whether they acted only as adjuvants to hormone treatment or influenced hormone synthesis directly, speeding up or retarding the progress of the disease and the effect of the treatment.

The effect on thyroid function of vitamins, particularly vitamins A, E and C, and to a lesser extent those of the B group, has been studied. The results with regard to the effect of vitamins B_1 and B_{12} on the activity of the thyroid gland are contradictory.

After administration of vitamin B_{12}, alone and in conjunction with propylthiouracil, Barbazza[1] observed no changes in the thyroid gland and concluded that the action of this vitamin in experimental hyperthyroidism is purely peripheral and antithyroxic and does not influence the hypophyseal thyrotropic hormone (antithyrotropic). Recently, Ferguson *et al.* (1957)[2] found that in chickens given a diet deficient in vitamin B_{12}, the growth of the thyroid gland was retarded and that a hypofunctional condition developed. There was also a fall in the fixation of radioactive iodine I^{131}.

According to some authors, vitamin B_1 affects thyroid function by interfering with thyroxine at the peripheral tissue level.

With regard to benzedrine and phenobarbital, Stefan Milcou *et al.*[4] showed that one day's benzedrine treatment produces a slight increase in the fixation of radioactive iodine I^{131}, whereas phenobarbital has a paradoxical effect, producing a large increase in radioactive iodine fixation after ten days of treatment.

In the research dealt with here, we studied the effect of vitamins B_1 and B_{12}, benzedrine and phenobarbital, on normal thyroid function and on experimental goiter induced in rats by a diet deficient in iodine maintained for a period of nine to ten months.

We believe the results of this research will contribute to an understanding of the mechanism involved and of the indications and counter-indications in the treatment of thyroid diseases.

Original language: French.

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EXPERIMENTS

The experiments were carried out with 100 male and female albino rats, weighing 89 to 95 g, divided into ten experimental groups as follows:

First group: ten rats of both sexes, with an initial weight of 90 g, were used as controls.

Second group: ten rats weighing 92 g were given vitamin B_1 (Merck thiamin) by intramuscular injection in doses of 10 mg per day per animal, three times a week for three months.

Third group: ten rats (male and female), weighing 95 g, were given vitamin B_{12} (Merck) by intramuscular injection in doses of 10 gamma per day per animal, three times a week for three months.

Fourth group: ten albino rats were given benzedrine orally in doses of 1 mg per day per animal, three times a week for three months.

Fifth group: ten rats were given phenobarbital (Luminal) in doses of 10 mg per day per animal, three times a week for three months.

Sixth group: ten rats, weighing 90 g, were fed for nine to ten months exclusively on an iodine-deficient diet, which was a modified form of Remington's diet: wheat starch 75%, fat 8%, liver (powdered) 8%, cellulose 5%, dried yeast 2%, sodium chloride 1%, calcium triphosphate $Ca(PO_4)_3$ 1%. Throughout the experiment the animals drank only distilled water. An estimation of the iodine in the food showed that the diet contained approximately 4.5 γ of iodine per 100 g of food, which meant that a rat consuming 18 to 20 g of this diet would ingest 0.66 γ of iodine daily.

Seventh group: ten rats, with an average weight of 93 g, were kept on the iodine-deficient diet for about six months, after which the same diet was supplemented with vitamin B_1 in doses of 10 mg per day per animal, three times a week for three months. The purpose was to study the effect of this vitamin on development of the experimentally-produced goiter.

Eighth group: ten adult rats, initially weighing 95 g, were also kept on the iodine-deficient diet for six months, after which the same diet was supplemented with vitamin B_{12} in doses of 10 g per day per animal, three times a week for three months.

Ninth group: ten rats (male and female) were kept on the iodine-deficient diet for six months, after which

the same diet was combined with benzedrine in doses of 1 mg per day per animal, three times a week for three months.

Tenth group: ten albino rats (male and female), with an average weight of 93 g, were kept on the iodine-deficient diet for six months, after which the same diet was combined with phenobarbital in doses of 10 mg per day per animal, three times a week for three months.

Five days before sacrificing the animals, the radioactive iodine fixation was determined by administering 4 μc of I^{131} to each rat by intraperitoneal injection. The measurements were made with a Geiger-Müller counter 4, 24, 48, 72 and 100 hours after the I^{131} injection. The thyroid, hypophysis and adrenals were removed and fixed in Bouin's fluid and 10% formalin.

At the end of the experiments, the basal metabolism was determined and the thyroid and body weights recorded; after fixation, the organs were embedded in paraffin, sliced into 3–4 micron sections and stained with haematoxylin-eosin and Masson's trichromatic. The internal Golgi reticulum was studied by da Fano's method.

RESULTS

In these experiments we observed: fixation of radioactive iodine I^{131}, basal metabolism, thyroid and body weights and histological structure. The results varied from group to group. In the controls, radioactive iodine fixation was 41% after 4 hours, 44% after 24 hours, 36% after 48 hours, 34% after 72 hours and 31% after 100 hours.

In the rats treated with vitamin B_1 there was a moderate fall in radioactive iodine fixation: 34.2% after 4 hours, 42.3% after 24 hours, 38.2% after 48 hours, 31% after 72 hours and 22.2% after 100 hours.

In the rats treated with vitamin B_{12} radioactive iodine fixation increased, reaching 58.3% after 4 hours, and then declined to 57.4% after 24 hours, 51.1% after 48 hours, 55% after 72 hours and 52.5% after 100 hours.

After the administration of phenobarbital, a marked increase in iodine fixation was observed: 64.2% after 4 hours, 67.4% after 24 hours, 63.2% after 48 hours, 61% after 72 hours and 59.1% after 100 hours. This was the highest radioactive iodine fixation recorded in our experiments.

Benzedrine gave a radioiodine retention of 45.3% after 4 hours, 54.1% after 24 hours, 48.2% after 48 hours, 43% after 72 hours and 37.2% after 100 hours.

In the rats kept for 9 to 10 months on an iodine-deficient diet, there was a rise in radioactive iodine fixation, which reached 55% after 4 hours, 56% after 24 hours, 54% after 48 hours and 51% after 72 hours, falling to 48% after 100 hours.

Where vitamin B_1 (thiamin) had been administered to animals on an iodine-deficient diet, the radioactive iodine fixation was lower than in animals kept on the diet alone, being 49.1% after 4 hours, 53.2% after 24 hours, 47.5% after 48 hours, 43% after 72 hours and 40.4% after 100 hours.

Vitamin B_{12} administered to rats on an iodine-deficient diet produced a marked increase during the first 24 hours (64.2% after 4 hours and 59.1% after 24 hours), followed by a progressive decrease to 51.2% after 48 hours, 42% after 72 hours and 34.1% after 100 hours.

Benzedrine administered to rats on an iodine-deficient diet produced a slight rise in radioiodine fixation, which was: 58.2% after 4 hours, 59% after 24 hours, 52.3% after 48 hours and 50% after 72 hours, falling to 40% after 100 hours.

Phenobarbital administered to rats on an iodine-deficient diet produced somewhat lower radioiodine fixation than was observed in those kept on the diet alone: 48.1% after 4 hours, 53.2% after 24 hours, 55.7% after 48 hours, 50% after 72 hours and 43.2% after 100 hours. These figures are represented in Fig. 1 and the radioactivity was measured in collaboration with Dr. A. Bojinescu.

Basal metabolism varied with the treatment given. Thus, in the rats treated with vitamin B_1 we found a decrease of up to 5.5% (in relation to the controls, taken as 0).

In the animals treated with vitamin B_{12}, metabolism showed a moderate increase: +2.1%.

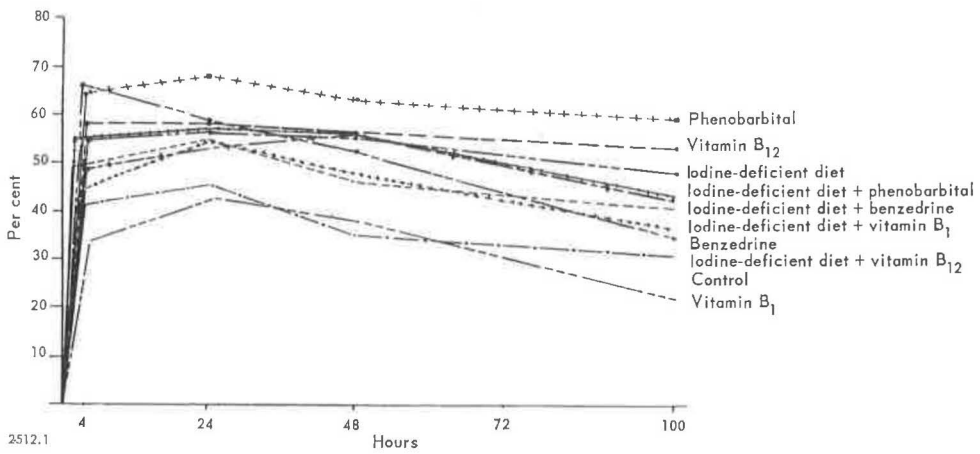

Figure 1. Fixation of radioactive iodine I^{131}

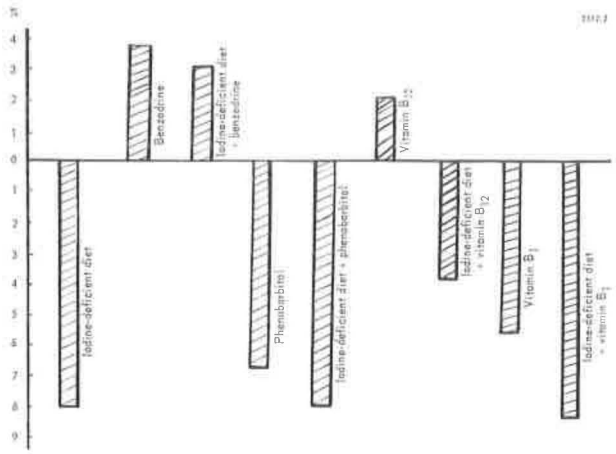

Figure 2. Variations in basal metabolism

Benzedrine produced the highest increase recorded in the experiments: +3.8% of the basal metabolism.

Phenobarbital reduced basal metabolism as much as 6.7%.

The iodine-deficient diet produced a marked fall in basal metabolism of up to −8.1%. Vitamin B_1 coupled with the iodine-deficient diet reduced basal metabolism still more, giving −8.3%, the lowest figure obtained in the experiments, whereas vitamin B_{12} in conjunction with the iodine-deficient diet gave a moderate fall: −3.8% in relation to the controls (Fig. 2).

Body and thyroid weights also underwent considerable changes. In the controls, the mean thyroid weight was 16 mg; it increased substantially in the rats on the iodine-deficient diet, reaching 42 mg (about three times that of the controls); in the rats treated with vitamin B_{12} it increased slightly, to 18 mg, and fell to 15 mg in those treated with vitamin B_1. Benzedrine increased the thyroid weight, while phenobarbital left it unchanged (Fig. 3).

Microscopic examination showed the thyroid controls to be made up of oval, average-sized follicles with a homogeneous colloid. The follicular epithelium consisted of cubic cells of 9 to 10 μ (Fig. 4a).

After treatment with vitamin B_1 the thyroid seemed to consist of larger oval follicles (macrofollicles), filled with homogeneous colloid; the follicular epithelium was made up of flattened cells of about 6 μ (Fig. 4e); inhibition of thyroid function was clearly visible.

After treatment with vitamin B_{12}, thyroid function was found to be stimulated; this was reflected in a predominance of microfollicles with little colloid and a follicular epithelium made up of long cells of 14 to 16 microns (Fig. 4f).

Stimulation of thyroid function was also observed in the rats treated with benzedrine. The colloid had diminished and become very pale, with several resorption vacuoles (Fig. 5c). On the other hand, phenobarbital resulted in moderate inhibition of thyroid function. The colloid was intensely eosinophilic (Fig. 5d).

The majority of the animals kept for 9 to 10 months on an iodine-deficient diet developed hyperplastic parenchymatous goiter, with predominance of microfollicles, hyperaemia of the gland and reduced colloid (Fig. 4b).

In other cases nodules had formed, distinct from the rest of the gland; these were follicular adenomas (Fig. 5c and d).

The administration of vitamin B_1 reduced hyperplastic goiter and thyroid tumors; the follicles became larger and filled with homogeneous colloid (Fig. 5a).

Vitamin B_{12} stimulated slightly the formation of parenchymatous goiter in which there was predominance of microfollicles with very dilute colloid (Fig. 5b).

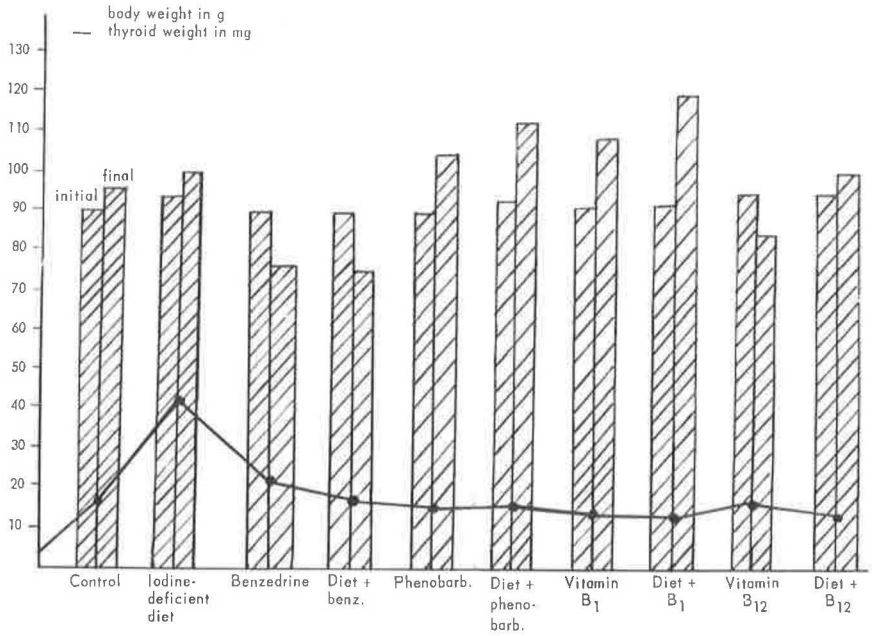

Figure 3. Variations in body and thyroid weight

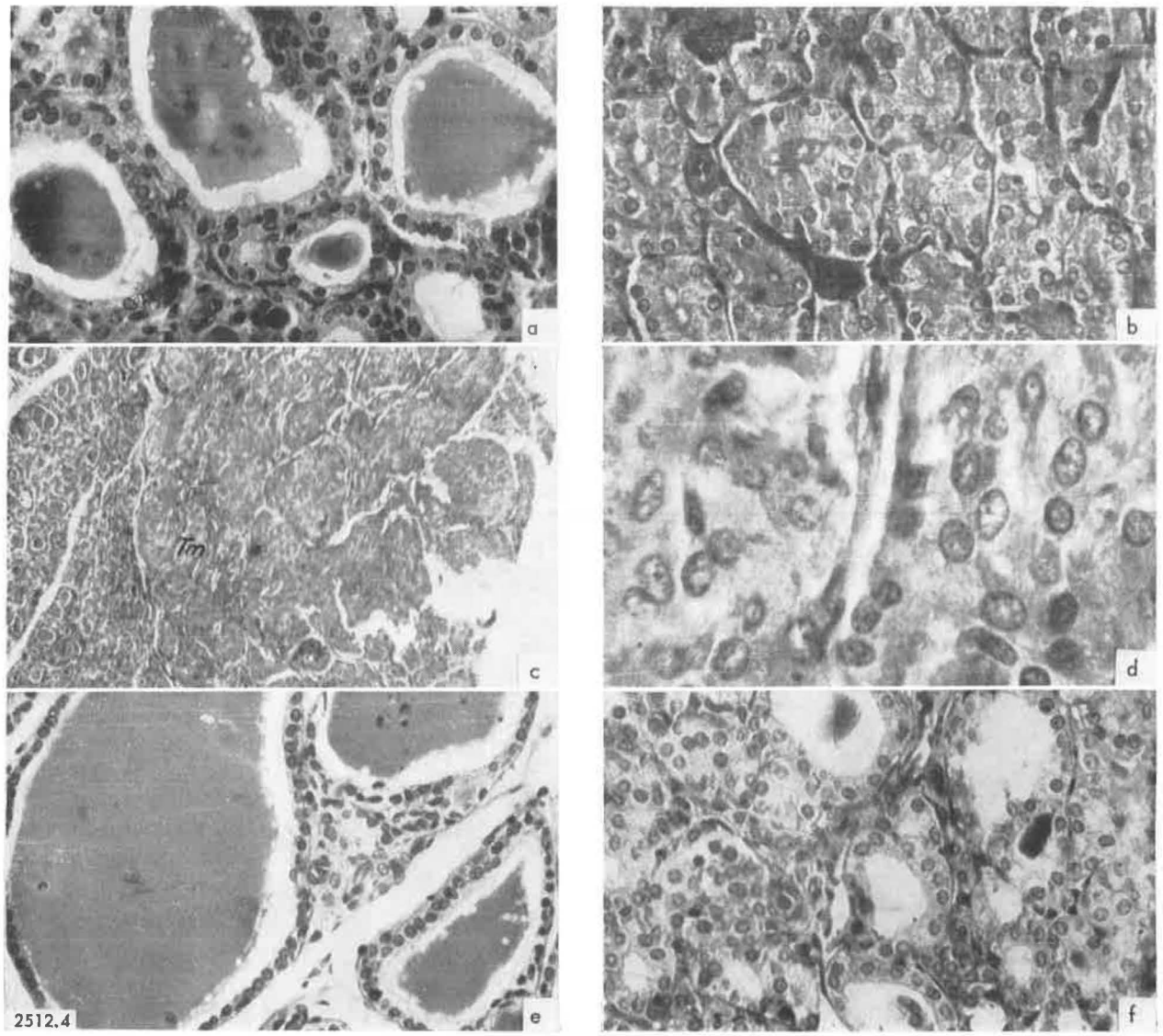

Figure 4. Histopathologic materials. a, thyroid: control rat; b, thyroid: iodine-deficient diet, hyperplastic microfollicular goiter; c, thyroid: iodine-deficient diet, thyroid tumor; d, thyroid: iodine-deficient diet, follicular adenoma; e, thyroid: vitamin B_1, inhibition of thyroid function; f, thyroid: vitamin B_{12}, stimulation of thyroid function

Benzedrine altered the development of experimental goiter, moderately stimulating it (Fig. 5e), whereas phenobarbital produced a slight inhibition; colloid was in evidence (Fig. 5f).

DISCUSSION

Our research has shown that the administration of vitamin B_1 results in hypofunction of the thyroid, reflected in a decrease in fixation of radioactive iodine (I^{131}), in basal metabolism and in the thyroid and body weights.

The administration of vitamin B_{12}, on the other hand, produces hyperfunction of the thyroid as reflected by an increase in radioactive iodine (I^{131}) fixation, basal metabolism and thyroid weight.

The antithesis between effects of the two vitamins at the thyroid level is also found in the development of hyperfunctional goiter and thyroid tumors induced in rats by an iodine-deficient diet. Our results recall those of Ferguson *et al.*[2] who found hypofunction of the thyroid gland in chickens given a diet deficient in vitamin B_{12}. Paper radio-chromatography reveals the presence of mono-iodotyrosine, di-iodotyrosine and thyroxine in the deficient thyroids. We do not agree with Barbazza[1] that vitamin B_{12} exercises no influence on the normal thyroid and that in experimental hyperthyroidism its action is purely antithyroxic. In our research, we have found, on the contrary, that vitamin B_{12} acts through the medium of the hypophyseal thyreotrope.

Vitamin B_1 has the opposite effect on thyroid function, producing an inhibition in the normal thyroid and in experimental goiter. Clinical observations confirm these findings and have demonstrated the beneficial effect of vitamin B_1 in hyperthyroidism.

With regard to the action of drugs which alter the excitability of the central nervous system, we found

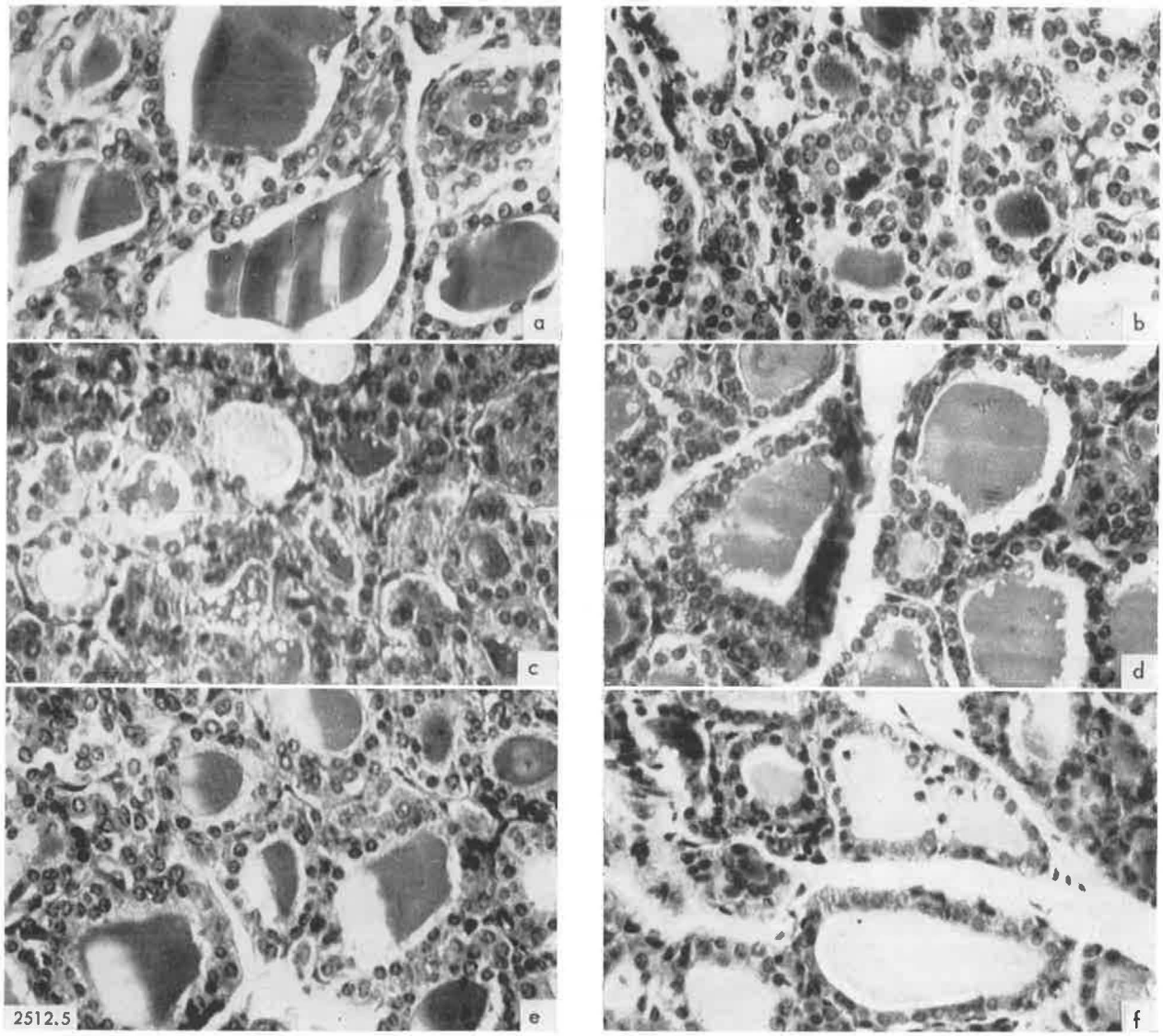

Figure 5. Histopathologic materials. a, thyroid: iodine-deficient diet + vitamin B_1; b, thyroid: iodine-deficient diet + vitamin B_{12}; c, thyroid: benzedrine; d, thyroid: phenobarbital; e, thyroid: iodine-deficient diet + benzedrine; f, thyroid: iodine-deficient diet + phenobarbital

that prolonged administration of benzedrine resulted in more pronounced stimulation of thyroid function than was produced by vitamin B_{12}, whereas phenobarbital had a paradoxical effect.

The results given here demonstrate the role played by these drugs and their importance in thyroid therapy.

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Investigation of Central Hemodynamics by Means of Selective Quantitative Radiocardiography

By Gabriele Monasterio and Luigi Donato*

The adaptation of the heart output to peripheral requirements takes place through variations of pressure and volumes of blood in the heart chambers. This implies that both pressure and volume measurements are needed to achieve a complete understanding of the hemodynamic behaviour of the heart in physiological and pathological conditions.

Reliable pressure measurements may be obtained by heart catheterization techniques, but correct volumetric estimations are almost impossible by means of traditional methods.

Volume changes affect pressure values in several ways: (*a*) diastolic pressure is related to the amount of blood in the cavity at the end of diastole, but this relation is not linear, because of the elastic characteristics of the myocardial walls; (*b*) the contracting energy, which is determined by the myocardium, yields different pressures and outputs depending upon the blood content of the contracting chamber.

The initial stages of valvular diseases produce a redistribution of blood in the heart chambers, and pressure changes occur secondarily and are not simply correlative to volume changes. Knowledge of pressure values therefore does not provide a complete picture of the central hemodynamic pattern.

The difficulty of measuring precisely and separately the volume of blood in the heart chambers and the changes in volume during cardiac action has been overcome very recently by the use of radioactive tracers. The methods of analysis already widely used in metabolic studies for the estimation of pool size and rate of renewal of body constituents have been successfully applied to the measurement of the amount of blood in the heart cavities and to its rate of transfer throughout the central circulation.

PRINCIPLES AND METHODS

Transfer of Tracer through the Cardiopulmonary Circulation Considered as a Series of Systems in Dynamic Equilibrium

The term *dynamic equilibrium* has been used in biology to describe a fundamental property of the so-called "steady state systems" whose constancy of composition is due not to functional rest, but to a continuous flow of components through the system itself, a fixed fraction of the constant number of constituent units being turned over per unit time.

With some simplification, central circulation may be considered as a series of systems in dynamic equilibrium with each other. In fact, if the duration of a heart cycle is taken as unit time, the volume of blood in each chamber and the flow rate through them may be considered constant.

Each chamber may be represented by a container of constant volume, open at both ends, through which a constant flow of liquid passes. Biological systems in dynamic equilibrium have an additional characteristic of basic importance in turnover studies, namely, the occurrence of complete mixing of newly formed components with those already present. Complete mixing occurs in the ventricles[1] as a result of the turbulence in the flow of liquid in them, but in the atrial cavities mixing does not take place to the same extent where a streamline flow occurs. Hence, the assumption that the heart cavities behave as a system in dynamic equilibrium implies the acceptance of a theoretical error for the atrial cavity. However, it will be shown that this error is of minor importance when compared with the importance of the data derived from the above assumption.

Mixing and the occurrence of dynamic equilibrium in the heart cavities implies that a radioactive indicator suddenly injected into any one of the four cavities should disappear from the cavity at an exponential rate given by the flow/volume ratio (F/V) in the cavity itself.

According to Zilversmit,[2] after injection into the atrial chamber, atrial blood may be considered the specific precursor of ventricular blood. Activity concentration in the ventricular blood will follow the curve for specific activities (see Fig. 1 (*a*)) given by Artom *et al.*,[3] and confirmed by Zilversmit[2] and Siri.[4] Total activity changes take place according to the curve in Fig. 1 (b) as the ventricular blood volume (V_B) is much higher than atrial blood volume (V_A).

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The mathematical expression for the disappearance of atrial activity (A_A) is given by:

$$A_{A(t)} = A_{A(0)}e^{-(F/V_A)t},$$

and assuming $K_A = F/V_A$; then

$$A_{A(t)} = A_{A(0)}e^{-K_A t}. \quad (1)$$

The activity changes in the ventricular blood (A_V) may be described by the Siri equation for transfer of tracer between two phases,[4] that is:

$$A_{V(t)} = \frac{K_V}{K_V - K_A} A_{A(0)}(e^{-K_A t} - e^{-K_V t}) \quad (2)$$

where K_V is the rate of emptying of the ventricle, that is, the ratio between flow and ventricular volume. The total activity $A_{T(t)}$ recorded by a counter facing both chambers is given by:

$$A_{T(t)} = A_{A(t)} + A_{V(t)}$$
$$= A_{A(0)}e^{-K_A t} + A_{A(0)} \frac{K_V}{K_V - K_A} (e^{-K_A t} - e^{-K_V t}) \quad (3)$$

By substituting $-R = K_V/(K_V - K_A)$, eq. 3 becomes:

$$A_{T(t)} = (1 + R)(A_{A(0)}e^{-K_A t}) + R(A_{A(0)}e^{-K_V t}). \quad (4)$$

The recorded curve will be given by the sum of two exponential functions, but it will not be a pure exponential function itself. The greater K_A in comparison with K_V, the faster will the first term of eq. 4 become negligible; the total curve will approach a pure exponential function, changing at a rate given by K_V. Total activity will hence be given by the following equation:

$$A_{T(t)} = R(A_{A(0)}e^{-K_V t}). \quad (5)$$

This theory applies to both sides of the heart considered separately.

Quantitative Evaluation of Radiocardiographic Curves on the Basis of Turnover Theory

In 1948 Prinzmetal *et al.*[5] and Waser and Hunzinger[6] proposed a technique which was called radiocardiography. Radioactive sodium (Na^{24}) was injected into an arm vein and time–activity curves were recorded by a collimated counter over the heart area. Under normal conditions the curve obtained showed two peaks, corresponding to the transit of the tracer through the two sides of the heart. These curves were analyzed in relation to time to obtain information concerning the transit times for the various sections of the cardiopulmonary circulation.

Several groups used the technique later, improving tracers and recording methods.[7–10] In 1954 Veall *et al.*[11] demonstrated the possibility of calculating cardiac output from the radiocardiographic curve just as from any other dye dilution curve. Measurement of blood flow by means of this technique has been reported by several groups.[12–14]

Our work in this field has been to ascertain the possibility of using the technique for measuring the amount of blood in the heart cavities and for measuring its rate of transfer from one cavity into another.

A scintillation counter directed towards the heart area "sees" at the same time all the cavities of the heart, or at least a fraction of each of them. Separation of right from left heart curve in the recorded tracings is due to the interposition of the pulmonary vascular bed (its greatest extent lies outside the counter field). It is, however, impossible to separate atrial from ventricular curve since both cavities are seen by the counter. The curves recorded for each side are then the sum of atrial and ventricular curves.

Practical application of the above theory to radiocardiographic tracings was shown by a study of the right curve of injection radiocardiograms.[15] It was found that under normal conditions the downslope of the curve was exponential starting from the peak, or shortly afterwards. The early appearance of a pure exponential downslope means that in a very short time the amount of tracer left in the atrium becomes negligible and that eq. 5 describes the disappearance curve. As shown in Fig. 1 (b) this means that activity changes take place at a rate equal to the right ventricle rate of emptying.

For eqs. 4 and 5 to be strictly valid under experimental conditions, counting efficiency should be identical for both atrium and ventricle. Certainly this is not the case, since, lying closer to the thoracic wall, counting efficiency must be higher for the ventricle. If C is the ratio of average counting efficiency for atrial blood to that for ventricular blood, eq. 4 becomes:

$$\bar{A}_{T(t)} = (C + R)(A_{A(0)}e^{-K_A t}) + R(A_{A(0)}e^{-K_V t}). \quad (6)$$

This correction does not invalidate the theory, but further reduces the relative importance of the atrial component, as C is 1.

On the basis of the above analytical and experimental evidence two points may be established: (1) The exponential downslope of curves recorded on one side of the heart after a sudden inflow of the tracer in the atrium represents the flow/volume ratio in the ventricle. (It may be calculated as $K_V = 0.693/T_{1/2}$, and it is referred to as ventricular rate of emptying.) (2) The interval between the initial peak concentration and the beginning of the exponential decrease is due to the persistency of an appreciable amount of activity in the atrium and its duration is proportional to the rate of emptying of the atrium itself. (This tract was called atrial delay time (ADT).)

Knowing the ventricular rate of emptying per unit time K_V, ventricular end-diastolic volume (VDV) may be calculated once the flow F per unit time is known:

$$VDV = F/K_V \quad (7)$$

Subtracting the stroke volume (SV) from VDV gives the residual blood volume in the ventricle at the end of systole (VRV):

$$VRV = VDV - SV \quad (8)$$

In vitro experiments (Donato and Debus[16]) on a glass phantom of cardiopulmonary circulation showed on graphic analysis that the exponential downslope

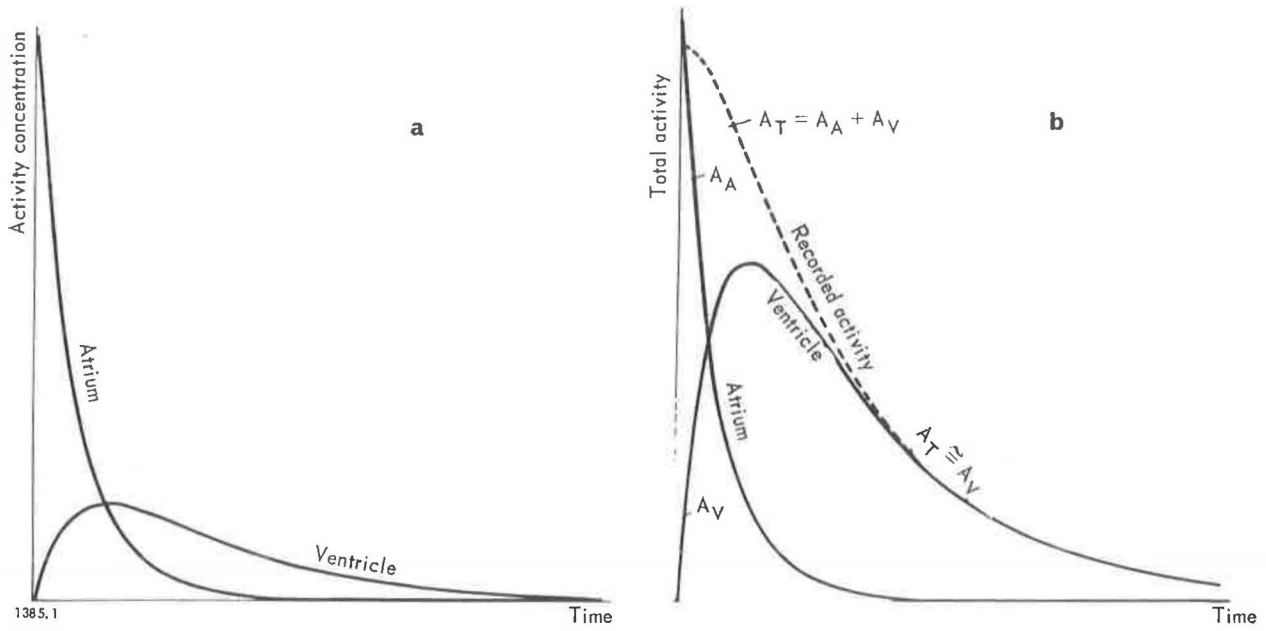

Figure 1. (a) Activity concentration in ventricular and atrial blood. Theoretical activity concentration–time curve in atrium and ventricle after injection of an indicator into the atrial cavity. Atrial volume is 100 ml and ventricular volume is 350 ml. Flow per unit time is 70 ml. (b) Theoretical total activity–time curve for the same condition. Dotted line represents the sum of both atrial and ventricular activity

appears when less than 10% of the initial peak activity is left in the atrium. It was therefore assumed that after a time ADT (eq. 1 for the atrial activity) could be written:

$$A_{A(ADT)}/A_{A(0)} = 0.10 = e^{-K_A(ADT)}, \qquad (9)$$

from which it is possible to calculate the conventional atrial rate of emptying (K_A) as:

$$-K_A = \frac{2.3}{ADT}. \qquad (10)$$

The corresponding ideal atrial volume—atrial washout volume (AWV)—is calculated as for the ventricle:

$$AWV = F/K_A. \qquad (11)$$

Technical Problems and Methods in Selective Quantitative Radiocardiography

In order to apply the above methods of calculation to the analysis of tracings recorded over the heart area during the passage of a gamma-emitting tracer, questions connected with the following technical problems had to be solved: (*a*) obtaining rapid and massive inflow of the tracer in the sections of the side of the heart under investigation; (*b*) counter collimation to include in the counter field most of the chambers under investigation; and (*c*) reliable methods of recording to permit accurate analysis of the tracings obtained.

Selection and Administration of Tracers

Rapid inflow of the tracer into the right side of the heart may be obtained by intravenous injection. In normal subjects change of the point of injection does not appreciably affect slope and timings of the right curve, but it may cause critical variations in patients with heart disease.[15] Injection of the tracer into the jugular vein gives reproducible tracings even in severe congestive failure, provided the injected volume is less than 0.3 ml and the injection is performed during inspiration.[13]

Two kinds of tracers are available for selective radiocardiography of the right heart (see Fig. 2). Radioiodinated human serum albumin (RIHSA) is commonly used and the first recorded curve (right) is analyzed. Radiogold-198 adsorbed on 30–50 microns carbon particles is used alternatively (Au–RCG) whenever avoidance of a left curve is required.[17] This may be important in severe congestive failure with extreme reduction of right ventricular emptying. The large

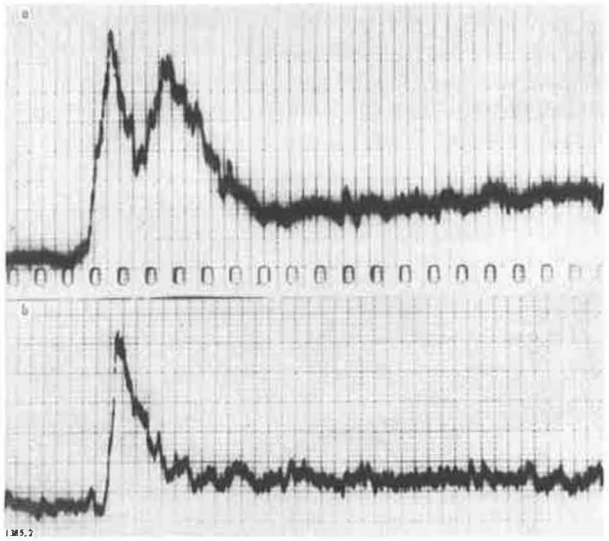

Figure 2. (a) Total radiocardiogram obtained by jugular injection of RIHSA into a normal subject; (b) right selective radiocardiogram obtained by jugular injection of radiogold-198 carbon particles into a normal subject. (From: Gigli *et al.*[26])

size radiogold particles are stopped in the lung capillaries and a pure right curve is obtained.

In the RIHSA–RCG the right exponential downslope is interrupted by the appearance of activity in the left side and, from this point on, the recorded curve is the sum of left time–activity and residual activity in the right side. Subtraction of an extrapolated right descending branch from the total recorded curve gives the pure left tracing. It is not possible to analyze the subtracted curve directly because the dilution of the tracer in the right heart and pulmonary circulation brings it to the left side at too slow a rate to permit reliable quantitative analysis.

The problem of avoiding the prediluting effect of the right section as the preliminary step to quantitative evaluation of left hemodynamics was first pointed out by one of us[15] and it was suggested that this might be accomplished by the use of a gaseous tracer administered by inhalation.

The problem was solved[18] by using radioiodinated methyl iodide (MI), which fulfills the conditions required of a gaseous tracer for the study of left heart hemodynamics. After inhalation of 20–30 microcuries of I^{131} as methyl iodide a small fraction is expired, a certain fraction remains in the respiratory tract, probably adsorbed by the mucus of the bronchial walls from which it is lost very slowly, and the main fraction of the tracer is rapidly absorbed by the alveoli and transferred to the left heart at a very high rate.

The curves obtained by recording the activity variations over the heart area after inhalation of methyl iodide (MI-RCGs) were shown to represent the passage of the tracer through the left sections of the heart, superimposed on a bronchial background; subtraction of this bronchial level yielded reproducible selective radiocardiograms of the left side of the heart (see Fig. 3).

Counter Collimation

Positioning of the counter is an important problem in quantitative radiocardiography. Large-opening collimators are required for quantitative analysis as it is necessary to have in the counter field a sizable fraction of each chamber of the section under study. The spatial

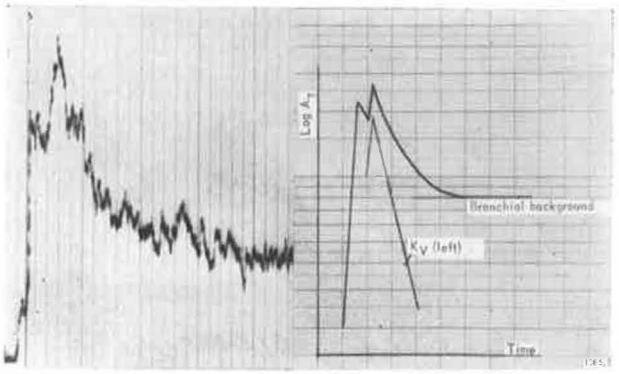

Figure 3. Original tracing and semilog plot of a left selective RCG obtained by inhalation of methyl-radioiodide in a normal subject. Subtraction of final bronchial background yields the true left downslope

Figure 4. Equipment for recording of radiocardiographic tracings in the Center of Nuclear Medicine, University of Pisa. Collimated scintillation counter, counting rate meter, pulse height analyzer and multichannel photographic recorder, including ECG

locations of the heart cavities suggest that for maximal geometrical efficiency on either side of the heart and for maximal reduction of extravascular interfering activity central collimation is best.

The model used by us is a commercial NaI (Tl) scintillation counter with a 1-inch-square crystal and heavy lead collimator with the following characteristics: a 12° collimating channel, 10 cm long, with an external diameter of 6 cm and an internal opening of 4.3 cm. The collimator is positioned close to the body surface with the counter axis directed towards the centre of the heart area.

Both sides of the heart are "seen" over a wide area by the counter and the lungs are almost completely out of the field. Small changes in collimation will result in variations of the fraction of the chambers seen by the counter, but will not change timing and slopes of the tracings as has been demonstrated in normal subjects and cardiac patients.

Recording Technique

Quantitative analysis of the tracing requires plotting on semilog paper for timing and extrapolation of curves. The critical factors which affect the accuracy of replotting are the statistical variations in counting rate and the duration of appearance of the parts of the tracts to be extrapolated.

Random variations of counting rate may be reduced by increasing the administered activity, by using longer time constants for the ratemeter and by excluding scattered radiations by means of pulse-height analysis. When using less than 50 microcuries of activity, optimal conditions are obtained with a 0.35 sec time constant of the ratemeter and a 3000-counts-per-sec scale. Pulse-height analysis has been recently introduced by our group for recording of radiocardiograms.

The duration of appearance of portions of the descending branches must be plotted with as many points as possible to permit proper extrapolation.

Relatively high-speed photographic recorders and large strips are necessary. In our model, paper (20 cm wide) is run at 0.5 cm per sec for coarse examination

of tracings and at 5 cm per sec when fine analysis is required. At the latter speed at least five points per sec are available for replotting the curves.

ECG tracings, taken at the same time and recorded on the same film, permit correlation of the time–activity curve with the heart cycle. The equipment used by our group is shown in Fig. 4.

APPLICATIONS

Quantitative Data from Radiocardiographic Curve

Three complementary techniques are actually available for radiocardiography: (1) RIHSA injection radiocardiogram (RIHSA–RCG), (2) radiogold-198 particles injection radiocardiogram (Au–RCG) and (3) methyl iodide inhalation radiocardiogram (MI–RCG).

By the above techniques, the following quantitative data may be obtained: cardiac output (CO), rates of emptying of heart cavities (K_A and K_V), blood content of heart cavities (VDV, VRV and AWV), and traversal time through the cardiopulmonary system.

Heart Output

RIHSA–RCG provides a simple method for measuring cardiac output. Theory and methods of calculation were first proposed by Veall *et al.*[11] and since then widely confirmed and used.

Blood flow through the heart cavities cannot be measured on Au– or on MI–RCGs. In both cases "calibration" of the curves is not possible since this would require a homogeneous distribution of the tracer in the vascular bed. This occurs with RIHSA. Radiogold particles are stopped in the lung circulation; methyl iodide largely diffuses through the systemic capillaries and its final level is mainly due to extravascular activity, i.e., in the left bronchus.

Rates of Emptying of the Heart Cavities

Right and left selective RCGs supply information on the rates of emptying for the cavities of the two sides of the heart. Analytical procedure is the same for both types of tracings, except for the required preliminary subtraction of the bronchial background for MI–RCGs.

On the semilog plotting, ventricular rates of emptying (K_V) are calculated from the exponential downslopes and the atrial rates of emptying (K_A) are measured by means of eq. 10.

Right K_V has been measured by this method in 17 normal subjects by Gigli *et al.*, and it has been found to average 23.1% in men and 22.8% in women.[19] In a mixed group of 34 normal subjects recently examined by us, right ventricle rate of emptying per cycle averaged 26.5 ± 7.96%.[20] Left ventricular rate of emptying (K_V) per cycle calculated on MI–RCGs[18] averaged 19.5 ± 2.4% in men and 23.4 ± 4% in women.

In both right and left selective tracings, the duration of the atrial delay time (ADT) was found to be shorter than 3 sec in normal patients, yielding, according to eq. 10, 77% per cycle as the slowest acceptable K_A in normal subjects.

Blood Content of the Heart Cavities

The calculated rates of emptying of the heart cavities (Ks), as reported above, give the F/V ratio in the heart cavities. The close values obtained for left and right rates in normal subjects (the flow passing through both sides being the same), led to the conclusion that blood content of the two sides of the heart was of the same order of magnitude.

Measurement of volumes, according to eqs. 7 and 8, requires a knowledge of blood flow and rate of emptying in the cavity being studied.

Right heart blood volumes are easily calculated from the RIHSA–RCG, on which cardiac output (CO) and right sections rates of emptying (Ks) are measurable. By this method blood volumes were calculated in 7 male and 11 female normal subjects.[19] Right ventricular end-diastolic volume (VDV) averages 355 ml in men and 343 in women, with a residual blood volume in the ventricles at the end of systole (VRV) of 284 ml in men and 265 in women. Atrial washout volume (AWV), calculated in the same group of individuals according to eq. 11, was found to be smaller than 100 ml. In a mixed group of 44 normal subjects recently examined by us, right VDV averaged 325.4 ± 81 ml and VRV 245.9 ± 71 ml.[20]

In the exceptionally rare cases where the right downslope of RIHSA–RCG is badly defined, pulse height analysis makes it possible to record simultaneously both Au– and RIHSA–RCGs. Right Ks calculated from the first are compared with cardiac output obtained from the second and volumetry of right heart may hence be calculated.

Left heart volumetry can not be directly measured on RIHSA–RCGs on account of the diluting effect of the preceding sections on the tracer inflow. Until now simultaneous recording of selective inhalation RCG and cardiac output measurement has not been undertaken, but several possibilities may be considered for this purpose, among which is the measurement of output from arterial dye or tagged cells dilution curves.

Left volume measurement might also be obtained by doing RIHSA–RCGs followed by MI–RCGs for calculation of left Ks after a few minutes when activity is uniformly distributed. Comparison of data would not be strictly valid, but the error would be acceptable if basal conditions were maintained throughout the test.

Pulmonary Circulation Time

Radiocardiography was first proposed for the measurement of pulmonary circulation time (PCT), and the distance between the two peaks was taken as its measure—the *Mittlere Lungenzeit* of Waser and Hunzinger.[6]

Later, Lammerant and De Visscher[10] proposed calculating the mean PCT as the difference between mean circulation time calculated on both right and left curves according to the Hamilton equation[23] for arterial dye-dilution curves. They also suggested that the Stewart–Hamilton principle could be used for the esti-

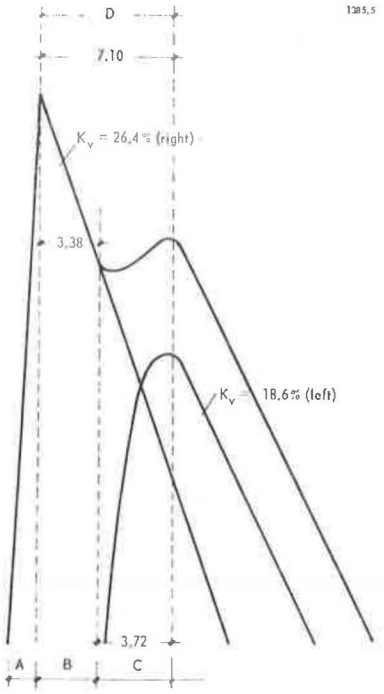

Figure 5. Normal values of RIHSA–RCGs. *A*—right filling time; *B*—minimum PCT; *C*—left filling time; *D*—peak-to-peak time; K_V—slopes of exponential tracts (Combined from Bartolomei *et al.*[21] and Bianchi *et al.*[22])

mation of pulmonary blood volume, that is, the product of PCT and cardiac output.

More recently, Huff and his group[24] extended the Lammerant theory to the study of transit time between the various sections of the central circulation by applying the Hamilton formulae to the analysis of curves recorded over the thoracic wall by multiple scintillation equipment. They also attempted to calculate the blood volumes between the explored points by multiplying cardiac output by the Hamilton mean transit time.

Our group[25] has pointed out that the measurement of the so-called mean transit time by the Hamilton equation can not be correctly applied to the analysis of curves recorded on mixing-volumes with fractional emptying. In fact the Hamilton principle assumes that each single particle of indicator is measured only once by the detecting instrument. This condition does not apply to curves recorded on mixing-volumes, where the persistency of each particle in the counter field is a random event purely related to the turnover rate of blood in the chamber itself.

The only reliable measurement of pulmonary traversal time on RIHSA–RCG is given by the time interval from appearance of activity in the right side to its appearance in the left. For practical purposes, since right inflow is very rapid, we measure the time interval between right peak and left foot, which we refer to as *minimum pulmonary traversal time*.[26] In 44 normal subjects Bianchi, Bartolomei and Cerri found that minimum PCT averaged 3.38 ± 0.79 heart cycles.[22]

Study of Left Hemodynamics

Left curves of RIHSA–RCGs have been recently submitted to a critical study on the basis of the data obtained from Au–RCG and MI–RCG.

By subtracting the extrapolated branch of the right downslope from the total recorded activity on the left curves obtained from RIHSA–RCGs, the first component (from foot of left curve to the beginning of the left exponential tract) is referred to as "left filling time." It is followed by a second component represented by an exponential downslope.

The outflow of tracer from left ventricle in RIHSA–RCGs should not yield a pure exponential function because left inflow of tracer probably continues over a long time. However, the final downslope of the tracing appears practically exponential by the usual graphic methods.

Forty-four normal tracings were recently examined in our department by Bartolomei, Bianchi and Cerri,[21] and the right exponential slope was found to average 0.264 ± 0.079 per cycle, with a left slope of 0.186 ± 0.056 per cycle; right–left slope ratio was 1.36 ± 0.53. This ratio appeared remarkably constant over a very wide range of CO values, and it was concluded that comparison of the slopes of the two exponential functions of RIHSA–RCGs could provide useful information concerning left ventricle blood volumes.

Bianchi, Bartolomei and Cerri[22] have also recently carried out a systematic study of the so-called "left filling time": in normal conditions its average value

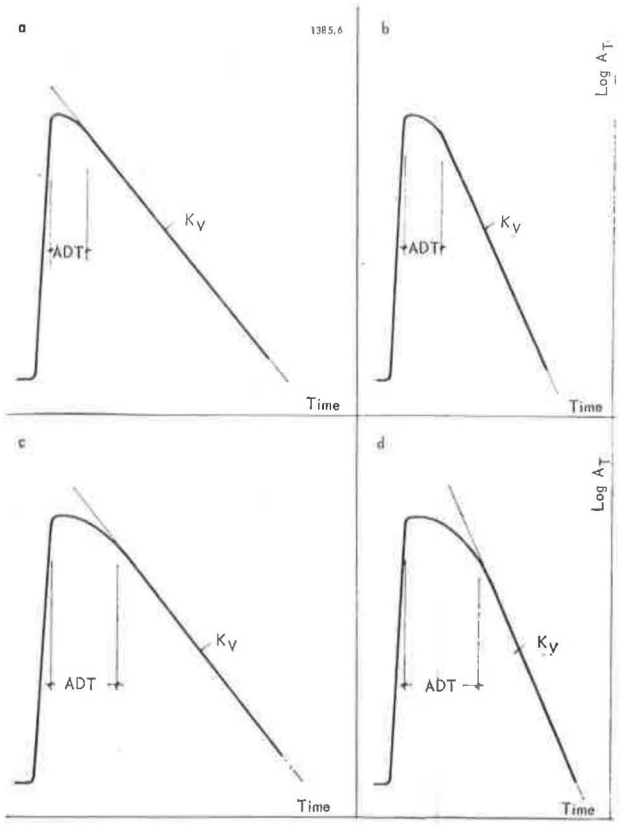

Figure 6. Elementary changes of selective RCG. (a) Normal tracing; (b) reduced ventricular emptying with normal atrial emptying; (c) reduced atrial emptying with normal ventricular emptying; (d) reduction of both atrial and ventricular rate of emptying. (From Gigli *et al.*[26])

has been found to be 3.72 ± 2.12 heart cycles. The high correlation observed between the values of this time interval and left atrial rate of emptying led these investigators to point out its importance for the approximate evaluation of left atrial volumes.

Figure 5 shows a semilog RIHSA–RCG whose timings and slopes represent the average normal values.[21,22]

Radiocardiography in Cardiovascular Physiology

The introduction of radiocardiography led to the clarification of some basic problems concerning cardiopulmonary physiology.

Heart systolic emptying involves about one-fourth of cardiac blood content. Cardiac output adaptation to conditions of increased demand or reduced venous return is better understood on the basis of the above evidence. Suggestive demonstration of the importance of ventricular residual blood was obtained from the study of the effects of physical effort on methyl iodide inhalation tracings. In trained subjects it was shown that increased output takes place as a result of reduction in left ventricle residual volume and appears in the tracing as the steeper downslope of the exponential branch.[19]

New information on the problem of pulmonary circulation is now available. It has been shown that *the pulmonary vascular bed can not be considered as a third mixing volume interposed between the two sides of the heart.* Newman's theory of pulmonary washout volume was shown to be incorrect on the basis of turnover equations[26] and this is supported by evidence derived from a series of experiments on a heart–lung model by Donato and Debus.[16]

The results of these analytical and experimental studies[26] showed that pulmonary circulation behaves like a system of channels of different length in which blood flow is of the laminar type. True mixing does not take place, but dispersion occurs according to the *random walk* theory of Sheppard,[28] the random distribution of right ventricle outflow into a great number of circuits of different traversal time.

Minimum right-heart to left-heart traversal time, obtained from RIHSA–RCGs, and minimum lung to left-heart time, calculated on the inhalation tracings, were found to be almost identical. This demonstrates that most of the time necessary for the blood to reach the left side of the heart from the right ventricle is spent in the venous side of the pulmonary circulation.

Systematic investigations are now being undertaken in our department to correlate flow, volumes and pressures in the heart chambers.

Clinical Use of Radiocardiography

Pathological changes in radiocardiographic curves may be due either to flow or volume variations. Provided the flow rate through all the explored cavities is the same, flow changes will affect all the components of the curve to the same extent, whereas volume changes will affect only the component related to the heart cavity where volume changes occur.

Elementary changes of selective RCG are shown in Fig. 6. Reduction in the atrial rate of emptying with normal ventricular emptying has the effect of increasing the duration of ADT, as happens, for example, in pure mitral stenosis; reduction of ventricular emptying alone reduces K_V without affecting the ADT, as, for example, in aortic valve disease with normal left atrial hemodynamics.

It must be pointed out that in routine testing of patients RIHSA–RCGs are far more useful than the selective techniques because a larger number of data may be obtained from the former procedure.

The practical importance of the double peak RCG described by previous workers was limited by a lack of knowledge concerning the hemodynamic mechanisms shaping the curves. Clarification of these previously unknown factors as a result of the splitting of the RCG in two selective tracings has made RIHSA–RCG a valuable tool for diagnosis and follow-up of cardiac patients.

In fact, as we have shown in previous paragraphs, RIHSA tracings supply at the same time cardiac output measurement, right selective data and valuable information concerning left heart hemodynamics.

More than 500 tests on heart patients suffering from acquired or congenital heart diseases have been done in the past three years by our group. The results obtained have been presented elsewhere[25,26,29] and will not be discussed in detail here.

Among the more interesting results is that RIHSA–RCG has been found particularly useful for the study of mitral diseases, especially for the identification of

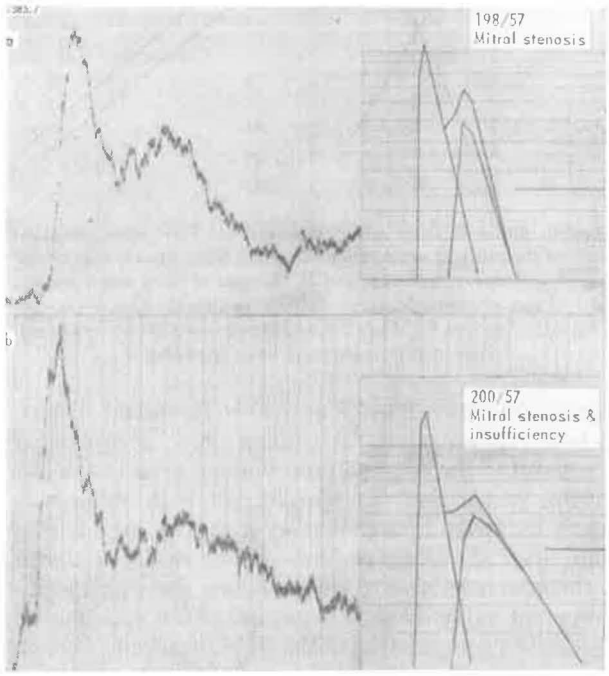

Figure 7. RIHSA–RCGs in mitral diseases: (a) Pure mitral stenosis (prolonged left filling time with normal left slope). (b) Mitral stenosis and insufficiency (prolongation of left filling time is associated with reduction of left slope). In both cases the right curve is normal. (From Donato *et al.*[25])

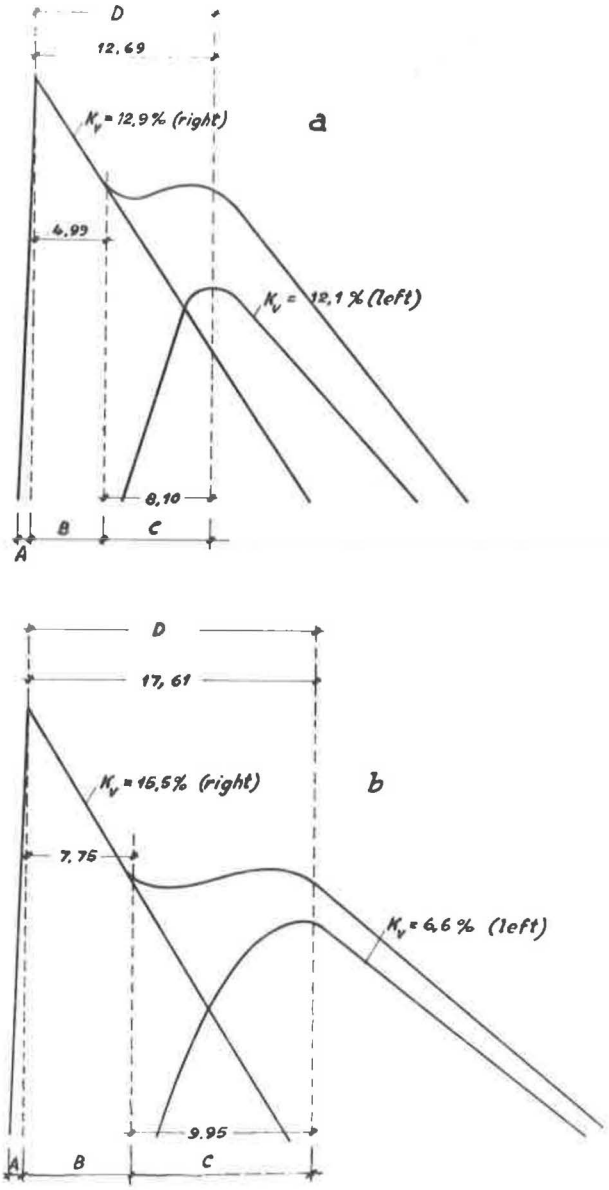

Figure 8. RIHSA–RCG in mitral diseases. (a) Pure mitral stenosis; (b) mitral stenosis and regurgitation. Tracings have been drawn on the basis of average values obtained in 18 cases of pure mitral stenosis and 19 cases of combined mitral diseases. Besides the typical changes of the left curve (see Fig. 7), *PCT* is prolonged and right K_V is reduced. Right *ADT* changes have been neglected

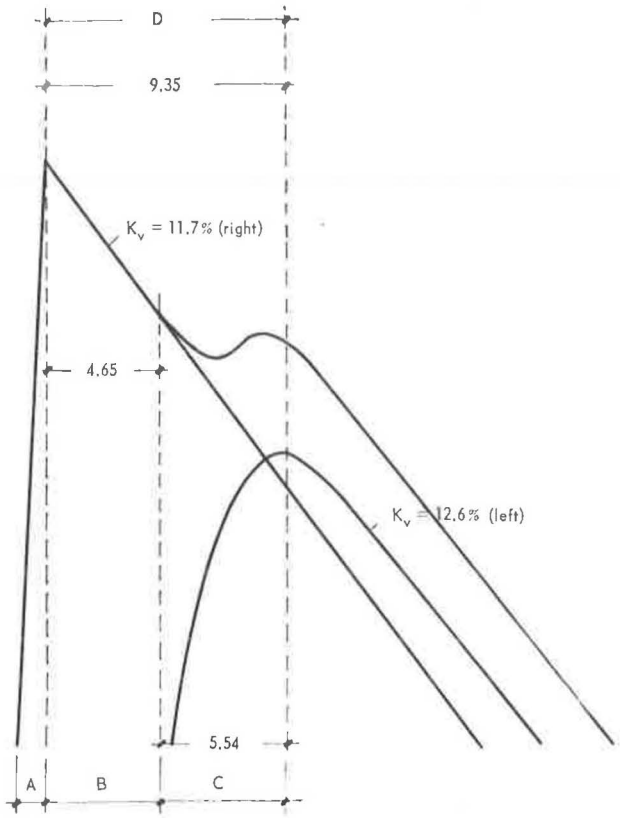

Figure 9. RIHSA–RCG in chronic cor pulmonale. Tracing has been drawn on the basis of the average data obtained in 34 cases of chronic cor pulmonale. Remarkable reduction of right ventricular emptying associated with a relatively short *PCT* is shown; left curve exponential slope is steeper than normal when compared with the right slope. (Combined from Bartolomei *et al.*[21] and Bianchi *et al.*[22])

regurgitant flow (Figs. 7 and 8).[25] In mitral disease without regurgitation, "left filling time" is prolonged as a result of the reduced flow–volume ratio in the left atrium; association of regurgitation with stenosis is clearly indicated by a reduction of the left exponential slope, since the effective flow–volume ratio is reduced in the ventricle, due to the backflow through the incompetent valve. In pure stenosis, the left exponential slope, when compared with the right, is normal or even increased for the reduced volume of blood in the left ventricle.

Right heart involvement in primary left-sided heart diseases is detectable early in RIHSA–RCGs, where it appears as a reduction of the right K_V, and eventually is associated with increased duration of *ADT* when tricuspid relative insufficiency occurs.

Figures 8 and 9 were drawn by plotting the average values of the components of RIHSA–RCGs performed in cases of pure mitral stenosis, mitral stenosis and regurgitation and chronic cor pulmonale at different stages of development.

Besides left curve changes, mitral cases show a typical prolongation of pulmonary circulation time and reduction of right ventricular rate of emptying.

The latter aspect is also found in chronic cor pulmonale, but in this condition the relative shortness of pulmonary circulation time compared with the reduction of the right ventricle outflow rate, points out the marked and typical reduction of the pulmonary vascular bed. Left curve components are obviously normal, right to left slope ratio being lower than normal for normal left ventricle hemodynamics.

Improvement of hemodynamics following medical or surgical therapy is easily and accurately evaluated by RCGs, as shown in Fig. 10 where tracings recorded in a severe case of mitral stenosis, before and immediately after valvulotomy, are shown for comparison.

Selective Au– and MI–RCGs are particularly useful for the study of congenital heart diseases. Shunts between the two sides of the heart are easily detected by

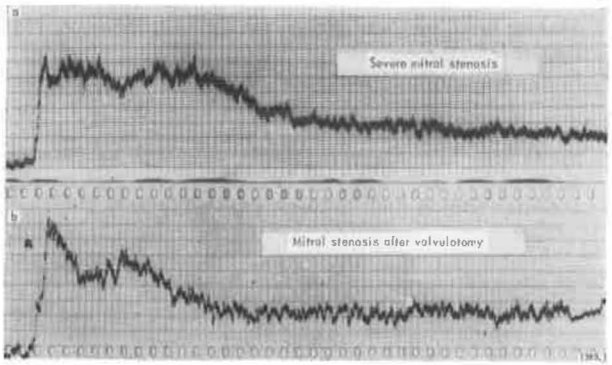

Figure 10. (a) RIHSA–RCG in a case of severe mitral stenosis. (b) RIHSA–RCG in the same case, shortly after valvulotomy. Improvement is shown by the disappearance of right *ADT*, which was markedly prolonged at the time of the first examination. (From Gigli *et al.*[26])

these techniques since the tracer passes with the shunted blood into the opposite side of the heart: Right-to-left shunts are shown by Au–RCGs but left-to-right shunts are better demonstrated by inhalation tracings. RIHSA–RCGs have also been found useful in the diagnosis of congenital heart defects and typical tracings have been reported elsewhere.[25]

These few examples demonstrate the usefulness of radiocardiography for proper individuation of the primary site of acquired or congenital heart diseases and for evaluating the degree of involvement of the various parts of the central circulation.

CONCLUSIONS

The volumes of blood in the cardiopulmonary circulation and their rate of renewal have been measured by quantitative methods of analysis of radiocardiographic tracings.

The techniques which have been developed along this line represent a new and accurate tool both for physiological investigation of cardiopulmonary circulation and clinical study of heart disease in patients.

Since it is well established that the hemodynamic constants measurable by means of quantitative radiocardiography play a leading role in the regulation of cardiovascular equilibrium, we hope that its widespread use will increase our knowledge concerning several still obscure points in heart physiology and physiopathology.

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Mr. Donato (Italy) presented P/1385, above, and added the following remarks:

As other reliable methods are available for measuring heart output, the basic importance of radiocardiography is the possibility of estimating the volumes of blood in the heart cavities and their rate of emptying from the slopes of the curves recorded on the heart after intravenous injection of a gamma emitter.

Quantitative radiocardiography represents a new approach to the study of central hemodynamics, and especially heart function. Not only is it new as a technique, but the factors which may be evaluated by this method were previously almost unexplorable.

Figure 11 shows the classical pressure–volume relation describing the hemodynamic behaviour of the ventricles: residual blood is brought up to the maximum or end-diastolic volume, almost without pressure changes, then pressure increases during isometric contraction and finally, during the emptying phase, both pressure and volume return to the initial level.

The data supplied by heart catheterization are shown in Fig. 12 and are limited to a record of pressure and to measurement of stroke volume by Fick's principle. The triangle which appears in the figure can not be located on a volumetric abscissa, which greatly limits the importance of the information obtained. In fact, it is known that pressure is a dependent variable whose values are determined by myocardial factors and volume changes which are really the primary factor in determining the hemodynamic behaviour of the heart. Volume changes are not simply correlated to pressure changes.

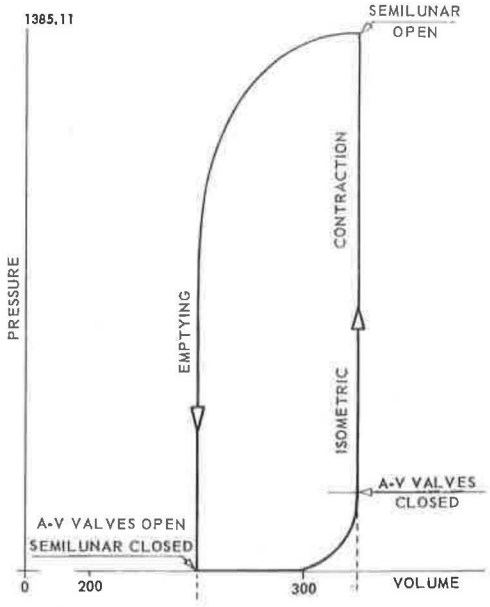

Figure 11. Pressure and volume changes in the ventricles during a heart cycle

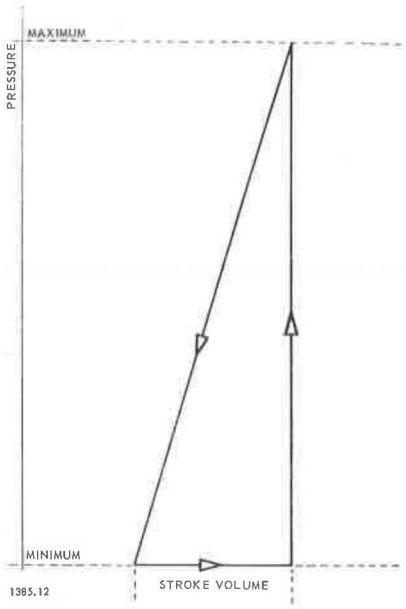

Figure 12. Evaluation of ventricular hemodynamics by heart catheterization

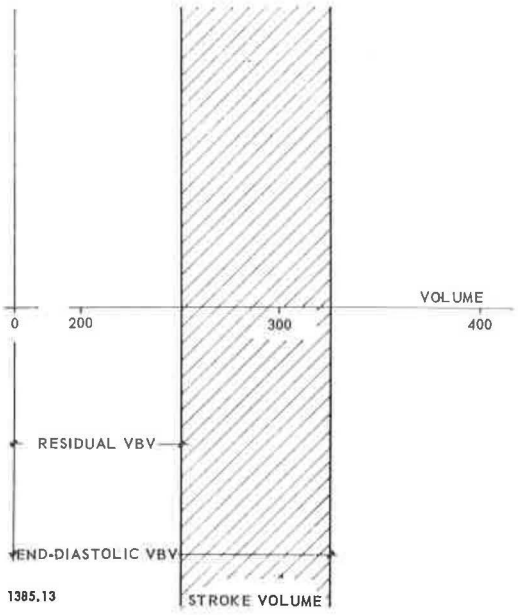

Figure 13. Evaluation of ventricular hemodynamics by quantitative RCG

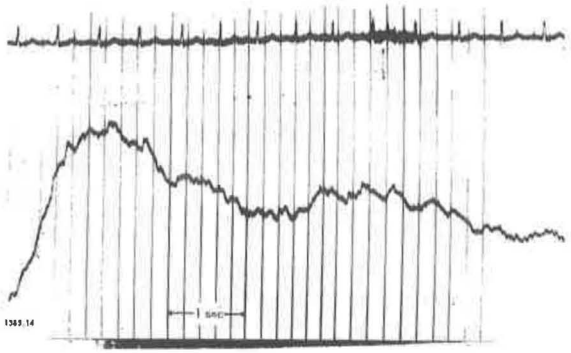

Figure 14. High-speed recording of radiocardiographic tracing

Figure 13 shows the data supplied by radiocardiography. It may be seen that this data gives an estimate of the independent variable (volume), and of the stroke volume which in turn depends upon volume, pressure in the ventricle and pressure in the arteries. The estimation of the end-diastolic volume quantitates the load imposed on the heart by the experimental or pathological condition, whereas the fraction ejected for a given volume gives an estimate of the other factors involved.

The importance of this new approach has been demonstrated by the study of normal subjects and heart patients. A report on this work has been prepared for the Third World Congress of Cardiology (Brussels).

A real improvement in the technique is the high-speed recording of radiocardiographic tracings. Figure 2 shows two tracings recorded by the traditional low-speed method. The upper is a "labelled-albumin injection tracing," the lower is a "radiogold-on-particles tracing." The interval between two vertical lines corresponds to one second, and on the original tracing to 2.5 millimetres. Downslopes are almost continuous and there is no evidence of the cyclic heart action.

In Fig. 14 a high-speed tracing is presented. Here the interval between two vertical lines corresponds to 0.2 seconds, and on the original tracing to 1 centimeter. Variations of activity synchronous with the heart cycles may be recognized in the tracing. They are limited to the descending branch of the right curve, and before an appreciable amount of tracer reaches the left side of the heart. Two of them clearly appear in this tracing.

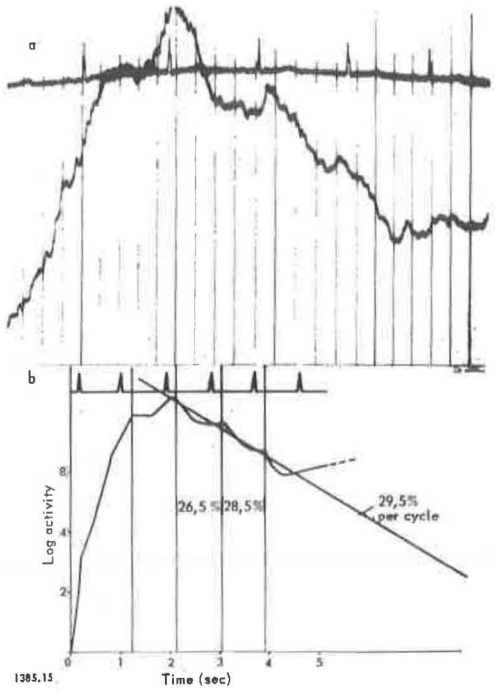

Figure 15. Right curve of RIHSA-radiocardiograph in a normal subject. (a) High-speed recording of RCG; (b) semilogarithmic plot of tracing

In Fig. 15 is seen (upper part) the right curve of a high-speed tracing recorded in a normal subject. In this tracing, and in the semilogarithmic plotting below, cyclical variations of activity are seen very clearly. The first systole which appears takes place during the inflow phase and it appears as an arrest in the filling process. Three clearly evident cycles follow. During the third cycle, activity rises again due to the fact that a detectable fraction has reached the left heart.

Percentage variations during each of two cycles agree with the fractional rate of emptying, calculated from the slope in the usual manner.

We feel that improvement of the technique and growing knowledge will further increase the importance of the method and the data derived from it. Our personal experience and the growing interest in this field, as evinced from the papers presented to this section, indicate that radioisotopes will occupy a very important place in heart-function investigations in the future.

Inhalation Radiocardiography

By C. H. Jaimet, R. H. Tomlinson and P. F. Nace*

This report deals with the investigation of several functions of the heart by means of inhalation radiocardiography. We have been particularly concerned with circulation in the left heart and myocardium. Our primary objective was the delivery of a radioactive isotope directly to the left heart in order to obtain records of pure left heart circulation. Various isotopes were considered, and our original work, recently reported,[1] dealt with the use of methyl radioiodide as the tracer in these hemodynamic studies. From this work there evolved the procedures to be described.

In the present work, we have developed improved methods of handling and administering the methyl radioiodide and have proceeded to the use of radiokrypton. The latter technique promises to give information concerning myocardial circulation which could not be obtained by using methyl iodide. It has also emphasized several of the important variables among patients and has led us to the planning of improved instrumentation which should permit correction or control of these individual factors.

EXPERIMENTAL METHOD

The equipment used is that described in our previous report.[1] It consists of a 2 × 2 inch (~5 × 5 cm) crystal scintillation counter, amplifiers, discriminator, rate meter and Esterline-Angus pen-recorder. The counter crystal is shielded with lead and faces an opening 7 cm in diameter. The crystal face is 20 cm back of the shield port and has a field nearly cylindrical in form, approximately 12 cm in diameter.

As in the previous study, the tracer was prepared by an exchange reaction between methyl iodide and sodium radioiodide. Approximately 1 ml of natural methyl iodide was added to 20 ml of aqueous sodium radioiodide with a specific activity of 1 mc/ml in a 50 ml standard taper Florence flask. A condenser was fitted to the neck of the flask after insertion of a magnetic stirring bar. Slow mixing was continued for several hours. The methyl radioiodide was separated from the aqueous phase by means of a precooled lambda pipette, transferred to a high vacuum assembly, outgassed by trap-to-trap distillation and stored *in vacuo*. The individual tracer doses were measured by a gas pipette with volume of 20 ml, including associated manometer. From the gas pipette, the methyl radioiodide was condensed with liquid air into glass vials 3 cm long and 1 mm in diameter, which were sealed from the vacuum system by flame. The dose was measured, relative to an iodine-131 standard, by means of a well-type ionization chamber and a vibrating-reed electrometer. After determining the activity associated with a given pressure in the gas pipette, glass vials containing any predetermined amount of activity could be prepared with reproducibility within 1%.

Doses of 15 μc methyl radioiodide were used in the present studies, and before inhalation of the tracer, patients' thyroids were blocked by administration of natural iodide. With the geometry of the earlier study, the patient was seated comfortably in front of the counter. This was centred at the fourth thoracic interspace, one inch (2–3 cm) to the left of the sternum. The patient maintained close thoracic contact with the counter face throughout the test.

The administration of the methyl iodide was accomplished with a respiratory mask equipped with two one-way valves. On the afferent side, 25 cm of 8 mm rubber tubing connected the mask to a 15 mm test tube with a sidearm near the bottom. The glass vial containing the tracer was placed in the sidearm extending across the bottom of the tube.

The tracer vial was broken with a glass needle. After allowing 30 seconds for the complete vaporization of the tracer and its diffusion through the hand-warmed tube, the mask was fitted to the patient who was instructed to inhale quickly and to resume normal breathing rhythm at once. The mask was removed on completion of the inspiration. An exhaust system carried away exhaled tracer.

For the krypton studies, slight modification of procedure was needed. Doses of krypton-85 were gas-pipetted in a vacuum system and adsorbed on 50 mg charcoal in thirty 1 mm glass vials cooled with liquid air. After each vial was sealed from the vacuum system with a flame, the millicurie strength of the dose was calibrated with the well-ionization technique described above for the methyl iodide. The krypton, in 5 mc doses, was then administered by the procedure used with the methyl iodide.

Interpretations of the experimental radiocardiograms have been carried out by comparison with the relations derived below. To obtain these equations, it has been necessary to assume that continuous functions can describe the intermittent physiological processes such as respiration and the cardiac cycle. With this limitation, the rate of accumulation and decay of radioactivity in the heart is obtained from the solution

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of the following simultaneous equations:

$$\frac{dN_l}{dt} = -(K_a + K_e)N_l$$

$$\frac{dN_a}{dt} = -K_aN_l$$

$$\frac{dN_h}{dt} = N_aK_a - N_hK_h$$

$$\frac{dN_m}{dt} = BN_hK_h - N_mK_m$$

Where N is the number of tracer atoms
K is the first-order rate constant
B is the fraction of blood leaving the left heart to enter myocardium.
l = lung, e = exhalation, a = absorption, h = left heart, m = myocardium.

Since the total tracer present in the heart is the sum of the amounts present in the left heart and myocardium, the total amount of tracer in the heart at any time, t, after the inhalation of N_0 tracer atoms to the lungs at $t = 0$, is as follows (provided no tracer returns to the heart during the period of observation):

$$N_{(\text{total heart})} = N_h + N_m$$
$$= \frac{K_a^2N_0(e^{-tK_h} - e^{-t(K_e+K_a)})}{(K_a + K_e)(K_e + K_a - K_h)}$$
$$+ \frac{K_hK_a^2BN_0}{(K_a + K_e)(K_a + K_e - K_h)}$$
$$\left[\frac{e^{-tK_m} - e^{-tK_h}}{(K_h - K_m)} + \frac{e^{-t(K_e+K_a)} - e^{-tK_m}}{(K_e + K_a - K_m)}\right] \quad (1)$$

For the conditions that the rate of absorption is large compared with both the rate of heart circulation and the rate of exhalation, and the rate of heart circulation is large compared with the rate of the myocardial circulation, i.e., $K_a \gg K_e$, $K_a \gg K_h$, and $K_h \gg K_m$,

$$N_{(\text{total heart})} = N_0e^{-tK_h} + BN_0e^{-tK_m} \quad (2)$$

if $tK_a \gg 1$.

RESULTS AND DISCUSSION

Several aspects of the new procedure, using pure methyl radioiodide without ether, were found to be improvements over the previous technique. Most important was the reproducibility of the tracer dose. The measurement of the ether solution in open systems had presented difficulties which the vacuum system eliminated. It was also found much more efficient to have the tracer doses prepared in advance and contained in sealed vials. This permitted closer scheduling of patients and avoided loss of the volatile tracer. A very important factor was the elimination of the ether. In a few cases, using doses of low specific activity, the ether solvent had produced coughing and apprehension.

In addition to the improved reproducibility of the determinations, the most obvious finding on the cardiograms was reduction in the time lapse between inhalation and the peak of radioactivity in the heart.

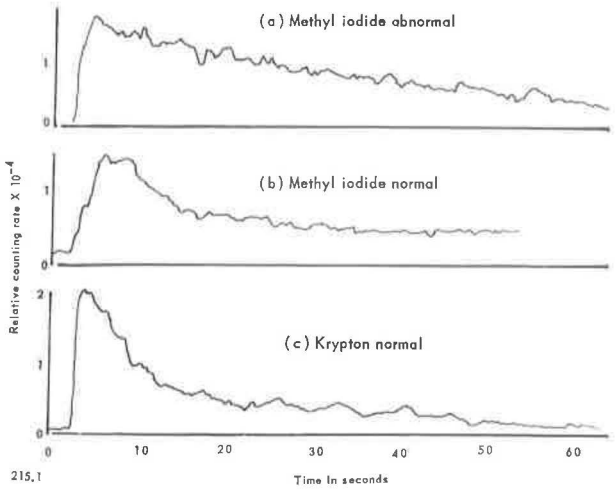

Figure 1

The use of a smaller tube connecting mask to tracer chamber reduced the dead air space of the system and assured that even a modest inspiratory effort would transfer the tracer to the lungs efficiently. Beyond these minor variations, the curves obtained with pure methyl iodide resembled those previously described for the ether solution of methyl iodide.

Typical methyl iodide inhalation radiocardiograms for cardiopathic and normal subjects are shown in Fig. 1 (a) and (b). The three chief features of the curves are the ascending limb, the descending limb and the final steady level. In the normal, Fig. 1 (b), the transit of the ascending limb required about 5 seconds to attain peak value. For most useful calculation, the dose and instruments were so adjusted that this peak represented 20,000 counts per minute and was recorded as a full-scale deflection of the pen. The descending limb of the curve occupied about twice the time of the ascending limb. Its low point occurred about 20 seconds after inhalation. This portion of the curve may be used to calculate the cardiac output, as percentage of cardiac volume by replotting on logarithmic graphs as previously described.[1] From the graphs shown in Fig. 1 (a) and (b), it may be estimated that the cardiac output per beat, expressed as percentage of the diastolic volume, is 18% for the normal subject and 5% for the cardiac patient. Our estimate of the functional impairment of this patient was confirmed by his recent development of severe cardiac failure although he was working without distress at the time when the test shown was done.

It may be seen in Fig. 1 (b) that the descending limb changed its path when it reached a level approximately half the peak value. From this point, there then continued a prolonged steady level. Originally, this was thought to represent activity in the respiratory mucus only,[1] but extensive studies with animals[2] have indicated that this persistent level derives, in part at least, from activity in the myocardium.† More will be said

† More detailed animal studies have continued with the support of the J. P. Bickell Foundation.

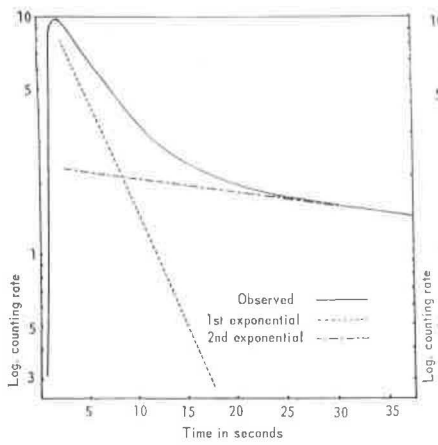

Figure 2. Normal

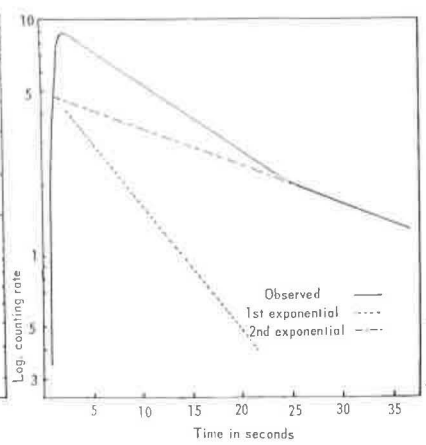

Figure 3. Angina

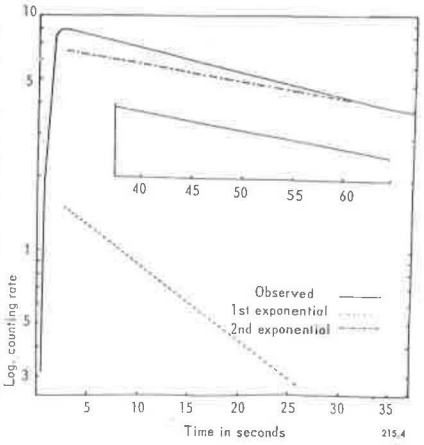

Figure 4. Severe Angina

of this when the krypton radiocardiogram is described. No precise identification of components of the curve with specific cardiac lesions will be attempted at this time, although there is evidence that this is possible.

The usefulness of krypton-85 as a tracer was investigated soon after the development of the pure methyl iodide method. A very obvious practical advantage of krypton, its long physical half-life, was apparent before its use was attempted. This isotope can be packaged in dose units, shipped and stored for long periods without appreciable loss of activity. Another important advantage, however, is a very short biological half-life. Tobias *et al.*[3] have shown three half periods of 6 minutes, 38 minutes and 320 minutes following saturation of the body with radiokrypton. Interpretation of this information in terms of a single inhalation indicates that most of the activity should be eliminated with the 6-minute half-life. This property, and the fact that krypton is not known to concentrate selectively in any organ, provide further reduction of radiation to even the most sensitive patients.

Qualitative comparison of the krypton and methyl iodide radiocardiograms is provided by Fig. 1 (b) and (c). The ascending limb of the curve for krypton is much more abrupt. While the methyl iodide reaches peak value in the heart in about 5 seconds, the krypton peak is attained too rapidly for measurement by our present instruments. The descending limb of the krypton-cardiogram, however, is markedly prolonged. In a normal subject, the exponential decay may be followed for 40 seconds or more. With methyl iodide, similar observation could be continued for only 10 seconds.

For the methyl iodide curve a final steady level of about 50% of peak value is obtained in most normal subjects, or at best 20–25% in a few trained athletes. The lower half of the descending limb is thus obscured by a final background, and nothing taking place in that portion of the curve can be discerned. In the krypton curves, the final background is nearly zero. We can, then, study the whole curve and measure factors invisible in the methyl iodide curves.

This improves calculation of cardiac output but it is not the sole virtue of this characteristic. Careful analysis of the curve discloses that it shows two exponential functions, rather than one. This is shown in Figs. 2, 3 and 4. Interpretation of the krypton cardiogram may be made by comparison with the equations derived above. Equation 1 represents the expected rate of accumulation and loss of an inhaled radioactive tracer from the left heart and myocardium from the time of inhalation until the time of appearance in the right heart.

Analysis of typical curves, as in Figs. 2, 3 and 4, indicates that the initial rise in activity is so rapid that the time constant of the recorder is the limiting factor. It is expected that improved instrumentation, such as the Honeywell Visicorder, may overcome this limitation and permit measurement of the lung-to-heart time. As the accumulation of activity in the heart is much more rapid than its loss, the analysis of the krypton cardiograms from 2 to 3 seconds after inhalation can be represented by the simplified equation 2, which has been reduced to the sum of two exponential terms. The first exponential represents the disappearance of activity from the left heart and yields the information previously obtained from the iodocardiogram (the percent cardiac output). The second exponential indicates, we think, the rate of decay of activity from the myocardium. Thus, we see, that the form of the experimental krypton cardiogram corresponds to the form expected. This correspondence can be real only if the tracer moves with the blood, and if all the activity observed originates in the heart.‡

The krypton may be absorbed to some extent and the interpretation of the second exponential in terms of myocardial circulation is not considered a proved fact. The second exponential has been found, however, to exist in the rabbit heart, exposed and shielded from the other thoracic viscera. This evidence suggests

‡ With methyl iodide, these conditions are not fulfilled. The iodide is absorbed and held in the myocardium.[2] Thus, with the methyl iodide, it is possible to observe only the total fraction of the tracer trapped in the myocardium. Other organs, such as parts of lung and bronchial tree lie in the field of the counter. Since these have absorbed methyl iodide during inhalation, they may very well contribute to the observed background.

probable identification of the second exponential with a heart function.

From equation 2 it may be seen that the ratio of the intercepts of the two exponentials should provide an estimate of the fraction of the cardiac output carried to the myocardium by the coronary circulation. When the experimental krypton cardiograms are interpreted in this manner the fraction appears much too large. Figures 2, 3 and 4 indicate values of 20% for a normal subject and 60% and 80% for known cardiac patients. This might be considered sufficient evidence to discard the myocardial theory of the origin of the second exponential. However, for the subjects examined, the relation between the intercepts was consistent with the clinical observations. To provide a possible explanation for these high values it is necessary to consider the radiation characteristics of krypton-85, and the method of observation. Only 0.7% of the disintegrations of krypton-85 provide a 0.5 Mev gamma ray. In order to obtain the required 20,000 counts per minute for a good radiocardiogram, even from a 5 mc tracer dose, it is necessary to make use of the Bremmstrahlen produced by the beta radiation. This radiation is very soft and is easily shielded from the counter by body tissues. The radiation from the left heart chambers is shielded more effectively than that from the myocardium, the large apex of which is close to the chest wall. If this interpretation is correct, it would be expected that the present krypton method can provide comparative estimates of coronary circulation, but not absolute fractions. This difficulty can, of course, be circumvented by use of harder radiation. If we were willing to use much larger doses of krypton, a pulse-height discriminator could be used to count selectively the 0.5 Mev gamma radiation of the krypton. This dose level seems inadvisable. Other nuclides, such as xenon-133, would be more suitable.

SUMMARY

The logarithmic form of the three krypton cardiograms in Figs. 2, 3 and 4 shows the normal sedentary subject with an intercept of about 20% of the total, while the patient with moderate angina reaches 55% and the severe angina patient a level of 80%. If the normal coronary flow is about 5%,[4] the above values should be divided by some factor of approximately 4. This interpretation of the experimental radiocardiogram suggests that a diseased heart receives, as coronary flow, a greater fraction of cardiac output than does a normal heart. This picture of a heart which we have clinically referred to as one with coronary insufficiency provokes serious contemplation. It may be suggested that such a diseased myocardium has to have a much larger fraction of the heart output fed to it in order to perform its basic function of maintaining adequate systemic circulation. It is, indeed, departing from the usual concept, formed on the basis of anatomic and pathologic observation, which has led to the belief that narrowed and hardened arteries would be incapable of receiving a larger percentage of the cardiac output. However, speculating further, since we cannot otherwise deny the apparent interpretation of our graph, it does seem, on mechanical grounds, to be logical that a weak or diseased heart must have more energy provided in order to continue its function. Since the blood is the source of this energy, an increased, rather than a decreased coronary flow may be expected until the heart fails. We have planned further study of this in the excised heart, maintained in the Anderson Heart Perfusion Apparatus. In this device, mechanical measurements of cardiac output and coronary flow can be compared with values calculated from the simultaneous radiocardiograms.

This discussion has been confined mainly to assessing the coronary flow obtained from the krypton cardiograms. However, in some 200 cases where patients were examined mostly by the older methyl iodide technique abnormalities were observed in the radiocardiograms of those with valvular and congenital diseases. Identification of these should be possible with further comparative studies with the new techniques on a larger series of patients.

At the purely clinical level, we would suggest that inhalation radiocardiography may prove of greatest value in comparative studies of heart function and change in response to specific heart therapy. There is, we think, a precedent for this suggestion as we are aware of the increased value of the electrocardiogram when serial studies are conducted. Since the inhalation radiocardiogram appears to measure heart function more directly, it is a useful supplement to other diagnostic cardiac tests.

ACKNOWLEDGEMENTS

To Dr. H. G. Thode, the authors express their appreciation for many suggestions and for encouragement in this work. The authors are also indebted to L. R. Murrell and L. Fucikovsky.

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ADDENDUM

Refinements of procedure and equipment now include a Sanborn 4 pen-recorder and electrocardiograph. This has clarified the contribution of lung activity to the observed heart curves.

It was recognized that our interpretation of the second exponential in the descending limb of the krypton cardiograms with the ratio of the intercepts indicating coronary flow was difficult to accept physiologically. The improved instrumentation and increased number of subjects studied have given further understanding of this phenomenon.

In Fig. 5 are shown simultaneous linear iodograms of the upper lobe of the right lung and the heart, using two directional scintillation probes. It may be seen that only in the ascending limb are there essential differences. The initial rise in the heart graph may be seen to result from activity in the lung which is viewed by

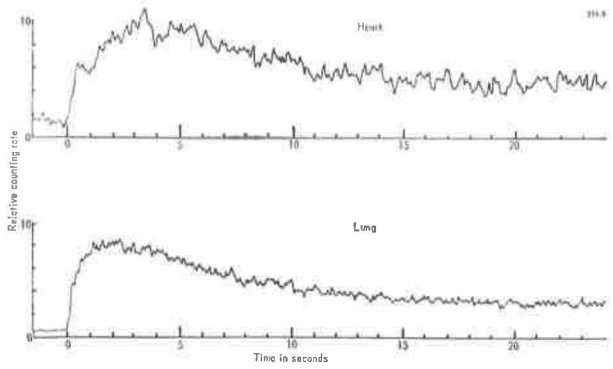

Figure 5

the heart probe. Only the second rise, after appropriate lung-to-heart delay, can be associated with heart function. The descending limbs of the heart and lung curves are similar so that a second exponential, if present, is hidden by the lung contribution.

Simultaneous kryptongrams, heart above lung, are seen in Fig. 6. The krypton-85 reaches a maximum in the lung in the incredibly short time of ¼ second, where it remains at constant levels during successive inspirations, but diminishes with each exhalation. On the ascending limb of the heart curve (upper graph), only the first half follows the lung curve; at this time the tracer begins to appear in the heart and the radioactivity increases more slowly during the next one second. The successive heart–lung changes are seen in the descending limbs—horizontal lines are drawn to accent this controlled comparison. (Note the lag in fall-off of activity from the heart after the earlier decline in lung curve during expiration.)

Methyl-radioiodide and krypton-85 have given useful but limited information in these preliminary studies. The experience gained, the improved tracer preparation and new instrumentation suggest that we will use higher efficiency gamma-emitting nuclides (e.g., nitrogen, argon and xenon) to obtain more basic and clinical information.

Although it now seems illogical to relate the second exponential in the kryptongrams to coronary flow, nevertheless, as these 'cardiograms and 'pneumograms now stand, the following are factual: (1) The second exponential has, with one exception, been present in our cardiac patients and not in our normals. (2) None of these patients has had any evidence of pulmonary disease or congestion. (3) The graphs obtained are reproducible and estimation by other methods has shown a quantitative relationship between the ratio of the intercepts and the degree of myocardial dysfunction. The 'cardiograms and 'pneumograms undoubtedly reflect some function of these organs, for they have provided additional valuable information about the clinical state of those patients in our series.

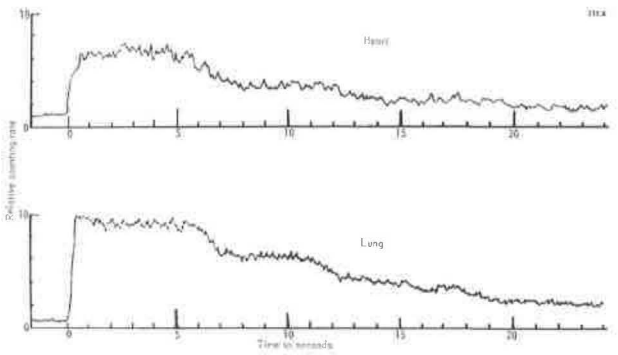

Figure 6

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A New Diagnostic Method in the Study of Congenital Heart Disease: The Krypton-85 Test for Circulatory Shunts

By R. J. Sanders and A. G. Morrow*

The accurate diagnosis and precise localization of congenital intracardiac anomalies has become of increasing importance, as the majority of such lesions are now amenable to complete surgical correction. Common to many types of defects are left–to–right shunts which result when an abnormal communication between the cardiac chambers or great vessels permits fully oxygenated blood from the left heart to mix with the less saturated blood in the right heart or pulmonary artery. The standard method for detecting left–to–right shunts takes advantage of the normal difference in oxygen content which exists in blood from the left and right sides of the heart. When, at cardiac catheterization, the blood oxygen content in the pulmonary artery or a right heart chamber is found to be higher than that in the proximal chamber, the presence of a shunt is suggested. However, inaccuracies and errors are not uncommon with this method since oxygen is a body metabolite and its concentration in venous blood may vary considerably in the course of the test. Furthermore, laminar flow and significant differences in the oxygen content of blood in the inferior and superior vena cava frequently make the accurate determination of the content of mixed venous blood proximal to the right atrium difficult. For example, the content of the oxygen samples obtained during cardiac catheterization in a patient with pulmonic stenosis is presented in Table 1.

Had it been impossible to sample the inferior vena cava (IVC) in this patient, not an uncommon difficulty, the increase in oxygen content from superior vena cava (SVC) into right atrium (RA) would be diagnostic of a left–to–right shunt at this level.

It has been demonstrated with N_2O that shortly after the inhalation of an inert gas, a large arteriovenous difference in gas content exists which is independent of the metabolic state.[1] Studies with radioactive inert gases have revealed that their inhalation results in even larger arteriovenous differences. In addition, the concentration of a radioactive gas in blood can be determined with ease by a Geiger counter, instead of with the laborious manometric methods necessary with N_2O. After preliminary evaluation[2,3] of gases containing I^{131}, Kr^{85} was chosen for experimental evaluation[4] and the present clinical study. Its long half-life (approximately ten years) permits storage with minimal decay, and the fact that it is almost entirely a beta emitter (99.4 per cent) renders it relatively safe for handling by laboratory personnel. The previous clinical application of Kr^{85} in the determination of cerebral blood flow also suggested its use for the purpose described.[5]

When inhalation of Kr^{85} is begun, the concentration of the gas in arterial blood rises rapidly (Fig. 1). In the absence of a left–to–right shunt, the concentration in venous blood, sampled from the pulmonary artery or right heart, does not begin to rise until one circulation has been completed; the rise after this time is slow because the gas is removed from arterial blood by the tissues. As saturation of the tissues is completed, the venous level approaches the arterial one thus diminishing the arteriovenous difference. In Fig. 1, the venous level, as measured in the pulmonary artery, is expressed as a percentage of the corresponding arterial level at 15-second intervals. The pulmonary arterial sample at 15 seconds is only one per cent of the systemic arterial sample, but by 60 seconds it has risen to 26 per cent of the arterial concentration.

In the presence of a left–to–right shunt, pulmonary arterial or right heart blood becomes mixed with shunted blood containing large amounts of Kr^{85}. Thus, when blood is sampled distal to the shunt, it is found to contain radioactivity almost immediately after the onset of Kr^{85} inhalation (Fig. 2). To determine the presence or absence of a shunt, samples are drawn simultaneously from the pulmonary artery or right heart during the first 30 seconds of inhalation. The ratio of the radioactivity of pulmonary arterial or right heart blood to systemic arterial blood thus reliably indicates the presence of a shunt and its magnitude.

METHOD

Kr^{85} was administered to 36 patients with proved left–to–right shunts, and to 45 patients without shunts who served as controls. A total of 132 tests was performed. In each patient, routine right heart catheterization was carried out through an antecubital or saphenous vein. Under fluoroscopic control, the tip of

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Table 1. Oxygen Samples (in vol per cent)
Patient with Pulmonic Stenosis and No Shunt

IVC	*SVC*	*RA*	*RV*	*PA*
18.4	14.9	14.1	17.1	17.3
18.5	15.2	17.3	17.2	17.3
		17.4	17.3	17.3

IVC = Inferior vena cava
SVC = Superior vena cava
RA = Right atrium
RV = Right ventricle
PA = Pulmonary artery

the catheter was first positioned in the main pulmonary artery. A needle was inserted into a femoral or brachial artery. The patient was then ventilated for 30 seconds with a mixture of air containing 0.1 to 0.4 mc Kr^{85} per liter. The gas was administered from either a spirometer or a compression cylinder† through a closed breathing system which included a three-way valve, a mask or mouthpiece, a nose clip, and a collection bag. If awake, the patient was instructed to breathe deeply and rapidly; if under anesthesia, the patient was hyperventilated by the anesthetist with a breathing bag previously inserted into the system. Blood samples were drawn simultaneously from the needle and the catheter between the 10th and 30th seconds of Kr^{85} inhalation. When the results of a test were considered inconclusive, it was repeated with an earlier sampling interval, during the 10- to 20-second period of inhalation. In an occasional patient with a very prolonged circulation time, the arterial sample obtained during the 10- to 30-second sampling period did not contain an adequate Kr^{85} concentration and the test was repeated with a later sampling period.

Blood samples of 2 cc were drawn into 10 cc oiled, heparinized syringes and analyzed immediately. Because krypton is far more soluble in air than blood, the gas was extracted from the blood in the following manner: 2 cc of air were drawn into each syringe and the syringes capped; the barrel of the syringe was pulled back to place the blood under reduced pressure, and the syringes were agitated by hand for one minute. The air, which then contained most of the Kr^{85}, was injected into a continuous gas-flow counter‡ and counted for one minute on a standard scaler. The sample was then washed from the counting chamber by applying gentle suction or compressed air for 5 or 10 seconds.

If the results of the pulmonary artery test indicated the absence of a left–to–right shunt, no further tests were done; if equivocal, the test was repeated with an earlier sampling period. If the test was positive, the shunt was localized by withdrawing the catheter and repeating tests in the right ventricle and right atrium. Following each test, the patient exhaled into a collection bag for five minutes. The bag was later emptied into a ventilated hood. Since Kr^{85} desaturation is more

† Obtained from New England Nuclear Corp., Boston, Massachusetts.

‡ From the Nuclear Corp. of America, Brooklyn, New York.

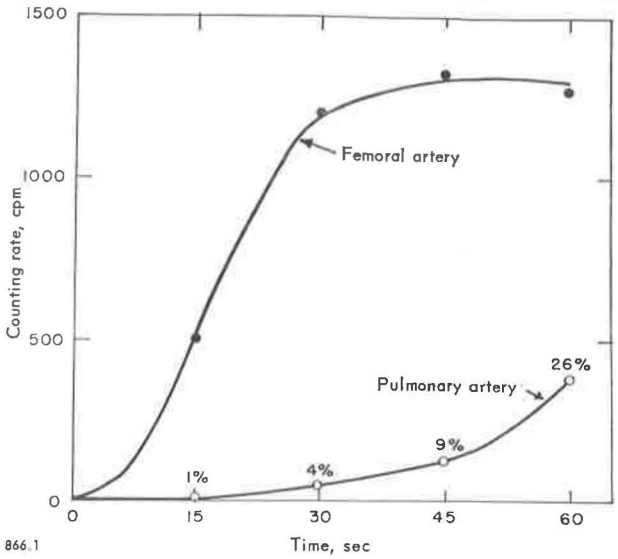

Figure 1. Concentrations in systemic arterial and mixed venous (pulmonary arterial) blood in a normal subject during inhalation of Kr^{85} (0.1 mc per liter). Percentages represent the ratio of venous to arterial concentration at the indicated intervals

than 90 per cent complete within five minutes, repeat tests were performed after this time. A blank sample was obtained from the catheter immediately prior to each test, and its value subtracted from that of each sample.

The procedure was carried out in a well ventilated room with an end-window Geiger-Muller tube and count-rate meter monitoring the atmosphere. Frequently, following each test, the radioactivity in the room increased several-fold, but only rarely did it exceed the recommended maximal permissible concentration recommended by the AEC. The rise in radioactivity in the room was presumably due to leaks in

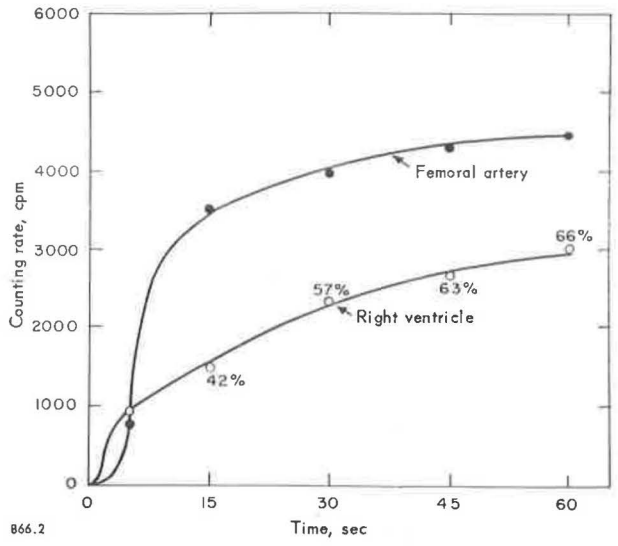

Figure 2. Concentration in systemic arterial and right ventricular blood following the inhalation of Kr^{85} (0.4 mc per liter) in a patient with atrial septal defect. Kr^{85} appears immediately in right heart blood and the ratio of the concentration in right ventricular blood to that in arterial blood is always high

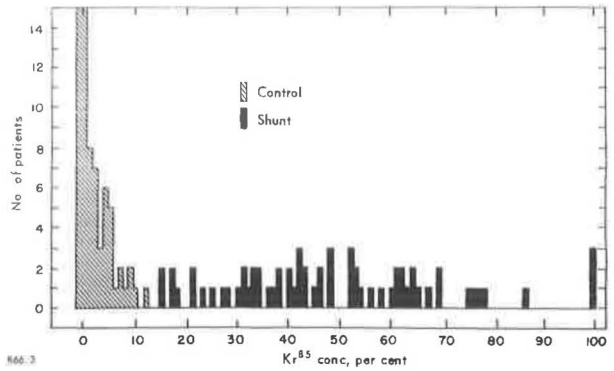

Figure 3. Results of Kr^{85} tests, 67 in control and 65 in shunt patients. The pulmonary artery (PA), right ventricular (RV) and right atrial (RA) Kr^{85} concentrations are expressed as percentages of their corresponding arterial (A) concentrations

$$\%\left(\frac{PA}{A}, \frac{RV}{A}, \frac{RA}{A} \times 100\right)$$

the breathing system, probably around the mask, mouthpiece or nose clip. However, the normal background count within the room was restored within 20 to 40 minutes. A hood has recently been installed over the catheterization table to further improve the rapid removal of contaminated air from the laboratory.

The tissue receiving the maximum amount of irradiation during the study is the trachea. The total exposure to this organ, following two minutes of inhalation of Kr^{85} in a concentration of 0.4 mc per liter is 0.011 rep.

RESULTS AND DISCUSSION

The results of 132 tests with Kr^{85} are presented in Fig. 3. All 67 tests in control patients gave values for the pulmonary artery or right heart samples that were less than 15 per cent of the corresponding arterial samples. Sixty-five tests were performed in patients with left–to–right shunts and in every instance samples at or beyond the shunt resulted in ratios exceeding 15 per cent. The presence of a shunt was thus established when the ratio of radioactivity in the pulmonary artery or right heart to that in the systemic artery exceeded 15 per cent. Because of possible errors in sampling and analytic technique the criterion for the positive diagnosis of a shunt has been established as 20 per cent or more, and the absence of a shunt is proved by a ratio of 10 per cent or less. Tests resulting in ratios between 10 and 20 per cent are considered inconclusive and should be repeated with an earlier sampling time.

In addition to localizing a left–to–right shunt, the results of the Kr^{85} test may also be used to determine its magnitude if blood is obtained from a chamber distal to the shunt so that opportunity is afforded for complete mixing of shunted and systemic blood. In terms of clinical evaluation, ratios of 20 to 40 per cent are associated with small shunts; ratios of 40 to 60 per cent are seen with moderate shunts where the ratio of pulmonary to systemic flow is 1.5 to 2.5:1; ratios exceeding 60 per cent are associated with large shunts. It is assumed that quantification of the magnitude of a shunt by the mixing formulae described for the N_2O test[6] will also apply with Kr^{85}, and such studies are now in progress.

In 52 patients, blood samples for oxygen determinations were also drawn during the same catheterization at which Kr^{85} tests were performed. A basis was thus provided for comparative evaluation of the two methods.

An example of such comparative data in a child with an interatrial septal defect is shown in Table 2.

From the O_2 samples in this patient it was impossible to establish the correct diagnosis. The high samples in the right atrium, as in the patient referred to in Table 1, could have represented sampling of a stream containing predominately inferior vena caval blood. Furthermore, even if the inferior caval samples were ignored, the over-all oxygen increase between superior caval and pulmonary arterial blood was only 0.8 vol per cent, not considered diagnostic of a shunt. The Kr^{85} test of 19 per cent in the pulmonary artery suggested a small shunt, and the right ventricular test was clearly positive. The large discrepancy between the two ratios could be explained by poor mixing of blood in the right ventricle. The right atrial test of over 100 per cent suggested that the catheter tip slipped into the left atrium during the test. The fact that the ratio exceeded 100 per cent was attributable to the delay of the circulation time since the Kr^{85} content of left atrial blood must exceed that of peripheral arterial blood when the levels are rising. At operation, this child was found to have an atrial septal defect measuring 2×3 cm.

Table 2. Atrial Septal Defect (comparative data)

Oxygen samples (vol per cent)

IVC	*SVC*	*RA*	*RV*	*PA*
15.9	13.5	13.0	14.6	14.4
16.0	13.8	15.9	14.7	14.8
		16.1	14.9	

Average oxygen values (vol per cent)

MVC[a]	*RA*	*RV*	*PA*
15.2	14.4	14.7	14.6

Kr^{85} tests

$$PA = \frac{PA}{A} = \frac{600}{3100} = 19\%$$

$$RV = \frac{RV}{A} = \frac{800}{1700} = 47\%$$

$$RA = \frac{RA}{A} = \frac{1000}{600} = >100\%$$

[a] Mixed caval O_2 values (MCV) were determined by weighting the inferior caval samples (IVC) as twice the superior caval samples (SVC). A = peripheral artery.

Table 3. Normal Patient

Oxygen samples (vol per cent)				
IVC	*SVC*	*RA*	*RV*	*PA*
13.0	11.7	10.3	12.9	11.7
13.8	12.3	12.2	13.0	12.0
		12.4	13.8	
Average oxygen values (vol per cent)				
MVC		*RA*	*RV*	*PA*
12.9		11.7	13.2	11.9
Kr^{85} test				
$PA = \frac{PA}{A} = \frac{141}{1500} = 9\%$				
N_2O test				
$PA = \frac{PA}{A} = \frac{0.64}{9.35} = 7\%$				

Table 3 presents the catheterization findings in a patient who proved not to have a shunt.

The large rise in O_2 content of the right ventricular samples suggested the presence of a small ventricular septal defect, but the decrease in the pulmonary artery made this diagnosis questionable. The pulmonary artery Kr^{85} test, however, was clearly negative. It should be noted that with only two blood samples the Kr^{85} test proved the absence of a shunt, while the 12 samples drawn for oxygen determinations yielded only inconclusive data. The nitrous oxide test was also performed in this patient and further confirmed the absence of a shunt.

The results in all of the patients in whom both tests were carried out are summarized in Table 4.

Table 4. Results in 52 Patients Having Both Tests

Patients	*No. having both tests*	*Oxygen errors*	*Kr^{85} errors*
With shunts	30	5	0
Controls	22	1	0
Totals	52	6	0

Among a total of 52 tests, there were six errors by the oxygen method, and none with the Kr^{85} test. In two patients with shunts, however, the krypton ratios were 16 per cent and 18 per cent, and therefore repeat tests were required.

An important additional advantage of the Kr^{85} method is that the results of the test are available within a few minutes, while the catheter is still in place. The results of manometric or spectrophotometric determinations of blood O_2 content are usually not available until after completion of the catheterization. When the results of a Kr^{85} test are inconclusive, or the arterial level is less than the required ten times background count, the test is able to be repeated and the diagnosis made certain before the patient leaves the laboratory.

SUMMARY

A new method is presented for determining the presence or absence of a left–to–right circulatory shunt in patients with congenital heart disease. In the course of right heart catheterization, patients inhaled a mixture of Kr^{85} and air for 30 seconds, as blood samples were drawn simultaneously from the pulmonary artery and from a systemic artery. It was found that when the radioactivity of pulmonary arterial blood was more than 20 per cent of the systemic arterial level, the diagnosis of a shunt could be made; when less than 10 per cent, the absence of a shunt was confirmed. Tests between 10 and 20 per cent were considered inconclusive and were repeated. The blood samples were analyzed with a gas-flow counter and scaler, and the results were available within five minutes. When the pulmonary artery test was positive, the test was repeated in the right ventricle and right atrium to localize the shunt. The advantages of the Kr^{85} test over the method employing blood oxygen differences was demonstrated in 52 patients studied by both methods. There were six diagnostic errors with the oxygen method and none with Kr^{85}.

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The Preparation and Use of Oxygen-15 with Particular Reference to Its Value in the Study of Pulmonary Malfunction

By N. A. Dyson,* P. Hugh-Jones,† G. R. Newbery* and J. B. West†

The short-lived radioactive isotope oxygen-15 potentially offers a safe and direct tracer method of studying both the intake of oxygen on inspiration and its clearance by the blood, in small regional volumes of lung.

Hitherto, bronchospirometry has been almost the only method of comparing gas exchange in different regions of the lungs. But, since it entails the passing of catheters into the bronchi under local anaesthesia, so that the gas can be collected, it is unpleasant for the patient and the conditions are hardly physiological. Moreover, only a comparison of the whole of one lung with the other is usually practicable. Thus the use of oxygen-15 could be an important advance.

Oxygen-15 is the longest-lived radioactive isotope of oxygen, yet it has a half-life of only two minutes. This short half-life means that a number of tests can be done serially with no residual activity, and it also means that the isotope must be prepared close to the patient. The cyclotron recently built by the Medical Research Council[1] was sited within a hospital for a number of reasons, one of which was to make available for medical research a further range of radioactive isotopes, beyond those obtainable from reactors, and particularly those with very short half-lives.

In common with many cyclotron-produced isotopes, oxygen-15 decays by positron emission and consequently the annihilation gamma radiation from the lungs may be measured by external scintillation counters. By using pairs of counters connected in coincidence, the volumes examined may be restricted to small cylindrical cores through the lungs.

Oxygen-15 has now been prepared at Hammersmith Hospital by bombardment of atmospheric nitrogen with the external deuteron beam from the Medical Research Council cyclotron. This paper describes the method of preparation and gives details of a preliminary investigation of its value for comparing the function of one part of the lung with another. The results are encouraging and the investigation is continuing.

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PHYSIOLOGICAL PRINCIPLES

The initial counting rate, after inspiration of oxygen-15 labelled air, is a measure of the intake of active gas to the part of the lung under examination and is almost proportional to the regional ventilation. The subsequent fall in the counting rate, due to clearance of oxygen-15 into the bloodstream during breath-holding, is chiefly determined by the regional blood flow.

Factors Affecting Initial Counting Rate

The counting rate is determined by the alveolar volume from which radiation is detected and by the ventilation of that volume. With the coincidence-counting method described in a later section, 95% of the counts come from a core of tissue 3.8 cm in diameter. The length of the core depends on the position of the counters over the thoracic cage. In the mid-zone of the lung fields it is about 20 cm, so that the volume of lung examined is some 225 cm^3. In comparing the ventilation of one side with the other, it is important to allow for any difference in anteroposterior measurements. In particular, when the counters are near the edge of the lung, small lateral movements of the subject will cause large variations in the volume being examined.

Large blood vessels in the core under examination will reduce the alveolar volume. Blood in the pulmonary artery will have no activity until recirculation of the oxygen-15 occurs, while the activity of the blood in the pulmonary vein is likely to be about 20% of that of the alveolar gas, volume for volume. The figure 20% arises because a litre of alveolar gas contains about 20% of oxygen, volume by volume, and a litre of blood has an oxygen capacity of about 200 ml, but of this only 20% will have been added in one passage through the lung.

For an observed volume of lung, the initial counting rate can be shown to be nearly proportional to the ventilation expressed as the volume of fresh gas (not dead space gas) entering a unit alveolar volume per breath. Strict proportionality is not achieved for two reasons. First, if anatomical dead space gas is preferentially distributed to some alveoli causing them to be poorly ventilated, as has been suggested,[2] the counting rate is reduced more than the ventilation. Secondly,

if anatomical dead space gas is evenly distributed, the counting rate and the ventilation are hyperbolically related, though the departure from a straight line is slight within the likely range of ventilation. These errors are relatively small and are in opposite directions, so that when comparing equal volumes of lung, the ventilation can be taken as proportional to the initial counting rate.

Ideally, the volume of the test inspiration should be the same as the normal volume used in resting ventilation. In practice it is difficult to ensure this, and a larger fixed inspiratory volume of one litre has been adopted. It is possible that the compliance of some parts of the lung is changed when the inspiratory volume is increased to this extent, and an error in the comparison of resting ventilations in different parts of the lung may be introduced.

Factors Affecting the Fall in Counting Rate

Oxygen-15 is removed from the lung by the pulmonary blood during breath-holding. In normal subjects the clearance rate from unit volume is nearly proportional to the perfusion (local blood flow) in litres per minute. The expected rate of fall of activity (after correcting for the natural decay) can be calculated from the resting oxygen consumption (about 300–400 ml/min) and the alveolar gas volume (about 2.5–3 litres). It is about 1.2 to 1.9% per second.

Several factors will modify this rate of fall. First, it will not remain constant as the alveolar oxygen concentration is reduced. However, the change is small because of the shallow slope of the oxygen dissociation curve in this range. Thus, assuming an oxygen saturation in the mixed venous blood of 75%, a reduction of alveolar oxygen tension from 100 to 75 mm (equivalent to about 15 seconds of breath-holding) will reduce the arterio-venous difference by only 4 volumes in 22, a reduction of about 20% in the rate of fall. Secondly, the perfusion will probably be altered during the breath-holding period. Holding the breath against a closed glottis is a Valsalva manoeuvre which will temporarily reduce the cardiac output. Thirdly, some 10 seconds after the beginning of inspiration, oxygen-15 will reappear in the pulmonary arterial blood thus reducing the observed rate of fall of activity. Utilisation of oxygen-15 by lung tissue oxidation and subsequent diffusion of the tagged water results in a negligible loss of activity during the period that the breath is held.

In abnormal subjects the clearance rate may be affected by two other factors. When the local alveolar oxygen tension is low, the arterio-venous difference is reduced to an extent determined by the oxygen dissociation curve. The local alveolar oxygen tension is determined by the ventilation-perfusion ratio so that the clearance rate is influenced by the ventilation. However, an abnormal ventilation-perfusion ratio alone will not introduce a large error. Thus, for typical conditions, a ventilation-perfusion ratio of one-half normal will reduce the arterio-venous difference by 5 volumes in 22,[3] causing a reduction of about 20% in the clearance rate. The reduction will become more marked during the breath-holding period.

The presence of a diffusion defect will also reduce the rate of oxygen removal. Again the effect of this alone is small; a fall in the diffusing capacity for oxygen to half the normal value will introduce an alveolar-end-capillary gradient of less than 5 mm Hg which will reduce the clearance rate by about 5%. However, an abnormally low ventilation-perfusion ratio in the presence of a diffusion defect will result in a marked underestimate of the perfusion as measured by the oxygen-15 clearance rate. For example, in a region in which both the ventilation-perfusion ratio and the diffusing capacity are reduced to one-half the normal value, there will be a reduction in clearance rate of up to 50%.

It would be possible to eliminate these two factors by using, instead of air, an oxygen-enriched mixture as the inspired gas. The resultant increase in alveolar oxygen tension would then be sufficient to raise the clearance rate to the normal value for the prevailing perfusion. Several minutes of breathing a similar inactive mixture would be essential to ensure that the subject was in a steady state. However, the measurement of clearance rate under nearly physiological conditions is in many ways more informative than a measurement of perfusion alone, since the former indicates the over-all performance of part of the lung in transferring oxygen to the blood.

PREPARATION AND ADMINISTRATION

A continuous flow of air labelled with oxygen-15 is produced by the $N^{14}(d, n)O^{15}$ reaction. Air is pumped through an aluminium target vessel having a thin window and placed in the external beam of 15-Mev deuterons from the cyclotron as shown in Fig. 1. Both

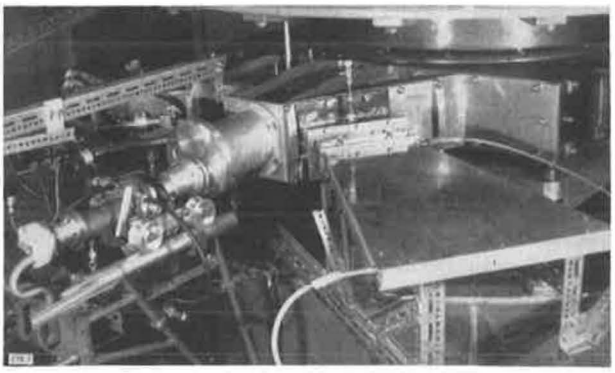

Figure 1. Target vessel for production of oxygen-15 on the cyclotron

open and closed circuits have been used, but the latter is preferred because there is less waste gas to be disposed of and the concentration of oxygen-15 is both increased and also made less sensitive to fluctuations in the deuteron beam current. The disadvantage is that the activity of any long-lived contaminant builds up with time and may have to be removed chemically.

The activity of the bombarded air is observed by passing it through a 500-ml flask in a brass-walled re-

entrant ionization chamber and recording the ionization current. The yields for open and closed circuits are shown in Fig. 2 as functions of total window thickness, and approximate deuteron energy on entering the air inside the target vessel. Beam currents up to 100 μa or more are available but about 20 μa is normally used, giving an activity of about 50 mc/litre in a closed circuit of total volume approximately 20 litres and with a flow rate of about 15 litres/minute.

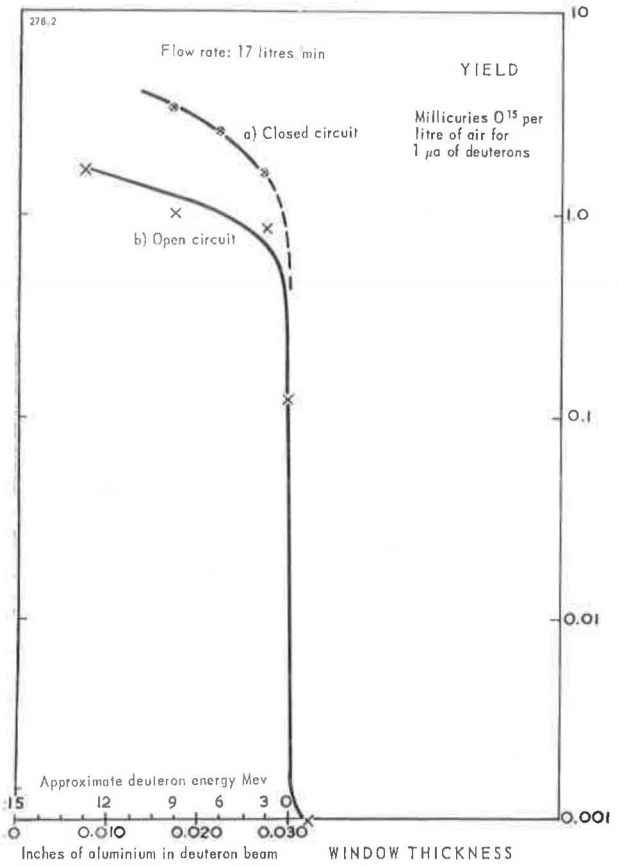

Figure 2. Yield of oxygen-15

For use, the active gas is led out of the circulating system through a control valve and mixed with inactive air to obtain the required concentration, usually about 4 mc/litre at the pumping station, which decays to 2 mc/litre at the clinical investigation room some 30 feet away. All gas flows are measured with rotameters and the flow rate to the clinical room is normally maintained at a fixed value (5 litres/minute) to keep the transit time constant between the two rooms. The activity is monitored at the pumping station and at the clinical room. The latter monitor is calibrated by collecting a sample of the final gas and observing the response due to it in the re-entrant ionization chamber, relative to a standard radium tube. Oxygen-15 decays entirely by positron emission to the ground state of nitrogen-15, and the specific γ-ray emission is 6.0 r/hour mc at 1 cm.

After final monitoring the gas is fed into a recording spirometer and then to waste. The patient takes a single breath from the spirometer through large-bore tubing with suitable valves and diaphragms (see Fig. 12). These enable the patient to breath air normally; then during an expiration the system can be flushed with active air so that on the subsequent inspiration the patient takes in up to a litre of the active air. He then holds his breath for about 10 seconds, after which he breathes normally, the expired active air being taken to waste.

Contaminants

The decay of a sample of active air prepared with a closed circuit and a total window thickness of 0.0175 in. aluminium is shown in Fig. 3. Relative to the oxygen activity there is nearly 4% of another isotope with a half-life of 20 minutes, which is attributed to carbon-11 produced by the $N^{14}(d, n\alpha)$ reaction.

The carbon-11 activity was found to be only partially removed when the gas was passed through caustic soda or over soda lime to remove $C^{11}O_2$. The remaining activity was not removed by a series of liquid air traps, but by passing the gas over heated cupric oxide or manganese dioxide to convert $C^{11}O$ to $C^{11}O_2$ and then through a second soda lime tube, it was possible to remove it completely. The decay curve is then as in Fig. 4, from which it can be seen that there is present another isotope of about 1% of the oxygen activity and with a half-life of 10 minutes. This is presumably nitrogen-13, produced by the reaction $O^{16}(d, n\alpha)$. A liquid air trap prior to the heated manganese dioxide collected a small amount of 10-minute activity but most passed through, so the nitrogen-13 is probably present as molecular nitrogen. There is also a fraction of a per cent of a longer-lived activity with a half-life of about 2 hours. This was at first thought to be fluorine-18 but γ-ray spectroscopy showed a γ line at 1.3 Mev and hence it is most probably argon-41, produced either by $A^{40}(d, p)$ or by $A^{40}(n, \gamma)$ reactions.

In order to remove ozone and oxides of nitrogen, an unheated manganese dioxide filled tube was added before the main purification system. All connectors and tubing are of glass, PVC or polythene, as rubber perishes rapidly when exposed to the ozone. It was also found that water condensed in the rotameters although the incoming air was dried by passage through a long tube containing silica gel. Additional silica gel tubes were therefore inserted in the system to remove water vapour. Finally, the outgoing low activity gas is passed over activated charcoal to remove any unpalatable vapour such as decomposed glycerine lubricant from the final pump. The over-all system as first used is shown diagrammatically in Fig. 5 and decay curves of the gas as administered to the patient are shown in Fig. 6. These curves were obtained with a pair of scintillation counters connected in parallel and in coincidence, and demonstrate that the 10-minute activity is due to a positron-emitting isotope and that the longer-lived contaminant is not. This supports the view that these activities are nitrogen-13 and argon-41.

Several runs were made with additional thicknesses

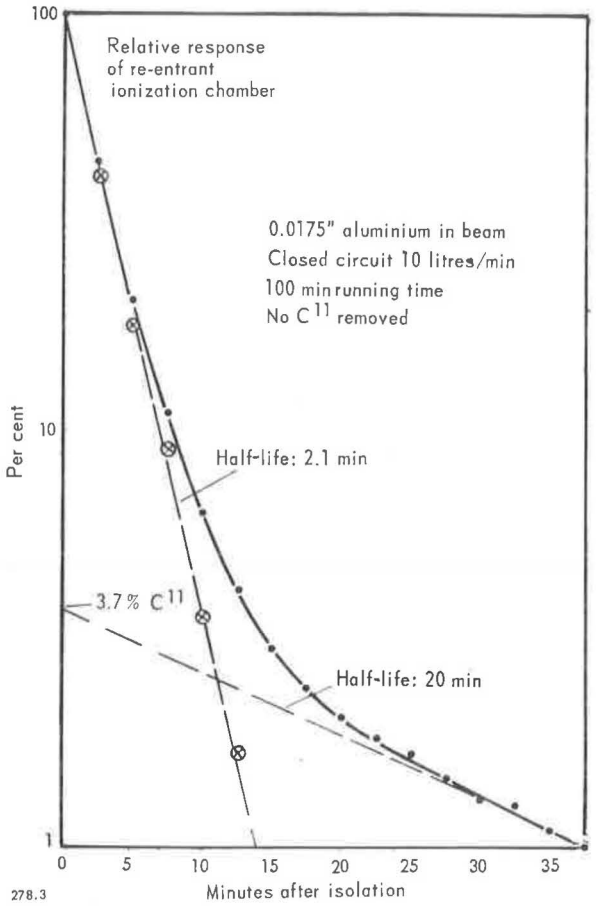

Figure 3. Decay curve of oxygen-15 sample

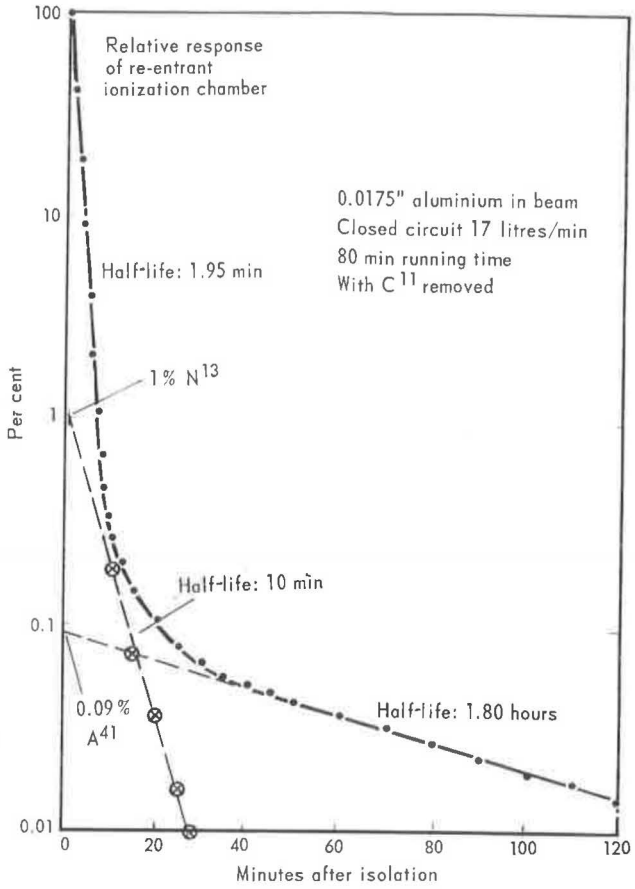

Figure 4. Decay curve of oxygen-15 sample with carbon-11 removed

of aluminium between the outlet window (0.0025 in. aluminium) of the cyclotron and the window (0.005 in. aluminium) of the target vessel. The amount of carbon-11 contamination present decreases with increasing thickness and most of the clinical work has been done with a total thickness of 0.0225 in. aluminium in the beam. This thickness does not completely remove the contaminating carbon-11 activity and chemical purification is still necessary. Recently 0.0275 in. aluminium has been tried and it was found that the yield of oxygen-15 is still very high as shown in Fig. 2 and that the contaminating carbon-11 and nitrogen-13 are eliminated in accordance with the thresholds of the (d, nα) reactions (5 and 7 Mev). The argon-41 remains, as can be seen in Fig. 7. The full theoretical range[4] of 15-Mev deuterons in aluminium is 0.0295 in. and the residual energy of the deuterons after passing through 0.0275 in. is approximately 3 Mev, which is therefore about the optimum for the production of pure oxygen-15. This means that lower-energy machines could be satisfactorily used for oxygen-15 production. When 2-Mev deuterons from the M.R.C. electrostatic generator are passed through the necessary windows they do not, however, give a very high yield.[5] In practice, on the M.R.C. cyclotron, magnesium is used in lieu of aluminium for slowing down the deuterons, in order to produce sodium-22 as a by-product from the reaction Mg^{24}(d, α)Na^{22}.

The mean value of five observations of the half-life of oxygen-15, each over at least three decades of activity, is 2.05 minutes with a standard error of 0.035 minute. It has been taken as 125 seconds for the calculations of absorbed dose, and for correcting clearance rate observations for radioactive decay.

ABSORBED DOSES OF RADIATION

In order to assess the radiation hazard associated with this test, it is important to know the absorbed doses in lung tissue, in blood and at the gonads, per breath of gas of known activity (G mc/litre) and volume (V litres). The effect of contaminant activities must be considered and a simple formula for calculating the total absorbed dose while the test is being carried out would be of great value.

For the purpose of calculating absorbed doses, it may be assumed that the whole of the activity appears instantaneously in the lungs on inspiration. This activity then decays because of clearance by the blood, radioactive decay and wash-out after normal breathing recommences. This decay will not be a single exponential process, but in practice it is possible, for the present purpose, to match an exponential decay (half-life τ sec) sufficiently accurately to the observed decay. The activity in the blood will increase because of transfer from the lungs (at a rate of p per second),

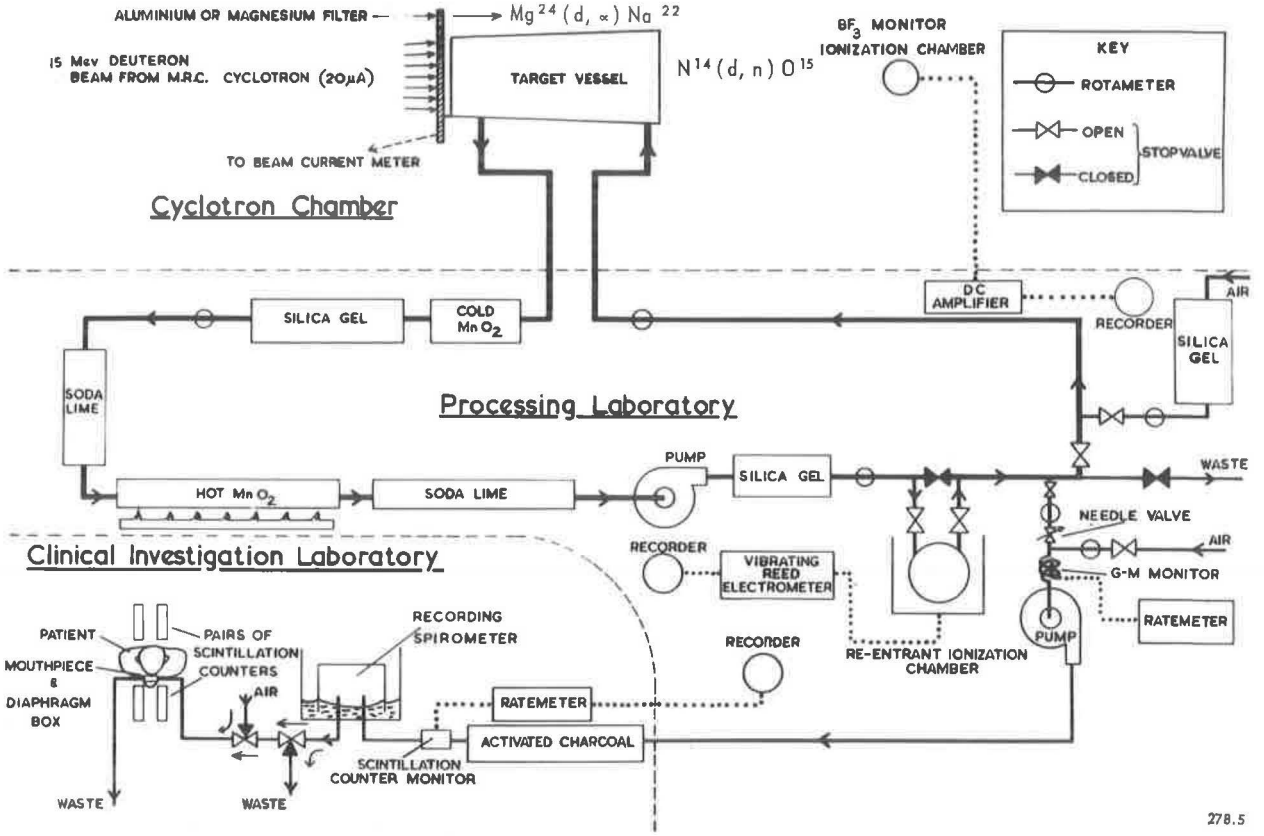

Figure 5. Over-all system for preparation of oxygen-15

but at the same time activity will be lost by transfer to body tissues (at a rate of q per second), and by radioactive decay (physical half-life t seconds). The effective half-life of this decay will be θ seconds, where

$$\frac{1}{\theta} = \frac{1}{t} + \frac{q}{0.693}.$$

Absorbed Dose in Lungs

β-Ray Dose

The usual formula[6] for β-ray dose (D_β) to a medium containing a uniformly distributed activity and of dimensions large compared with the maximum β-particle range, as applied to this case, is

$$D_\beta = 0.854\overline{E}_\beta \frac{GV}{M}\tau \times 10^3 \text{ millirads},$$

where $\overline{E}_\beta$ is the mean β-particle energy (Mev),
M is the mass of the lungs, which to a first approximation may be taken from the standard man (1953)[7] as 1000 g. for all patients. More accurately it could be assumed to be proportional to body weight.

For oxygen-15,

$\overline{E}_\beta = 0.7$ Mev, so
$D_\beta = 0.60\, GV\tau$ millirads.

For nitrogen-13,

$\overline{E}_\beta = 0.5$ Mev, and assuming an activity of 3% of that of the O^{15} (see Fig. 6),
$D_\beta = 0.013GV\tau$ millirads.

For argon-41,

$\overline{E}_\beta = 0.5$ Mev, and assuming an activity of 0.2% of that of the O^{15} (see Fig. 6),
$D_\beta = 0.0008GV\tau$ millirads.

γ-Ray Dose

Assuming uniform distribution of activity in tissue of uniform composition (density $\rho = 0.3$ g/cm³) the usual formula[6] for γ-ray dose (D_γ) is

$$D_\gamma = 0.372 \frac{GV}{M}\tau\rho kg \text{ millirads},$$

where k is the specific γ-ray emission (r/hour mc at 1 cm),
g is a geometrical factor, which may include the effect of tissue absorption (cm).

For the lungs it is reasonable to use the value of g for the centre of a sphere of 20 cm diameter, neglecting absorption, i.e., 126 cm.[6] This will give the maximum value of the absorbed dose in the lungs.

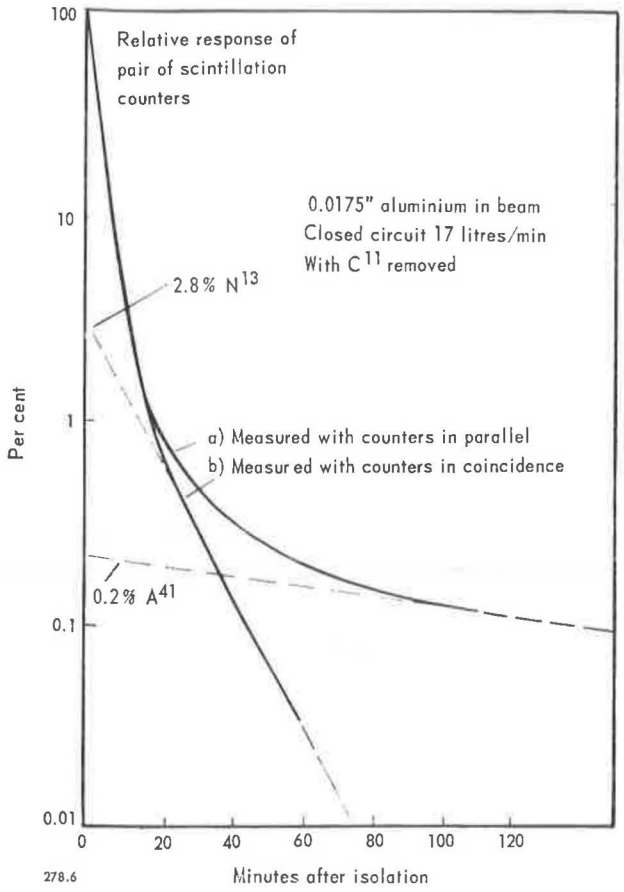

Figure 6. Decay curve of oxygen-15 sample as administered to patient

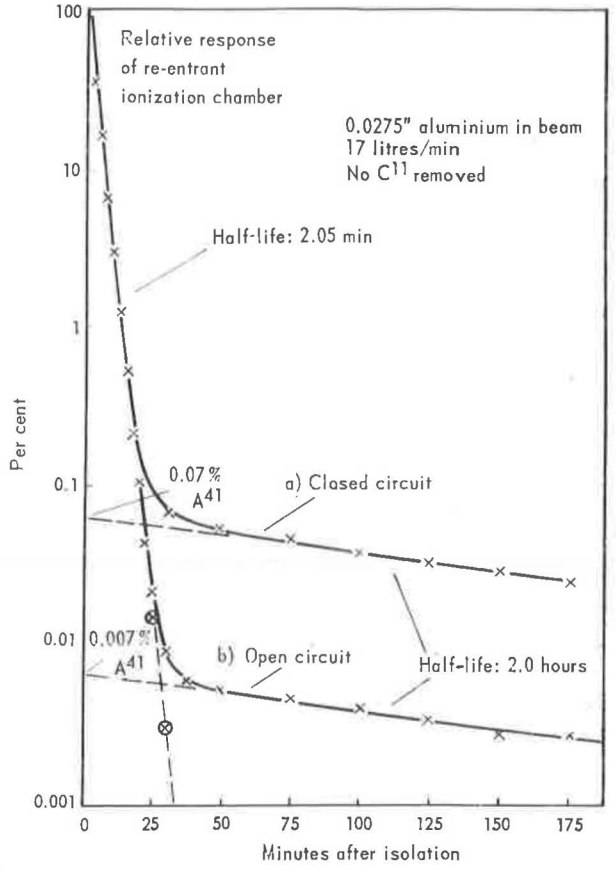

Figure 7. Decay curve of oxygen-15 sample with increased beam filtration

For oxygen-15,

k = 6.0 r/hour mc at 1 cm, so
$D_\gamma = 0.084GV\tau$ millirads.

For nitrogen-13,

k = 6.0 r/hour mc at 1 cm, so
$D_\gamma = 0.002GV\tau$ millirads.

For argon-41,

k = 7.1 r/hour mc at 1 cm, so
$D_\gamma = 0.0002GV\tau$ millirads.

Absorbed Dose in Blood

β-Ray Dose

It can be shown that the maximum β-ray dose to the blood will be given by

$$D_\beta = 1.24\bar{E}_\beta \frac{GV}{M} \tau p\theta \times 10^3 \text{ millirads.}$$

Factor p can be deduced from the counting records and for normal patients is about 0.015 per second. If it is assumed that 300 ml of oxygen are used by the body per minute, that the total blood volume is 5 litres (mass 5400 g) and that the blood carries 160 ml of oxygen per litre (at a mean saturation of 80%) then q is 0.006 per second.

For oxygen-15,

t = 125 seconds, θ = 60 seconds, so
$D_\beta = 0.15GV\tau$ millirads.

For nitrogen-13,

t = 600 seconds, θ = 97 seconds, so
$D_\beta = 0.006GV\tau$ millirads.

For argon-41,

t = 1.8 hours, θ = 114 seconds, so
$D_\beta = 0.004GV\tau$ millirads.

γ-Ray Dose

The absorbed dose due to γ rays arising in the blood itself will be small, but the γ-ray dose may still be appreciable because of γ rays arising from all over the body. The maximum value will be the same as that derived under gonad dose.

Absorbed Dose in Gonads

β-Ray Dose

This is not easy to calculate exactly but will probably not be greater than the maximum β-ray dose to

an intimate combination of blood and tissue in which the activity decays with the physical half-life of the isotope. In this case M is 70,000 g, and

$$D_\beta = 1.24\bar{E}_\beta \frac{GV}{M} \tau pt \times 10^3 \text{ millirads.}$$

For oxygen-15,

$$D_\beta = 0.023GV\tau \text{ millirads.}$$

For nitrogen-13,

$$D_\beta = 0.0023GV\tau \text{ millirads.}$$

For argon-41,

$$D_\beta = 0.0017GV\tau \text{ millirads.}$$

γ-Ray Dose

The γ-ray dose will vary throughout the body, but the maximum value will be given by taking g as 180 cm.[6] Such a value will be a fair estimate of the γ-ray dose to the ovaries, but is probably an overestimate of the male gonad dose. Assuming that the activity in the blood and the rest of the body tissue (of unit density) both contribute to the γ-ray dose, then

$$D_\gamma = 0.54 \frac{GV}{M} \tau tp\rho kg \text{ millirads.}$$

For oxygen-15,

$$D_\gamma = 0.015GV\tau \text{ millirads.}$$

For nitrogen-13,

$$D_\gamma = 0.002GV\tau \text{ millirads.}$$

For argon-41,

$$D_\gamma = 0.002GV\tau \text{ millirads.}$$

Values of Absorbed Doses

Typical Patient

If it is assumed that $GV\tau$ is 60 mc sec for a typical patient (G = 2 mc/litre, V = 1 litre, τ = 30 sec) then the resultant doses are as in Table 1. From this table it can be seen that

Table 1. Absorbed Doses (millirads) for Typical Patient ($GV\tau$ = 60 mc sec)

Isotope	*Relative activity*	*Radiation*	*Lungs*	*Blood*	*Gonads*
Oxygen-15	100%	β	36.0	9.0	1.38
		γ	5.0	0.90	0.90
Nitrogen-13	3%	β	0.78	0.36	0.14
		γ	0.12	0.12	0.12
Argon-41	0.2%	β	0.05	0.02	0.10
		γ	0.01	0.12	0.12
Total		β	36.83	9.38	1.62
		γ	5.13	1.14	1.14
		β + γ	42.0	10.5	2.8

(*a*) The effect of the contaminants is negligible.

(*b*) The total dose per breath to the gonads does not exceed 3 millirads and hence from the genetic point of view the test is reasonable, bearing in mind that the estimated annual gonad dose due to natural radiation is 95 millirads.[8]

(*c*) The maximum absorbed dose in lung tissue is about 40 millirads per breath and in the blood 10 millirads per breath, so that the number of breaths allowed to any patient must be kept to the minimum compatible with the obtaining of useful results.

(*d*) The absorbed dose in lung tissue or blood is largely due to β rays.

(*e*) An approximate formula for the maximum absorbed dose in the lung tissue is

$$D = 0.7GV\tau \text{ millirads per breath.}$$

The integral absorbed dose to the lungs is not more than 42 gram-rads and, to the rest of the body, not more than 250 gram-rads. The total integral absorbed dose is therefore not more than 300 gram-rads per breath.

Actual Patients

Using the approximate formula given above, the maximum absorbed doses in lung tissue for 11 patients actually receiving radioactive oxygen have been computed and are shown in Table 2. The average absorbed dose per investigation (330 millirads) is in fact slightly more than that from a chest radiograph[9] and comparable with the weekly maximum permissible dose for occupational exposure (300 millirads).[7] It is appreciably less than that due to normal X-ray screening of the chest.

Table 2. Absorbed Doses for Individual Patients

Patient	*Average absorbed dose to lung tissue per breath (millirads)*	*No. of breaths*	*Total absorbed dose to lung tissue (millirads)*
1	12.5	11	138
2	137	9	1234[a]
3	0.7	11	8[b]
4	39	6	235
5	35	8	281
6	39	7	273
7	37	6	224
8	44	7	306
9	66	4	267
10	50	8	402
11	50	6	302
Average value	46	7.5	330

[a] mc/litre used.
[b] Low inspired volumes.

COUNTING METHODS

General

The essential problem is to observe the radiation from within a defined cylinder of tissue, with an ap-

proximately uniform sensitivity throughout its volume. The use of single counters is of limited value, although of interest in the study of relatively superficial regions. The use of a pair of opposed counters connected in parallel offers the possibility of as uniform a response, along the axis of the pair, as may be desired (neglecting for the moment tissue absorption), provided that the counters are sufficiently separated. The problem then becomes one of choosing the best compromise between uniformity of response and a reasonably low absorbed dose of radiation to the patient. Parallel counting suffers from difficulties due to penumbra effects and penetration of the shielding, although the higher counting rates obtainable would be advantageous if adequate spatial resolution could be achieved.

The positron-emitting property of oxygen-15 in principle enables the coincident detection of the annihilation photons to be employed. This is the only method which offers inherently perfect collimation, though at relatively low counting rates. In addition, the effect of background radiation from the spirometer and the tubes carrying the active gas is completely negligible. Radiation from regions surrounding the defined cylinder can only be observed by virtue of the random coincidences produced, and these are always distinguishable from true coincidences by inserting a small delay into one of the pair of counting channels. For these reasons most of the clinical measurements reported below were obtained by this method.

Parallel Counting

For studies of counter response a standard collimator separation of 10 inches was used with a crystal separation of 22 inches. In the clinical work the collimators are brought as close as possible to exclude extraneous radiation and the crystal separation adjusted independently to approximately 22 inches, so that the uniformity of response remains unchanged. The design of the shielding and collimation is shown in Fig. 8.

Isocount curves for parallel counting under these conditions are shown in Fig. 9. For studies of the response in parallel a positron emitter is not needed, and it is convenient to use a small source of caesium-137, yielding gamma radiation with an energy (662 kev) not far removed from that of annihilation radiation (511 kev) so that the crystal sensitivities, collimator efficiencies, etc., will be nearly the same for the two radiations. By comparison with the coincidence

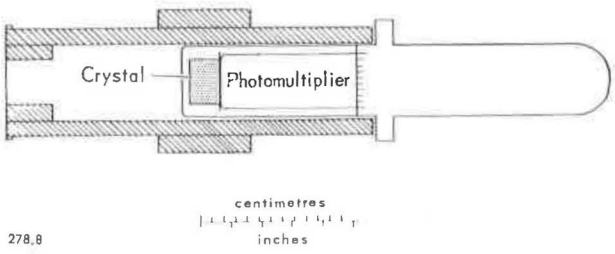

Figure 8. Shielding and collimation of single scintillation counter

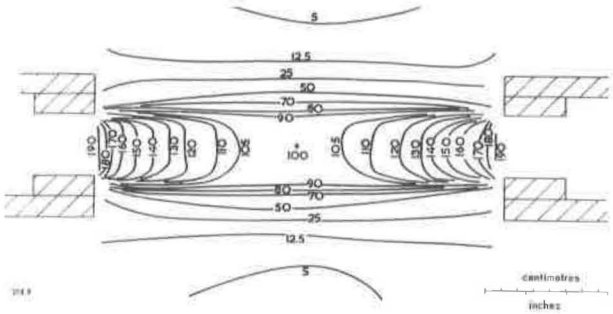

Figure 9. Isocount curves for counters in parallel (crystal separation 22 inches)

curves in Fig. 10, it will be seen that the response along the axis in the parallel case is markedly less uniform. This nonuniformity will be accentuated by tissue absorption, and it will be shown below that the coincidence method is free from this disadvantage.

At first sight it appears that, for parallel counting, collimation is adequate for the present purpose, but on closer analysis, the contributions from the penumbral region and beyond are very significant when considering an extended source filling all the space in the vicinity of the counters. It was found from experiments

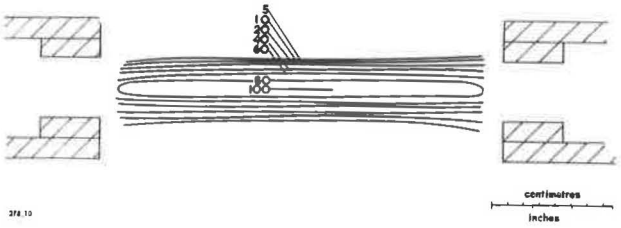

Figure 10. Isocount curves for counters in coincidence (crystal separation 22 inches)

with phantoms that the ability to detect small regions of inactivity is much less than when the coincidence method is used. It seems, however, that the limitation may be essentially a practical one, and recently the spatial resolution has been improved by using a different shape of collimator. These conditions are useful in circumstances where spatial resolution can be relaxed. However, if parallel counting could be developed to give a spatial resolution as good as that obtained by the coincidence method, it appears that the statistical accuracy obtained by the parallel method would be only slightly better than that available with coincidence counting. Therefore, the coincidence method is preferred except when the spatial resolution requirement can be relaxed.

Coincidence Counting

The main difficulty associated with the coincidence method is the correction for the random coincidences which occur when unrelated photons reach the counters. The principles of the coincidence method have been discussed by Brownell and Sweet[10] and applied by them to the localisation of brain tumours, using the positron emitter arsenic-74. In their application

the region of importance was one of increased activity relative to the surrounding tissue. In the present work, the problem of random coincidences is accentuated by the need for studying regions of low activity surrounded on all sides by areas of greater activity from which radiation can readily reach the crystals. Some degree of collimation is therefore particularly important in these circumstances.

Considering first the problem of a point source on the axis, midway between the two crystals, the individual, coincidence and random counting rates are given, respectively, by

$$N_1 = N_2 = 2N\Omega\epsilon, \quad \text{(i)}$$

$$N_C = 2N\Omega\epsilon^2, \quad \text{(ii)}$$

and

$$N_R = 2\sigma \cdot 4N^2\Omega^2\epsilon^2, \quad \text{(iii)}$$

where N is the activity of the source in disintegrations per second, Ω the fractional solid angle subtended by either crystal at the source, ϵ the crystal counting efficiency, and σ the coincidence resolving time. The ratio of real to random counting rates is given by

$$R = 1/4\sigma N\Omega \quad \text{(iv)}$$

and is seen to improve with decreasing N or Ω, ϵ being immaterial. Clearly a decrease of N involves a reduction in the statistical accuracy obtainable in the coincidence counting, and it is necessary to write the real to random ratio in terms, not of the source activity, but of the required coincidence counting rate

$$R = \epsilon^2/2N_C\sigma, \quad \text{(v)}$$

showing immediately the importance of a high detection efficiency.

At first it was thought advisable to use pulse analysers, to select the photoelectric peak only, and to eliminate pulses of reduced heights. In this way the true (but unwanted) coincidences due to scattered radiation can be reduced. But as collimators are in any case necessary to reduce the individual (and hence the random) counting rates, the number of scattered photons reaching the crystals will be reduced. The need for selecting the photoelectric peak is thus lessened. The detection efficiency of each channel can be increased considerably by using the whole of the pulse spectrum from the counters, so pulse analysis is not being used at present.

Random coincidences are usually not negligible, and in such cases measurement of both total and random coincidences is necessary, either simultaneously or in two separate breaths. It can be seen from equations (ii) to (iv) that the random counting rate increases with the square of the activity, whereas the true coincidence rate increases linearly. This involves a reduction in the ratio of true to random coincidences with increasing activity, but it can be shown that the statistical accuracy obtainable by counting over a given time, or alternatively by using ratemeters of a given time constant, does in fact improve when the activity is increased, although the improvement becomes less marked as R becomes less, reaching a limit of usefulness for values of R of the order of unity. Correction for random coincidences is particularly important in clearance rate measurements; the square law variation of random counting rate with source activity would introduce considerable systematic error if this correction were not carried out.

With an extended source, as in the present case, the random coincidences are more important than the above expressions imply. In fact, it can be shown that the effect of extending the point source so that it occupies a disc equal to the crystal diameter is to lower the true coincidence rate by a factor of 4, the individual counting rates (and hence the random counting rate) remaining essentially undisturbed. A further extension of the source would yield a further reduction in R because of penumbral effects and the inability of a practical collimator to exclude unwanted radiation completely. So the smallest possible resolving time is necessary for good results, even if this means the loss of some true coincidences, due to small variations in pulse rise time.

Isocount curves for coincidence counting (using the same geometrical arrangement as previously) are shown in Fig. 10. They were obtained using as a source a 1-cm-diameter glass bulb, through which the active gas was passed continuously. The response can be seen to be highly collimated, and uniform to a satisfactory degree along the axis of the system.

In practice, counting rates will be reduced by tissue absorption, but it is an important consequence of the coincidence method that the degree of uniformity will not be impaired by this effect. Considering Fig. 11, in which A and B represent the boundaries of an absorbing medium, the coincidence counting rate is given in the absence of absorption by

$$N_C = 2N\frac{\omega}{4\pi}\epsilon^2$$

where ω is the smaller of the solid angles subtended by the crystals at the source, and by

$$N_C = 2N\frac{\omega}{4\pi}\epsilon^2 e^{-\mu d_1} e^{-\mu d_2}$$

(where μ is the linear absorption coefficient of the medium) when absorption is taken into account. The product of the two exponentials is constant for all points along the axis, being equal to $e^{-\mu D}$.

The isocount curves of Fig. 10 were obtained in air and there is the possibility that these curves would be modified by some true coincidences arising from annihilation events occurring in the penumbral region of

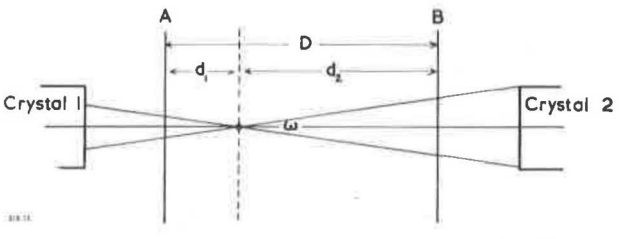

Figure 11. Diagram for illustrating effect of tissue absorpion

the crystals followed by "scattering-in" of one of the annihilation photons. Experiments using small bulbs (containing no activity) immersed in a suitable phantom material containing active gas have shown that this effect is small, but it is intended to investigate this aspect of the problem more fully in the future.

Coincidence counting rates of a few hundred counts per second are customary. Individual counting rates are in the region of 3×10^4 counts per second, and the coincidence counting rates are subject to the counting losses in the individual channels. For a paralysis time of 5 microseconds, this amounts to a correction term in the region of 1.2 for each channel, or the square of this quantity when considering the coincidence counts. The individual counting rates were not recorded separately, but were calculated from the random coincidence counting rate, using the assumption that the two individual counting rates are the same. This approximation introduces only a small error into what is itself a correction term. These corrections have been included in all measurements where their neglect would lead to significant error.

COUNTING APPARATUS

The detectors consist of four cylindrical sodium iodide crystals 1 in. thick by 1½ in. in diameter, each associated with a photomultiplier and cathode follower connected to a standard-type amplifier operated with a rise time of approximately 0.5×10^{-6} second and output pulse heights of up to 25 volts. Each pair of amplifiers supplies the input to a coincidence unit. It is necessary to use the minimum available coincidence resolving time of 10^{-7} second in the interest of low random counting rates but this involves sacrificing about 20% of true coincidences because of uncertainties in the timing of the input pulses to the coincidence circuit. The coincidence outputs are fed to standard ratemeters and a two-channel pen recorder. Time constants of 1 to 2 seconds are found to give the best compromise between rapidity of response and a reasonably low fluctuation.

For simultaneous comparison of corresponding regions of the left and right lungs as in comparative ventilation measurements two or three breaths are taken, one of which is used for determination of the random coincidences only. For clearance rate measurements it is better to use only one pair of counters, and to make ratemeter measurements of total and random coincidences simultaneously. It is convenient to supply the two signals to a simple mixer circuit which subtracts them (in the correct proportions to allow for differences in the resolving time of the two coincidence units) and yields an output signal proportional to the true coincidence rate only. In this way a relatively high random counting rate can be tolerated.

The counting rate at the end of inspiration will only be a true measure of the ventilation if the inspiration is instantaneous. In practice the inspiration takes 1 to 2 seconds and another second may elapse before the chest is held quite still. Thus, because the time constant of the ratemeter with its pen is about 1½ seconds, the tracing does not reach its peak until oxygen-15 has been in the lung for about 4 seconds, during which time some oxygen has been removed by the blood. Furthermore, the initial deflection is subject to a random variation which for the counting rates used was of the order of 10%. For these reasons it was considered useful to record, by means of scalers, the total coincidence counts during the 8 seconds after the pen had reached its peak and to use these rather than the initial deflections for measuring ventilation. It was thought that 8 seconds was the best compromise between errors due to random fluctuations in the counting rate and errors introduced by recirculation. The scaled count is clearly influenced by the rate of removal of oxygen by the blood. This varies from 0 to 2% per second, so the effect is small. Further work is needed to decide whether other methods of analysis (e.g., extrapolation of the tracing back to zero time) give a more reliable measure of ventilation.

The pairs of counters are supported on two gantries, each with independent movements allowing the counters to be positioned relative to the patient with ease and accuracy (Fig. 12). A specially designed chair with clamps to prevent the patient moving is now in use.

RESULTS

In order to make an initial assessment of the method, seven normal subjects were compared with four abnormal subjects. The normal subjects were patients who were undergoing radiotherapy but who had normal lungs. The abnormal subjects were as follows. One pa-

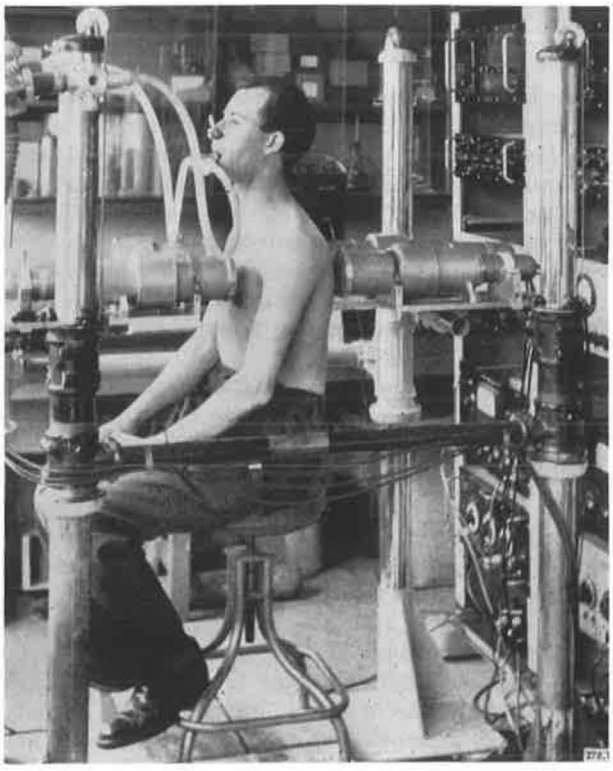

Figure 12. Clinical counting arrangement

tient (J) had extreme transradiancy of one lung (Macleod's Syndrome)[11] and was thought to have markedly reduced ventilation and blood flow on the affected side.[12] Another patient (H) was selected as an example of grossly reduced or absent blood flow but normal ventilation. This patient showed evidence of previous pulmonary emboli, and a reduced blood flow in the right mid-zone had been confirmed by angiography. Two cases showing severe unilateral fibrosis, following irradiation for bronchial carcinoma, were also included as examples of unilateral lung disease in which both ventilation and blood flow were likely to be reduced.

Ventilation

The repeatability of the ratios of scaled counts for corresponding regions of the right and left lungs in three normal subjects is shown in Fig. 13. In all of these

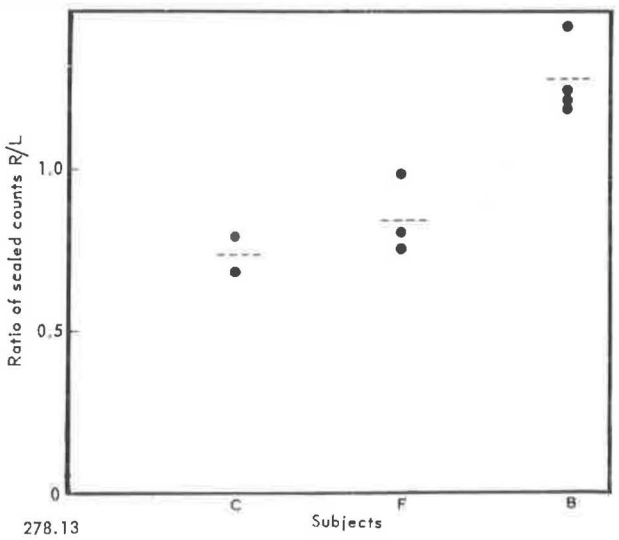

Figure 13. Ratios of scaled counts (ventilation) in normal subjects (dotted lines indicate the mean for each subject)

cases, and particularly with F and B, great care was taken to ensure similarity in positioning of the counters over the two lungs, and the variation of the mean values from each other and from unity may be taken as some indication of the variation to be expected from subject to subject.

In the relative ventilation measurements it is of the greatest importance to position the subject accurately and to ensure that the position remains fixed if good repeatability is to be achieved. This was illustrated on one subject by taking measurements before and after displacing the right-hand pair of counters one inch laterally. This showed a change in right to left ratio from 0.8 to 0.4. This is particularly significant because in this instance the counters were positioned on the mid-clavicular line to ensure that the variation of anteroposterior thickness of the lung, with transverse displacement, would be minimal. The effect of vertical displacement of the left-hand counters from the first intercostal space to the third rib was to reduce the left to right ratio from 1.3 to 0.5. In the upper zone, the anteroposterior thickness of lung is much reduced, and this is apparent from the marked change in the ratio of the counter responses. Once it was realised how critical was the exact placing of the counters (this was particularly difficult in obese subjects) their position was verified by radiography.

Two of the tracings obtained from the pen recorder in the case of abnormal transradiancy of the left lung are reproduced in Fig. 14. The ratio of initial counting rates (left lung to right) was 0.54 and 0.27 in two breaths, and 0.49 from two subsequent breaths in which left and right lungs were examined separately. An unexpected and interesting feature of one of the tracings (Fig. 14) from this patient was the failure of the subsequent normal respirations to wash out the active gas from the abnormal lung. Figure 15 shows the tracings from the patient with pulmonary emboli. The initial counting rates on the two sides are similar (right to left ratios of 0.91 and 0.85) but, as discussed later, the counting rates fall very differently. An example of gross difference in ventilation is shown in Fig. 16. This tracing is from one of the patients with severe postirradiation fibrosis. The mean ratio of left to right lung counting rate from three breaths was 0.05. A single breath was all that was necessary to establish the virtual absence of ventilation in the selected volume of the fibrotic lung.

No attempt has yet been made to measure ventilation simultaneously within many different parts of the lung, as has been done by Knipping[13] and his colleagues using xenon-133.

Clearance Rate

Compared with the measurements of ventilation the repeatability of the clearance rates both within and between different normal subjects is poor. Nevertheless, Fig. 17 shows that the means of the observations on each lung lie tolerably closely around a grand mean of 1.6% per second, which agrees well with the expected rate of fall of 1.2 to 1.9% per second. Some of the scatter is due to the variation in resting oxygen consumption and some is attributable to the random fluctuations in the tracing due to the comparatively low coincidence rates.

In most tracings the fall is approximately linear until the end of the breath-holding period, when oxygen-15 is washed out of the lungs by the breathing. A recirculation peak is rarely seen because of the relatively small number of counts which come from the blood, so that the whole of the breath-holding period can be used to estimate the slope of the tracing.

In one normal subject, strenuous bicycling provoked a faster decline of counting rate, from 1.0 to 3.5% per second, because of the rise in oxygen consumption. In another normal subject the counters were placed on the mid-line at the level of the third intercostal space in order to observe the activity coming from the mediastinum; but this was found to be negligible confirming the high degree of collimation of the counting system. In a third normal subject the counters were placed

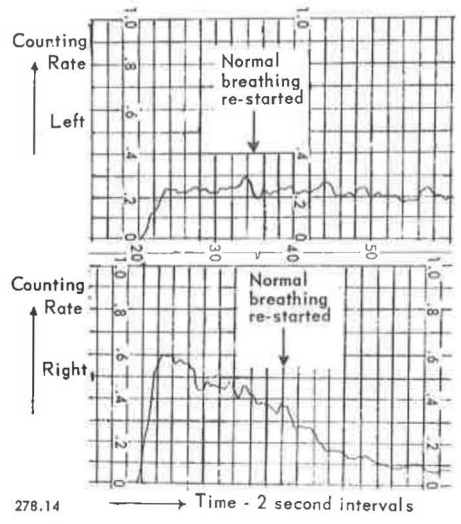

Figure 14. Tracing from patient J with unilateral radiotranslucency of left lung

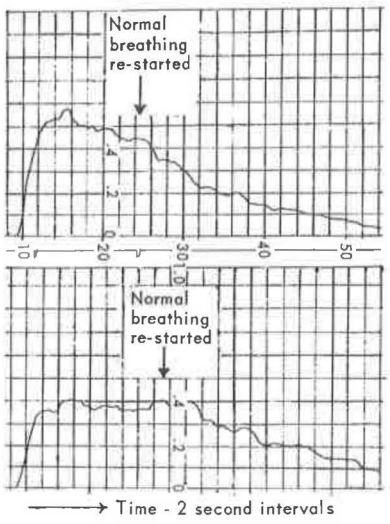

Figure 15. Tracing from patient H with previous pulmonary emboli in right lung

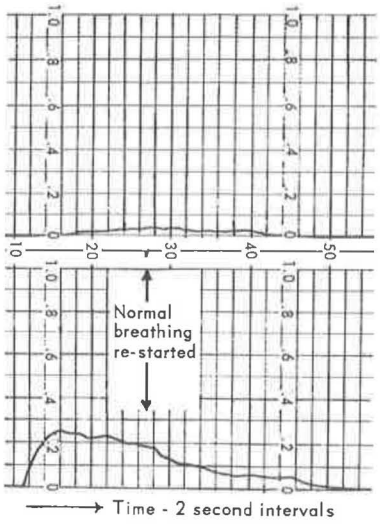

Figure 16. Tracing from a patient with post-irradiation fibrosis of left lung

just to the left of the sternum over the heart and the low clearance rate of 0.3% per second was obtained. Some lung tissue was included in this field.

Four abnormal subjects were studied. From the tracing shown in Fig. 14 it appears that the patient with abnormal transradiancy of one lung has no clearance on the affected side but a high clearance rate on the other. His results are plotted as J in Fig. 17. It can be seen that when the correction for the natural decay of oxygen-15 is made, the clearance rate is apparently negative, presumably because of error in judging the slope.

The tracing reproduced in Fig. 15 is from the patient with pulmonary emboli and shows no clearance in the right mid-zone but a rapid clearance in the left (H in Fig. 17). Her results are particularly striking in view of the normal ventilation on both sides. A third patient with severe unilateral fibrosis following therapeutic irradiation showed so few counts on the left that the clearance rate could not be estimated (Fig. 16). Measurements were made on a fourth subject with post-irradiation fibrosis using single counters, and clearance rates of 0.1% per second on the affected side as against 1.6% per second on the unaffected side were obtained. The degree of collimation here was poor and the results are not included in Fig. 17.

Thus, from Fig. 17, in the two abnormal subjects where one lung was expected to show no clearance and the other a normal or excessive clearance, the differences were 1.3% and 1.1% per second compared with a maximum difference between mean values for normal lungs of 0.4% per second.

CONCLUSIONS

It must be emphasised that this is a preliminary investigation, and that much more work will be necessary to explore the technique fully. The results in normal subjects and in patients chosen to represent examples of extreme abnormality of ventilation and blood flow in the lungs were generally as expected. They show that it is indeed possible to measure the ventilation and clearance by the blood of small volumes of lung with useful accuracy.

The ability to discriminate between small areas of lung is good, but the problem of examining a small, localised volume inside the lung (e.g., a cyst) is very difficult because normal lung tissue is inevitably included in the field.

The chief drawback of the technique as it stands is the poor repeatability of the measurements of clearance rate, and for these it may be necessary to use parallel counting with some sacrifice of spatial resolution in order to achieve higher counting rates.

The radiation hazard associated with this test, using either parallel or coincidence counting, is acceptable.

The advantage of being able to make measurements of function in different regions of the lungs, without intubation, is very considerable. The oxygen-15 test

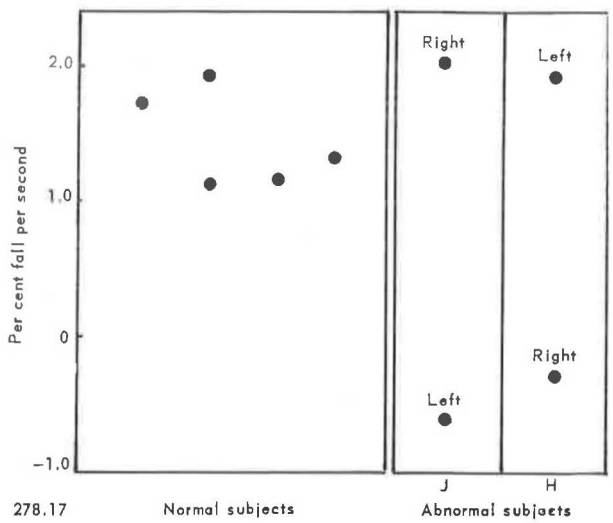

Figure 17. Mean clearance rates in four normal and two abnormal subjects (in three normal subjects, only one lung was studied)

shows such promise that it is being investigated clinically in greater detail.

ACKNOWLEDGEMENTS

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Techniques for Gamma-isotope-tracer Studies of Rapid Substance Movement in the Living Organism

By N. A. Gabelova and G. M. Frank

While artificial radioactive substances are widely used in various ways in biology, the stress has been on the application of radioactive tracers for the study of metabolism. The determination of the speeds of chemical reactions going on in the organism, the nature of intermediate processes and the mechanism of chemical transformations should be regarded as the main achievements in biology which are able to be reached by means of radio-isotopes.

Comparatively less attention has been paid to problems dealing not so much with the interpretation of chemical transformations but rather with substance movement, in the strict sense of the word, in the organism. These involve the study of such processes as blood circulation, lymphatic circulation, absorption, secretion, etc.

It is quite obvious that no definite line of demarcation can be drawn between these two trends in the use of tracers. The distribution of substances entering the organism—their absorption, secretion, concentration in certain organs and tissues, etc.,—is practically inseparable from the participation of these substances in metabolic processes.

Direct observation of the movements of a tracer and of the dynamics of its distribution in the organism has an independent significance.[1] Special emphasis in this field of research is given to blood circulation. Here, the registration of the rapid spread of substances carried by the blood flow is of very great interest to investigators and deserves intensive study. The possibility of observing and very accurately assessing the changes occurring in the process of blood circulation, absorption, secretion, etc., is really invaluable in the study of the mechanisms regulating physiological processes, not to mention the study of the effects of various pharmacological and physical agents.

It must be pointed out, however, that while biochemical tracer studies have been practised on a very wide scale, the physiological aspects of the problem have not been studied sufficiently. This is due to the fact that the solution of the problem, conditionally termed by us "physiological", requires technical approaches quite different from the methods adopted in chemistry and biochemistry, of measuring radioactive materials by means of universal scalers.

The specific feature of the present experiment is the preferential (if not exclusive) use of gamma-radioactive isotopes. By placing the detector outside the organism (near its surface), the increase of activity due to the isotope and its falling off in certain sites are registered continuously and simultaneously. This allows the nature and the speeds of redistribution of the isotopes introduced into the organism to be assessed on the basis of direct *in vivo* measurements, i.e., without drawing blood samples or doing tissue biopsy and without the removal and chemical processing of the organs of slaughtered test animals.

Such an experiment, naturally, requires an original technical approach in order to overcome experimental difficulties greater than those involved in routine chemical assays of samples. While scaler activity measurements of a sample taken from the organ of a test animal permits determination of the radioactivity of just that given tissue sample, localization of radiation under the conditions of an experiment *in vivo* and its measurement at a distance present certain difficulties. However, to overcome these difficulties and to work out and devise a method allowing easy and simple quantitative registration of substance movement in a living organism is important not only for the study of the above-mentioned physiological processes, but also for the observation of the dynamics and localization of certain biological processes.

The methodological prospects for the development of this field must take into account the following three considerations:

(1) Processes occurring within a few seconds should be registered when determining the velocity of the blood turnover, and those taking several minutes or even tens of minutes should be registered when studying the dynamics of substance accumulation and redistribution in certain organs and tissues.

(2) For an adequate understanding of the essential nature of the observed phenomena, measurements taken at any single location in the organism are not sufficient. A general picture of the processes mentioned above can be obtained only by simultaneous comparative analysis of phenomena in various parts of the organism.

(3) The problem is not only that of reducing to a minimum the contribution of whole-body diffuse gamma rays (background), but of being able to register even brief and slight changes of radioactivity at the

Original language: Russian.

site in question, or in comparison to its environment, even though the differences between the compared radioactivities might be relatively small (often within 10 to 30 per cent).

RADIOGRAPHY TECHNIQUE FOR TRACER STUDIES

Principles of the Method

To detect such small differences against the whole-body diffuse radiation background (considering that measurements over a long period of time are impossible on account of the more or less rapid changes of the estimated magnitudes) is not easy. To overcome this difficulty we applied the principle of accentuating the differences by means of nonlinear registration of gamma radiation. This is the basic principle adopted for the method which was given the name *radiography*. Using this method the dynamics of substance redistribution in the organism are estimated by means of a number of scintillation counters connected to power supplies and a special electronic design in a "multichannel radiograph".

The first model of the UNIR-1* apparatus (1955) was a two-channel device. The data presented in this paper have been partially obtained with the second model, UNIR-2, a three-channel radiograph, and with the third model, a four-channel unit (Fig. 1).

* UNIR-1: Universal Nonlinear Integrating Radiograph, model 1.

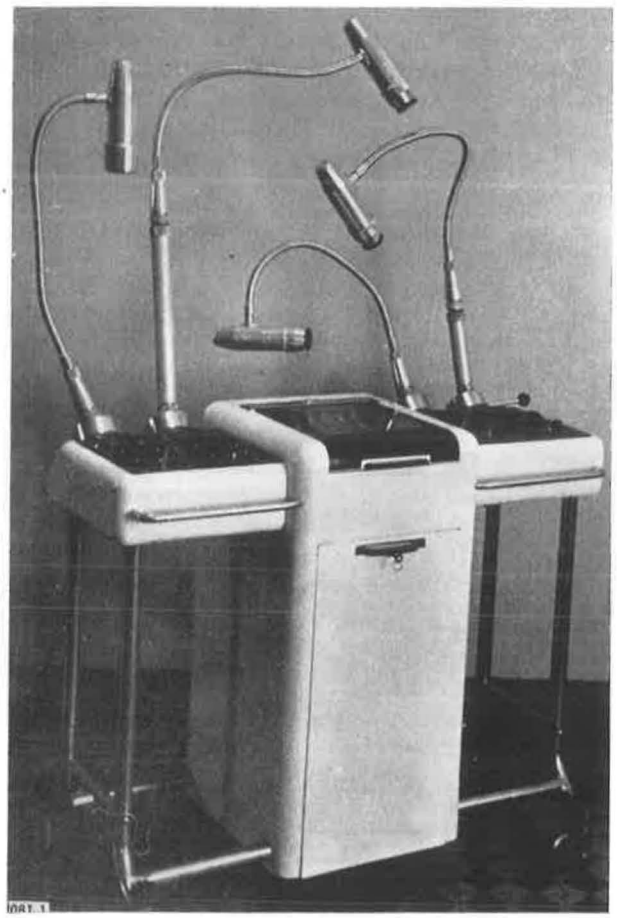

Figure 1. Four-channel radiograph; general view

The main feature of the radiograph is its nonlinear response to the intensity of the gamma radiation being registered. This means that readings for relatively low radiation intensities are diminished and that readings are exaggeratedly increased when intensities are relatively high (for a given operating range of the apparatus).

The radiograph is normally operated in the square-power mode; i.e., when the output current is proportional to the square of the gamma-ray intensity registered by the counter. This relation is determined by the equation

$$i = kI_\gamma^2$$

where i is the output current of the radiograph, I^2 is the gamma-ray intensity and k the conversion factor.

When a gamma-ray point source is being moved in relation to a counter, using conventional scalers, the readings change as the inverse square power of the distance between the source and the counter. The readings of the radiograph under the same conditions change as the inverse fourth power of the distance. Thus the increase and falling off of the readings with the approach or withdrawal of the source are much more sharp than is the case with ordinary techniques. Besides this, when compared with a conventional squaring computer the radiograph has the advantage in that the statistical fluctuations are not squared, but are determined by the common equipartition law.

The Radiograph

Besides its nonlinearity, the radiograph differs essentially from conventional radiometric equipment in having additional controls which allow adjustment of the operating mode of each channel in accordance with the conditions and the purpose of the experiment.

The unit has 3 or 4† independent channels and, correspondingly, 3 or 4 scintillation counters mounted on the ends of flexible armoured pipes having 6 degrees of movement. Readings are made by a pen-and-ink recorder on a common chart tape, providing for time marks (at 0.25 or 1 sec intervals), automatic recording of the moment of injection of the radioactive material and permitting necessary marks, such as changes in the experimental conditions, to be made manually.

The operation of each channel is controlled independently. Provision is made not only for the adjustment of the operational range in accordance with the radiation intensity at the site of each counter, but also for independent control of the amplification factor, of the time constant and of the gamma-ray intensity threshold, while the apparatus nonlinearly registers any excess of this threshold. This possibility to adjust the apparatus for optimum operation in accordance with experimental conditions and the possibility to discriminate against the whole-body background (in-

† An eight-channel model will soon be available.

cluding that due to a tracer introduced into the organism earlier) provide for sharp, distinct detection of small changes in the gamma-ray intensity not only during the first investigation, but also after repeated introductions of the isotope.

It should be noted that with the use of the conventional technique, investigations repeated immediately are impeded by the presence in the organism of gamma-emitting material introduced at the first test. This tends to prevent a wider application of gamma-emitting materials for physiological investigations in which repeated observations are of paramount importance.

The method of nonlinear gamma-radiation registration employed in the radiograph has an advantage over a collimator (combined with a usual scaler) since the nonlinear technique is more sensitive to slight changes in gamma-ray intensity and allows detection of even very brief and slight changes in radioactivity which are not registered by a collimator with a linear response. This advantage of the radiograph over the collimator can be of decisive significance not only for the measurement, for example, of blood flow rate as we shall show in detail below, but also for a good many other investigations *in vivo*.

The principle of nonlinear response with gamma-radiation intensity used in the multichannel design and the various controls for making adjustments to specific experimental requirements greatly extends the scope of gamma-isotope-tracer studies in the living organism.

EXPERIMENTAL INVESTIGATIONS

Model Experiments

Compared with conventional proportional registration, the advantages of nonlinear registration of gamma radiation for studies *in vivo* are clearly manifested even in model experiments. In these tests the dynamic conditions existing in a living organism are imitated by moving gamma-radioactive sources along counters arranged in a line.

For comparison one of the radiograph channels is switched over for conventional linear operation, while the other two channels register nonlinear performance.

The advantages of the nonlinear operation are clearly manifested when a number of point sources, which are equally spaced, are rapidly moved in relation to the counters.

Figure 2a shows the geometrical and dynamic conditions of such a model experiment, while Fig. 2b presents the chart with the results recorded.

As is seen in Fig. 2b, the nonlinear operation (curves 2 and 3) quite clearly shows the moment when the samples pass under the counters; the samples spaced at 8 cm are clearly detected even when moving at the speed of 20 cm per sec. At the same time it is practically impossible to tell from curve 1, corresponding to linear performance, the moment when the separate samples pass under the counter.

The advantages of the radiograph is even more unmistakable when it is desired to detect dynamically a slight increase of radioactivity against an average

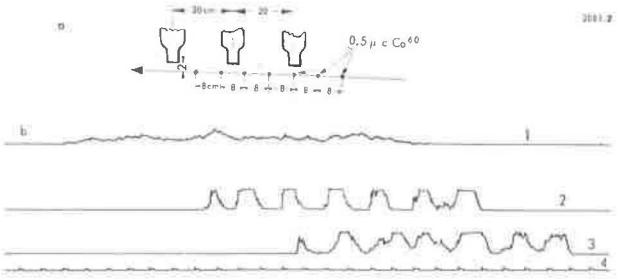

Figure 2. Test diagram (a) and typical record (b) of seven samples of 0.5 μc Co^{60} moved at a speed of about 20 cm/sec, 1, linear operation; 2 and 3, nonlinear operations; 4, time marks (0.25 sec)

background. This problem approximates the conditions of determining the second wave in a radiocardiogram as well as the conditions for repeated measurements of blood flow rate.

The geometrical and dynamic conditions of a model experiment are reproduced in Fig. 3a and the results in Fig. 3b. It is practically impossible to tell by curve 1, the linear operating channel in Fig. 3b, when a 0.5 μc source of Co^{60} situated among other sources two-times less active passes under the counter. Yet, both nonlinear channels (curves 2 and 3) unmistakably detect the two-times greater increase in radioactivity; this is achieved by appropriate operation adjustment of the channels and application of output discrimination.

And, finally, one more example of a model experiment showing the registration of a radioactive wave-front approaching a counter. For this purpose the radioactive wave (corresponding, for example, to the movement of radioactive material injected into the bloodstream) is depicted as a moving row of 10 small (0.25 μc of Co^{60} each) samples spaced too closely for

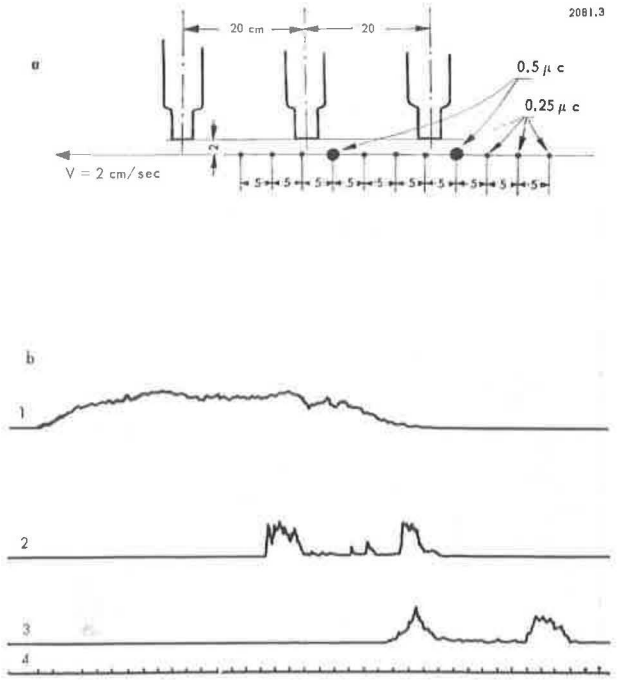

Figure 3. Test diagram (a) and typical record (b). A number of samples of varied activity are moving at a speed of 2 cm/sec, 1, linear operation; 2 and 3, nonlinear operation; 4, time marks (seconds)

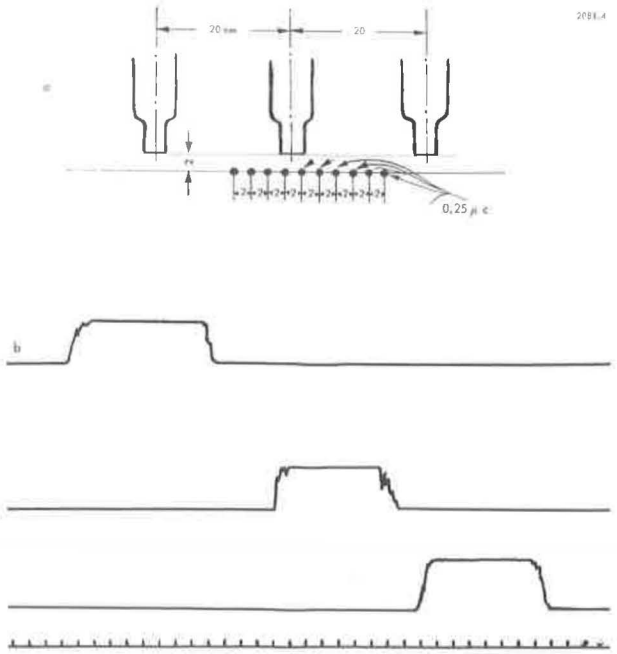

Figure 4. Test diagram (a) and typical record (b); a compact row of 10 samples of 0.25 μc Co^{60} moving at a speed of 2 cm/sec; nonlinear operation of all the three channels

the separate samples of the row to be "resolved." These conditions, provided the passage of the entire row under the counter is recorded, produce a table-shaped curve with an extraordinarily steep front of activity rise and drop (see Fig. 4b which presents data corresponding to a nonlinear performance of all the three channels).

The examples cited, showing the use of the radiograph in model experiments, prove that this apparatus therefore makes it possible to investigate dynamic problems which were beyond the scope of the conventional equipment to solve.

Investigations *in vivo*

Measurement of Blood Flow Rate

As has been mentioned above, radioactive isotope tracer studies *in vivo* may be extremely varied. The present paper describes some studies concerned with the determination of hemodynamic parameters and blood flow rates in different parts of the organism.

The problem of determining the blood flow rate has been posed long ago before clinicians and physiologists and has a long history. Yet, not one of the methods developed so far can be considered adequate from the standpoint of modern requirements.

The complexity of the problem can be seen from the fact that at present the use of "bloody" methods is advocated not only for tests in animals,[2] but even in clinical practice for diagnostic examinations in man.[3]

This situation is due to the fact that conventional radiometric equipment has proved utterly inadequate and practically unfit for determining, for instance, the moment when the counter is approached by radioactive material moving with the blood stream.

The use of a collimator for shielding against direct radiation from parts outside the area to be measured does not solve the problem completely. The main disadvantage of the collimator for the study of peripheral circulation is that it requires the introduction of relatively high doses of the radioactive tracer. An essential drawback of a collimator in combination with conventional radiometric equipment is its failure to detect slight and short-lived intensity changes in the radiation being registered. Thus, the usefulness of the collimator[4] for tumour metastases localisation by detection of the selective deposition of labelled material in them could be proved only if the isotope concentration in the tumour tissue was at least three times greater than the mean concentration of the surrounding tissues. In case of examinations involving dynamic measurements, even a threefold excess of isotope concentration would not be sufficient.

However, as we have demonstrated in our sample tests, such a problem can be definitely solved by using the method of nonlinear registration of gamma radiation (see Fig. 3). By this method a twofold increase of radioactivity is definitely detected in dynamic conditions.

An example of dynamic measurements *in vivo* is seen in Fig. 5 which shows a typical record taken when measuring the blood flow rate in a rabbit.

The test was conducted by means of the radiograph with nonlinear operation of all the three channels. Ten microcuries of I^{131}‡ was injected into the ear vein of the rabbit, the injection time being recorded automatically (Fig. 5, curve 1). Two counters were placed symmetrically over the middle of the right and left thighs (curves 2 and 3); the third counter was placed over the heart region (curve 4). As Fig. 5 shows, the moment the radioactive material coming from the ear appears at the locations under the counters is registered quite distinctly on curves 2, 3 and 4.

As has been mentioned already, the radiograph provides for the control of the threshold radiation, excess of which is nonlinearly registered by the unit. This

‡ For measuring blood flow velocity in animals, I^{131} with a longer half-life was substituted for the commonly used Na^{24}.

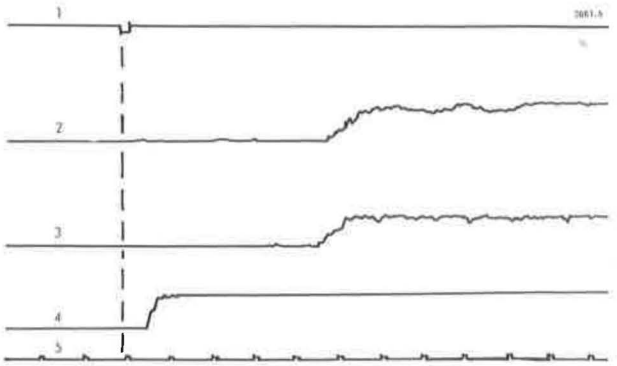

Figure 5. Typical record of blood flow rate in a rabbit. 1, shows moment of injection of 10 μc I^{131}; 2 and 3, readings from counters symmetrically set over right and left thigh; 4, record from heart region counter; 5, time marks (seconds)

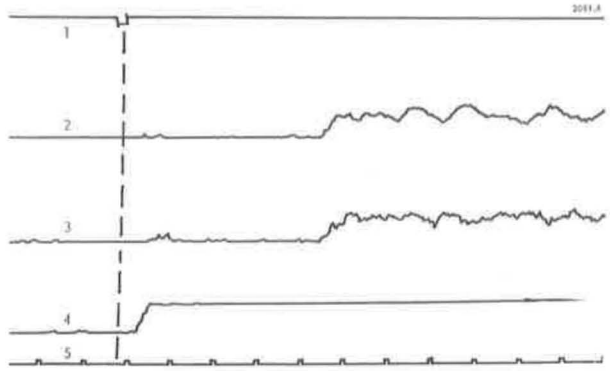

Figure 6. Repeated determination of blood flow rate in the same rabbit (repeated several minutes after the first measurement). Administered dose, counter settings and curve designations as in Fig. 5

makes it possible to conduct consecutive measurements of blood flow rate following repeated administration of the radioactive tracer, against the background of the isotope administered earlier.

Figure 6 presents an example of consecutive measurements of blood flow rate with the injection of 10 μc I^{131} several minutes after the first administration of the same dose. Arrangement of counters and, correspondingly, of curves is the same as in the test illustrated in Fig. 5. Figure 6 shows that when tracer injections are repeated, the moment the radioactive wave approaches the sites of counter disposals is detected as distinctly as with the first administration of the tracer.

The anatomical features of the rabbit prevent the taking of a radiocardiogram by means of a counter placed above the heart region. Therefore, when adjusting the operational range of the corresponding radiograph channel the aim was to obtain the most accurate detection of the moment when the labelled blood reaches the heart. This aim is best achieved under conditions providing for registration by a step curve, as is shown in Figs. 5 and 6. The great steepness of the front of this step curve is remarkable. Such a steep front ensures highly accurate registration of the moment when the labelled blood reaches the heart and

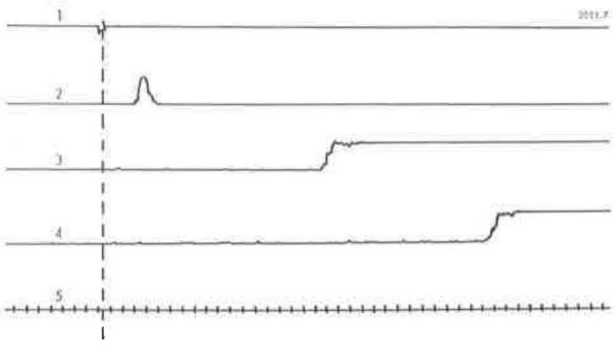

Figure 7. Radiocardiogram of the right heart in man and measurement of blood flow rate in the area "thigh–shank": 1, shows moment of injection of 50 μc Na^{24}; 2, readings from counter set at right border of heart; 3, readings from counter set at upper third of left thigh; 4, same, at lower third of left shank; 5, time marks (seconds). Counters at left leg are spaced at 50 cm; time of blood passage through the area corresponds to shift on curves 3 and 4 (13 seconds)

allows quantitative determination of one of the most essential blood circulation parameters—the time parameter.

Up to the present, it has not been possible to register simultaneously a radiocardiogram and the peripheral blood flow rate in man. Such data has been obtained only separately, by repeated examinations. Failure to obtain simultaneous data of this kind in a single operation was due to the absence (or scarcity) of multichannel units; great difficulties also arose because it is necessary to register a comparatively compact portion of labelled blood in the heart simultaneously with the rather diluted radioactivity in the peripheral blood flow in, for instance, the lower extremities. The independent control of the operational mode of each of the radiograph channels favours the solution of this problem. Figures 7–11 illustrate the results of examinations conducted in men following the administration of 30 to 50 μc of radioactive sodium, Na^{24}. (A 50 μc dose of Na^{24} is specially used for investigations of peripheral circulation; for radiocardiography the dose can be reduced several times.)

Figure 7 presents a typical record of such an examination. Curve 1 shows the automatic registration of the time of injection of 50 μc of Na^{24} into the cubital vein; curve 2, the readings of the channel with the counter placed over the right heart region (sensitivity of the channel is lowered and sharpness is high). The narrow peak corresponds to the labelled venous blood coming from the cubital vein to enter the right heart (ascending part of curve) and to the outflow of radioactive blood from the right heart to the lungs (descending part of curve). The return of the labelled blood from the lungs into the left heart is not registered because of the position of the counter and the given operational mode. Curves 3 and 4 show the passage of blood in the upper thigh and the lower part of the gastrocnemius muscle. The time differences between the ascents on curves 3 and 4 give the time for the passage of blood from the upper thigh to the lower third of the shank. The counters in this case were spaced at 50 cm and the time for the passage of blood along this route (according to the difference between the ascents on curves 3 and 4) was 13 seconds. These data allow us to determine the blood flow rate in this area, which in this case is about 4 cm per sec.

Figure 8 is a record from the examination of the heart region with the counter placed above the left ventricle near the midline. The two other counters were placed symmetrically over the lower third of the right and left gastrocnemius muscles (curves 3 and 4). The simultaneous rise of curves 3 and 4 shows that the blood flow in the lower extremities at the level of the lower third of the shanks is symmetrical. In the region of the heart (curve 2) the moment when the venous blood enters the right heart (ascending part of curve) and the arterial blood leaves the left heart (descending part of curve) is distinctly registered. The "saddle" on this curve, corresponding to the passage of the blood through the lungs, is expressed indistinctly, for the sharpness of the channel had been reduced pur-

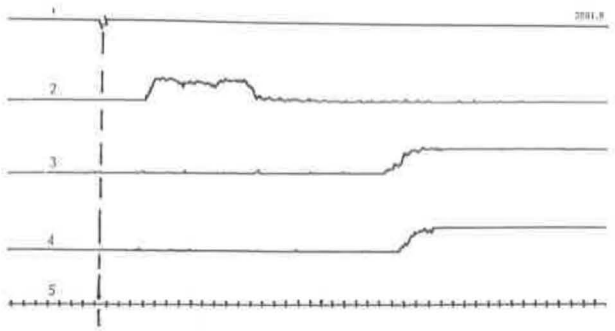

Figure 8. Radiocardiogram and measurement of blood flow rate in the right and left extremities in man. 1, shows moment of injection of 50 μc Na^{24}. Counter settings: 2, over heart; 3, over right shank (lower third); 4, over left shank (symmetrically to right); 5, time marks (seconds)

posely to permit the registration of radioactivity in both the right and the left heart. Nevertheless, the total length of this wide peak allows us to assess the rate of blood passage through the lungs.

Figure 9 gives an example of a multichannel radiocardiograph with three counters placed over the heart region and the fourth over the region of the right lung (curve 2). Curve 2 also shows the injection time of 30 μc Na^{24} into the cubital vein (rectangular burst). Curve 1 comes from the counter placed above the middle of the heart region, curve 3 from the counter at the right border and curve 4 from the counter at the left border of the heart. It is regrettable that the dimensions of the counters on this radiograph model prevented optimum arrangement of the counters for obtaining narrow peaks, similar to the peak registered on curve 2 of Fig. 7. The rather unfavourable arrangement of counters made it necessary to reduce registration sharpness not only for the counter set above the middle of the heart region, but also for the lateral counters; this resulted in much wider peaks than on curve 2 in Fig. 7. Nevertheless, the drop between the two peaks on curve 1, Fig. 9 (midheart counter) is shown quite distinctly and the general view of this curve fully corresponds to the "classical" radiocardiogram first obtained by Prinzmetal *et al.*[5]

Measurement of Blood Flow through Heart Cavities

A most important and novel feature of multichannel radiocardiography is the ability to register the passage

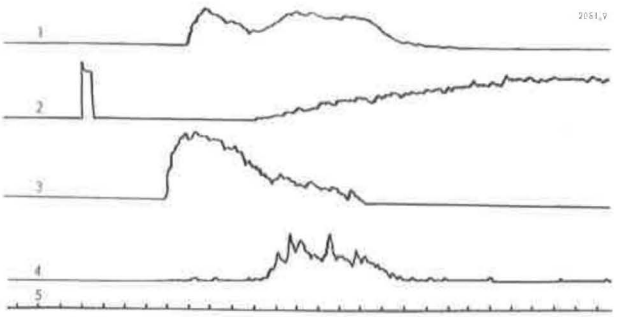

Figure 9. Multichannel radiocardiography. Counter settings: 1, over middle of heart region; 2, over region of right lung; the same curve shows the moment of injection of 30 μc Na^{24} into the cubital vein (rectangular pulse); 3, at right border of heart; 4, at left border of heart; 5, time marks (seconds)

of labelled blood through the various heart cavities individually, but simultaneously. Thus, for instance, the saddle-shaped radiocardiogram (curve 1, Fig. 9) can be compared with the simultaneously recorded entrance of labelled blood into the right heart (curve 3), into the lungs (curve 2) and into the left heart (curve 4).

The latest eight-channel model of the radiograph is still better designed for multichannel radiocardiography. The small-dimension counters of this model make possible exact settings of 4 counters above the required areas of the heart. Such optimum setting permits a sufficiently high sharpness of registration and conditions favourable for registering the appearance of the main portion of the labelled blood in the heart cavity under investigation. The process will be recorded as an acute single peak, similar to that on curve 2, Fig. 7. This will result in a radiocardiogram with 2 separate peaks, a goal once unobtainable with any arrangement of a single detector, i.e., in one-channel radiocardiography, by Lammerant and de Visscher.[6]

When using 4 small-dimension detectors for multichannel radiocardiography, 2 of them can be placed over the right heart area and 2 over the left heart. This, presumably, will eliminate the necessity of roentgenoscopic control usually practised when using a single detector.[6] At the same time it will ensure regular registration of radiocardiograms with two separate peaks—under optimum conditions drawn twice from each pair of symmetrically set counters.

Measurements of Substances in Circulating Blood

Radiographic technique is also applicable for measuring the rate of substance intermixture in the circulating blood, as well as the rate of substance escape from the blood vessels. This is achieved by continuous registration of radioactivity in the heart region. According to obtained data, intermixture of sodium chloride in the blood is practically complete within 40 seconds; then follows a rather slow drop of the radioactivity level due, probably, to the sodium leaving the blood system. Equilibrium of isotope correlation between the sodium content of the blood and that of the tissue fluids is reached only within tens of minutes.

Registration of radioactivity in the heart region has also been found quite useful for measuring the rate at which substances injected, for instance, subcutaneously, are absorbed into the circulating blood (here the second counter can be set above the site of injection). We have observed the gradual appearance (starting 15–20 sec after subcutaneous injection) and increase of blood radioactivity following a subcutaneous injection of 50 μc Na^{24} in the region of the cubital vein. In this case the radioactivity level in the heart region, approximately equal to the level reached 30–40 sec following the same dose injected intravenously, was observed in 2 to 3 min following the subcutaneous injection of the Na^{24}; at the same time the site of injection still retained a high radioactivity level.

In this way the rate of absorption has been found to be much higher than was assumed earlier. This fact alone is of great interest and deserves further study.

Study of Asymmetry in Peripheral Circulation

Radiography proved extremely fruitful when applied for the detection and study of circulation asymmetry in the extremities. For this purpose two counters (two pairs with the four-channel radiograph model) are set at symmetrical points over the extremities, for instance, at the middle of the gastrocnemius muscles. If there is a difference between the moments when the radioactive waves approach the sites under the counters, blood circulation asymmetry is indicated. Two-channel examination by means of a two- or three-channel radiograph (in the latter case the third counter, being unpaired, is not used) detects the presence or absence of blood flow asymmetry at the level of the counter settings. Four-channel examination permits comparison of asymmetry at different levels, with simultaneous comparison of blood flow rate in the two symmetrical regions (for instance, "knee–ankle", or "knee–middle of shank") of the right or left extremities. Four-channel examination is much more fruitful than two-channel work; this is especially important in cases of obliterating endarteritis, gangrene, frostbite, etc., and, particularly, in surgery when the minimum amputation height is to be determined.

Nevertheless, even the three-channel model (in this case used as a two-channel unit) has proved highly valuable for diagnostic purposes in complex laboratory and clinical examinations. Figures 10 and 11 are examples of examinations which detected distinct blood flow asymmetry[7] in the case of cerebral tumours.§ In these figures, curve 1 designates the moment of injection; 2, channel readings of the counter set at mid-region of the left shank; 3, the same for the right extremity; and 4, the time marks, in seconds. Comparison of radiography data with the results of other clinical diagnostic examinations (rate of propagation of pulse wave, skin temperature, capillaroscopy, plethysmography, etc.) makes for a better understanding of the nature of pathological processes and in particular, the differential diagnosis of neurogenous blood flow asymmetry becomes possible. Such asymmetry is manifested by asymmetry (*a*) of the vascular wall tension and (*b*) of the capillary network.

§ This work has been conducted at the Burdenko Institute of Neurosurgery, USSR Academy of Medical Sciences.

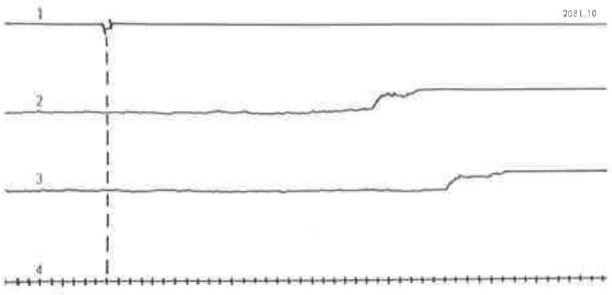

Figure 10. Detection of blood flow asymmetry in the lower extremities in a case of functional disturbance of the central nervous system. 1, injection time of 50 μc Na^{24}; 2, readings from counter set at the middle of left shank; 3, same, of right shank; 4, time marks (seconds). At the midlevel of the shanks, blood flow rate in the right extremity is 7 sec slower than on the left side

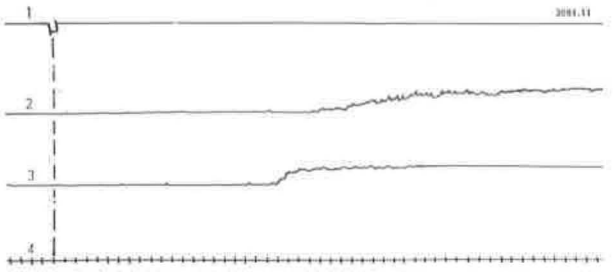

Figure 11. Detection of blood flow asymmetry in the lower extremities by disturbance in blood flow rate and by other specific features in a case of functional disturbance of the central nervous system. Curve designation as in Fig. 10. At the midlevel of the shanks, blood flow rate in the left extremity is slower than in the right, while the front of activity increase in the left extremity is less steep

Of special interest are the results of a few examinations in which blood flow asymmetry, detected by radiography, occurs side by side with complete symmetry by other criteria. Such data are not only an indication of the high specificity and sensitiveness of the radiographic method, but also suggest that in cases of central nervous system disturbances the development of a peripheral pathologic process may be started off by dynamic changes in the blood supply, and only then with development of the process does more stable asymmetry of other kinds appear.

Another interesting observation in some patients is the peculiar nature of blood flow asymmetry manifested by a difference between the moments when the radioactive wave reaches the symmetrically set counters and by a gradual increase of activity in one of the extremities while a more or less steep front is usually observed in the other. An example of such asymmetry is illustrated by Fig. 11 where the curve designation is the same as in Fig. 10.

There is no doubt that the analysis of such findings and comparison with clinical data and other examination results may help us to penetrate deeper into the nature of pathological processes. Even more complete data on the nature of blood flow asymmetry can be obtained by multichannel radiography employing four and more detectors.

Use for Tumour Localization

The last example to be given of the diagnostic application of the radiograph is concerned with the exact localization of a tumour of the spinal cord prior to operation.[8] Following the administration of gaseous radon (at present radioactive xenon is used) by lumbar puncture into the vertebral column, the patient was kept in a vertical (sitting) position for two hours. The radiograph was moved in such a manner that one of the counters travelled strictly along the vertebral column. Marks corresponding to the passage of the counter over each vertebra were registered on curve 1, Fig. 12 (in previous figures, curve 1 usually automatically recorded the moment the tracer is injected into the blood stream), the counter moving from the lum-

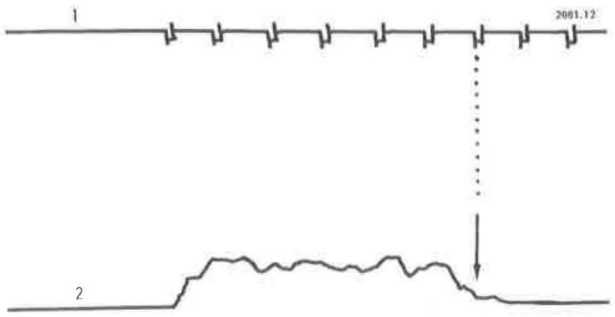

Figure 12. Spinal cord tumour localization by moving a detector along the vertebrae following administration of gaseous radon into the vertebral column. 1, shows the marks corresponding to passage of detector over each vertebra from lumbar region to occiput; 2, indicates activity distribution along the vertebral column 2 hours after injection of gaseous radon by lumbar puncture. Tumour localization is determined by the place where the ascent of the radon stops (marked by arrow) in the vertebral column. (Data from F. M. Lyass[8])

bar region to the occiput. During the 2 hours following the administration of radon, the latter partially dissolves in the cerebrospinal fluid and the remaining gas bubble gradually ascends until it meets an obstacle. In this case the obstacle is the tumour of the spinal cord. Thus localization of the tumour is determined by the place where the radon propagation is stopped, marked by an arrow in Fig. 12.

The method described gives a curve of the activity distribution along the vertebral column for a given time, as is shown in Fig. 12. When a four-channel radiograph is available another method can also be used—that of setting all the four counters along the vertebral column in the region of the presumed locality of the tumour. In this case radioactive levels and changes in them are registered at each site. This method also allows us to study the appearance, uptake and movement in the cerebrospinal fluid of labelled materials, administered suboccipitally, by lumbar puncture or into the blood stream.

CONCLUSION

As has been stated above, the examples described have by no means exhausted the possibilities of applying the radiograph. It is hoped that the suggested method of nonlinear registration will facilitate the development of studies connected with observations of the movement of gamma-emitting isotopes administered into the organism.

The method of nonlinear registration of gamma radiation can be also used in scanning systems to register the distribution of isotope tracers in the organism (radiotopography). In this case nonlinear registration will sharply accentuate and thus facilitate identification of nonuniformities in the isotope distribution, which will make readily perceptible even slight differences in the local concentration of the tracer in comparison to the surrounding tissues.

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Coronary Blood Flow Determinations with Radioactive Rubidium

By R. E. Mack, D. D. Nolting, M. Kirsch, E. Luethy, J. Duttachoudhury, C. E. Hogancamp and R. J. Bing*

The isotope of rubidium (Rb^{86}) has been extensively applied to biological studies since it is a univalent alkaline element. Because potassium is an adjacent member of the Group I alkali member series, the use of Rb^{86} has been suggested as a tracer of potassium. A comparative study of potassium and rubidium was carried out by Burch, Threefoot and Ray[1] in patients with and without congestive heart failure. They found that although rubidium was not a precise tracer of potassium, the biological decay rates of Rb^{86} seemed applicable to those of potassium within certain limits. Further, since Rb^{86} has a much longer half-life (19.5 days) than does K^{42} (12.4 hours), certain information relative to potassium turnover was much more readily available using radioactive rubidium.

The application of Rb^{86} to myocardial potassium turnover and the calculation of coronary blood flow was reported by Love and Burch.[2,3] The rate of Rb^{86} uptake by the heart was measured by means of an external radiation detector positioned over the precordium. This is possible because 20% of the disintegrations of Rb^{86} result in a gamma ray of 1.08 Mev. Their data suggested that the myocardial uptake of rubidium has an exponential relationship with time. Assuming an average percentage extraction of Rb^{86} by the heart of 70%, these authors were able to calculate coronary blood flow based on estimates of potassium turnover rate.

Studies were initiated in this laboratory to compare the value for coronary blood flow determined by the method of Love and Burch with a simultaneous estimation by means of the nitrous oxide method. During the course of these experiments it appeared that the myocardial uptake of Rb^{86} was not exponential but linear with time. This suggested the possibility that the Fick principle could be applied to myocardial rubidium uptake provided a means could be devised for the determination of Rb^{86} uptake of the entire heart.

METHODS

Dogs varying in weight from 10 to 18 kilograms were anesthetized with sodium pentobarbital. The coronary sinus was intubated with a No. 7 Birdseye catheter under fluoroscopic control.[4,5] A femoral artery and vein were then intubated with a No. 7 catheter which was tied in place. Prior to the counting procedure the chest of the animal was fluoroscoped and the midpoint of the cardiac shadow was located. A second point, 2 cm superior to the arch of the aorta, was also identified and marked over the chest wall. The counting system consisted of an RCL recording spectrogammeometer and a scintillation-probe counter with a multichannel collimator. For additional shielding, a movable lead plate of one-inch thickness in which a hole was drilled to receive the tapered head of the collimator was employed. When positioned over the midpoint of the cardiac silhouette, the probe counter was able to perceive only a portion of the entire heart and its content of radioactivity. Therefore, a calibration factor had to be determined which related the actual quantity of the radioactive rubidium in the whole heart to the counting rate recorded by the external counting system.

This calibration factor was determined by two methods. In the first, two balloons were placed into the right and left ventricles, respectively, by means of catheters inserted through the carotid artery and the external jugular vein. By this method variations in the total volume and in Rb^{86} content in the two balloons could be studied. The volume in the left ventricular balloon exceeded that in the right by a factor of 1.4 in order to maintain the usual relationship of the muscle mass of the two ventricles. Balloons containing 10 and 14 cc of Rb^{86} solutions of increasing concentrations were placed into the right and left ventricles of the dead dogs and the precordial activity was monitored. The exact concentration of each solution was determined in the well-type scintillation counter (54,144 counts per minute per microcurie of Rb^{86}). A straight-line relationship was found to exist between the precordial count and the concentration of Rb^{86}.

The calibration factor was calculated as the ratio of the counting rate per microcurie in the well-type counter over the counting rate per microcurie of the external counting system. This factor did not change appreciably despite variations in the quantity of Rb^{86} in the solutions.

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The second method for determining the calibration factor was based upon a comparison of the specific radioactivity of homogenized heart suspensions with the counting rate of the probe counter positioned over the whole heart *in situ*. To accomplish this, in four experiments Rb^{86} was infused for periods ranging from 23 to 30 minutes. The animals were then sacrificed with sodium pentobarbital and the net precordial count was determined. The heart was removed and homogenized in water in a Waring blender. The counting rate of 2 grams of the homogenized suspension was then determined in the well-type counter. The calibration factor was obtained from the ratio of the total myocardial radioactivity divided by the precordial counting rate (Table 1). The two methods used in the determinations of the calibration factor gave similar values, i.e., 2610 with the intracardiac balloon and 2320 with homogenized heart suspensions.

One hundred to 400 microcuries of a stock solution of Rb^{86} (Abbott) were diluted to 50 cc with physiologic saline. Ten cubic centimeters of this rubidium solution were injected rapidly as a priming dose. The remainder of the solution was infused into the femoral vein by means of a constant infusion apparatus (at a rate varying from 2 to 3 cc per minute in order to maintain a stable arterial concentration). Arterial and coronary sinus blood samples were drawn simultaneously at five-minute intervals during the 20-minute infusion period. Aliquots of 1 cc of plasma were counted in the well-type scintillation counter. Coronary blood flow using N_2O was determined by the desaturation method previously described.[6] Inhalation of nitrous oxide commenced about four minutes before the beginning of the rubidium infusion. Desaturation and determination of the coronary blood flow with nitrous oxide was started 10 to 15 minutes following the onset of Rb^{86} infusion.

In six experiments hypothermia was used to lower coronary blood flow. Anesthetized dogs were given artificial respiration and cooled in ice water until their rectal temperature had fallen to 27°C. The experimental procedures described above were then carried out.

Table 1. Standardization Constant Determined from Homogenized Heart Suspensions (*A*) and Intracardiac Balloons (*B*)

A	*Cpm/whole heart, counted in well-type counter*	*Precordial cpm, background counted with probe counter*	*Standardization constant*
	1,125,120	450	2496
	1,459,200	765	1907
	908,800	450	2022
	1,209,600	429	2816
		Average standardization constant	2310

B	*Cpm, total 24 cc vol Rb^{86} in balloon, counted in well-type counter*	*Precordial cpm, background/ 24 cc vol Rb^{86} in balloon*	*Standardization constant*
	7.58×105	250	3040
	14.8×105	620	2390
	22.2×105	850	2610
	29.6×105	1100	2400
		Average standardization constant	2610

Prior to each experiment the external counting system was standardized by finding the peak voltage for a Rb^{86} standard. This peak voltage was also checked against Co^{60}, a better calibration standard because of its longer half-life. Prior to the onset of infusion the aperture of the probe counter was placed over the point marking the upper chest and remained there for the first four minutes of the infusion in order to obtain the background count. After four minutes the counter was centered over the precordium and remained there until the determination of coronary flow with nitrous oxide had been completed. Following this, the collimator was again centered over the upper chest for the final determination of background counting rate.

The average increment of background activity over the chest was obtained by subtracting the background count at the onset of the experiment from that at its termination and dividing the difference by the time interval between the two counts:

$$\text{Background count} = \frac{\text{Final background} - \text{Initial background}}{\text{Final time} - \text{Initial time}}.$$

In a similar manner the average increment of precordial radioactivity was obtained by subtracting the precordial count at the onset of the determination of coronary flow from that at the end of the determination, a time period of four minutes' duration. The average increment therefore is the difference between the two counting rates divided by four. The increase in counting rate resulting from the uptake of Rb^{86} by the heart alone was then calculated as the difference between the two average increments.

The standardization constant of the external counter was calculated directly in terms of the sensitivities of the respective counters. It is determined as follows:

$$\text{Standardization constant} = \frac{\text{Cpm}/\mu\text{c } Rb^{86} \text{ (well counter)}}{\text{Cpm}/\mu\text{c } Rb^{86} \text{ (probe counter)}}.$$

The mean percentage extraction of Rb^{86} in the blood was determined from the concentrations in the simultaneously-obtained arterial and coronary sinus blood samples:

$$\text{Mean \% Extraction} = \frac{\text{Mean arterial concentration} - \text{Mean coronary sinus concentration}}{\text{Mean arterial concentration}} \times 100.$$

The coronary flow is then calculated from the Fick principle:

$$\text{Flow} = \frac{\text{Increase in counting rate/min (probe counter)} \times \text{Calibration factor}}{\text{Arterial blood (cpm/cc)} - \text{Coronary sinus blood (cpm/cc)}}.$$

All counting rates were corrected for radioactive decay.

RESULTS

The mean percentage extraction of Rb^{86} by the heart as measured by the A–V difference is 47% with a standard deviation of ±9.3% (Fig. 1). Statistical studies demonstrate that the percentage extraction of rubidium by the heart is independent of variations in arterial concentrations. On the basis of these calculations a mean value of 47% for the myocardial extraction of rubidium has been accepted.

Figure 2 illustrates a tracing of the precordial radioactivity. The increase appears to be linear with time. This might be expected from the observation that the per cent myocardial extraction of rubidium does not vary with time.

In 23 experiments the coronary flow was determined simultaneously using radiorubidium and N_2O (Table 2). The correlation coefficient between the two methods where the myocardial extraction of rubidium is directly determined is 0.8462 with a P value of less than 0.001. When the coronary flow was calculated from the extraction ratio average of 47%, the correlation coefficient between coronary flow by the two methods is 0.830 with a P value of less than 0.001. Thus, a definite relationship exists between coronary flow as determined with nitrous oxide and with Rb^{86}.

Table 2. Comparison of Coronary Flows Determined by the Nitrous-Flow Method, Rb^{86} Method with Observed A–V Extraction, and Rb^{86} Method with A–V Extraction Calculated from 47% Arterial Level

N_2O flow method	*Rb^{86} method (observed A–V extraction)*	*Rb^{86} method (calculated A–V extraction)*
130	113	100
200	90	109
390	225	211
26	37	58
22	14.5	25
44	28	29
57	65	47
96	70	89
127	173	181
271	298	284
87	110	107
187	285	235
266	242	222
85	140	100
158	92	126
186	190	176
330	260	180
210	201	234
350	284	166
348	274	244
96	93	81
117	139	146
150	71	94

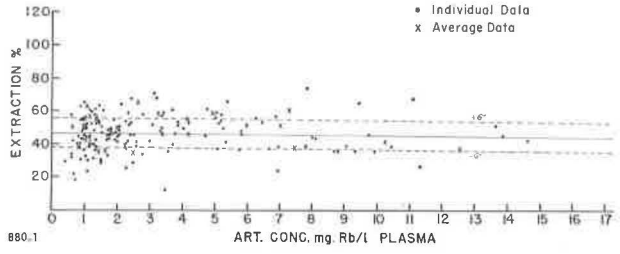

Figure 1. Relationship of arterial concentration Rb^{86} (mg/l) to percentage extraction. The arterial concentration of rubidium was calculated from the known specific activity of the infused Rb^{86}

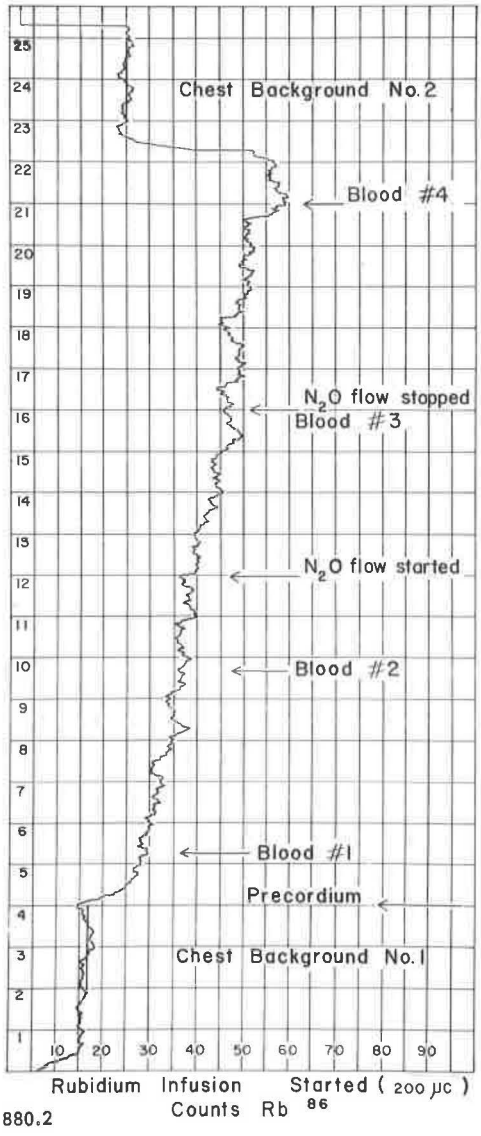

Figure 2. Precordial radioactivity. The time–course of Rb^{86} uptake over the precordium appears linear

DISCUSSION

The measurement of coronary blood flow with Rb^{86} as reported in this paper is based on an application of the Fick principle. The data suggests that one need not catheterize the coronary sinus in order to evaluate the myocardial extraction percentage of radioactive rubidium. Rather, one can determine the arterial concentration during the experimental procedure and calculate the A–V difference on the basis of the average extraction of 47%.

The ability to quantitatively determine the concentration of radioactive rubidium in the myocardium must be inspected critically. Burch, for example, is of the opinion that the time–course of precordial activity has an exponential relationship with time and has calculated the uptake of Rb^{86} by the heart based on this assumption. Experiments described in this report suggest that the time–course of precordial radioactivity is a linear function with time, at least for the duration of these experiments. The kinetics which ultimately determine the disappearance rate of the isotope from blood are not completely understood. For K^{42} and also possibly for Rb^{86}, much of the loss might occur by initial diffusion from the capillaries. However, the possibility of a selective intracellular binding of the isotope or an inward transport system must also be considered. The data reported herein permit no definite conclusions on the mode of disappearance of rubidium from the blood and into the heart muscle. The determination of the actual concentration of Rb^{86} by the heart is by necessity an indirect one in these experiments. Using intracardiac balloons, it has been found that within certain limits neither the quantity of radioactive material present nor the heart volume or size influence the calibration factor. However, the distance of the heart from the precordial counter does alter this standardization constant. To permit a more complete independence from variation in the volume and size of the heart, the counter must be capable of detecting the radiation emitted from the entire heart. The collimator therefore should be one whose diameter is equal to the maximal diameter of the heart and at the same time should have sufficient shielding to exclude extracardiac sources of radiation (liver) which may be of importance. Such a counting system will be constructed in order to use this procedure on the human subject.

An ideal method for the determination of coronary blood flow in the nonanesthetized animal or human is one which will measure blood flow in all of the coronary arteries from moment to moment under normal physiologic conditions. Thus, one should be in a position to measure the coronary blood flow with the heart *in situ* and its nervous and humoral control intact. The method described in this report appears to fulfill these requirements. Since the precordial activity shows rapid changes reflecting alterations in the myocardial uptake of rubidium[7] and since both activity of Rb^{86} and arterial blood, and the extraction of Rb^{86} by the heart remain relatively constant, it may be possible to detect not only an over-all but even rapid changes in coronary blood flow by this method.

SUMMARY

The adaptation of the Fick principle to determinations of coronary blood flow from myocardial Rb^{86} uptake in dogs was studied. This method was found to give results comparable to simultaneously determined coronary flows by the established nitrous oxide method. Since the mean myocardial extraction rate of 47% was shown to be independent of arterial Rb^{86} concentration, determination of coronary blood flow without coronary sinus catheterization is possible by the rubidium method.

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New Radiodiagnostic Techniques for Investigating Parenchymal and Obstructive Liver and Kidney Diseases

By G. V. Taplin, O. M. Meredith Jr., H. Kade, C. C. Winter and D. Johnson*

New radioisotope tracer tests have been developed during the past four years for investigating the underlying pathophysiological disturbances in diseases of the liver and kidneys.[1–3] Following the intravenous injection of minute (μg) doses of the I^{131}-labeled liver- and kidney-specific agents[4,5] Rose Bengal and Diodrast, the dynamics of blood clearance, organ uptake–excretion and translocation of these tracers are measured externally with gamma-ray scintillation detection equipment. The data obtained permit evaluation of vascular capacity, parenchymal cell function and patency of the excretory passages of the liver and of each kidney separately.

Most biochemical tests for hepatobiliary tract disease are not organ-specific and frequently provide equivocal results in the face of clinically apparent liver disease and/or acute biliary tract obstruction.[6,7] Methods for estimating liver blood flow by the Fick principle are likewise complicated and results are variable.[8] Samples of hepatic vein blood must be obtained by passing a catheter through the heart down to the liver using fluoroscopy to aid in localization. Standard methods for estimating individual kidney function include intravenous urography and measurement of the clearance of various agents by each kidney separately after ureteral catheterization.[5] Renal vascular lesions are localized by aortography,[9,10] which is a technically difficult and somewhat hazardous procedure.[11] Standard urological diagnostic procedures are traumatic and many may require hospitalization, anaesthesia, cystoscopy and radiography.

By contrast, the radioisotope hepatogram and renogram tracer tests are relatively simple, painless, rapid and reproducible office procedures. They are unique in providing information on multiple functions simultaneously and have the added advantage of freedom from drug reactions. The radiation exposure is many times less than from radiography of these organs.[12] Rapid removal of the tracer materials from the body permits repetition of the tests whenever necessary, even in the presence of severe jaundice and in patients too ill or children too small to undergo urological study.

The major part of this paper is concerned with recent advances in Rose Bengal I^{131} tracer techniques consequent to pathophysiological studies in animals and parallel investigations in patients with various diseases of the liver. These include the development of (1) the Rose Bengal I^{131}–BSP stress or loading test which is capable of detecting minimal liver damage; (2) a dual blood clearance technique for estimating functional impairment of the portal circulation; (3) the Rose Bengal I^{131} hepatogram, a multiple-purpose tracer procedure which is useful in the differential diagnosis of jaundice. It provides data on liver vascular capacity, polygonal cell function, and bile flow interference from either functional or organic causes.[13,14]

The final section of this report is limited to a review of the clinical investigations with the Diodrast I^{131} renogram in the field of urology and to its use as a rapid screening test for detecting unilateral renal disorders in patients with hypertension.

MATERIALS AND EQUIPMENT

The I^{131}-labeled Rose Bengal and Diodrast supplies are available commercially† as sterile solutions having a relatively high specific activity ranging from 0.1 to 0.5 mc/mg. These concentrated solutions may be diluted with normal physiological saline to prepare individual test doses of the desired strength (1 to 2 μc/15 kg for Rose Bengal and 1 μc/5 kg for Diodrast). Dilutions up to 1/500 do not alter the dynamics of their uptake or excretion by either the kidneys or the liver.

The arrangements of gamma-ray scintillation counting and recording equipment as used for performing the Rose Bengal I^{131} hepatogram in animals and man are shown in Fig. 1 (a and b) and for the Diodrast I^{131} renogram in Fig. 1 (c and d). Reports have been published previously which contain descriptions of the techniques, precautions and interpretations of both of these tracer tests in detail.[1,3]

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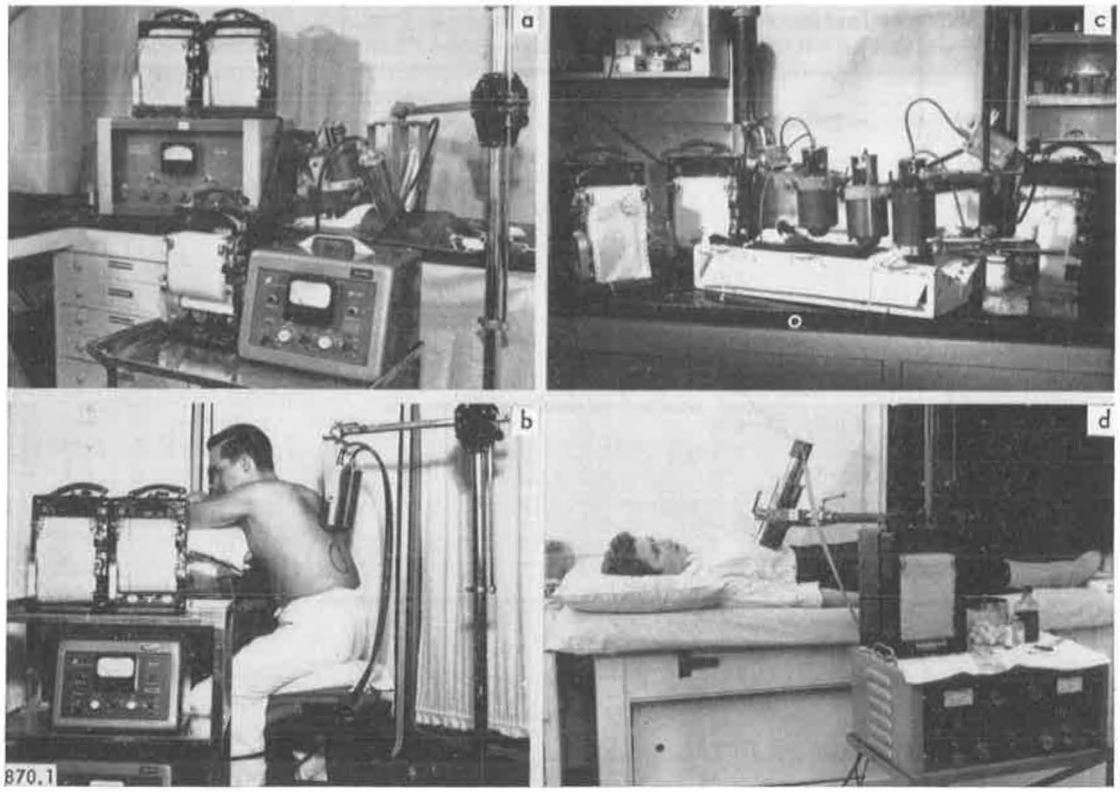

Figure 1. Gamma ray scintillation counting and recording equipment; (a,b)—for Rose Bengal I^{131} hepatogram; (c,d)—for Diodrast I^{131} renogram

ROSE BENGAL I^{131} TRACER TECHNIQUES

Pathophysiological Studies in Animals and Man

Since it is well known that most biochemical liver tests are relatively insensitive and nonspecific,[6,7] efforts have been made to increase the sensitivity of the Rose Bengal tracer test by placing the liver under stress or loading the polygonal cells with various physiological agents. These have included bromsulphalein (BSP), glucose, glycine and other amino acids. BSP has been shown to be an effective and practical stress-producing agent. This dye is extracted from the blood by the polygonal cells of the liver much the same as is Rose Bengal.[15] When both dyes are injected simultaneously in a mixture containing microgram amounts of Rose Bengal and 3–5 mg/kg doses of BSP, the normal liver is able to extract each agent separately and at nearly the same rate. However, in patients with asymptomatic liver disease and in animals with minimal liver damage from CCl_4 poisoning, blood clearance of Rose Bengal in the mixture is much slower than it would be if the tracer dose had been administered separately and not as a mixture.

LIVER PATHOLOGY AND ROSE BENGAL I^{131} TESTS

Acute CCl_4 Poisoning in Rabbits

Data presented in Table 1 show the correlation between Rose Bengal blood clearance rates and liver pathology in a large group of animals during the development of and recovery from acute CCl_4 poisoning (50 mg/kg). The findings indicate that physiological disorders and histological changes develop within 6 hours and reach a maximum during the next 24 to 72 hours. Considerable recovery occurs by 7 to 8 days and is nearly always complete by 14 days. Separate tracer test results in the same animals are entirely negative by 9 to 10 days. However, during this same period and for a few days prior to it, the stress test findings are more positive in most instances than tracer test results. After recovery has occurred (14 to 28 days) results of both types of tests are negative. This pathophysiological correlation demonstrates the reliability of the Rose

Table 1. Stress Test[a] Blood Clearance Values and Liver Pathology in Rabbits During Development and Recovery from Acute CCl_4 Poisoning (all animals were poisoned with CCl_4 in olive oil (50 mg/kg) by gastric intubation)

Time after poisoning	*No. of animals*	*$BCT_{1/2}$ (min)[b] (av. values)*	*Pathological classification*
Controls	106	3.6	1
6 hr	6	7.4	2
18 hr	6	7.7	3
24 hr	13	15.3	4
72 hr	9	14.0	3
7–8 d	15	6.3	2
13–14 d	7	4.0	1
20–21 d	8	3.7	1
27–28 d	6	3.7	1

[a] Stress test—I.V. injection of Rose Bengal I^{131} (6.0 μc/kg) + BSP (5 mg/kg).
[b] Blood clearance half-time.

Table 2. Tracer versus Stress Test Results with Rose Bengal I^{131} and BSP in Rabbits Poisoned with CCl_4 Once a Week (Rose Bengal I^{131} tracer and stress tests performed 7 days post-poisoning)

Animal	*Control values*	*Days after onset of poisoning*							
		7	*14*	*21*	*28*	*35*	*42*	*49*	*56*
		1. Blood clearance half-times in minutes							
L-7	2.0	3.0	3.5	3.0	3.5	*7.5*[a]	Dead	—	—
M-8	3.0	3.0	4.5	6.5	5.0	*9.5*	3.0	*7.0*	6.0
R-9	1.5	3.0	3.0	2.0	5.0	*7.0*	5.0	*3.5*	3.0
S-10	2.5	4.0	3.5	3.0	3.0	*9.5*	7.5	*11.0*	11.0
T-11	3.0	2.0	3.0	4.0	3.5	*10.0*	4.0	*10.0*	6.0
U-12	2.0	2.0	2.0	2.5	4.0	*4.0*	4.0	*8.0*	5.0
Av. values	2.3	2.8	3.2	3.5	4.0	*7.9*	4.7	*7.9*	6.2
		2. Minutes to maximum liver uptake							
L-7	7.0	8.0	8.0	8.5	5.5	*15.5*	Dead	—	—
M-8	5.5	11.0	8.5	11.0	7.0	*14.0*	8.5	*13.5*	11.0
R-9	9.0	6.5	7.0	6.5	6.5	*9.5*	14.5	*8.5*	8.0
S-10	7.5	7.0	9.5	9.0	8.0	*11.5*	9.5	*19.5*	10.0
T-11	7.5	8.0	8.0	8.5	7.5	*8.0*	7.5	*10.0*	8.0
U-12	6.0	8.0	7.5	6.0	6.5	*5.5*	10.0	*7.0*	7.5
Av. values	7.1	8.0	8.0	8.2	6.6	*10.6*	10.0	*11.7*	8.9

[a] Values for stress tests are in italics.

Bengal tests in reflecting the degree of liver injury and the ability of the BSP–Rose Bengal stress test to detect minimal liver injury in rabbits.

Chronic CCl_4 Poisoning in Rabbits

Data presented in Table 2 demonstrate that there is progressive impairment of liver function in rabbits poisoned once a week with CCl_4 administered at a dose level of 10 mg/kg. The average values of blood clearance half-time and time-to-reach-maximum liver uptake increased gradually. After 28 days, stress tests are more positive than those for tracer procedures in most instances. Similar findings are shown in Table 3 for animals poisoned with 5 mg doses twice weekly. The blood clearance half-time appears to be a more sensitive index of liver damage than the time-to-reach-maximum liver uptake. Histological examinations reveal the development of pathological changes which are characteristic of early cirrhosis.

Tracer versus Stress Tests in Humans

Tracer and stress hepatogram findings from a normal subject are presented in Fig. 2. It shows that there is little difference between the blood clearance and liver uptake rates, whereas in a 53-year-old man with chronic alcoholism having relatively normal biochemical findings the results of the stress hepatogram (see Fig. 3) are distinctly positive while those of the tracer test are within the lower limits of normal. Tabulated data from normal subjects compared with patients

Table 3. Tracer versus Stress Test[a] Results with Rose Bengal I^{131} and BSP in Rabbits Poisoned with CCl_4 Twice Weekly (Rose Bengal I^{131} tracer and stress tests performed 3 days post-poisoning)

Animal	*Control values*	*Days after onset of poisoning*							
		7	*14*	*21*	*28*	*35*	*42*	*49*	*56*
		1. Blood clearance half-times in minutes							
J-1	3.0	3.0	3.5	3.5	—	4.0	*5.5*	8.0	*6.5*
K-2	2.0	2.0	2.0	2.0	—	4.0	*3.0*	3.5	*10.0*
N-3	2.0	2.5	2.0	2.5	—	3.0	*8.0*	7.5	*20.0*
O-4	1.5	3.0	2.5	1.5	—	3.0	*7.5*	7.0	*9.0*
P-5	3.0	3.0	2.0	1.5	—	4.0	*4.5*	8.0	*9.0*
Q-6	1.5	2.5	2.5	2.5	*4.5*[b]	dead	—	—	—
Av. values	2.2	2.7	2.4	2.3	*4.5*	3.6	*5.7*	6.8	*10.0*
		2. Minutes to maximum liver uptake							
J-1	8.5	11.0	10.5	6.5	—	6.0	*7.5*	8.5	*13.0*
K-2	7.0	7.5	5.5	6.0	—	5.0	*6.5*	6.5	*16.0*
N-3	9.0	8.5	5.0	7.0	—	9.0	*9.0*	9.0	*17.5*
O-4	7.5	7.5	8.0	9.5	—	5.0	*9.0*	6.0	*8.5*
P-5	8.0	6.5	10.0	5.0	—	5.0	*11.0*	8.5	*16.5*
Q-6	6.5	4.0	6.0	5.5	*9.0*	dead	—	—	—
Av. values	7.7	7.6	7.6	6.6	*9.0*	6.0	*8.6*	7.7	*14.3*

[a] Stress test—5 mg/kg BSP injected simultaneously with the tracer dose of Rose Bengal (6 μc/kg).
[b] Values for stress tests are in italics.

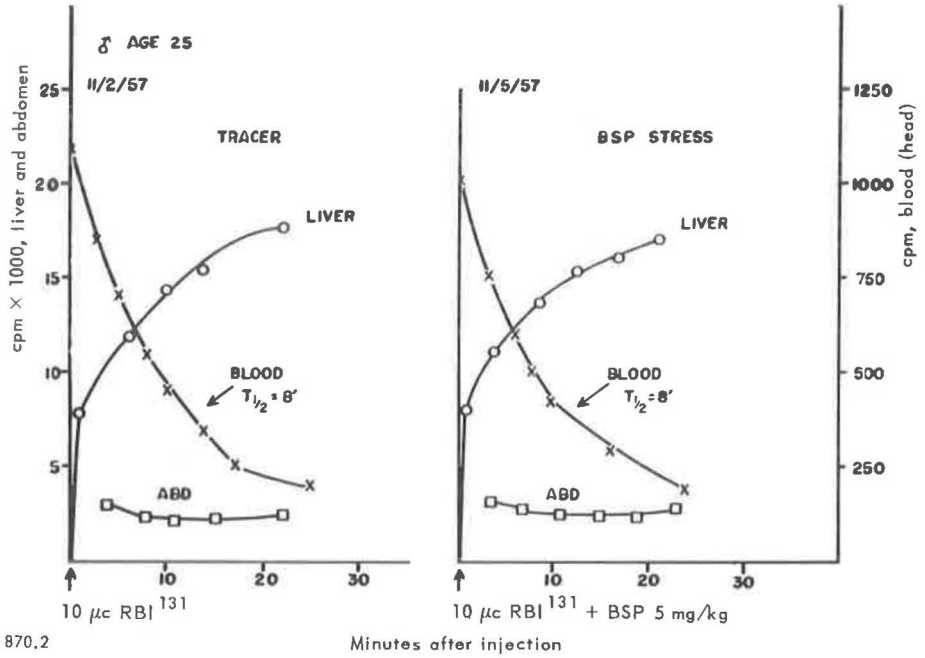

Figure 2. Tracer and stress hepatograms (normal subject)

Abbreviations, Symbols and Values Used in the Figures and Tables:		*Normal values*
Alk Phos	—Serum alkaline phosphatase (Bodansky units)	2–9
Bili	—Serum bilirubin in milligrams per cent	0–0.3
CF	—Cephalin—cholesterol flocculation test (0–4+) at 24 and 48 hours	0–+
TT	—Thymol turbidity and flocculation test (Neefe's units)	0–5
II	—Icterus index (Icterus units)	4–7
VDB	—Van den Bergh (direct and indirect reacting bilirubin)	0.3–0.8
Protime	—Prothrombin time (per cent of normal)	
BSP	—Bromsulphalein blood retention in milligrams per cent at 45 minutes after intravenous dose of 5 mg/kg	0–Trace
Alb	—Serum albumen milligrams per cent	4–5.5
Glob	—Serum globulin milligrams per cent	2.0–2.5
TP	—Serum total protein milligrams per cent	6.0–8.0
↑μcRBI^{131}	—Dose of I^{131}-labeled Rose Bengal in microcuries injected intravenously	
♂	—Male	
♀	—Female	
CD Stone	—Common bile duct stone	
CBD	—Common bile duct area in right upper quadrant of abdomen	
GB	—Gall bladder area in right upper quadrant of abdomen	
ABD	—Midabdominal area, below liver edge	
Liver	—Counting area over anterior surface of the liver above gall bladder and liver edge	
Blood T½	—Time in minutes for 50 per cent blood clearance of Rose Bengal—I^{131}	
T-Tube	—T-shaped catheter for common bile duct drainage	
cpm	—Counts per minute corrected for background levels	

having known or suspected liver disease are presented in Table 4. Patients having histories of chronic alcoholism and persistent liver enlargement from previous hepatitis frequently show strongly positive stress test results although there is negligible bromsulphalein retention. Patients with moderate liver damage associated with cirrhosis or long-standing liver congestion from cardiac disease have abnormal BSP retention and positive stress tests. In such patients the delayed Rose Bengal blood clearance and high BSP retention both reflect not only the defective extraction capacity of the liver cells but also the impairment of liver circulation.

TRACER STUDIES OF LIVER BLOOD SUPPLY

The blood flow in the portal circulation of patients with advanced portal cirrhosis is 30 to 70 per cent below the normal values (1500 ml/min).[16] These findings and the simple external measurement of initial liver vascularity made with Rose Bengal I^{131} correlate well. However, both of these procedures fail to measure functional impairment of the portal circulation separately from its arterial supply. The arterial circulation predominates[6,7,16,17] in cirrhosis and progressive portal hypertension develops causing, along with other factors,[17] hemorrhage from esophageal varices, which is one of the most serious complications of this disease. Portal hypertension can be corrected by various surgical procedures which bypass the liver and provide portal decompression.[16,17] Most patients do not receive the benefit of prophylactic surgery for several reasons, one of which is lack of a simple functional test for the detection and evaluation of such vascular defects early in the course of the disease. To meet this need, experiments were conducted to develop a tracer technique to measure impairment of portal blood supply and to evaluate the relative importance of the portal venous versus arterial circulation of the liver.

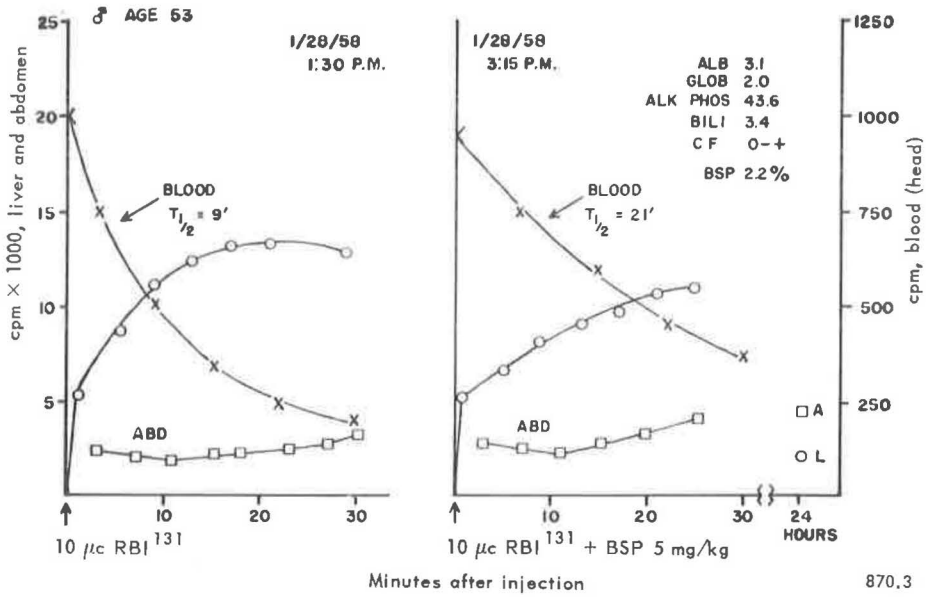

Figure 3. Tracer and stress hepatograms. Patient with chronic alcoholism of 20 years' duration

Importance of Portal versus Arterial Blood Supply

The capacity of the liver to extract Rose Bengal I^{131} is reduced three- to fivefold by portal vein ligation in rabbits, but hardly altered by ligation of the hepatic artery. Furthermore, portal vein and hepatic artery ligation have different effects on bile excretion rates and on bile flow response to a hydrocholeretic agent in rabbits. Data in Table 5 show that a rabbit with its hepatic artery tied off continues to form bile at a normal rate and responds to injection of sodium dehydrocholate with a sharp increase in bile volume, whereas in an animal with its portal vein ligated there is reduced bile flow and an inability to respond to the same agent. These findings demonstrate the major importance of the portal supply in rabbits.

Dual Blood Clearance Tests for Impaired Portal Function

Progressive impairment of the portal circulation occurs during the production of experimental cirrhosis in rabbits. This obstructive vascular defect manifests itself by gross differences in the rates of Rose Bengal blood clearance measured over portal (abdominal) versus nonportal (head) areas. These defects were observed in 9 of 12 rabbits chronically poisoned with CCl_4 for 10 weeks. Tracer studies were repeated at weekly intervals throughout this period. The findings from a typical rabbit presented in Fig. 4 demonstrate the manifestations of this portal vascular defect. It is apparent that as cirrhosis is induced, the Rose Bengal blood clearance rates measured over the abdominal portal area decrease much more than the nonportal blood clearance rates measured over the head. There is also progressive reduction in liver vascular capacity during this time to levels similar to those seen in cirrhotic patients. This dual blood clearance technique is readily adaptable for clinical application.

DIFFERENTIAL DIAGNOSIS OF JAUNDICE USING THE ROSE BENGAL I^{131} HEPATOGRAM (CLINICAL STUDIES)

A large portion of recent clinical work has been directed toward evaluating the effects of complete and partial obstruction of the biliary tract on liver functions and on the use of Rose Bengal I^{131} for estimating interference with bile flow in the presence of associated liver disease. Jaundiced patients with evidence of biliary obstruction plus liver cell damage pose some of the most difficult differential diagnostic problems in medicine.[6] In the past 18 months over 100 patients with a variety of hepatobiliary tract disorders have been studied thoroughly. Fifty surgical patients have been tested either pre- or postoperatively, and many have had repeated pre- and postoperative studies. The complete Rose Bengal I^{131} hepatogram procedure has been performed on all of these patients in order to establish its diagnostic features, reproducibility and reliability in comparison with other liver tests and also with the patients' course in the hospital and with the final clinical and pathological diagnoses. Parallel studies in conjunction with these clinical investigations have been made of rabbits with partial and/or complete surgical occlusion of the common bile duct.[14] The diagnostic value of the tracer hepatogram is best demonstrated by presenting the comparative results of repeated hepatograms and biochemical liver tests performed in individual patients in whom a definite diagnosis has been established.

Case 1. Data presented in Fig. 5 were obtained from a young woman with a recurrent attack of jaundice occurring 3 months after cholecystectomy and common bile duct exploration. A clinical diagnosis was difficult because the patient had received several transfusions at the time of operation. The second hepatogram indicated a spontaneous release of a partial bili-

Table 4. Tracer versus Stress Test[a] Results with Rose Bengal I^{131}–BSP in Normal Subjects and Those Having Known or Suspected Liver Disease

Patient	*Age*	*Sex*	*Diagnosis*	*$BCT_{1/2}$ (min)*		*Blood retention BSP at 45 min, %*
				RBI^{131}	*RBI^{131}+BSP*	
LB	27	M	Normal	6	6	0.0
JDT	25	M	Normal	8	8	0.0
FW	59	F	Normal	8	10	0.0
HS	53	M	Coronary H.D.	10	12	4.0
BS	39	F	Diabetes, enlarged liver	10	15	1.8
AW	67	M	Alcoholism	9	14	6.0
BS	39	M	Rheumatic H.D.	7.5	13	5.0
IC	72	M	Diabetes	5	12	0.0
LB	47	M	Recent cor. occl.	10	20	0.0
WM	41	M	Cirrhosis	7.5	20	8.0
WG	64	M	Alcoholism	5.0	18	0.0
PS	38	F	Portal cirrhosis	30	105	42
WM	53	M	Alcoholism	8	23	2.2
VM	42	M	Alcoholism	10	25	0.0
MJ	59	M	Cardiac hepatomegaly	7	14	—
ES	68	F	Cardiac hepatomegaly	9	18	0.0
EP	26	M	Ac. pancreatitis	7	14	0.0
AA	22	M	Res. hepatitis	6	12	0.0
AK	51	M	Cirrhosis	18	—	22
MS	46	M	Alcoholism	10	18	12
CB	41	F	Alcoholism	12	—	17
ES	20	M	Chr. hepatitis	—	100	53
JK	63	M	Cirrhosis	35	—	36
EM	40	F	Res. hepatitis	—	18	10

[a] In stress tests, 5 mg/kg of bromsulphalein (BSP) are injected simultaneously with the tracer dose (10–50 μc) of Rose Bengal I^{131} (1.0 μc/25 lb).

ary obstruction and these findings correlated with the clinical picture. However, biochemical evidence for obstruction increased during this period and did not reflect the true condition of biliary tract patency until two weeks later. The clinical and laboratory findings in this patient are consistent with a diagnosis of transient obstructive jaundice from recurrent common duct stone which was passed spontaneously.

Case 2. An example of intermittent biliary obstruction again demonstrated by repeated preoperative hepatograms is presented in Fig. 6 along with postoperative findings. As in the case of the previous patient, the obstruction had been low-grade and transient, and there was relatively little associated parenchymal liver damage. The underlying pathophysiological disturbances were reflected accurately in the hepatograms in both of these cases.

Case 3. Findings in a 71-year-old patient with partial obstructive jaundice of three weeks' duration are shown in Fig. 7. In this patient, recovery was slower and there was more severe secondary liver injury which was not indicated by the biochemical tests. The severe liver injury was demonstrated by the very slow Rose Bengal I^{131} liver uptake and blood clearance rates which correlated closely with the clinical picture and with the liver biopsy findings.

Case 4. An example of acute complete biliary obstruction from common duct stone (12 hours' duration) in a young woman is shown in Fig. 8. Initial findings by the BSP and the hepatogram indicated high-level obstruction with severe impairment of liver function. The patient was in a critical condition, verging on shock, which persisted for 24 hours in spite of supportive measures. At operation, complete obstruction from a stone impacted in the pancreatic portion of the common duct was found. It is likely that the slow Rose Bengal I^{131} blood clearance and liver uptake rates were related largely to an associated acute impairment of liver circulation. This explanation is supported by the increased liver vascularity detected in the postoperative hepatograms and by the sudden improvement in liver function following release of biliary obstruction. In this patient the indirect biochemical liver test results did not provide strong evidence for obstruction, whereas the first hepatogram demonstrated gross impairment of dye excretion into the intestine.

Case 5. The data from a patient having nearly complete biliary obstruction of several weeks' duration

Table 5. Effects of Portal Vein and Hepatic Artery Ligation on Bile Secretion and Response to Decholin in Rabbits[a]

Status of blood supply to liver	*Vol of bile secreted in 15-min periods (ml)*	
	Before injection	*After injection with sodium dehydrochlorate*
Portal vein intact	1.95	4.3
Portal vein ligated	0.75	0.45
Hepatic artery intact	1.5	4.2
Hepatic artery ligated	1.5	3.6

[a] Bile samples collected by cannulation of the common bile duct.

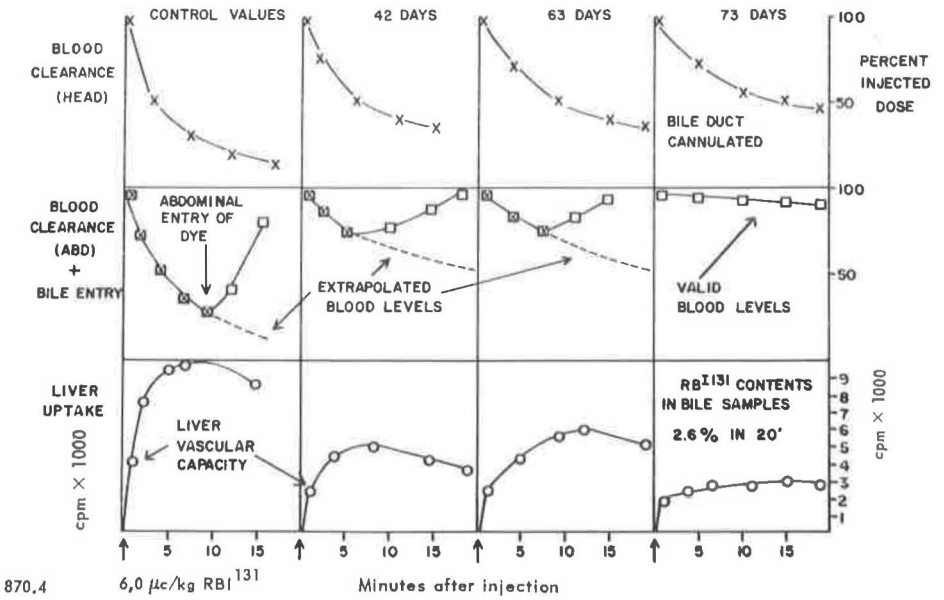

Figure 4. Development of portal vascular functional impairment and cirrhosis during chronic CCl_4 poisoning in the rabbit (10 mg/kg once weekly)

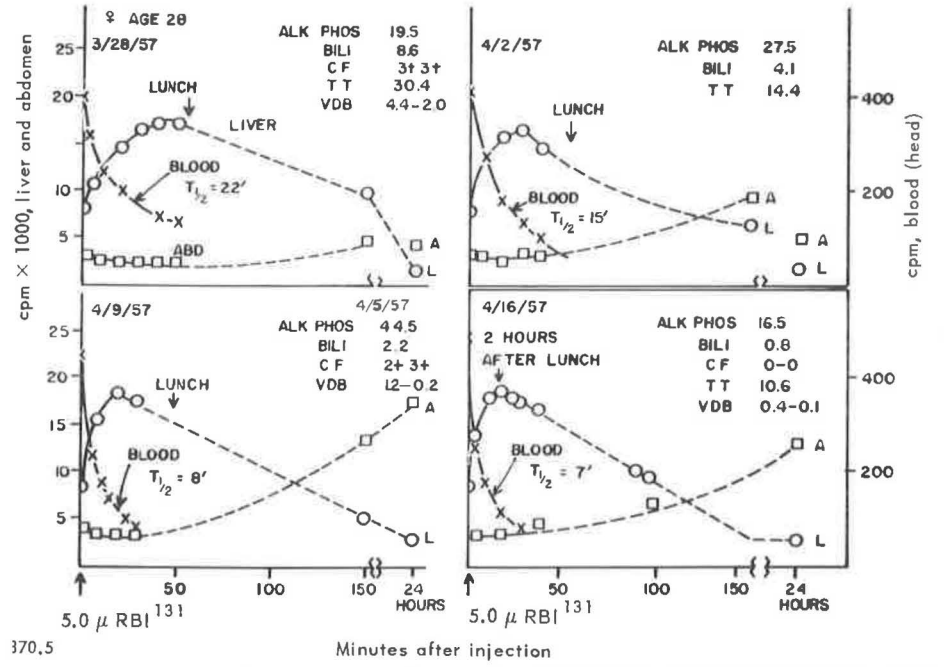

Figure 5. Patient with transient recurrent jaundice from common duct stone, 3 months after cholecystectomy

from carcinoma of the head of the pancreas are shown in Fig. 9. The hepatogram findings pre- and postoperatively reflected accurately and quickly the effects of the surgical correction of biliary obstruction. Again, the alkaline phosphatase results lagged behind the hepatogram findings after release of the obstruction. Although little indication of secondary parenchymal change was indicated by flocculation tests, the recovery of liver function in this patient with jaundice of long duration was slower than in the previous cases and paralleled the clinical course and operative findings.

Case 6. Findings in another patient with long-standing obstructive jaundice from carcinoma of the head of the pancreas are shown in Fig. 10. The hepatogram gave direct evidence of a complete biliary obstruction: dye did not enter the intestine for 24 hours and dye retention was prolonged in both the liver and the blood. The latter findings are consistent with intrahepatic regurgitation of bile and dye. The standard liver test results indicated obstruction and mild parenchymal cell damage. The hepatogram indicated more severe polygonal cell damage by the slow blood clearance and liver uptake rates—especially in view of the normal liver vascular capacity. The latter results mirrored the clinical picture more closely and were confirmed by liver biopsy.

Case 7. In Fig. 11 are shown the results of repeated hepatograms and biochemical liver tests in a patient

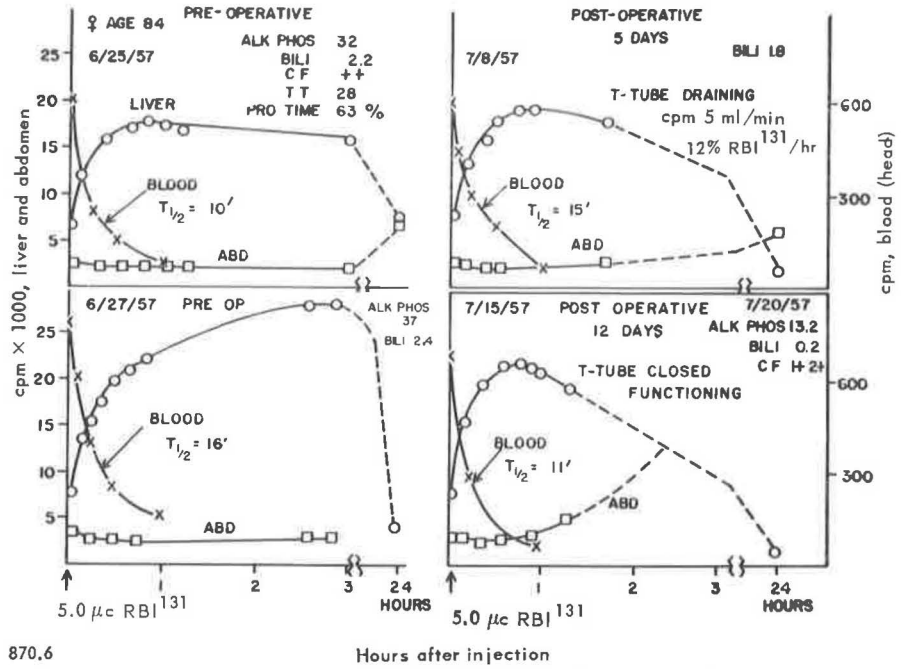

Figure 6. Patient with intermittent biliary obstruction from common duct stone

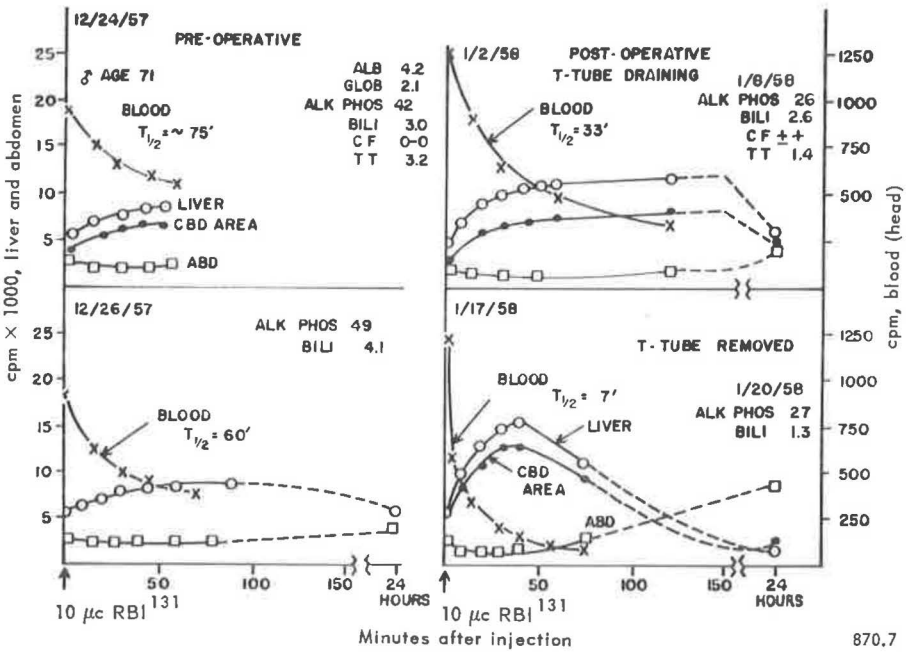

Figure 7. Patient with partial obstructive jaundice, 3 weeks' duration

with severe acute infectious hepatitis. Again the changes revealed by the hepatogram followed the clinical picture more closely than did the results of the other liver tests, particularly the cephalin flocculation which remained the same in spite of reduction of bilirubin and thymol turbidity. The high alkaline phosphatase at the height of the disease and its subsequent lower levels may have reflected a transient period of partial intrahepatic obstruction. The low level of Rose Bengal I^{131} liver retention at 48 hours proved there was not a high degree of biliary obstruction. The subsequent clinical course and results of repeated liver tests confirmed the diagnosis of infectious hepatitis.

Case 8. The reproducibility of the hepatogram is demonstrated by Fig. 12 which shows the similarity in test results (2 months apart) from a patient having advanced but stabilized portal cirrhosis 5 years after a portal-caval shunt operation for bleeding esophageal varices. In addition, these findings show the greater sensitivity of the BSP and hepatogram tests over the cephalin flocculation test in cirrhosis. The advantage of the hepatogram over the BSP lies in the fact that the hepatogram also reveals the marked reduction in liver vascular capacity. Furthermore, from the data

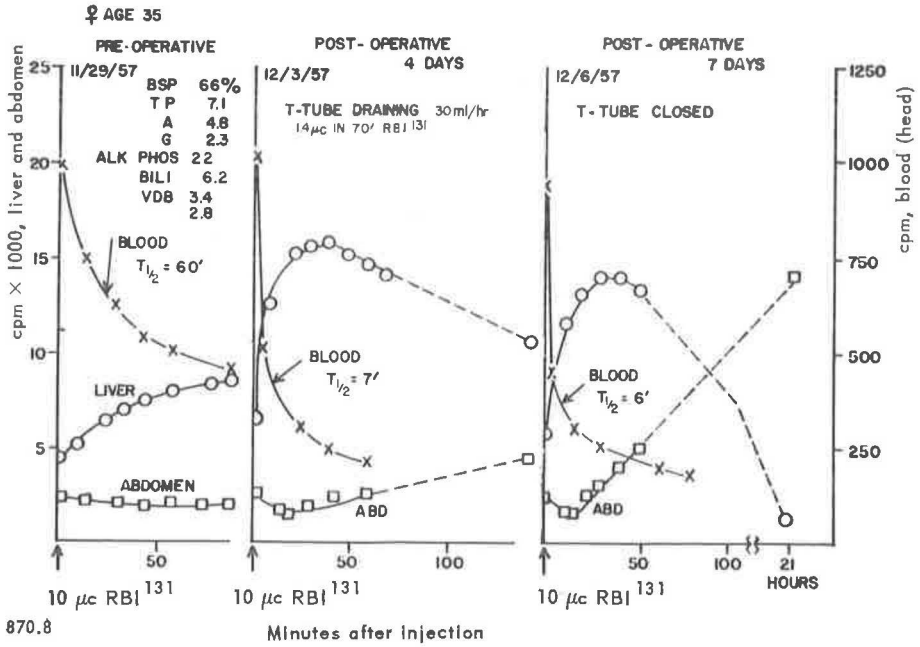

Figure 8. Patient with acute complete biliary obstruction due to common duct stone

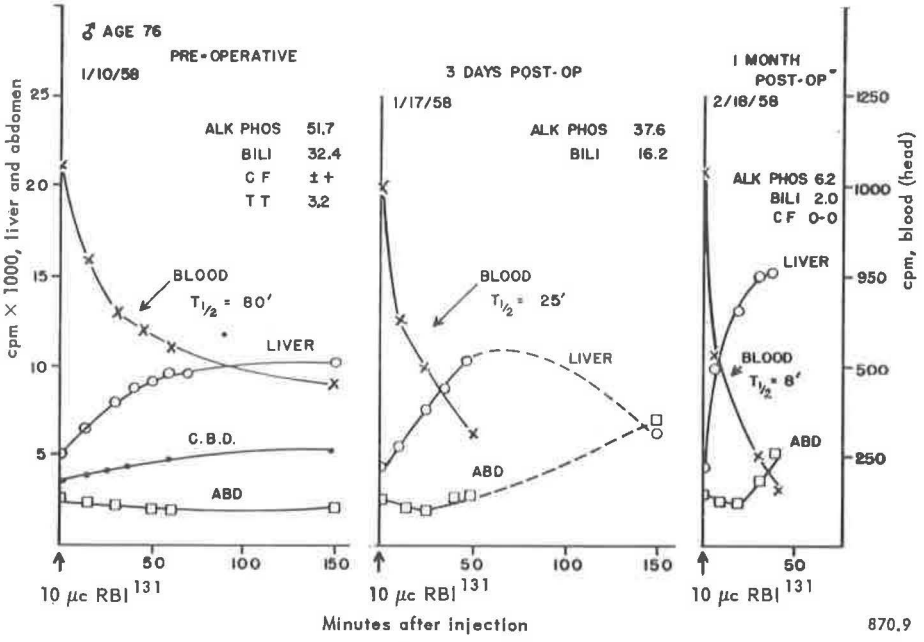

Figure 9. Obstructive jaundice from carcinoma of the head of the pancreas

presented in the previous cases, it is apparent that Rose Bengal I^{131} blood clearance and liver uptake rates are not directly related to the degree of bilirubinemia,[18] but reflect changes in polygonal cell function and liver vascularity.

Case 9. Findings presented in Fig. 13 show again the reliability of the hepatogram in mirroring the changes in parenchymal and vascular function of the liver in a cirrhotic patient recovering from hepatic coma brought on by severe hemorrhage from esophageal varices. The Rose Bengal results showed a distinct improvement in the ability of the liver to extract dye from the blood and a definite increase in liver vascular capacity. Furthermore, the hepatograms also demonstrated an absence of interference with bile flow by showing a progressive reduction in 24-hour values for liver retention and an associated improvement in the rates of dye entry into the intestine. Although the patient recovered dramatically, the indirect biochemical liver test results indicated a progressive deterioration of function in respect to protein metabolism. It is most likely that liver functions were reduced below critical levels by temporary reduction in hepatic blood supply during severe hemorrhage. The initial hepatogram indicated the true severity of the situation by a ten- to fifteenfold reduction in blood clearance and liver up-

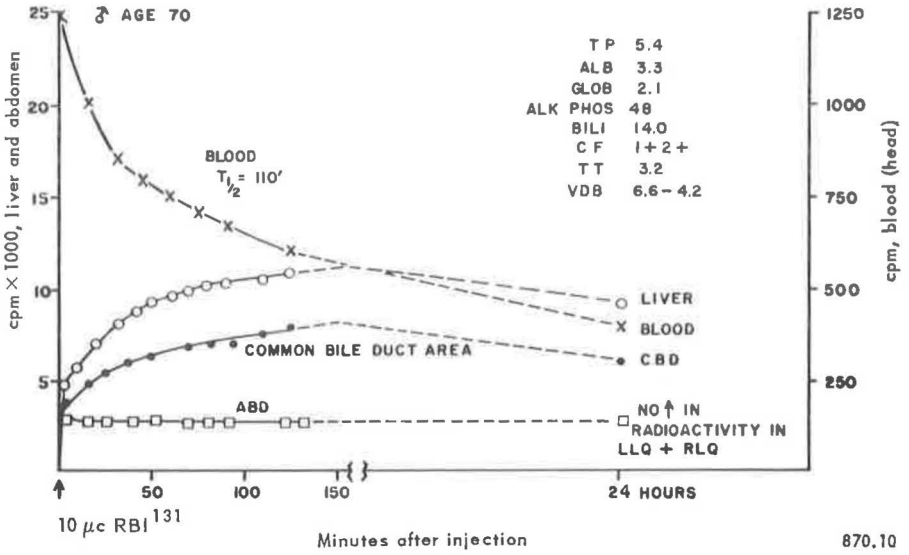

Figure 10. Patient with obstructive jaundice of 2 months' duration from carcinoma of the head of the pancreas

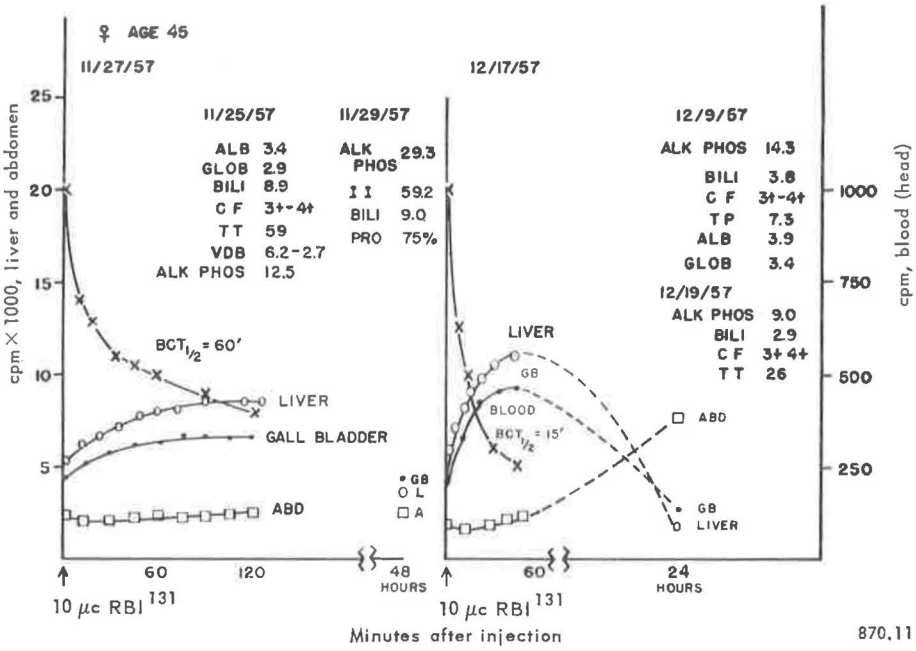

Figure 11. Patient with severe acute infectious hepatitis

take rates and by a threefold decrease in liver vascular capacity when compared with normal values.

Case 10. Comparison between repeated hepatograms and the results of biochemical liver tests in a patient with an unusually protracted and severe case of obstructive jaundice from chlorpromazine is presented in Fig. 14. Liver biopsy showed cholangiolar bile stasis, normal triads and no dilation of the intrahepatic bile ducts. Although the patient was uncomfortable from severely pruritic jaundice, there were no complaints referable to the gastrointestinal tract except for loose, light-colored, fatty stools. Appetite remained exceptionally good, and the patient felt and behaved well in spite of the severe jaundice, excoriative dermatitis and secondary furunculosis. The laboratory findings before and after a course of cortisone (Aristocort) and tetracyline (Terramycin) are presented in Fig. 14. The hepatograms show a slight improvement in liver function and freedom of bile flow, but no significant change is revealed by the biochemical tests. Clinically there was definite improvement in bowel function and complete recovery from the furunculosis and pruritis, but no change in the jaundice. The hepatograms indicated unimpaired liver vascularity and incomplete biliary obstruction that improved during medical management.

Resume of Clinical Studies

The hepatogram findings in over 100 patients with common hepatobiliary tract diseases are compared with the findings in 50 subjects having normal liver functions (see Table 6). The blood clearance half-time and liver vascular capacity values provide reliable in-

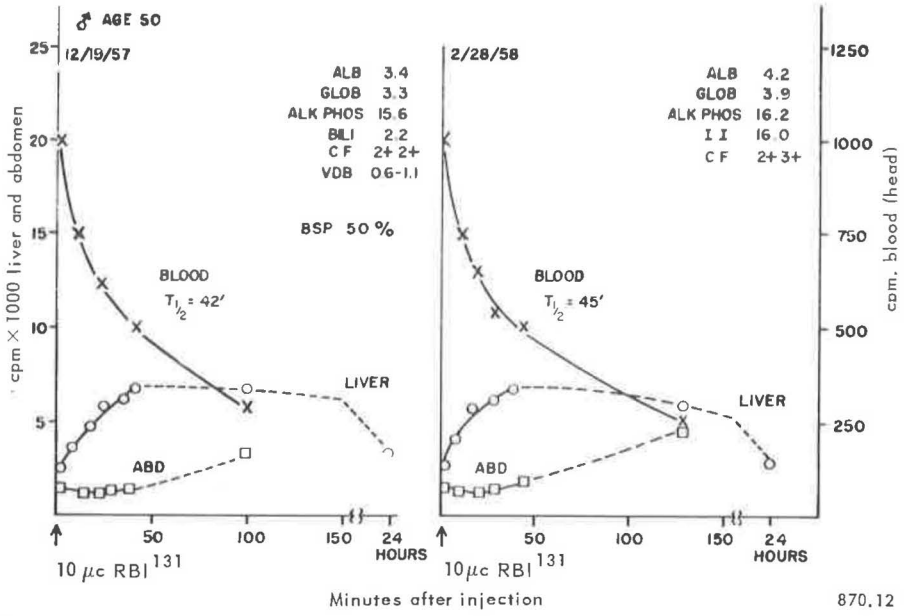

Figure 12. Hepatograms taken 2 months apart. Patient with advanced portal cirrhosis 5 years after a portal-caval shunt operation

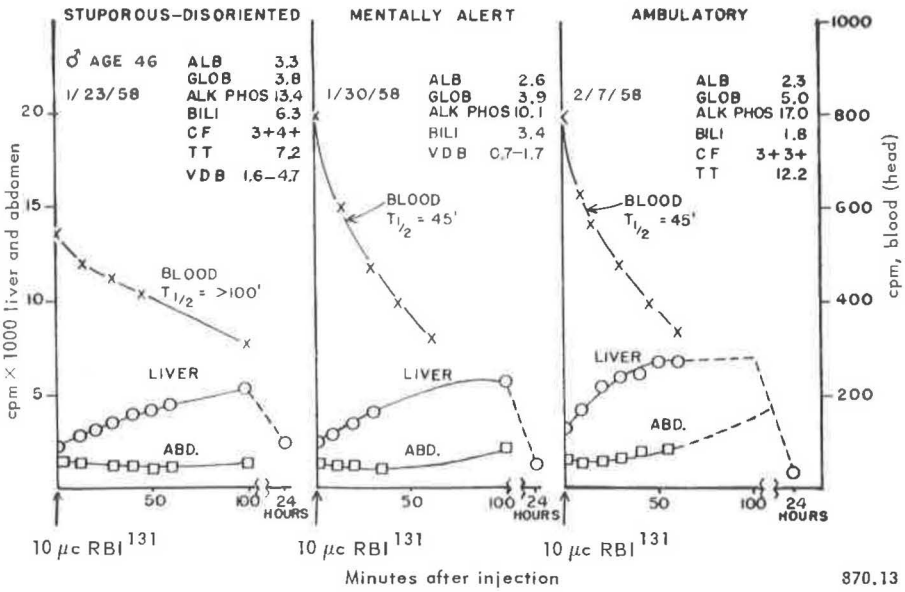

Figure 13. Patient with cirrhosis of the liver. Hepatic coma brought on by severe hemorrhage from esophageal varices; hepatogram findings through stages of recovery

dices for evaluating polygonal cell function and disturbances of liver blood supply. Repeated measurements over the abdomen and liver provide data from which estimates of bile flow interference may be made on a purely mechanical basis. In nearly all jaundiced patients these features of the hepatogram are sufficient to differentiate medical from surgical causes, especially when the test is repeated during critical periods. In our experience, there have been only 3 patients in whom the results of serial tests did not reveal some diagnostic differences. These were patients with severe jaundice of long duration who were first tested after liver function had deteriorated to the point where either the liver cells were unable to remove dye from the blood or the dye was regurgitated with bile into the circulation.[6] Such conditions may develop after prolonged complete extra- or intrahepatic obstruction and may also be the result of severe primary liver disease. Because of this, liver biopsy and surgical exploration are hazardous procedures. The physician and surgeon must lean heavily on clinical experience because laboratory findings may give conflicting data.

In most of the diagnostic problems, serial hepatograms have reflected changes in polygonal cell function and biliary obstruction more quickly and accurately than have biochemical liver tests. In addition, the hepatogram indicates severe impairment of hepatic blood supply (liver vascular capacity) in patients with portal cirrhosis. The moderate reduction of Rose Bengal blood clearance rates found in patients with con-

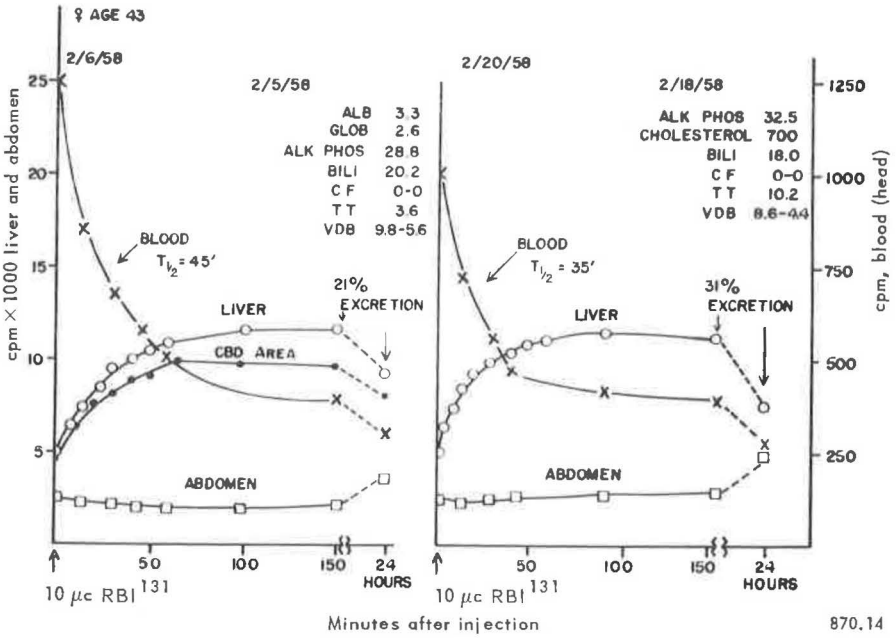

Figure 14. Patient with jaundice from chlorpromazine

gestive cardiac failure indicates the influence of impaired blood flow on the dye extraction capacity of the hepatic cells. Clinical investigations are being made to evaluate the dual blood clearance test for impaired portal function in cirrhosis and other diseases of the liver with an important vascular component.

DIODRAST I^{131} RENOGRAM STUDIES

Findings in Subjects with Normal Kidney Functions

After intravenous injection of a tracer dose (1 μc/5 kg) of Diodrast I^{131}, there is an initial rapid increase in radioactivity, the height of which provides an estimate of renal vascular capacity (segment A). During the next 3–6 minutes radioactivity levels continue to rise to peak values and coinciding with this increase in renal radioactivity there is a reciprocal fall in blood concentration. This second increase (segment B) in renal radioactivity represents the active secretory process (tubular cell function) of the kidney. In normal individuals renal radioactivity levels then fall rapidly from peak to near background values in fifteen to twenty minutes, indicating patency of the upper urinary passages (segment C).

The dynamics of renal uptake–excretion and blood clearance of Diodrast I^{131} following injection of tracer

Table 6. Summary of Rose Bengal I^{131} Hepatogram Findings in Patients with Common Hepatobiliary Diseases

Hepatobiliary tract diseases	*Hepatogram findings*				
	LVC[a] *cpm × 1000*	*BCT½*[b] *(min)*	*AET*[c] *(min)*	*AER*[d] *cpm × 1000*	*Liver retention % LVC*
Subjects having normal liver functions	5.0–8.0	5–10	10–25	1.5–6.0	15–50
Acute, primary liver disease	4.0–7.0	10–60+	10–30	0.5–8.0	15–100
Chronic hepatitis and portal cirrhosis	2.2–5.0	10–60+	10–30	0.5–5.0	25–100
Biliary obstruction: acute, severe	3.5–5.0	10–60+	>90	<0.2	100–300
Biliary obstruction: partial or intermittent	3.5–8.0	5–50	>30	<1.5	50–100
Biliary tract disease without clinical jaundice	5.0–8.0	5–10	>30	1.5–5.0	15–50
Chronic hepatomegaly, cardiac origin	5.0–9.0	15–50	10–30	1.0–5.0	25–100

[a] LVC—liver vascular capacity in cpm × 1000, measured for one minute beginning 30 seconds after injection of Rose Bengal I^{131} (1 μc/25 lb).

[b] $BCT_{1/2}$—time in minutes to reach 50 % blood clearance measured with a separate counter over the side of the head and plotted continuously with an Esterline-Angus recorder.

[c] AET—abdominal entry time, i.e., when initial downward slope begins to rise, indicating arrival of dye in area counted.

[d] AER—abdominal entry rate in cpm per hour during the first 1–2 hours.

doses are nearly identical for man and the rabbit[19] (see Fig. 15). In studies which included 410 patients with normal renograms, only 8 (or 2 per cent) were shown by standard methods to have renal disease. These false negative results were found mainly with the right renogram and are attributed to problems of geometry. The incidence of false positive results is somewhat higher (6 per cent). Most of these errors also occur with the right renogram and are due to positioning of the detector and/or interference from the liver.

Acute Ureteral Obstruction

The renograms in man with sudden ureteral obstruction produced by a ureteral bag catheter and in the rabbit after ureteral ligation are similar and entirely different from the normal. The second segment of the renal uptake curve representing tubular cell function continues to rise and, provided the opposite kidney is functioning normally, finally reaches a plateau in about 20 minutes (see Fig. 16). The renograms from a patient tested before and after surgical removal of a ureteral calculus are shown in Fig. 16.

Hydronephrosis

Forty-nine patients with this diagnosis have been studied with the renogram, and the results correlate well with those from standard urological diagnostic procedures. Hydronephrosis develops from long-standing partial obstruction in the upper urinary passages due to a variety of lesions. The renogram usually shows reduced vascular capacity, an abnormal secretory lag and impairment of excretion manifested

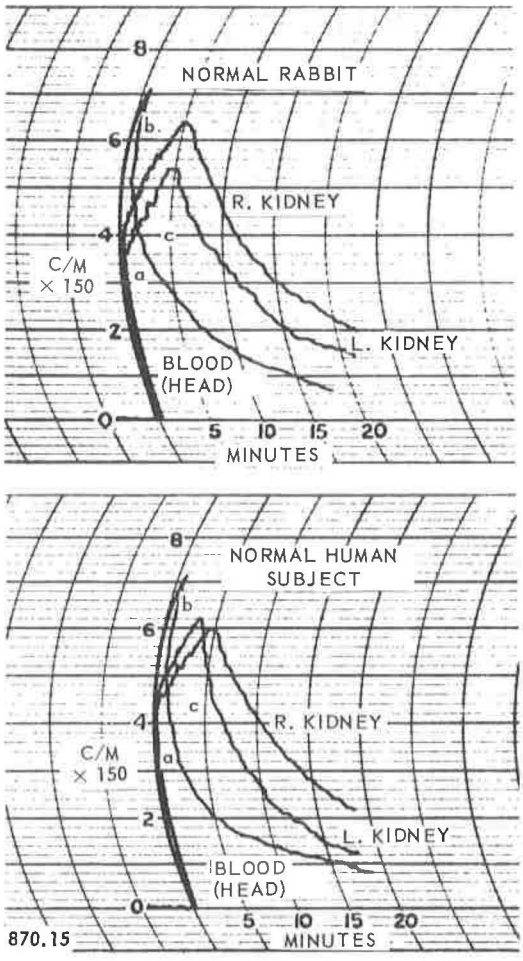

Figure 15. Renal uptake–excretion and blood clearance of Diodrast I^{131} in man and the rabbit

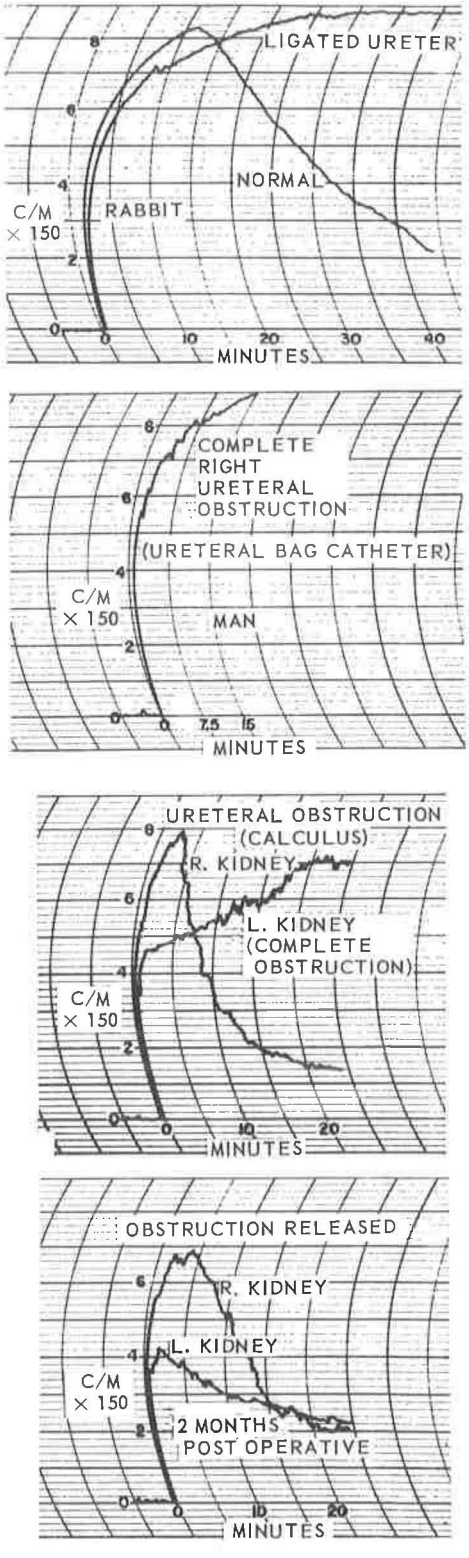

Figure 16. Renogram studies in ureteral obstruction in man and the rabbit

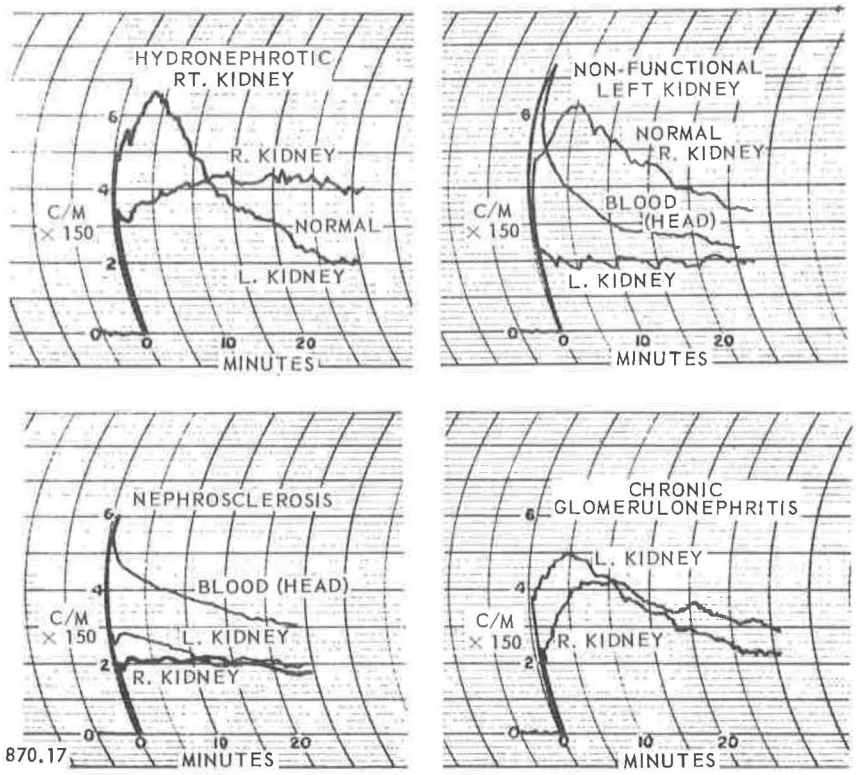

Figure 17. Renograms with Diodrast I^{131} in different diseases of the kidney

by a slowly declining excretion segment. (See Fig. 17, which also shows a nearly normal renogram for the unaffected kidney.)

Nonfunctioning or Absent Kidney

The renogram findings on 45 patients having these abnormalities have been confirmed in all instances either by intravenous or retrograde urography. The renogram results indicate the absence of tubular cell function and reduced vascular capacity in the renal area. The excretion segment of the curve parallels the blood clearance curve (Fig. 17).

Nephrosclerosis and Chronic Nephritis

The renogram findings for 35 patients with these diagnoses show variations of the findings from those shown in Fig. 17. These patients have abnormalities of renal vascularity and tubular cell function, and the excretory segments of the renograms follow the blood clearance curves. Such findings have diagnostic significance only if they occur unilaterally.

Neurogenic Shock

This condition has been observed twice in patients during performance of the renogram test. In both instances the reaction was most probably induced by repeated venipunctures and not by reaction to the test agent. The clinical picture in both cases was similar. The patients appeared pale, apprehensive and complained of feeling faint. Pulse rates were slow and the blood pressure readings fell to low levels. Recovery occurred rapidly and spontaneously as the result of bed rest only. In the first patient the reaction occurred during a tracer test, which was made 10 minutes after injection of a priming dose of 25 ml of a 70 per cent Urokon solution (see Fig. 18). In the second patient the reaction was less severe and occurred during a tracer test with Diodrast I^{131}. In both instances the renograms showed a continuing accumulation of test material in both renal areas similar to curves found in animals and man with complete bilateral ureteral obstruction. However, in the second patient a sudden fall in renal radioactivity occurred after about 20 minutes —as if there had been a sudden release of a ureteral obstruction. At this time the patient's blood pressure increased and symptoms of shock subsided. The two most likely explanations for these findings are (1) bi-

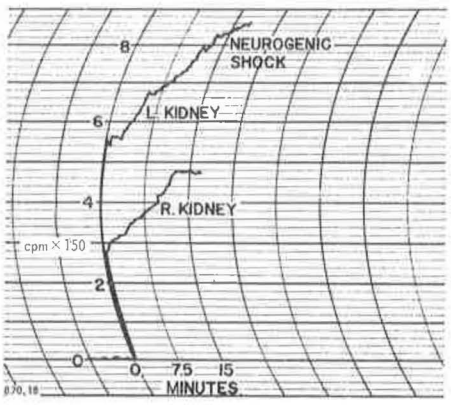

Figure 18. Neurogenic shock during renogram with Diodrast I^{131}

Table 7. Diodrast I^{131} Renogram Findings in Hypertensive Patients with Unilateral Renal Disorders Determined by Standard Methods

Case	B.P.	Renogram		Final diagnosis	Therapy	Results	
		R	L			Period observation, mo.	Remarks
1	220/120	N	Abn	Partially calc. L. kidney	Nephrectomy	14	Cured
2	150/116	N	Abn	Partial infarc. L. kidney	Observation		Spont. cured
3	230/130	Abn	N	Coarcted R. renal art.	Resection	24	Cured
4	240/130	Abn	N	Contracted R. kidney	Nephrectomy	24	Improved
5	148/92	N	Abn	Pyelonephritic L. kidney	Nephrectomy	24	Cured
6	250/165	N	Abn	Agenesis L. kidney	Nephrectomy	30	Improved
7	280/160	Abn	N	Pyelonephritic R. kidney	Observation	16	Unchanged
8	150/100	Abn	N	Hydronephrosis R. kidney	Observation		Unchanged
9	150/100	N	Abn	Hydronephrosis L. kidney	Lithotomy	30	Cured
10	180/100	N	Abn	Absent L. kidney Prostatic obstr.	Prostatectomy	30	Improved
11	190/120	Abn	N	Pyelonephritic R. kidney	Nephrectomy		Improved
12	210/120	N	Abn	Pyelonephritic L. kidney	Nephrectomy	7	Improved
13	200/100	Abn	N	Pyelonephritic R. kidney	Nephrectomy	4	Improved
14	210/130	N	Abn	Pyelonephritic L. kidney	Nephrectomy	4	Improved
15	190/120	N	Abn	Pyelonephritic L. kidney	Nephrectomy	1 week	Died
16	184/115	N	Abn	Pyelonephritic L. kidney	Observation		Unchanged
17	250/130	N	Abn	Pyelonephritic L. kidney	Observation		Unchanged
18	188/118	Abn	N	Congenital rotation R. kidney	Observation		Unchanged
19	190/120	N	Abn	Pyelonephritic L. kidney	Nephrectomy	5	Cured
20	220/150	N	Abn	Essential hypertension	Observation		Unchanged
21	190/100	Abn	N	Pyelonephritic R. kidney	Nephrectomy	2	Cured
22	127/80	N	Abn	Pyelonephritic L. kidney	Observation		Unchanged

lateral ureteral spasm and (2) depression of urine formation with accumulation of test material in the tubular cells as a result of reduced blood flow.

DETECTION OF UNILATERAL RENAL DISORDERS IN HYPERTENSIVE PATIENTS

The pathogenesis of renal hypertension remains incompletely resolved despite an enormous amount of experimental work stimulated by the work of Goldblatt *et al.*[20] more than twenty years ago. Interest in this disease is revived periodically by reports of dramatic cures following nephrectomy for unilateral renal disease.[21–24] Homer Smith found 262 cases from a review of the literature[5] up to 1948, but only 19 per cent were reported cured by nephrectomy. Attention has been focused again on unilateral renal disease and hypertension as a result of the development of renal aortography[9,10] and other means of detecting individual kidney disease.[24,25] The bulk of evidence implicates pyelonephritis and various vascular lesions as the main causes of renal hypertension.[9,10] Among hypertensive patients in general it is estimated that in only 2–5 per cent is unilateral renal disease the sole cause of the hypertension.

The Diodrast I^{131} renogram test has been used along with standard urological diagnostic procedures in the study of 75 hypertensive patients. The renograms revealed definitely abnormal unilateral findings in 22 individuals, abnormal bilateral findings in 30 cases, and in the other 23 persons the tracings were normal. When compared with one or more standard tests for individual kidney function, the renogram correctly local-

ized the lesion in 73 of the 75 patients. The renogram gave a false positive result in one patient in each of the two groups with renal disease, but all 23 patients with essential hypertension had normal tracings.

The information presented in Table 7 summarizes the findings in 22 patients with unilateral renal disease diagnosed by standard methods. More complete information on the first 10 patients has been published previously by one of us.[25] The diseased kidney was removed surgically in 13 patients; in 6 the blood pressure readings have returned to and remained at normal levels for the duration of the observation period (2–30 months); in 6 others there has been improvement, but a mild to moderate hypertension has persisted; one patient died 7 days after nephrectomy. The remaining patients refused surgery or operation was deferred for various reasons. One of these (2) experienced a spontaneous cure after partial infarction of the left kidney.

From this limited series it is apparent that unilateral pyelonephritis is a common cause of renal hypertension and that nephrectomy is an effective treatment. However, it may be fortuitous that there were so many temporarily successful results.[23] The most remarkable cure followed resection of a coarctate right renal artery in a young woman (3) who had developed severe hypertension during the preceding 12 months. Her right renogram showed reduced vascular capacity, decreased tubular cell function and impaired drainage. The excretory urogram and retrograde pyelograms were both normal. Diagnosis was made by aortography and was confirmed by abnormal individual kidney clearances and dye excretion tests. Her postoperative renograms were negative and her blood pressure has remained normal for 30 months.

The excellent correlation between Diodrast renogram findings and the final diagnoses made by standard procedures in this group of 75 patients demonstrates the reliability of the renogram and its usefulness as a rapid screening test for the detection of unilateral renal disorders. Hypertensive patients with normal renograms may be spared the discomfort, time and expense of extensive urological investigation in most instances, and the more complete urological investigations would be limited to those relatively few patients who have disease of one kidney, as indicated by an abnormal renogram.

DISCUSSION

In spite of extensive investigations of liver structure and functions[6] the present-day physician is frequently puzzled by patients with nonhemolytic jaundice. The multiplicity of liver tests belies our knowledge of liver functions. The manifestations of liver disease are poor indicators of the severity of the underlying pathophysiological disorders.[6,7] Jaundice from cholangiolar obstruction may be severe, but even these patients may have relatively little liver damage and are surprisingly free of symptoms. On the other hand, severe impairment of liver function may go unrecognized for years in nonjaundiced patients with portal cirrhosis.[7] A cirrhotic patient may be catapulted from an apparently healthy ambulatory state into hepatic coma and then recover, and during this period standard biochemical liver tests may show no changes other than those of a static impairment of several functions. The flapping tremor[26] is not pathognomonic for liver disease, and the same may be said for palmar erythema and spider angiomata. An enlarged nontender liver may possess either excellent or greatly impaired function. These wide discrepancies among signs, symptoms and laboratory findings are noted, not to belittle the value of biochemical liver tests which are useful in the great majority of patients,[6] but to point out the need for sensitive organ and cell-specific test procedures and a knowledge of the influence of altered liver circulation on test results. Some of the most important unknown aspects of hepatic disease are related to the effects of defective circulation on the functions of the polygonal and von Kupffer's cells.

However, based on data from a study of more than 200 patients and several hundred rabbits plus the work of others,[18,27,28,29] Rose Bengal I^{131} tracer tests are practical procedures for estimating liver vascular capacity, polygonal cell function and bile flow interference.

The new Rose Bengal–BSP stress test procedure increases the sensitivity of the tracer test and is capable of detecting minimal liver damage in animals and asymptomatic liver disease in man. However, further clinical investigation including liver biopsy is needed to assess its sensitivity in patients suspected of having mild liver disease. Related tracer techniques are needed to measure disturbances in the venous and arterial components of the hepatic circulation. Tracer techniques for estimating functional impairment of the portal system in man are being developed on the principle of dual blood clearance demonstrated in studies on animals and described in this paper.

The difficulties and dangers of standard methods for estimating individual kidney function and renal vascular defects summarized in this paper have been reported in the published works on the advantages and disadvantages of the Diodrast I^{131} renogram.[12,19,25] It should be re-emphasized that the renogram was developed as a rapid clinical procedure for use primarily in the field of urology to detect *qualitative* abnormalities of individual kidney function.[12,19] Little effort has been made so far to increase its sensitivity as an over-all renal function test. Emphasis has been placed instead by one of us (C.C.W.) on evaluating its clinical usefulness in urology[12] and its reliability as a screening test in the investigation of renal hypertension.[25] Since the bulk of current evidence indicates the importance of renal vascular lesions as causes for renal hypertension, studies are now in progress to increase the accuracy of the renogram as a measure of renal vascular capacity. In addition, other related test agents such as Hypaque, Miokon and Urographin have been employed in place of Diodrast. These test materials have the advantage of being removed from the blood by the kidneys exclusively and not partially by the liver as is Diodrast. However, their slower excretion is a disadvantage.

Thus, Diodrast remains the most suitable tracer test material for general use. The other agents may be substituted in instances where interference from the liver produces an abnormal Diodrast renogram.

Probably the most significant aspect of these investigations is that external tracer techniques, which permit simultaneous measurement of multiple physiological events on a dynamic basis, have indicated a new approach to the study of renal and hepatic diseases and to related problems in other organs or organ systems.

SUMMARY

Recent advances in the development and clinical evaluation of external tracer techniques for measuring multiple functions of the liver and kidneys with I^{131}-labeled Rose Bengal I^{131} and Diodrast are described. The Rose Bengal I^{131} blood clearance–liver uptake tracer test provides reliable indices of polygonal cell function and liver vascular capacity. The sensitivity of the tracer test is increased by the simultaneous injection of bromsulphalein in stress doses of 3–5 mg/kg. Normal tracer and stress test findings indicate the absence of significant liver pathology. A dual Rose Bengal I^{131} hepatogram, a multipurpose tracer procedure, is useful in the differential diagnosis of medical versus surgical jaundice. When the hepatogram is used repeatedly in patients with hepatobiliary diseases results correlate well with the clinical findings and indicate changes in the underlying pathophysiological disturbances more quickly and accurately than do indirect biochemical liver tests.

The Diodrast I^{131} renogram developed as a logical corollary to the hepatogram has been evaluated through extensive clinical investigations in more than 800 patients with a variety of urological diseases. Although the sensitivity for measuring tubular cell function is no greater than most of the other dye excretion tests, its advantages as a simple nontraumatic method for measuring multiple functions of each kidney separately make it a valuable procedure in the practice of urology. Furthermore, it has been demonstrated that the renogram is a reliable and rapid screening test for hypertensive patients suspected of having unilateral renal lesions. It provides a simple diagnostic tool which will extend the investigation of renal hypertension into the field of pediatrics. Most hypertensive patients having normal renogram findings may be spared the discomfort and expense of extensive urological investigations sometimes considered as essential.

ACKNOWLEDGEMENTS

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The Differential Diagnosis of Jaundice with Radioactive Rose Bengal

By R. A. Nordyke and W. H. Blahd*

A simple and sensitive method of demonstrating the presence of extrahepatic biliary tract obstruction is possible with the use of intravenously injected I^{131}-labeled rose bengal dye followed by external scintillation monitoring. Since rose bengal is quantitatively removed from the blood by the liver, secreted into the bile ducts and gall bladder and passed on through the common duct into the intestine, obstruction to its flow can readily be demonstrated by external counting.

METHOD

Non-fasting patients were placed in a comfortable supine position. Two slightly collimated and well-shielded scintillation probes were positioned as follows: (1) horizontally against the head, centered at the ear and (2) over the mid-abdomen directed 30° inferiorly, making certain that it was considerably below the liver (Fig. 1). After obtaining a background count in each position, 25 μc I^{131} rose bengal in 2–5 ml of normal saline were injected intravenously. Counts were then taken at each site every two minutes for 30–60 minutes. Certain patients were also studied in the fasting state.

In order to compare the rates of change of dye concentrations in the different body sites, a semilog plot was used. Net counts (gross minus background) at each position were plotted and the best line drawn through the observed data (Fig. 2). Each curve was moved—by simple parallel geometric displacement—to start at 5 minutes and 100 counts per second for better visual comparison.

RESULTS

Figure 2 shows the results obtained in a normal human in the fasting and nonfasting states. Previous studies in patients with normal and abnormal functions[1] have demonstrated the following:

(1) The slope of the head curve represents the rate of disappearance of dye from the blood. It is essentially the mirror image of the uptake of dye by the liver and is in itself a sensitive index of liver polygonal cell function.

(2) The mid-abdomen curve represents declining radioactivity levels in the blood so long as it parallels the head curve; the point of divergence of the curves denotes the arrival time of the first dye in the intestinal lumen, and the difference between the two curves represents the rate of accumulation of dye in the intestine.

Figure 2A demonstrates the rapid flow of dye into the intestine in the normal postprandial human. During fasting (Fig. 2B) less dye flows, and food causes an immediate increase of dye into the bowel from the gall bladder and common bile duct. The arrival time of dye in the intestine is the same in both instances.

To demonstrate pharmacologic effects on bile flow, studies were done with a number of drugs, both alone and in combination, including neostigmine, morphine, nitroglycerine and amyl nitrite. The effect of neostigmine administered subcutaneously is seen in Fig. 2A. Figure 3 demonstrates the effect of intravenously administered morphine sulfate—the accumulation of dye in the intestine ceased. This state was not overcome by sublingual nitroglycerine but was temporarily relieved by amyl nitrite.

Two elements in the dynamics of intravenously injected rose bengal[1,2] and sulfobromophthalein (BSP)[3–5] are of special interest in determining the presence of extrahepatic obstruction. The first is the rate of disappearance of dye from the blood, indicating the ability of the liver to clear the dye and by inference an indication of liver cell function. The second is the time of arrival of dye in the intestine. Patients with extrahepatic biliary tract obstruction have relatively

Figure 1. Positioning of scintillation probes at the head and mid-abdomen

* Radioisotope Service, Veterans Administration Center, Los Angeles, California.

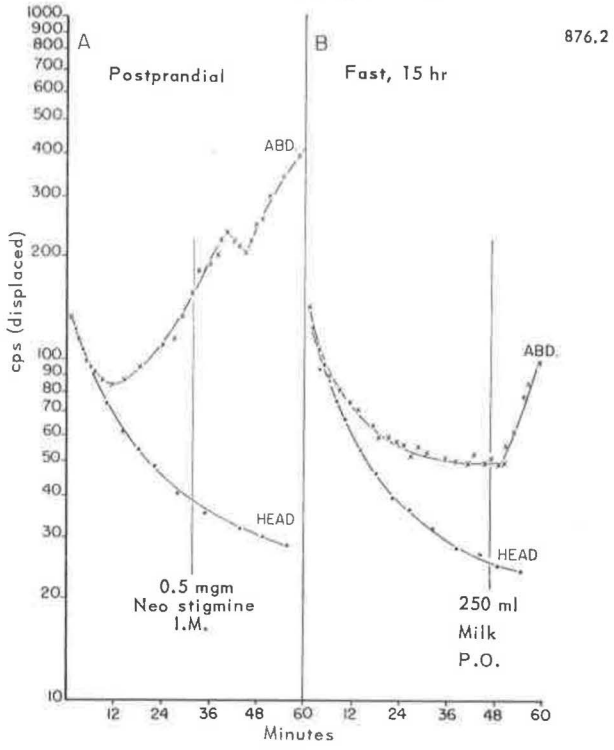


Figure 2A. Normal postprandial curves of counting rates obtained at the head and mid-abdomen, geometrically displaced for visual comparison to 100 cps at 5 minutes. Neostigmine was given at 32 minutes
Figure 2B. Normal fasting curves. Milk was given at 46 minutes

normal liver cell function coupled with a delayed arrival time of dye in the intestine (Fig. 4A), while patients with intrahepatic disease have relatively poor liver function with normal or early arrival times (Fig. 4B). Figure 5 is a graph of these two variables in 37 normal persons, 50 patients with known acute or chronic intrahepatic disease, 9 patients with partial obstruction of the common duct due to stones or stenosis, and 8 patients with common duct obstruction by carcinoma. The following factors are noted:

(1) The ratio of the 20 to 5 minute counting rates, expressed as per cent, is 51% or less in all normal persons.

(2) In all six instances where this ratio was over 90% the patients had severe decompensated Laennec's cirrhosis or viral hepatitis (i.e., intrahepatic jaundice).

(3) In all instances of an arrival time greater than 17 minutes the patients were shown, with one exception to have extrahepatic biliary tract obstruction.

(4) In eleven patients with severe jaundice there was no detectable arrival of dye in the intestine up to one hour. Seven of these were cases of intrahepatic and 4 were cases of extrahepatic jaundice.

(5) Two cases of partial extrahepatic obstruction had arrival times of less than 17 minutes.

The equivocal cases (see 4 and 5 above) are a small percentage of the number examined, but are important diagnostically. The largest group is the one in which no dye arrives in the intestine and therefore no arrival time can be noted. In order to differentiate the intra- and extra-hepatic patients in this group, an additional technique has been developed based on the response of the normal biliary tract to food. Figure 6A shows data obtained from a patient with jaundice due to cancer at the ampulla of Vater. Despite fairly good dye clearance from the blood (i.e., good liver function), there is no response to food. In comparison, the patient shown in Fig. 6B had severely decompensated Laennec's cirrhosis; there was minimal clearance of dye from the blood (i.e., markedly poor liver cell function) but food caused a prompt increase of dye in the intestine. For this phenomenon to occur, a patent common bile duct would seem to be necessary. The other difficult diagnostic group, patients with stones in the common duct, may be differentiated by this method, but sufficient data is not presently available.

DISCUSSION

Most previous methods for determining the presence of extrahepatic biliary tract obstruction have been indirect and nondynamic. A more direct approach for measuring the arrival time of BSP dye in the duodenum after intravenous administration was suggested in 1952 by Caroli, Tanasoglu and Cohen[3] and elaborated by others.[4,5] This method was technically rather difficult, involving duodenal intubation, fluoroscopic placement of the tube in the duodenum and pharmacologic sphincter relaxation. However, the results

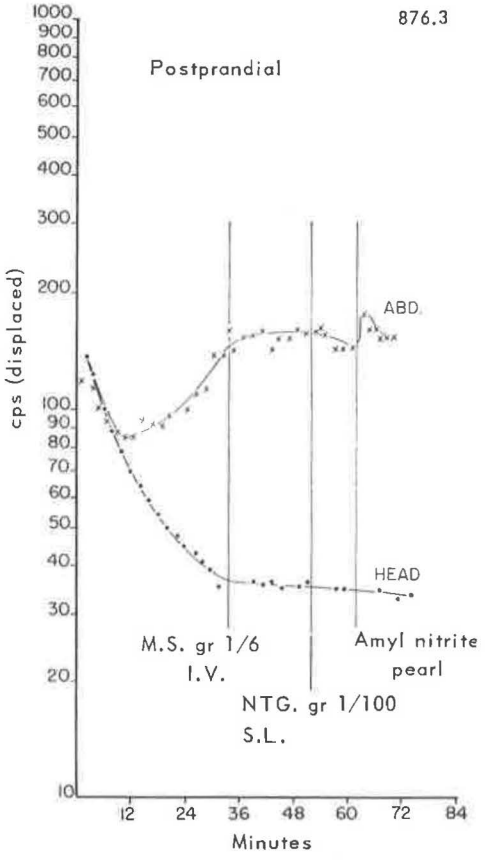
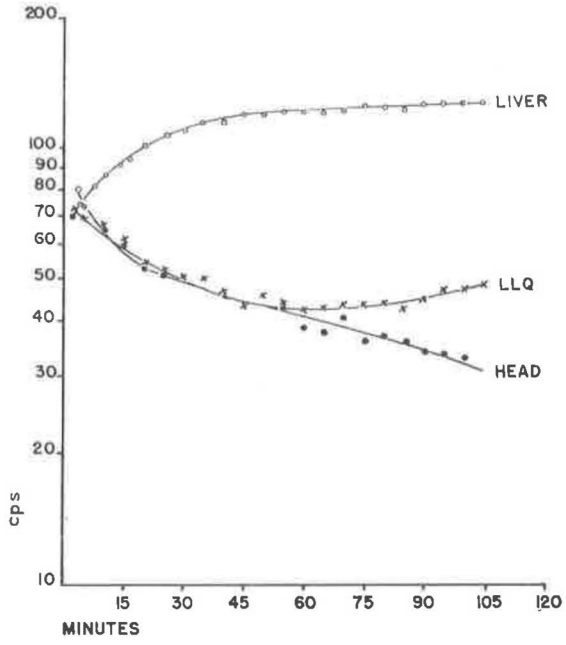


Figure 3. Postprandial curves in a normal patient. Morphine sulfate was given intravenously followed by nitroglycerine and later by amyl nitrite



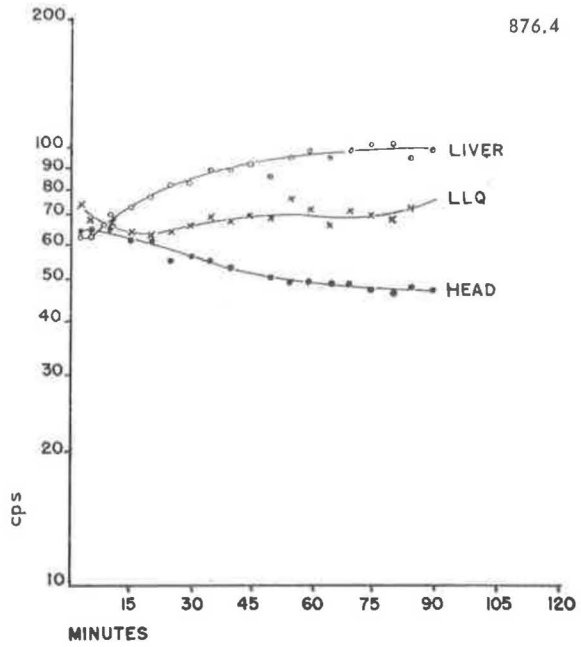


Figure 4A (left). Curves of counting rates at the head, left lower abdominal quadrant and lower edge of liver in a patient with extrahepatic obstruction of the common duct of 5 weeks' duration caused by carcinoma of the pancreas. Figure 4B (right). Severe intrahepatic disease due to decompensated Laennec's cirrhosis

seemed to indicate that this method was superior to standard methods. It was found that the dye arrived late in cases of extrahepatic biliary tract obstruction whereas in intrahepatic disease the time of arrival was normal or early. A few false negative and false positive cases were found.

We have attempted to simplify and extend this direct method by observing the changing concentrations of radioactive rose bengal over the abdomen below the outlet of the common bile duct by the expedient of serial external scintillation counting after intravenous injection of the dye.

We have been able to quickly obtain an accurate and reproducible arrival time of the dye in the intestine and our results in clinical cases have been similar to those obtained with the BSP method. To differentiate instances in which no dye arrives in

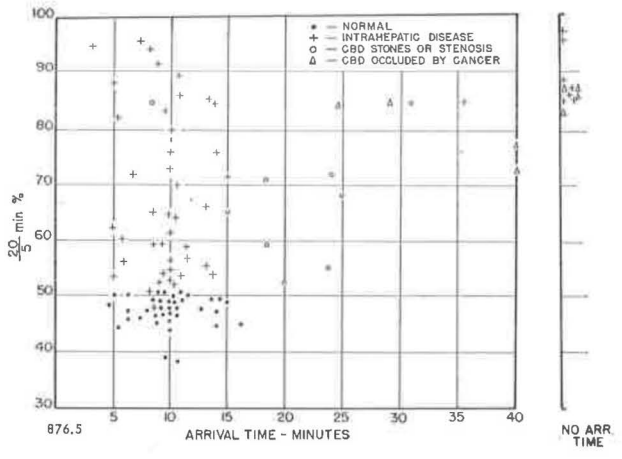


Figure 5. Rate of disappearance of dye from the blood (ordinate) expressed as a per cent of the 20/5 minute counting rates, and time of arrival of dye in the intestine (abscissa) in normal persons and in patients with intrahepatic disease and extrahepatic biliary tract obstruction

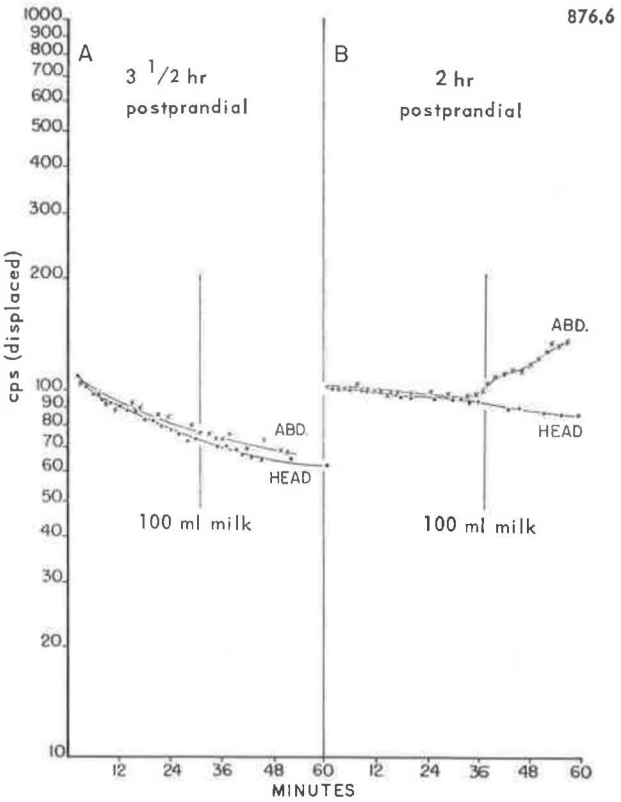


Figure 6A. Carcinoma of the ampulla of Vater. No response to ingestion of milk

Figure 6B. Severe decompensated Laennec's cirrhosis. Marked response to ingestion of milk

the intestine, the technique of giving food during the test to the fasting patient is promising. The few instances where the arrival times of the dye is normal although stones are present in the common duct remain an enigma at this time.

SUMMARY

A direct method is presented for determining the presence of extrahepatic biliary tract obstruction, using intravenously administered radioactive rose bengal followed by external scintillation monitoring.

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The Value of Rose Bengal-I^{131} as a Liver Function Test in Hepatic Bilharziasis

By F. Sallam, H. Daw, K. A. Mahmoud, A. Mamoon, I. Hazzaa and F. G. Zaki*

Urinary and intestinal bilharziasis are endemic in Egypt. Hepatic bilharziasis occurs as a complication of the intestinal form of bilharziasis. The ova of *Bilharzia*, usually Mansoni, reach the liver as emboli through the mesenteric veins in the same way as the amoeba reaches the liver in amoebic liver infection.

Reaching the liver via portal radicles, these ova provoke a reaction consisting of congestion, eosinophil and histocyte infiltration and granular tissue formation that encroach on parenchymal liver cells. This stage of infiltration is followed, after a variable period, by fibrosis which is typically located around the mouths of the portal radicles. The fibrous strands extend in a tapering manner along the small subdivisions of Glisson's capsule to meet similar ones from other portal tracts with parial enclosure of one or several hepatic lobules. The lobular pattern of the liver is still preserved, but the Kupffer cells, containing bilharzial pigments, become hypertrophic. The liver cells near the fibrous strands show atrophic necrosis.

The fibrotic tissue may be condensed as cord-like masses around the large portal tracts, or may be diffused throughout the small portal tracts, due to embolisation of ova through fine radicles, to give a relatively homogeneous appearance.

The bilharzial ova are usually present in all the early cases of infiltration, but they are present in only about three-fourths of the fibrotic cases. Splenomegaly develops towards the end of the hepatic infiltrative stage and is common during the fibrotic stage. Enlargement of the spleen is usually due to gradual portal obstruction, to deposition of the bilharzial ova in the spleen and to reaction of the spleen to infection by proliferation of the reticulo-endothelial system.

In the late stages of this liver disorder, ascites develops due to portal obstruction or partial thrombosis, to bilharzial peritonitis and sometimes to hypoproteinemia. Though the bilharzial hepatic affection starts at the portal radicles, no biliary obstruction has been encountered in any case.

Clinically, the development of hepatic bilharziasis passes through four stages, *viz.*:

(1) hepatic infiltration (hepatomegaly),

(2) hepatic infiltration with enlarged spleen (hepatosplenomegaly),

(3) hepatic fibrosis and

(4) hepatic fibrosis associated with ascites.

Recently, radioactive I^{131}-Rose Bengal has been used successfully as a measure of hepatic function and biliary patency.[1–14]

The present work is a preliminary study of the uptake–excretion of this dye by patients with hepatic bilharziasis. For this purpose a group of 19 patients with this disease as confirmed by biopsy and 15 normals (controls) were examined.

METHODS AND TECHNIQUES

Liver function tests such as icterus index (II), thymol turbidity (TT), serum alkaline phosphatase (AP) and bromsulphalein (BSP) together with liver biopsy (aspiration method) were performed on patients with hepatic bilharziasis. The urine and stools were also tested for the presence of bilharzial ova and for blood in order to differentiate between active and nonactive bilharziasis. Blood examination was also carried out to check for anemia, eosinophilia and lymphopenia.

The Rose Bengal used in this work contained 1 mg of the dye per 1 millicurie of I^{131}. Dilution was made with saline. Each patient received a dose of 25 μc. The γ-ray activity was measured by the use of a collimated scintillation probe attached to a scaler. The crystal of the probe was placed over the epigastric portion of the liver, 5 inches away from the surface. The position of the patient and the probe remained unchanged throughout the test. After intravenous injection of the dye, 5 minute counts were registered for 60–90 minutes. The counts were plotted against time on semilogarithmic paper after the method devised by Lowenstein.[12] (See Figs. 1 and 2.)

The uptake–excretion curve obtained was usually analysed qualitatively and quantitatively. Qualitative analysis gives a rapid idea about:

(*a*) The vigour of blood circulation in the liver, from the height of the peak in the curve.

(*b*) The functional capacity of the liver parenchymal cells to take up the dye, from the gradient of the dye uptake.

(*c*) The functional capacity of the liver parenchymal cells to excrete the dye as well as the patency of the biliary system, from the gradient of the dye excretion.

In the quantitative analysis[12] the uptake half-time $U_{\frac{1}{2}}$ is the time interval in which the liver collects half of the circulating radioactive dye; whereas the excre-

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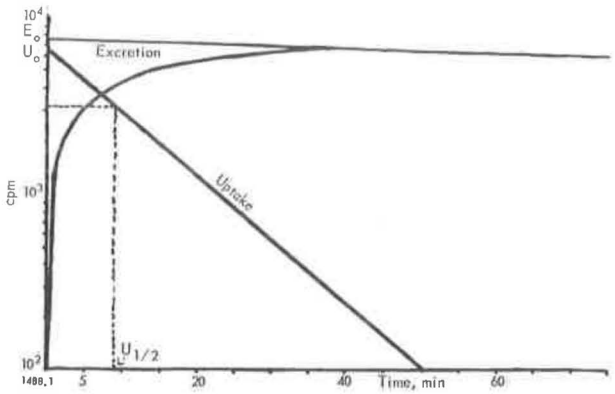

Figure 1. Uptake–excretion curve of a normal subject (case 15). $U_{½}$, 5 min; $E_{½}$, 103 min; R, 17%

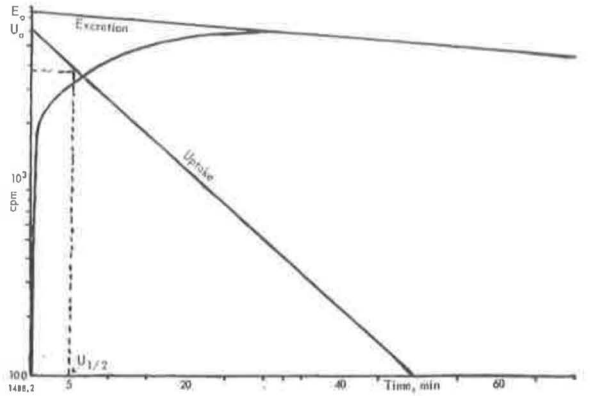

Figure 2. Uptake–excretion curve of a patient with hepatic bilharziasis (case 13). $U_{½}$, 9 min; $E_{½}$, 170 min; R, 19.2%

tion half-time $E_{½}$ is the time interval taken by the liver to excrete one-half of the dye it collected into the biliary tree. From this quantitative analysis, one can also collect information about the hepatic blood volume (HBV) in relation to the volume of the total circulating blood (TBV).

Table 1. Values Obtained with Radioactive Rose Bengal Test in Patients with Hepatic Bilharziasis and in Normal Subjects

Case No.	*Age*	*Sex*	*Stage*	$U_{½}$[a] *min*	$E_{½}$[b] *min*	*Hepatic blood vol index (R)*[c] *%*	*Other liver function tests*			
							II	*TT*	*AP*	*BSP retention %*
					Patients					
1	21	M	I	5.5	101	19	3	1	6	0
2	32	M	I	6.0	75	18.5	0.5	2	13	0
3	24	M	I	7.0	125	21	8	2.6	10	0
4	22	M	I	8.0	200	20	4.8	2.4	7.8	0.5
5	35	M	I	3.0	170	80	3.2	2.8	5.3	0
6	20	M	II	4.0	290	30	6.0	6	14	1
7	21	M	II	12.0	133	53	5.0	2	13	11
8	13	M	II	10.0	85	65	4.2	5.8	7.4	6
9	13	M	II	10.0	120	33	3.9	2.5	6.3	0
10	27	M	II	20.0	190	29	4.2	3.6	4	0
11	12	M	II	12.0	220	24	5	2.4	8.6	6
12	22	M	III	8.0	110	14.7	7	8.6	18	2
13	24	M	III	9.0	170	19.2	4	5.5	6.5	0
14	19	M	III	4.0	135	24	3.8	4	7.2	6
15	27	M	III	22.0	310	21	10.7	7.8	10.7	2
16	35	M	IV	15.0	320	20.5	4.6	5.2	7.4	3
17	42	M	IV	17.5	300	75	8.2	11	7.6	2
18	28	M	IV	10.0	215	58	12	9.2	9.4	0.5
19	36	M	IV	15.0	200	50	5	8	5.4	2
					Normal subjects					
1	18	F		5.0	80	7.5				
2	30	M		10.5	83	20				
3	23	M		18.0	55	26.5				
4	31	M		3.5	108	34				
5	32	M		5.0	60	23				
6	36	M		8.0	69	23.5				
7	33	M		9.5	53	19				
8	25	M		13.0	70	16				
9	54	M		8.0	85	18				
10	28	M		8.0	103	34				
11	36	M		12.5	107	20				
12	28	M		7.5	92	25				
13	30	M		8.0	90	16				
14	26	M		7.0	85	21				
15	29	M		5.0	103	17				

[a] Uptake half-time.

[b] Excretion half-time.

[c] Hepatic blood volume index (R) = $\frac{\text{hepatic blood volume (HBV)}}{\text{total blood volume (TBV)}}$.

RESULTS

In the course of hepatic bilharziasis, there is no sharp demarcation between the pathological pictures at the various clinical stages as the term "stage" might lead one to expect. The uptake–excretion curve of the radioactive Rose Bengal did not show a specific pattern for each of the 4 stages of this disease as can be seen in Table 1.

Table 1 shows that the mean half-time of the dye uptake by the normal controls was 8 minutes, whereas in patients with hepatic bilharziasis it was 10 minutes. In the normals, the excretion half-time varied from 53 to 108 minutes with an average of 75 minutes; in the bilharzia patients it varied from 75 to 310 minutes with an average of 188 minutes. There was no retention of the dye in the bilharzia cases since there is no biliary obstruction.

The present preliminary data indicate that the uptake–excretion curve of the radioactive Rose Bengal is a valuable test for liver function, notably the excretion portion of the curve. The test, with the exception of case 8, showed delayed dye excretion when other liver function tests revealed either normal or defective functions.

CONCLUSION

Use of Rose Bengal labeled with I^{131} proved to be a sensitive means for detecting liver damage in bilharziasis. The radioactive Rose Bengal, however, does not give a specific pattern for each of the clinical stages of hepatic bilharziasis.

From the data available it appears that the excretion portion of the curve is a more important index of hepatic cell function than the uptake portion. The value of the hepatic blood volume index (R) as mentioned by Lowenstein[12] is not clear in the present cases. In addition to its wide range in the normal controls, it did not increase uniformly in the infiltrative stage of bilharziasis nor did it decrease uniformly in the fibrotic stage.

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Radiocolloids in the Study of Hepatic Circulation in Man

By K. Fellinger, R. Höfer and H. Vetter*

Phagocytes of the reticulo-endothelial system are known to be capable of removing colloid particles from the blood stream. The observation that phagocytes of the liver and spleen are highly efficient in removing colloid particulate matter of a certain particle size from the blood perfusing these organs, and that as much as 90% of an intravenously injected colloid could be recovered in the liver and spleen, led to the assumption that the disappearance rate of such a colloid could be used to observe the state of liver circulation.

If it is assumed that the liver and spleen are the only organs which remove colloid particulate matter from the blood, that they do this with a 100% efficiency during the first passage of the colloid through these organs, and that the concentration of the colloid in the blood is representative for the concentration in whole blood volume, then the rate of disappearance of colloid observed in the peripheral blood should represent that fraction of the blood volume which perfuses these organs in unit time.[1]

This principle has been put to test by Dobson *et al.*[2] who used as the particulate matter colloidal chromic phosphate labelled with radiophosphorus. They injected small amounts of this colloid into a cubital vein and by frequent sampling of arterial or venous blood from the other arm determined the change of concentration of the radiocolloid with time. The disappearance rate constant is obtained from a semilogarithmic plot of the concentration against time after separating the fastest component of the multicomponent curve observed. This procedure has been thoroughly described by Dobson and Jones.[3] The rate of liver blood flow could then be calculated as a fraction of the whole blood volume by multiplying the disappearance rate constant with the blood volume. This was obtained from a plasma volume measurement using T-1824 and the peripheral hematocrit.

TYPE OF COLLOID

The chromic phosphate labelled with radiophosphorus used by Dobson and other workers has a very suitable average particle size of about 1 μ. However, a distinct disadvantage of this colloid is that because of the short range of the P^{32} beta particles the radioactivity of the peripheral blood can only be determined *in vitro;* this requires frequent blood sampling. Moreover, preparation of a chromic phosphate colloid of suitable and uniform particle size is such a laborious procedure that a satisfactory product has not yet been put on the market for general sale.

The use of colloidal radiogold was first advocated in this laboratory.[4] Its principal advantage is that Au^{198} is a gamma-ray emitter and therefore that radioactivity of the peripheral blood can be determined using external counting by simply placing a counter against the skin of the patient's leg. This feature not only makes blood sampling superfluous but also enables the use of semilogarithmic counting rate meters and chart recorders for wholly automatic registration of the disappearance rate. A second advantage is that colloidal radiogold is a commercial product practically always on hand since it is constantly used for therapeutic purposes. When this colloid was obtained from AERE Harwell it had an average particle size of 25 μ which, although about one-fortieth of the mean chromic phosphate diameter, was still satisfactory. The error introduced by further reduction of the particle size occuring when production of this material was transferred from Harwell to the Radiochemical Centre, Amersham, will be discussed later. One might consider it a disadvantage that the inert gold particles removed by liver and spleen will remain in cells of the reticulo-endothelial system indefinitely with possible subsequent damage.

Colloidal iron saccharate labelled with Fe^{59}, which has been used to some extent for this purpose in this laboratory,[5] has all the desired properties. It can be prepared relatively easily with a satisfactory particle size and, being a gamma-emitter, can also be followed by external counting. It is rapidly metabolized so that, despite its longer half-life, which permits convenient storage, radiation hazard problems do not arise.

Heat-denatured human serum albumin labelled with I^{131}, the use of which has been advocated by Halpern and colleagues,[6] also appears to be a colloid of excellent properties for estimation of liver blood flow. At present, it is probably (for reasons discussed below) the colloid of choice for measurement of liver blood flow, although it is not as easy to prepare as iron saccharate and the degree of error caused by the rapid return of free I^{131} into the circulation[7] remains to be explored.

SOURCES OF ERROR

Before discussing the practical results obtained with the colloid disappearance methods, it is essential to

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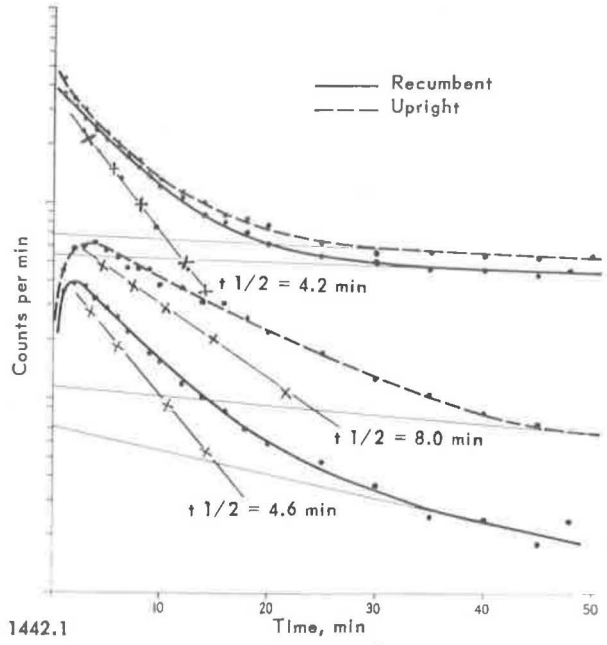

Figure 1. Disappearance curves of colloidal radiogold from the circulation observed in the same subject in the recumbent and in the upright position, using two scintillation counters—one directed towards the head (two upper curves) and one towards the thigh (two lower curves)

note the sources of error arising from the fact that the assumptions outlined above are not strictly valid.

The term liver blood flow is usually taken to denote that amount of blood which enters the liver bed via hepatic artery and portal vein and leaves it through the hepatic veins. However, it is now held by many workers that even under normal conditions a small fraction of the blood entering the liver bypasses the sinusoids and is therefore nonfunctional; this fraction greatly increases in pathological conditions such as liver cirrhosis. It should be noted that the liver blood flow as measured by colloid disappearance methods only estimates that fraction of the blood volume which is exposed to the action of the Kupffer cells; the use of the term "functional liver blood flow" therefore seems to be appropriate.

Under normal conditions almost all the blood passing through the spleen enters the liver bed. If this condition is not fulfilled, such as in the presence of oesophageal varices, spleen and liver are no longer connected in series and splenic blood flow will to a considerable extent determine the disappearance rate constant. In the case of liver cirrhosis with a grossly enlarged spleen this effect will lead to a figure for liver blood flow which is excessively high.

Using simultaneous injections of labelled chromic phosphate and T-1824, Dobson *et al.*[2] have established that in normal subjects the mixing of injected material is so rapid that its influence on the disappearance rate of the colloid could be neglected. In similar experiments with colloidal gold somewhat larger individual effects of delayed mixing were observed in patients with liver cirrhosis, but on the average these effects cancelled out.[8] Both observations were made with blood drawn from a cubital vein or artery.

When *in vitro* determinations of radioactivity were replaced by external counting over the legs, it was assumed that complete mixing in these parts of the body could be attained as rapidly as in the arm. This, however, is not the case, particularly in diseased subjects.

Bauman and Rothschild,[9] in a study on the intravascular equilibration of I^{131} labelled human serum albumin, have demonstrated that equilibrium levels in the blood are reached earlier in the head and chest than in the lower part of the body. If two scintillation counters are used simultaneously to observe the disappearance of radiogold over the head and over the leg, it is usually found that, even in normal patients, the disappearance rate calculated from the curves obtained is slightly slower over the leg than over the head. This effect is more pronounced in patients with circulatory disorders, especially if the same experiment is repeated with the subject in the upright position (Fig. 1). The maximum value of these curves is reached over the head, within the first minute and is indeed higher than the equilibrium value which would be observed if there were no rapid disappearance of the colloid from the circulation; the maximum value over the leg is reached later in the recumbent and is still more delayed in the upright position. It therefore appears essential that the patient be placed in the recumbent position and that the scintillation counter be directed towards his head. Positioning the counter towards the chest is inadvisable because of difficulty in excluding the rapidly increasing background radiation due to accumulation of the colloid in liver and spleen.

Since all colloidal preparations contain a small fraction of particles that are so minute that they escape removal by the reticulo-endothelial cells of the liver and are only very slowly eliminated from the circulation by other organs, the influence of this fraction on form of the disappearance curve has to be corrected by graphical separation. It should be stressed here that observation of the disappearance curve for at least 45 minutes is essential. If the disappearance curve is followed for only 20 minutes or less, as has been done by some workers, grossly erroneous results will be observed. This is illustrated by an experiment with an

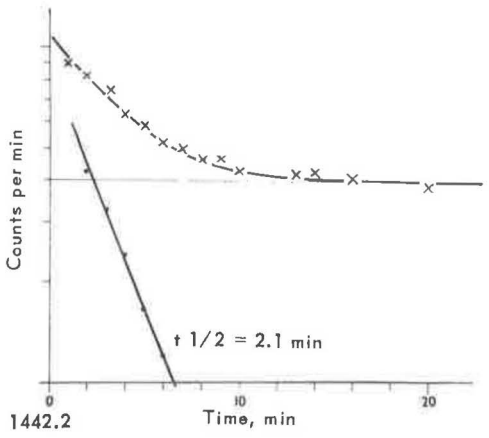

Figure 2. Disappearance curve of an I^{131} labelled India ink preparation containing a substantial fraction of very small particles

I^{131} labelled India ink preparation which contained a large fraction of very small particles (Fig. 2).

Halpern *et al.*[10] have shown that above a so-called "critical dose" the disappearance rate of a colloid will no longer be independent of the amount injected. In the case of colloidal radiogold this critical dose has been established to be 250 μg[4] and with the present specific activity less than 100 μg can be used.

Experiments in human subjects, using hepatic vein catheterisation and colloidal radiogold having an average particle size of 25 μ, have shown that this colloid is removed by the liver with an efficiency of about 80% within a single passage.[4] Similar values have been observed in various animal species.[11] Hence liver blood flow values calculated from disappearance curves of these colloids were 20% too low and it was rather the minimal than the true liver blood flow which was calculated. Observations with the Amersham gold which has an average particle size of only 5.5 μ[12] have shown that for this colloid the extraction efficiency is only 50 to 60%. It is therefore believed that the colloidal radiogold as supplied by the Radiochemical Centre Amersham cannot be used for quantitative estimations of the liver blood flow, although it is still useful if it is only desired to obtain some insight into the state of the liver circulation.[14]

PRACTICAL APPLICATIONS

Most published results, whether they have been determined with Harwell gold,[4] with Amersham gold[13] or with I^{131} labelled heat-denatured human serum albumin[15] agree in that values for liver blood flow in cirrhosis of the liver are in the majority of cases grossly below normal, whereas Nardi's values obtained with chromic phosphate are mostly well within the normal range.[16] The reason for these differences is not yet clear.

Simultaneous measurements of portal venous pressure have revealed the fact that in cases of liver cirrhosis, liver blood flow as calculated from radiogold disappearance curves is inversely proportional to the portal venous pressure (Fig. 3).[13,14]

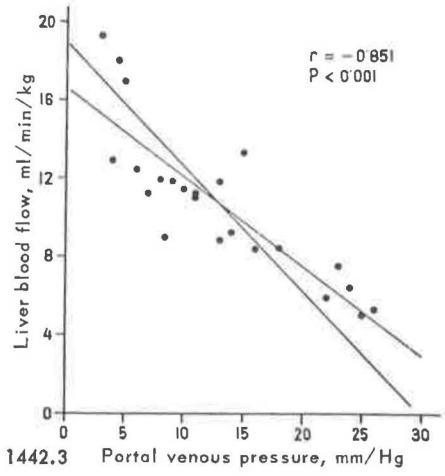

Figure 3. Relation between liver blood flow and portal venous pressure in 23 cases of liver cirrhosis. (By courtesy of the Editors, Proceedings of the 3rd Gastein Isotopes Symposium)

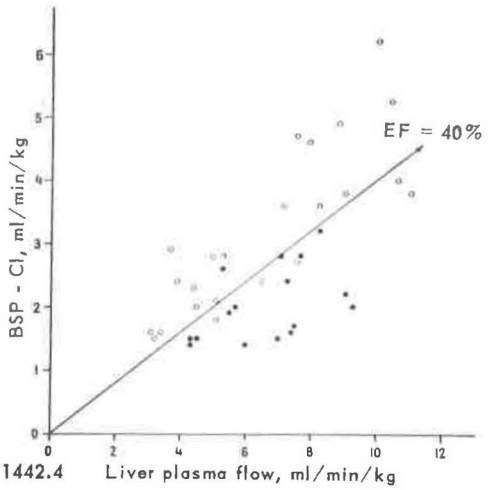

Figure 4. Relation between the bromsulphalein clearance and the liver plasma flow in 39 cases of liver cirrhosis with ascites (closed circles) and without (open circles). The straight line corresponds to a bromsulphalein extraction factor of 40%. (By courtesy of the Editors, Proceedings of the 3rd Gastein Isotopes Symposium)

It has been found particularly useful to combine determination of the colloid disappearance rate with measurement of the rate of disappearance from the plasma of an intravenously injected standard dose of the dye bromsulphalein, which is selectively taken up by cells of the liver parenchyma. The so-called "bromsulphalein clearance" has long been used as a clinical liver function test, but it could never be ascertained whether a given decrease of this clearance was due to a decreased ability of the liver parenchyma to extract the dye from the blood stream—that is, to impaired liver cell function or to a reduction of blood supply to the organ due to constriction of the liver vascular bed. By expressing bromsulphalein clearance as a fraction of the dye actually entering the liver, it has been possible to define a "bromsulphalein extraction factor" which permits a better understanding of liver cell function than the bromsulphalein clearance alone.[17,18] For example, it has been demonstrated that in cases of liver cirrhosis without ascites, bromsulphalein extraction by the liver cell is usually within the normal range, whereas in decompensated cases (that is, with ascites) the extraction factor is below normal (Fig. 4). This indicates that decrease in the bromsulphalein clearance generally observed in all cases of liver cirrhosis may, however, in a considerable number of cases, be due only to the reduction of blood flow while a normal cell function is still maintained.[14]

CONCLUSIONS

Observations of the colloidal disappearance rate before and after spleno-renal shunts have shown that if liver blood flow has been reduced by this operation the chances of survival for these patients are poor; they die of liver failure within six months. When the flow increased despite splenectomy, the patients did well.[16]

Apart from their much greater simplicity, it is a particular advantage of the colloid disappearance

methods over the methods using hepatic vein catheterisation that they permit repeated estimations of liver blood flow over any desired period. It has been possible, for example, to follow in cases of liver cirrhosis the effects of a raw liver extract therapy over a year by carrying out repeated observations of the radiogold clearance and the bromsulphalein extraction factor at two month or three month intervals.[19] This, however, is by no means the only way to make use of the particular advantage emphasized and there is no doubt that as soon as the magnitude of the errors mentioned has been fully appreciated and possibly some of their sources been eliminated, this method will be applied on a rapidly increasing scale in routine clinical work, especially since results of diagnostic importance can be secured which cannot be obtained otherwise.

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Study of the Liver Blood Flow Using Gamma-emitting Radionuclides

By A. M. Baptista and J. Silva Carvalho*

Measurement of the circulation of blood through the liver in human beings became possible with advent of the hepatic vein catheterization technique used in conjunction with bromsulphalein and urea excretion measurements. Leaving aside all debated questions associated with these methods, the technique employed heretofore cannot be considered a simple one and even less appropriate as a routine diagnostic procedure. Recently a different method was developed based on the assumption that phagocytes of the liver and spleen are highly efficient in removing particulate matter from the blood stream. It appears that Dobson[1] was the first to measure disappearance rate of colloidal chromic phosphate labelled with P^{32} as a parameter related to liver blood flow.

METHODOLOGY

Let us assume that at a given instant a mass m of a colloidal substance is uniformly mixed within the circulating blood of volume V. At this instant the concentration of colloidal substance is

$$C = m/V. \tag{1}$$

Let v be the blood volume that, per unit time, is perfusing the liver and a the fraction of colloid particulate matter removed from the blood in a single passage through the liver. We can call a the clearance coefficient for colloid removal from the liver. Then, in the time interval dt, the mass dm which disappears from the circulation is given by

$$dm = -avC\,dt. \tag{2}$$

Dividing by V and looking at (1) we can write,

$$\frac{dC}{dt} = -a\frac{v}{V}C. \tag{3}$$

For a given patient $a(v/V)$ is a constant and has been termed the colloid disappearance rate constant k,

$$k = a\frac{v}{V}. \tag{4}$$

Integrating (3) we obtain the final expression

$$C = C_0e^{-kt} \tag{5}$$

where C is the concentration at a given instant t, and C_0 at the instant t is equal to zero.

The exponential relation (5) is valid, of course, for the specific activity of blood samples withdrawn at intervals following intravenous injection of a labelled colloidal substance such as chromic phosphate labelled with P^{32}.

We have assumed that particles of the colloidal substance were uniform in size, or, although of different sizes, the clearance coefficient a was the same for all the particles. In general, this is not so and the disappearance curve is not given precisely by equation (5), but by a multicomponent curve (Dobson and Jones[2]), since there are many different values for the disappearance rate constant

$$k = av/V, \qquad k' = a'v/V, \qquad k'' = a''v/V, \ldots .$$

Then instead of (5), we have

$$C = C_0e^{-kt} + C_0'e^{-k't} + C_0''e^{-k''t} + \ldots . \tag{6}$$

By the method of preparation of the colloid, it is possible to consider only the initial portion of the multicomponent exponential curve without the error of k being significant. This is true since it was shown with chromic phosphate,[3,4] that the contribution of slower components due to smaller sized particles can be neglected. This method, although very interesting and useful, is not as simple as one would want for a routine diagnostic procedure. Preparation of the chromic phosphate labelled with P^{32} is a laborious operation, and while we think this colloidal substance can be prepared much more simply,[4] still the necessity of withdrawing serial blood samples at frequent intervals, the loss of a considerable amount of blood, and the time consuming radioactivity counting, makes desirable a simpler method.

A further simplification would be to use a labelled substance incorporating a gamma-emmiting nuclide. This was done by Vetter *et al.*[5,6] using colloidal gold (Au^{198}) and substituting for the *in vitro* measurements of blood samples radioactivity measurements carried out by means of a Geiger-Müller detector placed between the calves of the subject's legs. The principle of the method remains the same in essence and the disappearance rate constant k is determined in essentially the same way from the fastest component of the complex of disappearance curves by the usual graphic separation method.

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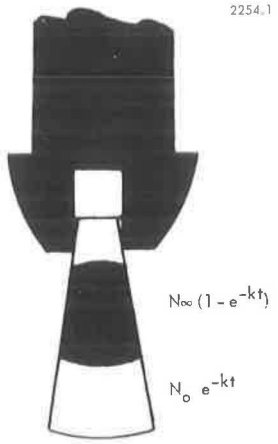

Figure 1. Illustration showing liver tissue in which radioactivity is increasing, and other tissue in which radioactivity is decreasing, that lie in the volume restricted by the counting aperture of the scintillation detector

It was our thought that by making external measurements of the gamma radioactivity over the liver region we could devise a method which is much more direct and with possible advantages and simplifications. It is the purpose of this paper, therefore, to present the first results of experiments performed with the newly devised method.

PROCEDURE

After intravenous injection of a radioactive colloidal substance, according to the newer procedure for removal of such substance from the blood, radioactivity of the liver follows the equation

$$N = N_\infty(1 - e^{-kt}) \tag{7}$$

where N is the radioactivity measured at any time by a counter placed directly over the liver region so that it detects only hepatic tissue and N_∞ the activity at infinite time. Presumably this equation was used for mice by Dobson and Jones,[2] employing colloidal chromic phosphate and detecting the beta radiation of P^{32}.

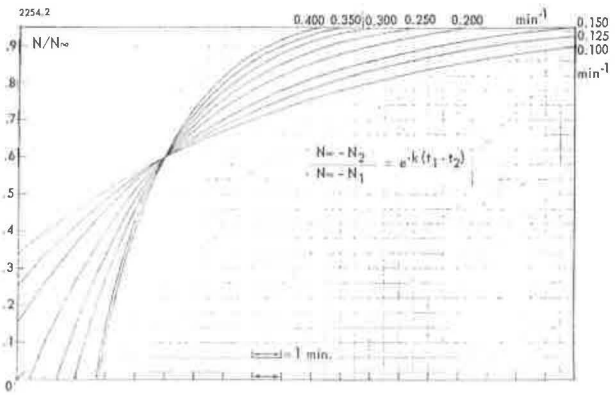

Figure 2. Theoretical curves for radioactivity measured externally over the liver region by a collimated radiation detector after injection of a radioactive colloidal substance labelled with a gamma-emitting radionuclide (variation with time of N/N_∞ normalized for $N/N_\infty = 0.60$)

After injection of a gamma-emmiting colloidal substance and measuring radioactivity over the liver region with a collimated scintillation detector, the measurement can be considered to reflect both the activity corresponding to the liver and also to other tissues inside the counting aperture of the detector. This is shown schematically in Fig. 1. If this picture is correct, the radioactivity measured by the detector can be said to follow the equation

$$N = N_\infty(1 - e^{-kt}) + N_0e^{-kt} \tag{8}$$

where N is the radioactivity at any time t, N_∞ the radioactivity corresponding to $t = \infty$ and N_0 to the instant $t = 0$, that is, assuming the colloidal substance is uniformly mixed with the blood immediately after the intravenous injection.

We see that the uptake curve will depend on the counting geometry (collimation of the detector and its position relative to the patient as well as "volume" of the subject). From external measurements over the liver region alone, it is possible to compute the disappearance rate constant k. From (8) we can write

$$N_\infty - N = (N_\infty - N_0)e^{-kt}. \tag{9}$$

If N_1 and N_2 are the radioactivities measured at the instants t_1 and t_2, respectively, it is

$$\frac{N_\infty - N_2}{N_\infty - N_1} = e^{k(t_1 - t_2)}. \tag{10}$$

From this equation then the value of k can be computed easily.

Figure 2 shows the theoretical curves which follow from equation (10) using different values for the disappearance rate constant k. The curves have been normalized for the point $N/N_\infty = 0.60$.

RESULTS AND DISCUSSION

When measurements are made, the patient should be comfortably supine and lie completely still.

The collimated scintillation detector is placed against the right lateral thoracic wall over the liver region as shown in Fig. 3. In this Figure is shown also

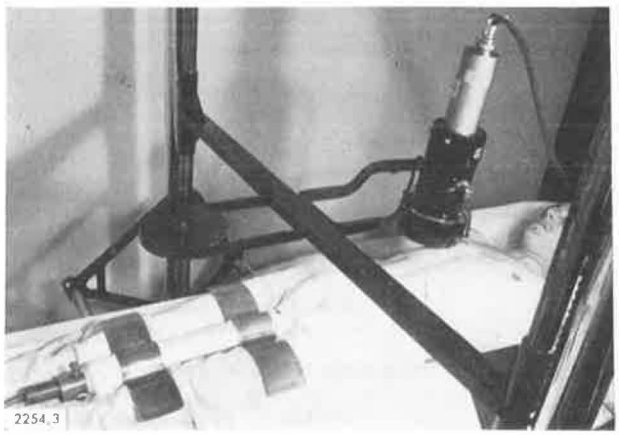

Figure 3. Patient in position for measurement of radioactivity over the liver region and of the blood by a collimated scintillation detector and a shielded Geiger-Müller tube, respectively

a Geiger-Müller detector placed between the calves of the patient, since, in some cases, we wished to obtain the disappearance rate constant from the disappearance curve for colloid in the blood.

The experiments were performed with colloidal gold (Au^{198}) obtained from the Radiochemical Centre, Amersham, England—that is, prepared as a colloidal suspension of metallic gold stabilized with gelatin. The usual specific radioactivity was about 100 mc/cm³ and the gold concentration 10 mg/cm³. The total solids were less than 0.5 g/cm³. The particle size as shown from electron microscope measurements were on the average between 200–300 Å with a small percentage being as little as 50 Å and as large as 600 Å.

After suitable dilution with sterile pyrogen-free isotonic saline, a radioactivity of about 50 μc was injected containing less than 150 μg of colloidal gold. It should be noted that this amount of radioactivity is not essential for the experiments, but since in some cases, as indicated above, measurements were made of the disappearance of radioactivity from the blood by external detection, it was necessary to use the higher amounts.

It is our purpose, in this paper, to describe fundamentals of the method, reserving for future publications the application to certain clinical situations.

Table 1 shows values for the disappearance rate constant k and the corresponding half-time $T_{½} = 0.693/k$ for 21 normal patients. This average value for k (0.296 ± 0.013 min^{-1}), is in good agreement with the value reported by Dobson *et al.*[3] for 29 normal young men ($k = 0.287 \pm 0.007$, using chromic phosphate), but somewhat higher than the value reported by Vetter *et al.*[5] for 25 normal patients ($k = 0.262 \pm 0.010$ min^{-1}, using colloidal gold and measuring the disappearance of radioactivity from the circulation with a Geiger-Müller detector).

It is disturbing, to say the least, that using the method of Vetter and co-workers except for employment of scintillation detector instead of the G.M. tube, Krook[7] found for 30 normal subjects $k = 0.153 \pm 0.021$ min^{-1}.

It has been our experience that sometimes the graphic separation of exponential components from the complex disappearance curves is difficult, and although, in some cases, the values for k determined by the two methods were in agreement, in many cases also this agreement was not verified, causing us not to have very great confidence in use of the disappearance method.

The good agreement between our results and the results reported by Dobson and collaborators, led us to make a more direct test, determining in the same patient the disappearance rate constant with chromic phosphate labelled with P^{32} and with colloidal gold making radioactive measurements over the liver region.

The agreement was again remarkable. With the chromic phosphate, $k = 0.245$ min^{-1} and with the colloidal gold, $k = 0.239$ min^{-1}.

We have seen above that the parameter k is, by definition, the product of clearance coefficient of the liver for the colloidal substance a and the fraction of blood volume perfusing the liver per unit time. Usually we cannot separate the two factors and for that reason the liver blood flow v of equation (2) can be known accurately only if a and the blood volume V are known. For this reason it is assumed that $a = 1$ in all of these studies.

Along with other workers, we believe that k is of greater physiological importance for the study of circulatory problems than is blood liver flow v.

It is necessary for interpretation of results obtained with the different methods to recognize that phagocyte efficiency of the liver is directly related with the value of a (clearance coefficient). It is important, furthermore, to note that determining the value of k for normal patients appears to be practically the same for chromic phosphate as computed by Dobson and Jones[2] for the dog, rabbit and mouse ($a = 0.78$ to $a = 0.88$), and for the radiogold method of Vetter *et al.*[5] applied to three human subjects using hepatic vein catheterization with the values 0.87, 0.81, 0.78, respectively, also that it is in close agreement with results of animal experiments with colloidal radioactive gold performed by Little and Kelly.[8] It is to be expected, therefore, that the average value of k would be the

Table 1. The Disappearance Rate Constant and Apparent Half-time for 21 Normal Patients

Initials	$T_{½}$ (min)	k (min^{-1})	Initials	$T_{½}$ (min)	k (min^{-1})
J. G. C.	3.48	0.199	R. A. S.	2.31	0.300
H. P.	3.46	0.200	M. G. F.	2.27	0.305
M. L. N.	3.38	0.205	L. F. L.	2.24	0.310
M. L. V.	3.15	0.220	A. M.	2.20	0.315
A. N.	2.90	0.239	G. M. J.	2.11	0.329
A. R. M.	2.65	0.262	M. L. A.	2.10	0.330
G. A. G.	2.50	0.277	M. C. S.	2.00	0.347
M. D. J.	2.42	0.287	M. M. C.	1.90	0.365
			J. A. M. M.	1.86	0.372
A. F.	2.33	0.297	I. S.	1.83	0.378
A. M. A.	2.31	0.300	M. L. C. M.	1.80	0.385

†Average for $k = 0.296 \pm 0.013$

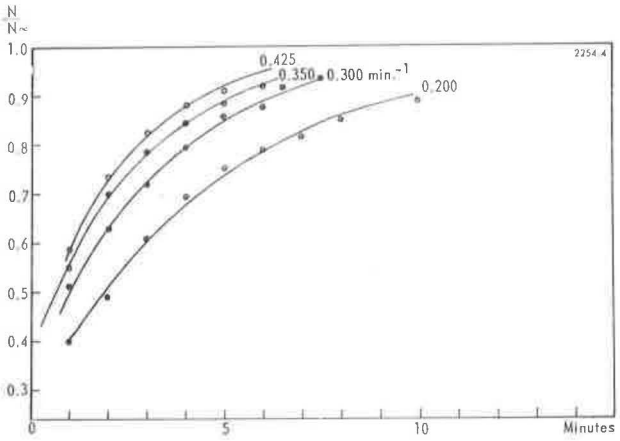

Figure 4. Theoretical curves and experimental points obtained for normal patients with the method described measuring gamma radioactivity over the liver region

same for the normal subject with respect to the two substances.

Figure 4 shows for three normal patients, the experimental points and the theoretical curves calculated from equation (10). Similarly Fig. 5 shows the experimental points and theoretical curves for three abnormal cases. The upper curve was obtained for a patient with constrictive pericarditis, the middle curve for a patient with liver cirrhosis and the lower for a patient with an acute mitral stenosis.

Figure 6 shows the results obtained with a polycythemia vera patient. With the value of $k = 0.125$ min^{-1} and the total blood volume (as determined with sodium chromate labelled with Cr^{51}) 9.2 litres, the liver blood flow (assuming $a = 1$) is $v = 1.115$ l/min. Although the value for V is definitely low, it is still within the range of normal, which indicates the greater significance of k. The value is in good agreement with the arm-tongue circulation time (Fig. 7) which was determined by injecting P^{32} and making register with an end-window Geiger-Müller tube placed directly

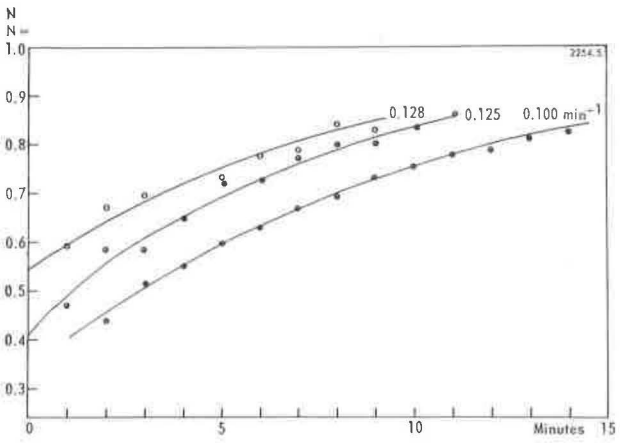

Figure 5. Theoretical curves and experimental points obtained for abnormal patients with the method described. The upper curve was obtained from observations on a patient with constrictive pericarditis, the middle curve from a patient with liver cirrhosis, and the lower curve was obtained from a patient with mitral stenosis

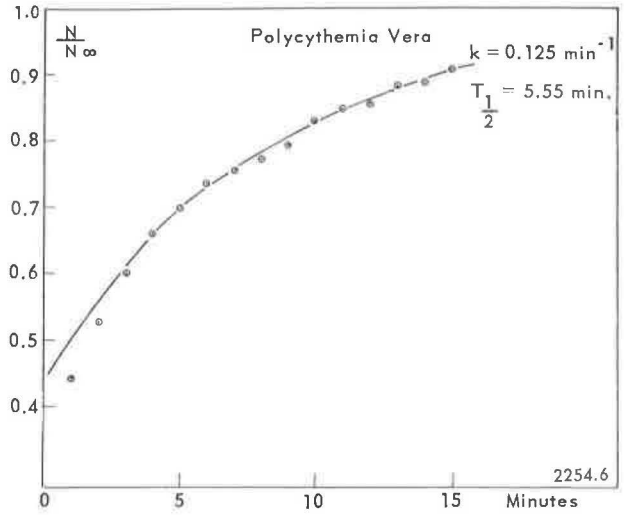

Figure 6. Theoretical curve and experimental points obtained from observations on a polycythemia vera patient

over the tongue. The value obtained (20 sec) was very low indeed.

CONCLUSIONS

In our view, determination of the disappearance rate constant k by measuring radioactivity over the liver region after injection of a colloidal substance labelled with a gamma-emitting nuclide, such as the Au^{198}, has various advantages.

First of all, withdrawal of blood samples is not necessary. The method is simple, reliable and harmless to patients, and it allows the use of much smaller quantities of radioactivity than the method based on external measurements of the activity of blood. In order to obtain equivalent statistical accuracy, ten times less injected radioactivity is needed.

The method is much more rapid since the time required to observe a constant activity level, N_∞ of equation (10), is about 15 minutes for a normal patient and 20–30 minutes for patients with very low values of the parameter k. This is much less than the time necessary to obtain such values by other methods.

Proper equations cannot be applied in any of the methods until the injected material is completely mixed within the blood.

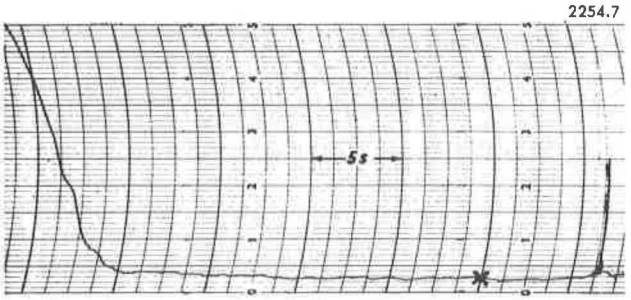

Figure 7. Arm-tongue circulation time; the cross indicates time of injection of P^{32}; detection was made with an end-window G.M. tube placed directly over the tongue (polycythemia vera patient of Fig. 6)

Dobson's group[1,2] uses a dye as indicator of mixing and corrects the radioactivities observed accordingly. Although, for the most part, we agree with other workers that this is not imperative, we must state that for our method this problem is of some importance for very high values of k (normal patients). It is perhaps an interesting possibility to consider using simultaneously two radionuclides, one labelling the colloidal substance and the other in such form that dilutes within the blood plasma, the two having a gamma spectrum so different in energy level that with a two channel pulse analyser it would be possible to discriminate and measure separately activities of the two radionuclides. In such a case, it should be possible to correct for mixing time the activities measured over the liver region.

ACKNOWLEDGEMENTS

It is our privilege to thank Professor Francisco Gentil for his continued support of the Isotope Laboratory; Professor Julio Palacios and Professor Jacinto M. de Bettencourt for the kind interest always shown during this work; Dr. M. A. Perez Fernandez and Dr. M. L. Martins for their assistance with respect to measurements; and V. Xavier and S. Nogueira for their technical assistance in preparation of this paper.

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Investigation of the Physiopathology of Uncinariasis

By Marcel Roche*

The rural population of tropical countries is greatly affected by ankylostomiasis. We often see in hospital practice the pale and tired peasant who comes in with an urgent need for treatment. The role of ankylostomiasis in the genesis of tropical anemias has been much discussed and even denied. For instance, Foy[1] working in India investigated 300 adults among whom the infection was 52% and found in these cases a mean hemoglobin level of 9.4 g/100 ml, whereas in another group in which the infection was only 12%, the mean level of Hb was 9.0 g/100 ml or about equal. He concludes that ankylostoma does not cause anemia, at least not statistically.

As a direct consequence of this attitude, anti-ankylostoma campaigns have not been carried out with the energy and conviction needed for success. It seems well, therefore, to have another look at the problem of the physiopathology of uncinariasis with the help of the radioactive isotopes, Cr^{51} and Fe^{59}, which make possible a quantitative measurement of the various factors which affect the absorption and synthesis of iron and the final fate of the red corpuscles. In this work, we wish to present some of the research conducted up to the present on this problem.

THE ANEMIA OF ANKYLOSTOMIASIS

Speaking *a priori*, the anemia due to ankylostomiasis may be produced by one of the following factors:

(*a*) Inadequate absorption of iron and proteins from food;

(*b*) Defects in intestinal absorption;

(*c*) Inadequate synthesis of hemoglobin from the iron and proteins in the absence of some factors, or as a result of the presence of hypothetical toxins produced by the worms;

(*d*) Loss of the duodenal mucosa caused by the ankylostoma;

(*e*) Hemolysis of circulating blood due to the hypothetical toxins produced by ankylostoma, and

(*f*) Loss of blood *via* the fecal route.

The first factor, i.e., the ingestion of proteins and iron, is difficult to evaluate and information on this point should come from nutritional investigation and balance studies which have not been possible up to the present. Investigation of the intestinal absorption of iron from certain foods is currently under way and will be dealt with briefly at the end of this paper.

The other factors have been studied and will be discussed in this paper.

LABELING OF ERYTHROCYTES WITH Cr^{51}

When red corpuscles are incubated with a solution containing radioactive chromium, the latter penetrates into the cell and unites with it in a practically irreversible form[2] in such a way that, within limits, the chromium is not liberated until the cell has been hemolyzed. Studying ankylostomiasis patients by this method and measuring simultaneously and comparing the radioactivity in the feces and in the blood, we obtain a quantitative measurement of the spoliation of blood by the ankylostoma located in the upper regions of the intestine, in the duodenum. However, this method is sound only if: (*a*) the chromium united with the erythrocytes is not excreted in appreciable quantities in the intestine and (*b*) if the chromium contained in the lumen of the intestine is not absorbed by the mucosa.

It was necessary, therefore, to conduct a preliminary investigation to justify the method, which was done as follows:[3] the red corpuscles of 10 uninfected subjects were labeled with radioactive chromium and the fecal excretion of radioactivity was measured. In another group, tagged red corpuscles of eight patients were introduced into the duodenum through a Levine tube and the total activity in the feces was measured.

Table 1 shows the results of the first investigation. We see that when the circulating erythrocytes of an uninfected patient are tagged, we recover in the feces, on the average, radioactivity equivalent to scarcely 1.27 cc of blood per day, which is minimal. The main part of the radioactivity escapes *via* the kidneys, an average of 33.33 cc per day. On the other hand, from the patients who received radioactive chromium united to their own erythrocytes by the duodenal route (Table 2), we recover in the feces 97.7% of the radioactivity with a range of 90.7 to 103% and from the urine a mean value of 1.7%. In none of these patients did we find a significant activity above the background in the red corpuscles. Thus, we can conclude that, within certain limits, the methods proposed to measure the amount of spoliation of blood by the ankylostoma are valid.

Original language: Spanish.

* Instituto Venezolano de Investigaciones Científicas. (This work was done in the Institute of Medical Research, Fundación Luis Roche.)

Table 1. Urine and Fecal Excretion of Cr^{51} from the Erythrocytes in Uninfected Patients

Patient and sex	*Diagnosis*	*Feces*		*Urine*		*Blood hemoglobin, g/100 ml*
		Blood/d ml	*Blood mass/d %*	*Blood/d ml*	*Blood mass/d %*	
JS M	Cutaneous leishmaniasis	0.71	1.22×10^{-2}	24.85	0.43	15.2
AR M	Chromoblastomycosis	1.05	2.03×10^{-2}	38.80	0.75	15.4
JM M	Cutaneous leishmaniasis	1.76	5.74×10^{-2}	49.09	1.40	14.4
JR M	Erythema induratum (Bazin)	1.04	2.01×10^{-2}	32.91	0.64	13.8
LO F	Bronchopneumonia (cured)	1.54	3.45×10^{-2}	28.33	0.59	12.5
MB F	Chronic cholecystitis	0.28		37.53		12.1
AA F	Erythema multiforme	2.14	6.72×10^{-2}	28.30	0.89	13.8
VS F	Cutaneous leishmaniasis	1.79	4.50×10^{-2}	26.82	0.67	14.0
LM F	Placenta previa, acute hemorrhage	0.42				6.1
JF M	Acute leukemia	1.98				4.2
	Mean	1.27	3.67×10^{-2}	33.33	0.77	
	Range	0.28 2.14	1.22×10^{-2} 6.72×10^{-2}	24.85 49.09	0.43 1.40	

Measurement of Blood Spoliation by the Ankylostoma

In order to obtain an idea of the amount of blood consumed by the ankylostoma, we made the following study: the erythrocytes of patients were tagged in the customary fashion and after a three day wait we began to gather all the feces, and this was continued for three periods of 4 days each, as a minimum. Blood was withdrawn every four days and its radioactivity was compared with that of the feces of the corresponding period.

The amount of blood lost was then calculated. Once this first 12-day period was finished, provided the condition of the patient permitted, we gave him 3 cc tetrachlorethylene followed by a saline cathartic. All the feces were examined until no more worms were seen, generally after three days; the worms were extracted and counted one by one. Then, a new study was made for 12 days and the mean per day obtained was subtracted from the first period; the result was divided by the number of worms recovered, which gave the amount of blood extracted per worm per day.

In Table 3, we see the results obtained in 14 patients with a pure infection of *Necator americanus:* the mean is of the order of 0.03 cc of blood per day per worm, with a range of 0.012 to 0.06 and standard deviation of 0.017.

In practice, an approximate idea of the amount of blood lost by each patient can be had by making a semiquantitative count of the eggs following homogenization of the feces with water, using the method of Caldwell and Caldwell.[4]

In Fig. 1, if we compare the amount of blood lost by the radioactive chromium method with the number of eggs per day, we see that in the last 15 cases investigated there is a good correlation between these two measurements of the biological activity of the worm, the mean loss being 13.6 cc of blood per million eggs per day. However, it is not practical for the clinician to recover the feces quantitatively over long periods of time, so that the same data were computed in terms of eggs per gram of feces.

Figure 2 shows that this method does not give as close a correlation. There is greater dispersion of the data, but one can get an approximate idea of the amount of blood lost and therefore of the degree to which the ankylostoma is contributing to the anemia. Counting the eggs in this form, the mean loss of blood is 6.08 cc $\pm$ 0.76 (standard error) per thousand eggs per gram of feces per day. It is difficult to believe that such loss does not contribute significantly, particularly in weakened, undernourished patients, to the anemia.

Table 2. Percentage of Recovery in the Feces and Urine of Cr^{51} Bound to Erythrocytes Introduced into the Duodenum of Patients with Uncinariasis

Patient and sex	*Blood hemoglobin g/100 ml*	*Excreta*	*Recovered percentage*[a]									*Total*	*Accumulated total*
			Days after administration										
			1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*		
AR[b] M	15.4	Feces	0	—	95.3	—	2.0	—	0			97.3	97.6
		Urine	0.3	0	0	0	0	0				0.3	
JS[b] M	15.2	Feces	—	0.4	29.8	—	42.5	—	18.0	0.01		90.7	92.2
		Urine	1.3	0	0	0	0	0	0	0.2		1.5	
JA M	15.2	Feces	4.7	50.8	24.3	11.2	0.1	0				91.1	91.5
		Urine	0.1	0.1	0.1	0	0					0.4	
PB M	12.4	Feces	32.6	58.9	11.8	0						103.3	
		Urine	0.9	0.8	0.7							2.4	105.7
MR F	5.9	Feces	67.5	25.4	12.1	—	0					94.5	
		Urine	4.1	0	0	0	1.2					5.3	99.8
JV M	6.2	Feces	84.2	14.7	0							98.9	
		Urine	0	0	0							0	98.9
AG F	5.4	Feces	0	83.5	19.0	1.0	0	0				103.5	
		Urine	1.3	0.3	0.2	0	0					1.8	105.3
JJM M	11.5	Feces	0	0	0.8	90.8	—	2.1	—	0.5	0	94.2	
		Urine	Not examined										
Mean		Feces										96.7	
		Urine										1.7	98.7

[a] Legend: 0 = no radioactivity in the sample;
— = no feces sample collected.
[b] Patient not infected by *Uncinaria*.

Table 3. Loss of Blood Due to *Necator* and the Relation between Blood Loss and Number of Eggs in Pure Infections of *Necator americanus*

	Fecal loss of blood ml/d period[a]		*No. of* Necator *recovered*	Necator *eggs, mil/day period*[a]		*Blood lost*	
	A	*B*		*A*	*B*	*ml* × 10^{-2} Necator/*d*	*ml*/10^4 *egg/d*
2 (1)	43.17	7.36	2,586	2,983	379	1.38	1.38
2 (2)	7.36	0.96	457	379	75	1.40	2.11
3	96.94	3.47	1,641	6,748	138	5.69	1.41
4 (1)	65.00	8.13	1,023	1,639	147	6.35	3.81
4 (2)	8.13	5.73	98	147	47	2.44	2.40
5	29.02	3.33	1,684	1,708	27	1.53	1.53
6	51.30	8.75	840	3,281	240	5.07	1.40
13	17.87	1.45	417	440	0	3.94	3.73
15	15.40	0.73	609			2.41	
16	7.74	1.84	189	482	0	3.12	1.22
17	7.26	1.23	509	1,060	0.9	1.18	0.57
18	4.41	0.53	109	421	1	3.55	0.92
19	3.49	0.17	80	160	0	4.15	2.08
20	2.74	1.81	67	38	13	1.39	3.72
	Mean					3.11	2.02
	Range					1.18–6.35	0.57–3.73
	Standard deviation					±1.73	±1.12

[a] A = Investigation immediately before giving a vermifuge; B = study after vermifuge.

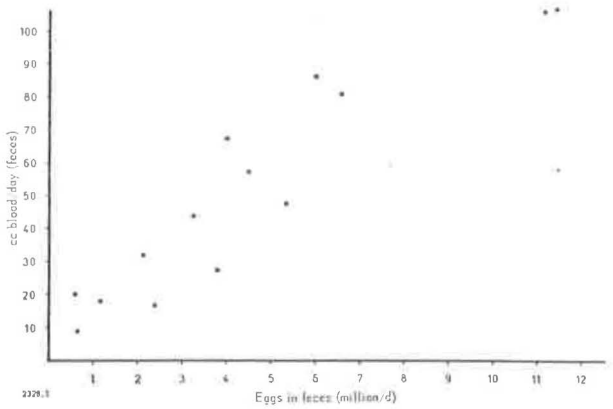

Figure 1. Comparison of amount of blood lost per day (by the radioactive chromium method) with the number of eggs per day in feces

During our investigation, we observed that immediately after transfusions in patients whose hemoglobin was very low, fecal radioactivity came down considerably, and that when the hemoglobin is increased (in a patient with low hemoglobin and given fecal excretion of radioactivity), the same number of parasites being maintained, the radioactivity also went down.

Even when the chromium method gives a reliable idea of the amount of blood loss due to ankylostoma in the duodenum, this does not indicate the percentage of various elements, particularly iron, which are reabsorbed from this blood. It has been possible in the last 14 patients we investigated to measure the amount of iron reabsorbed, using a method of double-tagging with isotopes.[5]

DOUBLE-LABELING OF ERYTHROCYTES WITH Cr^{51} AND Fe^{59}

Reabsorption of Iron from Feces

It is possible to tag the erythrocytes with chromium *in vitro* and with iron *in vivo*. The ankylostoma ingests these cells and ejects them into the duodenum. As we have seen, the chromium is excreted through the feces almost proportionately, but we did not know whether a part of the iron had been reabsorbed. Using a pulse-analyser which enables us to measure the activity due

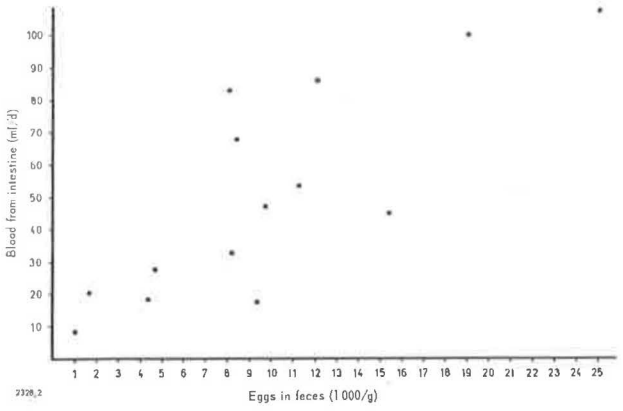

Figure 2. Comparison of amount of blood lost per day from the intestine with the eggs computed per gram of feces

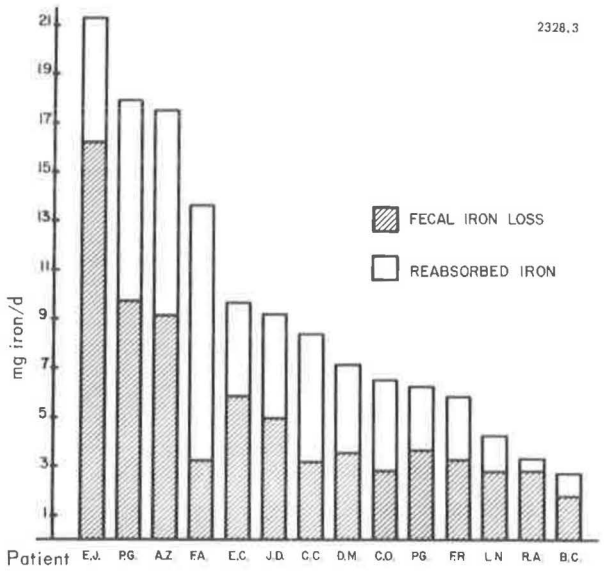

Figure 3. Iron lost through feces and reabsorbed per day

to chromium and iron individually, in the same sample, the observer may:[6]

(*a*) Measure the amount of chromium in the blood and in the feces, which makes it possible to compute the amount of blood consumed per worm, and

(*b*) Measure the amount of iron which is directly lost in the feces. Subtracting (*b*) from (*a*), the amount of iron reabsorbed is obtained.

Figure 3 shows these results for 14 patients suffering from ankylostomiasis. They lose, by the fecal route, large amounts of iron which vary from 3 to 21 mg per day, but an appreciable amount of this iron, 13 to 70%, is reabsorbed and (it is assumed) is utilized by the patient for the synthesis of new erythrocytes. This accounts, in part, for the fact that these patients are able to survive, despite the loss of such large amounts of iron through the duodenum.

Synthesis of Red Corpuscles

By injecting radioactive iron in the form of citrate by the intravenous route, it is possible to measure the time of disappearance of this iron, and thereafter its reappearance in the circulating hemoglobin molecule. We have not yet finished the analysis of this material, but it appears that we may correctly state that there is no significant defect in the synthesis of hemoglobin or in the utilization of the iron, so that these patients behave in a fashion very similar to that of patients with other types of iron deficiency anemia.

Half-life of the Red Corpuscles

Since the red corpuscles of these patients have been tagged with radioactive chromium, it is possible to follow this radioactivity in the blood day by day, and thus to observe decay and to measure the erythrocyte half-life. In 25 patients investigated we observed that the half-life averages 19 days, which is rather short if we compare it to the mean reported by other authors (25 days more or less). However, this fact does not

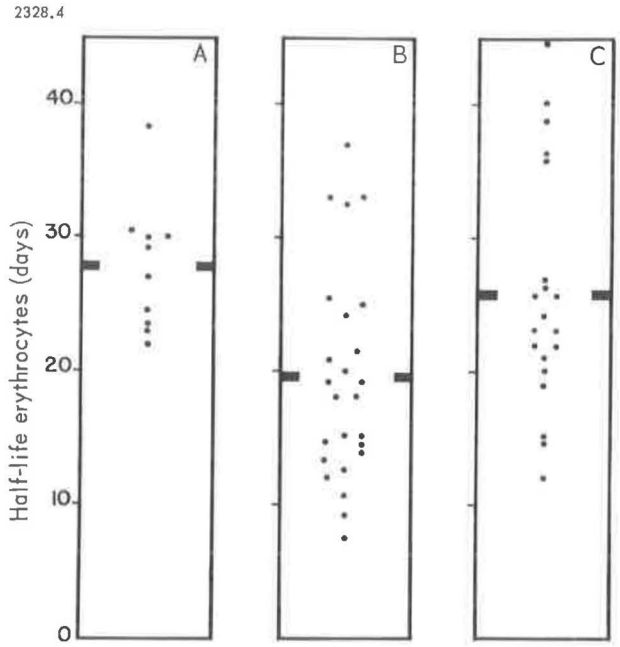

Figure 4. Half-life of erythrocytes, measured with radioactive chromium. A, normal subject; B, 25 subjects with ankylostoma and C, the same patients with values corrected for fecal loss

permit us to conclude that there is a hemolytic factor in ankylostomiasis since, as we have already seen, a large part of the radioactive chromium appears in the feces as a result of the spoliative effect of the worm. Since we have a quantitative measurement of the chromium in the feces of these patients, we may correct the curves in the following manner: if we label the erythrocytes in the patient on day zero and call the radioactivity in the blood 100%, we see that the experimental points follow exponential decay; the day when the activity reaches 50% of the initial is considered the half-life. This amount is lost by various mechanisms and may be due to (1) hemolysis (physiological or pathological) and (2) to fecal losses. If the blood volume of the patient is measured and the fecal losses are known, we can compute the percentages of the total blood mass lost by the intestinal route. If we add this percentage to the half-life observed, we obtain its real theoretical value.

The results can be seen in Fig. 4, which shows the erythrocyte half-life in the subject free from parasites (A), in 25 subjects with various degrees of infection (B), and lastly in the same subjects with a correction due to the fecal loss (C). The percentage in these last graphs falls within the limit of the normal values mentioned by other authors and those of our own control group. However, there are still some cases in which, despite the correction, the half-life is short. In the future we shall make more complete hemolytic studies of these cases.

Study of the Absorption and Utilization of Iron with Fe^{59}

The absorption and utilization of iron from analyzed food need study. We are currently beginning a study of this matter; in the investigation of iron absorption, the radioactive isotope is of great interest since it can be administered in small quantities which do not affect the physiology of absorption. We already know that the absorption of iron is very different, depending upon whether it is given in aqueous solution or in food; it is of greater interest, since it is much closer to conditions of life, to administer it in food. In order to meet this requirement, we are making hydroponic cultures of black beans (the basic food of our peasant population and probably its main source of iron) enriched with radioactive iron.

Administering these pulses, prepared in the same manner as in rural households, with a standard meal allows us to compute the total amount absorbed after recovering the feces and taking blood samples. We can not give results as yet, since these investigations are only in their preliminary phases.

Finally, we are interested in the physiology and the biochemistry of the worm and hope to complete investigations on these aspects during the coming year, using some *in vitro* methods which we are developing.

Even though these investigations may not seem to contribute much immediately to the problem of ankylostomiasis, we believe that here, as in all other scientific fields, quantitive results will contribute greatly to a solution. We also hope that our results may help authorities to take a strong position with respect to a more dynamic and more complete eradication of this parasitosis.

ACKNOWLEDGEMENTS

We wish to extend our thanks to Dr. M. E. Perez-Gimenez for her collaboration in this work.

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Isotopic Measurements of the Life Span of Human Erythrocytes, Leukocytes, and Platelets

By Myron Pollycove*

Though the life span of human erythrocytes, leukocytes and platelets has long been the subject of considerable investigation and interest, it is only recently that relatively accurate, quantitative physiologic studies have been made of the formed blood elements. These studies are a result of the development and application of artificially produced isotopes. Previously, measurements of erythrocyte survival have been obtained by specific differential agglutination of red corpuscles,[1,2] thereby identifying erythrocytes transfused into a recipient. All other procedures involving homologous transfusions and cross-circulation of leukocytes or platelets have been unsatisfactory. These procedures are subject to considerable criticism, because it has been shown that leukocytes and platelets are easily damaged by manipulation, that poorly understood immunologic cross-reactions are involved and that following transfusion such bodies are promptly removed by lungs, liver and spleen. During the past decade these difficulties have been circumvented by *in vivo* labeling of erythrocytes, leukocytes and platelets with isotopes.

Immature erythrocytes of approximately the same age have been labeled *in vivo* by incorporation of N^{15}-glycine,[3,4] C^{14}-glycine,[5,6] iron-59,[7–17] and iron-55[7–10] into heme. N^{15}-glycine was first used by Shemin and Rittenberg[3] to label heme in maturing erythrocytes (see Fig. 1). Life span of erythrocytes is determined by analysis of the rates of increase and decrease of the isotope circulating as heme (Fig. 1). C^{14}-glycine has also been used to label and to measure erythrocyte life span by Berlin, Lawrence and Lee.[5,6] Since isotopic glycine also labels constituents that leave the cell before its death, this method requires hemin crystallizations for specific-activity determination. A greater disadvantage in the use of C^{14}-glycine is that cell labeling continues for more than three weeks. This causes disappearance of labeled cells to be spread over at least three or four weeks more than the normal spread of life span, with a corresponding loss of accuracy in life span determination. Three normal subjects studied in this way showed life-span distributions (expressed as the mean plus twice the standard deviation) of 109 ± 47 days (skewed), 120 ± 52 days (skewed) and 127 ± 42 days (symmetrical). The unduly prolonged apparent life-span distribution obtained probably results from prolonged labeling of heme and from neglect in the mathematical analysis of reutilization of the isotope in further hemoglobin synthesis, probably from sources other than destroyed erythrocytes.[18] The mean life span of red cells in a patient with polycythemia vera was 131 days; one with pernicious anemia, 72 days; and one with sickle-cell anemia, 40 days.[4] Eight patients with leukemia were studied: three with chronic lymphatic leukemia had mean red-cell life spans of 113, 102 and 18 days, respectively; five with chronic myelogenous leukemia had mean red-cell life spans ranging from 100 to 70 days.[6]

Erythrocyte radioiron is present in significant amounts only as heme and does not leave the intact cell. Cell survival can thus be measured by direct counting of intact red cells. Labeling with radioiron is relatively rapid; 80% of the labeled cells appear in the circulation within a 3- to 4-day period and maximum blood concentration occurs in approximately one week. Though radioiron, under normal conditions, is almost completely reutilized after cell death, a transient decrease of erythrocyte radioiron occurs at the end of the finite life span[12] (see Fig. 2). By appropriate mathematical analysis, life-span distribution may be determined accurately. Three young normal subjects studied in this way showed symmetrical life-span distributions with means and two standard deviations of 115 ± 17 days, 119 ± 12 days and 122 ± 24 days, respectively. A skewed life-span distribution with a mean of 120 days was obtained in one middle-aged subject. Finch and co-workers have shown that permanent reduction of erythrocyte radioiron occurs at the end of finite life span in certain abnormal conditions of iron excess, such as hemochromatosis or hemosiderosis, and in conditions in which erythropoiesis is considerably decreased.[19]

Erythrocyte life span can also be determined indirectly with radioiron within a two-week period by relating hemoglobin synthesis to body hemoglobin. Hemoglobin synthesis may be quantitated by mathematical analysis of plasma radioiron for a period of 10 to 14 days in accordance with appropriate kinetic models (Figs. 3 and 4).[13–17] Total body hemoglobin is measured at the beginning and end of the study period by red-cell volume determinations with P^{32}-labeled red cells. Daily hemoglobin loss is calculated as the sum of daily hemoglobin synthesis and daily net decrease

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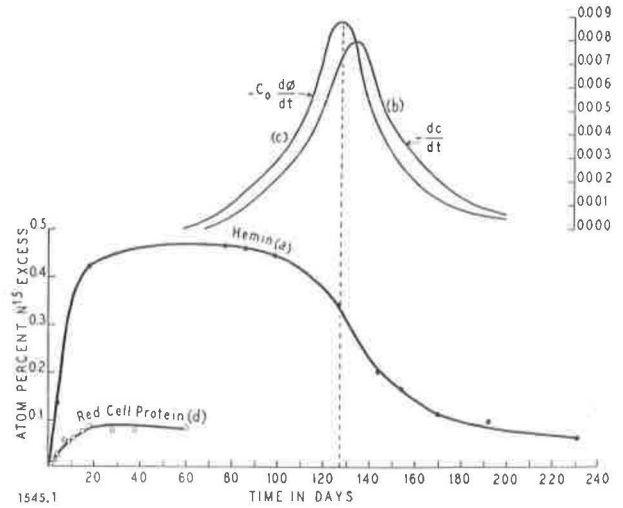

Figure 1. N^{15} concentration in hemin after feeding N^{15}-labeled glycine for 3 days (from Shemin and Rittenberg, J. Biol. Chem., 166: 628, 1946)

in body hemoglobin. Mean erythrocyte life span is determined by the ratio of body hemoglobin to daily hemoglobin loss. Twelve normal subjects studied in this way showed life spans of 104 to 129 days (mean, 117 days).[13–17] These measurements in more than 240 patients with anemia, polycythemia, leukemia or hemochromatosis show life spans varying from 133 days to as little as 3 days (in a patient with thalassemia major).[13–17]

Red cells of all ages have been labeled *in vitro* with Cr^{51}–sodium chromate and *in vivo* with P^{32}–diisopropylfluorophosphonate (DFP^{32}). Ebaugh, Ross, and Emerson[20] have shown that, despite the impermanence of the label and the somewhat variable elution of Cr^{51}, auto- and cross-transfusion of erythrocytes labeled *in vitro* may be useful in the clinical study of various anemias. The disappearance of Cr^{51} may be correlated with simultaneously performed Ashby studies to give a rough empirical relationship between persistence of

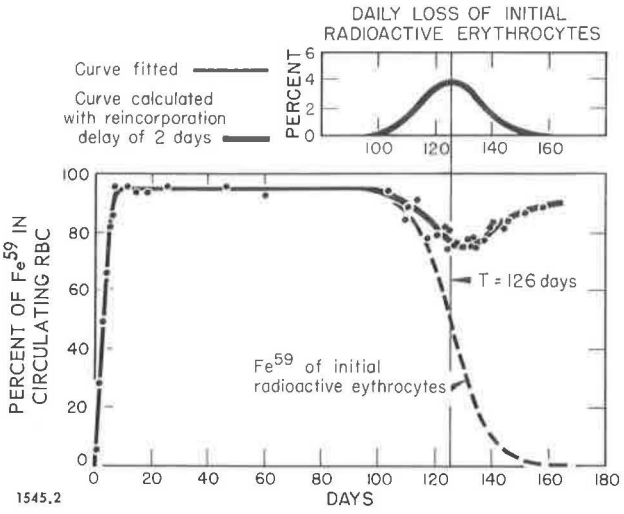

Figure 2. Per cent of administered Fe^{59} in red cell volume after intravenous injection of Fe^{59}-transferrin in plasma in normal male, age 35 years, weighing 80 kg. (mean life span (L) = time in days (T) minus mean labeling time: L = 126 − 4 = 122 days)

Cr^{51} in circulating red cells and erythrocyte life span. In normal subjects the half-time for the exponential disappearance of Cr^{51} from circulating erythrocytes varies from 23 to 40 days, depending somewhat upon the technique used: 23 to 30 days in one laboratory[21] and 25 to 40 days in another.[22]

More recently, Cohen and Warringa have used P^{32}-labeled diisopropylfluorophosphonate (DFP^{32}) as a labeling agent in the study of red cell survival.[23] This compound rapidly and irreversibly binds intracellular enzymes, yet P^{32} activity in erythrocytes of normal subjects decreases in linear fashion, resembling Ashby survival curves (Fig. 5). Cohen and Warringa[23] and Klaus and Ley,[24] using intramuscular injection of DFP^{32} in peanut oil, obtained life spans of 116 to 129 days in five hematologically normal subjects. Life spans of 104 to 127 days were obtained in 10 normal subjects by Pollycove, Dal Santo and Lawrence[25,26] after intravenous administration of DFP^{32} in propyl-

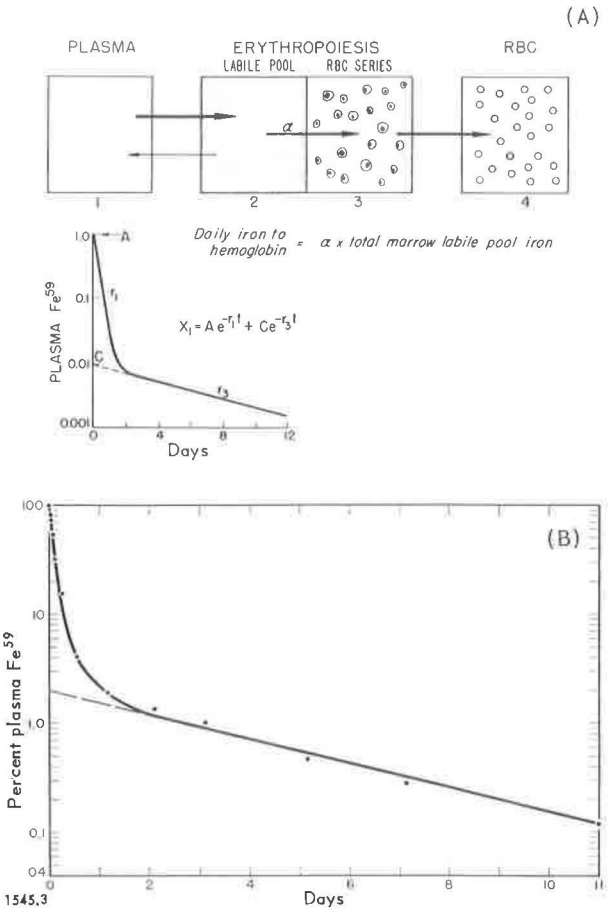

Figure 3. Analysis of plasma radioiron data in accordance with normal model shown. Storage compartment has been omitted because the plasma-storage iron exchange is negligible in the normal (cf. Fig. 4). Rigorous solution of the corresponding simultaneous differential equations makes possible quantitative determination of hemoglobin synthesis. (A), iron-kinetics model showing normal flow; (B), normal plasma iron removal in normal male, age 31, weighing 70 kg. Iron leaving plasma = 36 mg/d, labile erythropoietic pool = 90 mg, iron for hemoglobin = 22 mg/d, hemoglobin synthesis = Hb Fe/3.4 = 6.6 g/d, mean RBC life span $= \frac{\text{Total Hb}}{\text{Daily Hb loss}} = \frac{808}{6.6} = 122$ d

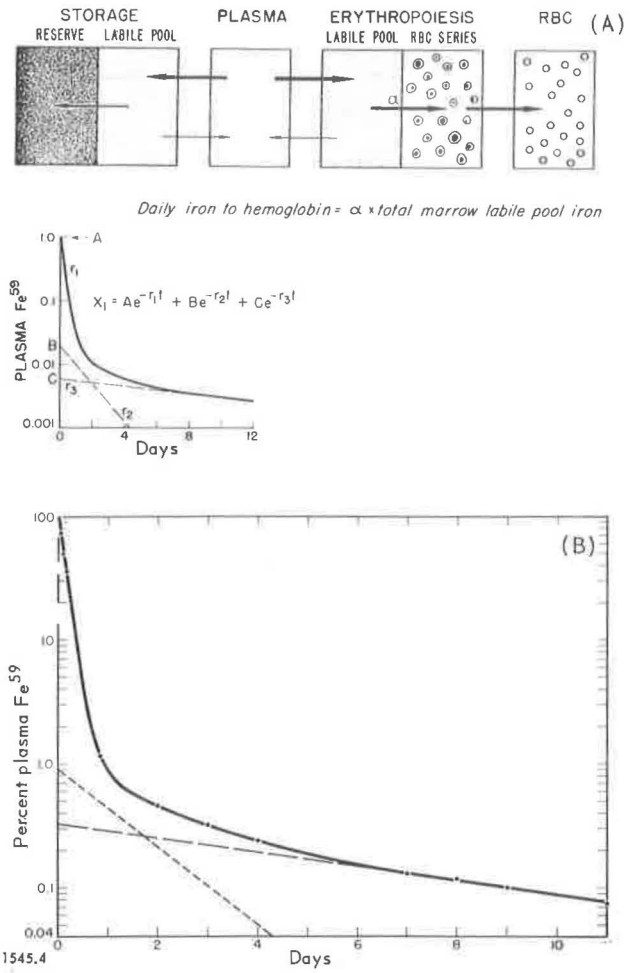

Figure 4. Analysis of plasma radioiron data in accordance with the storage exchange model shown. Rigorous solution of the corresponding simultaneous differential equations makes possible quantitative determination of hemoglobin synthesis. (A), iron-kinetics model showing storage exchange; (B), plasma iron removal in a case of endogenous hemachromatosis. Hb = 15.0, serum iron = 278 μg/100 ml, iron leaving plasma = 49 mg/d, labile erythropoietic pool = 187 mg, labile storage pool = 26 mg, iron for hemoglobin = 23 mg/d, hemoglobin synthesis = Hb Fe/3.4 = 6.6 g/d, mean RBC life

$$\text{span} = \frac{\text{Total Hb}}{\text{Daily Hb loss}} = \frac{700}{6.6} = 105 \text{ days}$$

ene glycol[26] (see Fig. 5). These data show that, in the amounts used, DFP^{32} is a permanent label and does not significantly shorten erythrocyte life span. These basic desiderata combined with ease of *in vivo* labeling and simplicity of measuring intact erythrocytes suggest that the use of DFP^{32} is at present the preferred method for study of red cells of all ages in their own environment.

White cell survival involves certain problems not encountered in red cell survival. White cells comprise a mixed population normally composed chiefly of neutrophilic granulocytes and lymphocytes. To determine survival of each specific cell type it is necessary to separate them in relatively pure form. This technical problem is still largely unsolved. Ottesen described a method of separating lymphocytes from granulocytes[27] which, in the hands of others, is difficult and gives variable results. Other problems in analysis of labeled leukocytes concern their adherence to blood-vessel walls and their transcapillary migration into tissues, their various modes of functional loss and destruction and their possible re-entry into the circulation. These considerations seem to make the concept of a finite life span inapplicable. A descriptive term such as "survival of leukocytes in circulating blood" seems more appropriate.

Immature leukocytes of approximately the same age have been labeled *in vivo* with inorganic radiophosphorus and S^{35}–*l*-cystine. Phosphorus exchange occurs in the intact leukocyte, with the result that P^{32} activity does not represent cell survival. Desoxypentose nucleic acid (DNA), however, in mature cells is metabolically inert, making possible the use of P^{32}–DNA as a permanent cell label. Ottesen[27] and Kline and Cliffton[28] determined survival of leukocytes in the circulation by analysis of P^{32} concentration in leukocyte DNA in the way that Shemin and Rittenberg[3] analyzed N^{15} concentration in erythrocyte hemin. These studies in nine subjects with normal leukocytes showed that granulocytes appear in the circulation after 4 to 6 days' maturation in the marrow, then remain in the blood 8 to 15 days, the mean age of circulating granulocytes being 13 days. Lymphocytes of two subjects studied by Ottesen appeared to be composed of two groups, 10 to 20% having a mean age of approximately 3 to 4 days and 80 to 90% having a mean age of 100 to 200 days. Christensen and Ottesen studied three patients with chronic lymphatic leukemia in whom the mean age of lymphocytes was calculated to be 1000 days.[29] Weisberger and Levine obtained similar results by measuring the concentration of radiosulfur (S^{35}) in leukocytes, probably not a permanent label, after the subjects had ingested S^{35}–*l*-cystine.[30] Survival of acute leukemic leukocytes (five patients) seemed considerably shorter than that of normal leukocytes; survival of leukocytes in chronic myelogenous leukemia (three patients) seemed only slightly shorter.

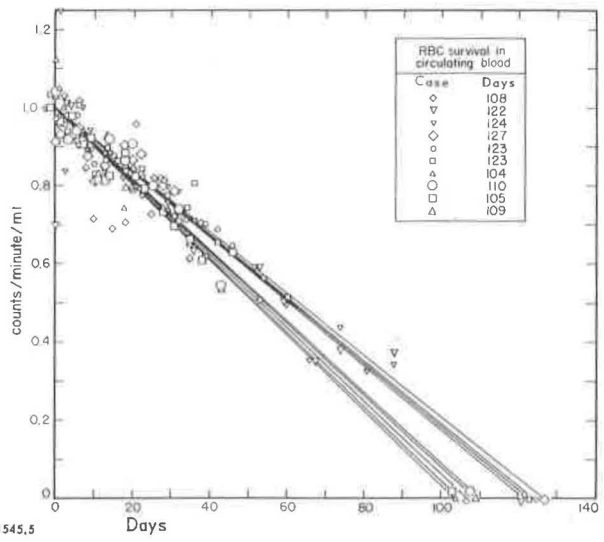

Figure 5. P^{32} concentration in red cells of 10 normal subjects after one intravenous injection of DFP^{32}

White cells of all ages recently have been labeled *in vivo* with P^{32}–diisopropylfluorophosphonate (DFP^{32}) by Mauer, Athens and co-workers[31,32] and subsequently by Pollycove, Dal Santo and Lawrence.[25,26] Labeled leukocytes were virtually absent from the circulation 15 to 20 days after parenteral administration of DFP^{32}, which is chiefly a granulocyte label, since lymphocytes appear to bind little, if any, DFP. The mode of disappearance of labeled granulocytes from the circulation suggests that labeled circulating granulocytes equilibrate in 1 or 2 days with a large noncirculating pool of labeled granulocytes, many of which are maturing in the marrow, and that after the labeled reserve is depleted (5 to 12 days), a final isotopic decrease occurs, reflecting removal of granulocytes from the circulation (Fig. 6).

Platelets of all ages have been labeled *in vivo* with DFP^{32} and *in vitro* with Cr^{51}–sodium chromate. Leeksma and Cohen, after intramuscular injection of DFP^{32} into five subjects without hematologic abnormalities, found linear decreases of radioactivity extrapolating to zero at 9 to 11 days.[33] Pollycove, Dal Santo and Lawrence, after intravenous injection of DFP^{32} into 13 normal subjects, obtained similar results showing platelet life span of from 8 to 14 days.[25,26] Aas and Gardner, despite some manipulative damage evidenced by transient sequestration of platelets from the circulation, obtained similar results with autotransfused platelets labeled *in vitro* with Cr^{51}–sodium chromate.[34] Adelson, Rheingold and Crosby studied the survival of polycythemic platelets labeled *in vivo* over a period of 7 days following one injection of 3 to 5 millicuries of P^{32} and then transfused into two normal recipients.[35] Transient sequestration of platelets occurred after transfusion and was followed by a rapid exponential disappearance of labeled platelets (half-life, 2.0 and 2.5 days). This effect is probably due to heavier labeling of older platelets, to possible shortening of life span

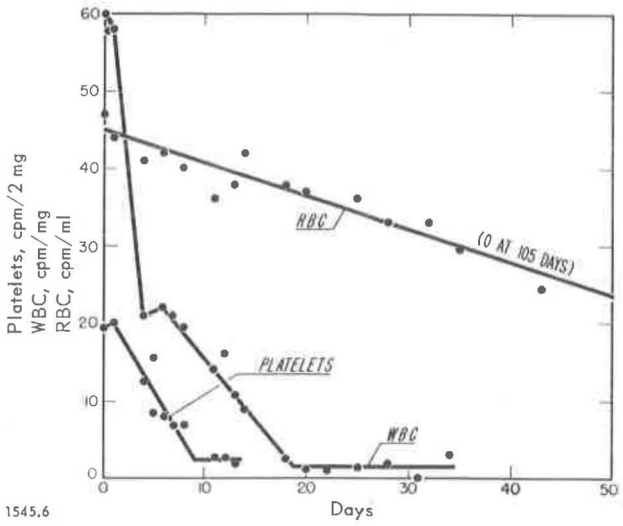

Figure 6. P^{32} concentration in red cells, white cells, and platelets of a normal male subject, age 34, after one intravenous injection of DFP^{32}. Days survival of DFP^{32}-labeled blood cells appear on abscissa

of polycythemic platelets, as shown previously,[25,33] and to possible permanent manipulative damage.

Recently Pollycove, Dal Santo and Lawrence have shown that DFP^{32} can be used in a practical, relatively simple manner for simultaneous determination of erythrocyte, leukocyte and platelet survival in circulating blood[25,26] (see Fig. 6). Erythrocyte, leukocyte and platelet radioactivity in 22 normal subjects decreased in approximately linear fashion, with end points at 104 to 129 days, 15 to 19 days and 8 to 14 days, respectively.

The widespread use of radioisotopes has made it possible to measure the life span of erythrocytes, leukocytes and platelets. These measurements are not only fundamental contributions to our knowledge of physiology but also are extremely useful in medical diagnosis and therapy.

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Application of Cr^{51} in the Study of Human Erythrocytes

By F. M. Bragança Gil and F. A. Carvão Gomes*

The life-span of human erythrocytes has been determined recently through application of the knowledge either of the total survival-time of the red cells or of their half-life, using Cr^{51} to label the erythrocytes, whose disappearance from the circulation can then be measured.[1,2]

Essentially, two techniques have been employed for this determination. One consists in withdrawing a certain volume of heparinized blood from the patient, incubating it in the presence of Cr^{51} (valence of 6) and then separating by centrifugation the red blood cells which will later be used for injection. The red cells are made up to the initial volume with isotonic saline solution and plasma from the same patient.

The other technique employs *in vivo* labelling of red blood cells for which hexavalent chromium is injected intravenously. In both methods, the disappearance of the labelled red blood cells from the circulation is checked by activity measurements on red blood cell samples obtained at different periods of time. Both methods have been used and the techniques and results are discussed in the present paper.

EFFECT OF VITAMIN C ON Cr^{51} UPTAKE

The use of chromium (valence of 3) for labelling red blood cells introduces this radioelement into the plasma proteins. On the other hand hexavalent Cr^{51} is fixed by the red blood cells and remains there due to the impermeability of the cell wall to the cation.

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The addition of a reducing agent to whole blood leads to the labelling of the blood proteins by the chromium and the inhibition of its uptake by the red blood cells. This point needs experimental confirmation since various investigators do not agree on the effect of vitamin C on Cr^{51} uptake by the erythrocyte. Among the different reducing agents that may be employed, ascorbic acid is the most practical and Read[3] was among the first investigators to use it.

In order to study the effect of this reducing agent on the labelling of red cells by Cr^{51}, therefore, we performed the following experiment.

Twenty-five milliliters of heparinized blood were withdrawn and divided into five centrifuge tubes. The red blood cells in two tubes were separated from the plasma by centrifugation. The whole blood and red cell samples were then treated with vitamin C (50 mg) and Cr^{51} (50 μc) as follows: (i) to one whole-blood sample (tube 1) 50 mg of vitamin C was first added and then 50 μc of Cr^{51}; (ii) to the second sample of whole blood (tube 4) the same quantity of Cr^{51} was added before the 50 mg of vitamin C; (iii) to the last sample of whole blood (tube 3) only Cr^{51} was added; (iv) to one erythrocyte sample (tube 5) the vitamin C was added after the Cr^{51}; and (v) to the other sample of erythrocytes (tube 2) only the radiochrome was added.

The samples containing the radioisotope were incubated, then those containing whole blood were centrifugated to separate the red cells from plasma. Each sample was washed with sterilized isotonic saline solution, and again the erythrocytes separated by centrifu-

Table 1

Tube	*Samples containing*	*Fractions*	*Measurement of activity (cpm)*
1	Whole blood, vitamin C, Cr^{51}	Erythrocytes	0
		Supernatant plasma	35.000
		Washing liquid	0
2	Erythrocytes, Cr^{51}, no vitamin C	Erythrocytes	7.900
		Washing liquid	25.000
3	Whole blood, Cr^{51}, no vitamin C	Erythrocytes	7.900
		Supernatant plasma	27.100
		Washing liquid	0
4	Whole blood, Cr^{51}, vitamin C	Erythrocytes	1.500
		Supernatant plasma	30.000
		Washing liquid	1.600
5	Erythrocytes, Cr^{51}, vitamin C	Erythrocytes	2.900
		Washing liquid	31.000

gation. Measurements for radioactivity were made on the different fractions obtained from these procedures (i.e. erythrocyte, supernatant plasma and washings) of each sample to determine the chromium distribution. The results are summarized in Table 1.

From the data presented in Table 1, it can be seen that in sample 1 where vitamin C was added before Cr^{51}, all the radioactive chromium passed into the supernatant plasma. In samples 4 and 5, where vitamin C was added after the radioelement to whole blood and erythrocytes, respectively, there is a distribution of activity between red blood cells and plasma and the fluid recovered from the washing. The samples to which no vitamin C was added showed a high degree of activity in the cellular fraction although some activity in the plasma, which can be explained by an unfinished incubation, is noticed.

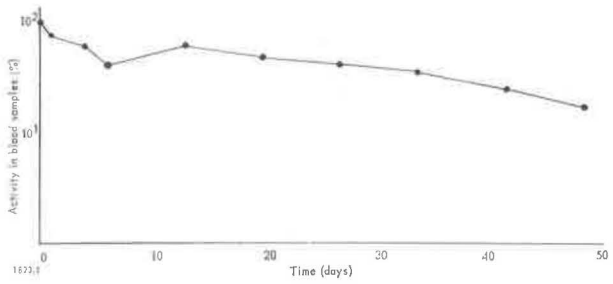

Figure 1. Decay of radioactivity in Cr^{51} labeled whole blood

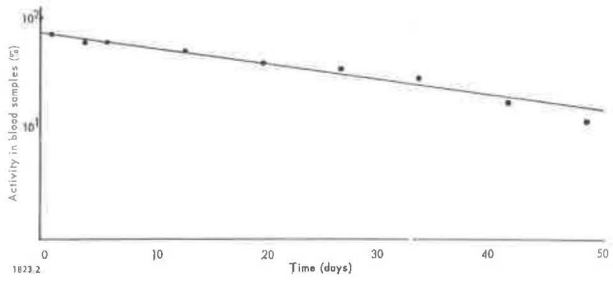

Figure 2. Decay of radioactivity in Cr^{51} labeled whole blood corrected for variations in hematocrit values

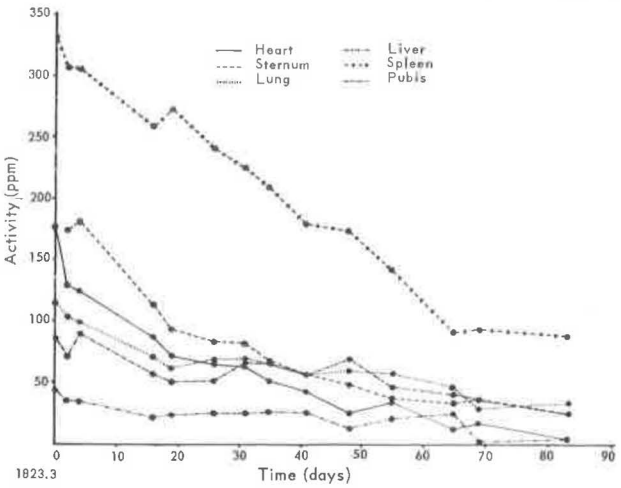

Figure 3. Radioactivity of Cr^{51} determined by external counting over different organs

METHODS OF MEASURING ERYTHROCYTE LIFE-SPAN

For the two methods of determining erythrocyte life-span mentioned above, we could find no reference giving the details of the technique for performing these measurements on samples of blood withdrawn. As the method for the determination of length of erythrocyte life is based on the labelling of these cells, we were of the opinion that measurements should only be made on the erythrocytes and not on whole blood. There are two practical methods for making these measurements: (1) separation of red cells from plasma by centrifugation, followed by washing of the cells and the determination of radioactivity of the cells, plasma and wash-water fractions, and (2) determination of radioactivity on a known volume of whole blood which is then expressed as a function of the red blood cells per volume

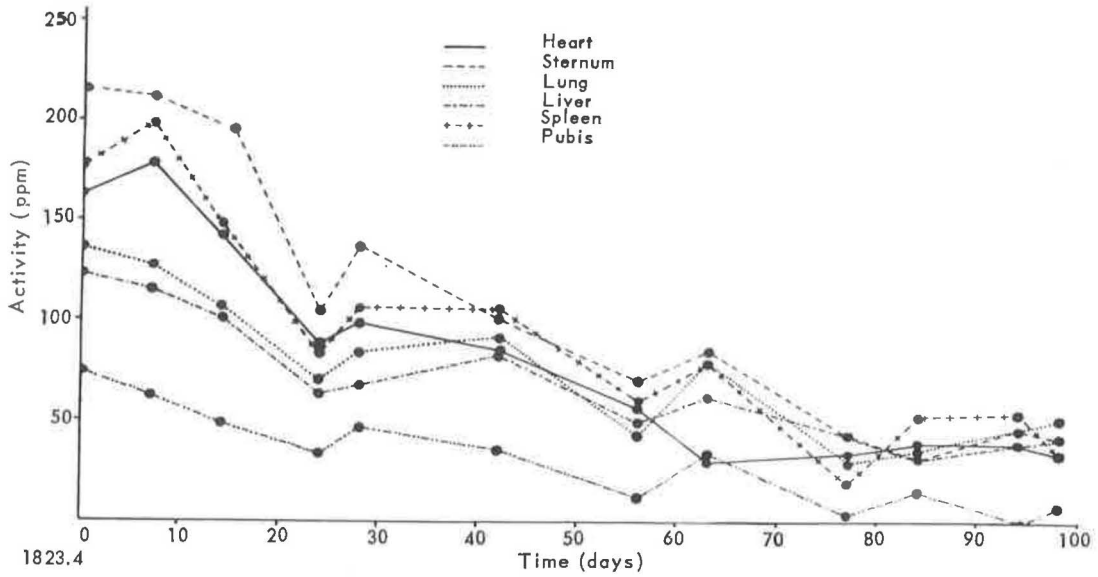

Figure 4. Radioactivity of Cr^{51} determined by external counting over different organs

units, the volume of the red cells being determined by the hematocrit method. The first method involves greater experimental manipulation, but errors in the measurement of erythrocyte activity due to the presence of radioactive chromium in plasma are avoided. Errors are likely to occur in the second method unless activity in the plasma is completely absent.

Experiments have shown that the amount of activity in the plasma can be determined, and we have been using this method. Up to now, we have no practical experimental data on plasma radioactivity from *in vivo* labelling. However, it is always possible to determine rapidly and accurately the activity in plasma by measurements made on a blood sample. Finally, the equation below expresses the activity in a ml volume of red blood cells as a function of the activity measured in the whole blood, knowing the red blood cell volume (in ml) from the hematocrit determination H:

$$A_0 = \left[\frac{100A}{HV} - \frac{A_1}{V_1}\left(\frac{100}{H} - 1\right)\right] \times e^{kt}$$

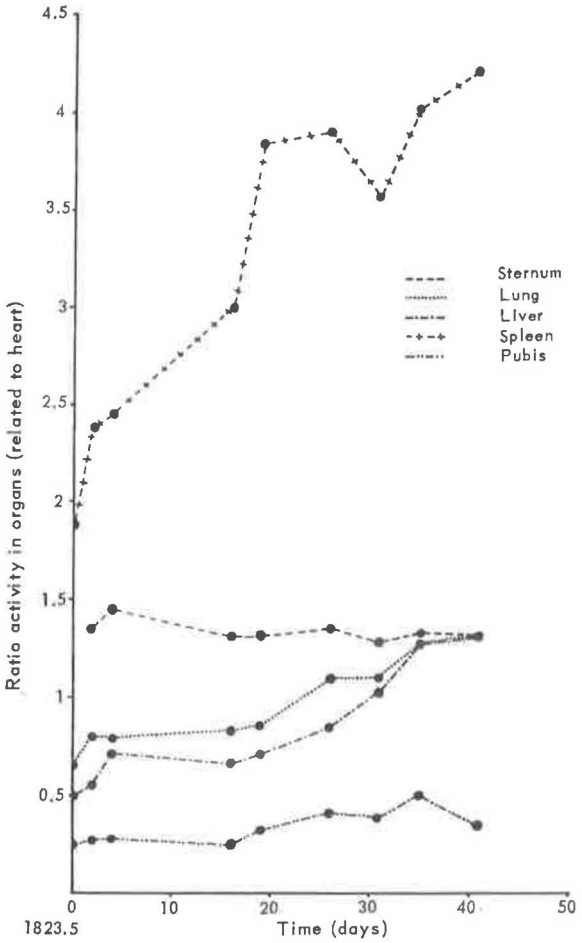

Figure 5. Ratio of activity of Cr^{51} over different organs in relation to activity over the heart

where V = volume of the blood sample; A_1 = activity of the plasma; V_1 = volume of plasma whose activity was measured.

These activities are corrected for "dead time" and for "background" in the counting system.

The factor e^{kt} is used to correct for the physical decay of the Cr^{51} employed in labelling the red blood cells. Ordinarily when there is no activity of the plasma, the previous equation becomes:

$$A_0 = \frac{100A}{HV} \times e^{kt}$$

Figure 1 shows the decay of activity on millilitre samples of whole blood.

The results obtained from the use of the above formula are corrected for temporary variations in hematocrit values and the curve is presented as a smooth line in Fig. 2.

In this case some correction also had to be made for plasma activity. The experimental results treated in this way show that red blood cell decay is exponential and this leads us to conclude that it is the half-life, rather than the life-span, of the red cells that is able to be determined.

EXTERNAL MEASUREMENTS OF Cr^{51} CONCENTRATION

Since chromium-51 is a gamma emitter, it is possible to determine its concentration in selected internal organs by external detectors without the necessity of withdrawing blood. Although the results may not be completely conclusive they are satisfactory.

Figures 3 and 4 show the results of measurements of activity determined for different organs over the same periods of time.

The ratio of radioactivity over various organs in relation to the radioactivity over the heart taken as a reference organ is shown in Figs. 5 and 6.

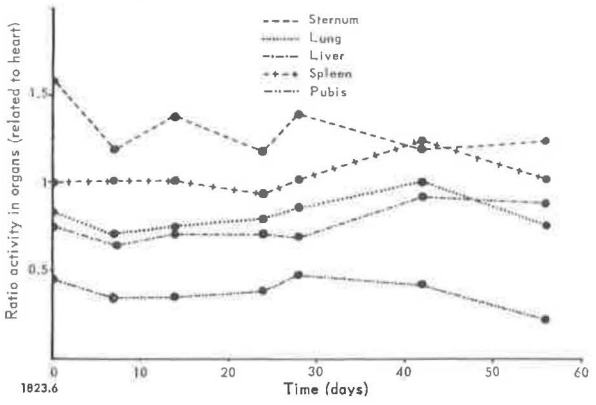

Figure 6. Ratio of activity of Cr^{51} over some organs to activity over the heart

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Uptake of Radioactive Ce^{144} by White Blood Cells

By A. Aeberhardt*

A study of the mode of transport of cerium in the blood of different laboratory animals following intravenous injection of carrier-free Ce^{144}–Pr^{144} has served to demonstrate the role played by white blood cells in the transport of fission products through the blood.

We were, therefore, led to an *in vitro* study of different aspects of the uptake of cerium by white blood cells in order to explore the possibility of utilizing this property to label leukocytes, inasmuch as current methods for labeling white cells are not entirely satisfactory.

Employing the method for separating blood components which we published in 1956,[1] we have studied the uptake of cerium in (i) rabbit leukocyte suspensions, (ii) human leukocyte suspensions and (iii) rabbit leukocytes in whole blood.

EXPERIMENTAL METHODS

Preparation of Leukocyte Suspensions

Our method of separating blood components allows the fractionation of 5 to 10 ml samples of blood into three fractions, viz., plasma, red blood cells and white blood cells, without the addition of any other substance. There is very little contamination of white blood cells with erythrocytes, and the cells have undergone minimal handling with the result that their physiological state is essentially unaltered.

Our method of separation is based on the principle of controlled centrifugation in a special apparatus composed of two concentric tubes, the lower ends of which communicate with one another. The blood is kept in the central tube during centrifugation by means of a small quantity of mercury placed in the bottoms of the tubes. After centrifugation, mercury is introduced into the outer tube in such a way as to cause the contents of the inner tube to rise slowly. This permits successive separation of the different fractions—plasma and cellular—from the upper portion of the column of liquid in the inner tube.

Rabbit leukocyte suspension was prepared by collecting 10 to 20 ml of blood from a heparinized rabbit using a trocar treated with heparin or silicon into a siliconed tube and kept at a temperature of 0°C. The blood is immediately placed in the apparatus for separating and centrifuged in the cold at 1500 *g* for 20 minutes. The various fractions are separated and the leukocyte fraction is washed with isotonic saline and the white cells are then suspended in 1 ml of 0.9% physiological saline (pH 7.4).

The suspension of human white blood corpuscles (500,000 per cubic cm^3) used in our studies was provided by the Army Blood Center (Clamart) and was prepared from blood obtained from a large number of donors. It was practically free of red blood cells.

Cerium Uptake by Leukocytes in Saline Suspensions

Rabbit Leucocytes

The carrier-free stock solution of Ce^{144}–Pr^{144} was suitably diluted in 0.9% saline solution and brought to the correct pH. For every 1 ml leukocyte suspension 0.1 ml diluted Ce^{144}–Pr^{144} solution was added and incubated at 37°C with constant shaking for varying periods. The leukocytes were then separated by centrifugation, washed twice with physiological saline solution and resuspended in 0.5 ml saline. The radioactivity of the leukocytes, of the supernate (incubation medium) and of the washings was then determined with the aid of a flow counter (Geiger-Müller tube with thin end window).

In another series of experiments the Ce^{144}–Pr^{144} solution was used to label the plasma collected in the course of fractionation. In this experiment the leukocyte suspension was added to 5 ml of the labeled plasma and incubated under the conditions described above.

Human Leukocytes

To 1 ml of the suspension of human leukocytes was added 19 ml 0.9% physiological saline solution (pH 7.4), and to this was added 1 ml diluted Ce^{144}–Pr^{144} solution ($CeCl_3$) in saline. The resulting suspension was incubated and the distribution of the radioactivity in the various fractions was then determined following the procedure outlined for rabbit blood.

Cerium Uptake by Leukocytes in Whole Blood

Blood was collected from rabbits as described previously. To 10 ml blood was added 0.1 ml diluted carrier-free Ce^{144}–Pr^{144} (either the chloride or nitrate) and the mixture incubated for varying periods (30 min to 2½ hr) with continuous shaking. Specific activity of the whole blood was determined both before and after incubation to check on the possibility of adsorption on the glass wall. The blood fractions were then sepa-

Original language: French.

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Table 1. *In Vitro* Uptake of Cerium by Rabbit Leukocytes

Type of salt	Medium	Conditions of incubation: pH	Duration hr	Temp °C	Distribution of radioactivity (per cent total): WBC[a]	Medium	Washings: 1	Washings: 2
$CeCl_3$	0.9% saline	5–6	1	37	25	75	1–3	1
$Ce(NO_3)_3$	0.9% saline	4	1	37	25	75	1–2	1
$Ce(NO_3)_3$	0.9% saline	7.5	1	37	20–25	65–70	5–10	2
$CeCl_3$	citrate–phosphate	5	1	37	1–2	98	—	—
$CeCl_3$	citrate–phosphate	7.5	1	37	1–2	98	—	—
$CeCl_3$	citrate–phosphate	8	1	37	15	85	1–2	1
$CeCl_3$	plasma	—	2½	37	25	75	1–3	1

[a] Fraction fixed after washing

rated, the white blood cells washed twice with physiological saline and the distribution of radioactivity among the various fractions was determined by measurements on aliquots of plasma, red cells and total number of white cells recovered after digestion with a mixture of perchloric and nitric acids.

EXPERIMENTAL RESULTS

In Vitro Uptake of Cerium by Rabbit Leukocytes

The uptake of cerium by isolated rabbit leukocytes was studied under different conditions of incubation—nature and pH of incubating medium and duration of incubation.

Table 1 summarizes the results which are expressed as per cent of the total radioactivity found in the different fractions—white blood cells, incubating medium and washings.

Cerium Uptake by Human Leukocytes

Bearing in mind the results obtained with rabbit leukocytes, we studied the uptake by human leukocytes under the conditions that gave us the best results, i.e., using a solution of $CeCl_3$ in 0.9% physiological saline solution at pH 6.

The distribution of radioactivity was studied as a function of duration and temperature of incubation. Table 2 summarizes the experimental results. The uptake by the leukocytes is expressed as a percentage of the initial activity in the suspension.

Table 2. *In Vitro* Uptake of Cerium by Human Leukocytes after Incubation in a Solution of $CeCl_3$ in 0.9% Physiological Saline, pH 6

Conditions of incubation: Duration min	Temp °C	Distribution of radioactivity (per cent initial dose): WBC	Medium	Washings: 1	Washings: 2
15	37	35	57	5	2.7
30	37	29	62	8	1
60	37	28	60	8	4
120	37	38	59	1	1
60	20	10	85	5	1
24 hr	20	31	48	13	7

Under these conditions uptake by human leukocytes was rapid at 37°C. It reached 25 to 35% of the initial activity after two washings. At 20°C uptake was slow, amounting to only 10 per cent after 60 min incubation and reaching a maximum after 24 hours. The amount of activity appearing in the water of successive washings was appreciably greater after incubation at 20°C than after incubation at 37°C. It was also proportionately greater after short periods of incubation than after longer periods, regardless of the temperature of incubation.

In Vitro Uptake of Cerium by White Blood Cells Suspended in Rabbit Whole Blood

Uptake of cerium by rabbit white cells suspended in rabbit whole blood was studied as a function of the nature of the anion ($CeCl_3$ and $Ce(NO_3)_3$) and of the pH of the Ce^{144}–Pr^{144} solution after incubation for a period of 1½ hours.

For $CeCl_3$ solution at pH 5 to 6, the incubation period varied from 30 min to 2½ hours. No studies were carried out with buffered solutions in view of the results obtained in the *in vitro* experiments with rabbit leukocytes. The results are summarized in Table 3. They are expressed as percentage of the initial radioactivity found in the different blood fractions and in the wash waters.

After the incubation of whole rabbit blood at 37°C, the cerium uptake is comparable to the uptake found in analogous experiments when the white cells are suspended in either a 0.9% physiological saline or in homologous plasma. However, certain differences in the rate and quantity of uptake are apparent.

Uptake by leukocytes suspended in whole blood is slower than in saline, requiring an incubation period of 1½ hours to attain a maximum of 15 to 25%. Uptake under these conditions is stable, inasmuch as successive washings remove only a small per cent of the activity fixed before washing. The quantity fixed, although not constant, is nevertheless significant (15–25%), varying apparently with the source of the blood, i.e., from different rabbits.

When the cerium used is in colloidal form ($CeCl_3$ at pH 11 and $Ce(NO_3)_3$ at pH 8), a larger fraction is taken up by the leukocytes (up to 30–50%) but some cerium is found also in the erythrocyte fraction. The distribution between plasma and red blood cells varies greatly from one experiment to the next and is apparently due to the colloidal nature of the cerium which in this case was unequally distributed between these two fractions. The activity found in the erythrocyte fraction is readily removed by dilution followed by gentle centrifugation, indicating that the cerium is not bound by the red blood cells.

On the other hand, uptake by the white cells is stable, resisting not only two successive washings with physiological saline but also exposure to physiological saline for 24 hours at room temperature, or exposure for 25 hours at 37°C to nonlabeled homologous plasma obtained in the course of fractionation of nonlabeled blood. In the latter case, 96% of the activity originally fixed on the leukocytes remain on the cells, only 4% having been liberated in the plasma.

INTERPRETATION AND DISCUSSION

Our experimental results indicate that a significant fraction of cerium is bound by the leukocytes, whether suspended in saline solution or in plasma.

This uptake is quantitatively significant, amounting to 25% of the initial radioactivity, and is stable. Optimum conditions for isotope uptake are realized with the incubation of a suspension of washed leukocytes in 0.9% saline solution with the cerium salt ($CeCl_3$) at pH 6 for one hour at 37°C with continuous shaking.

The absence of uptake in a medium buffered with citrate must have been due to the formation of a stable complex between the citrate and the cerium, thereby preventing the uptake of cerium by the white cells. In a solution of 0.9% NaCl in the absence of interfering agents, the uptake of cerium by the white cells can be attributed perhaps to the formation of a compound of cerium and the nucleic acids which are present in large quantities in white cells.

When the carrier solution is at alkaline pH, however, another mechanism may play a role. At neutral and alkaline pH, the cerium is partially changed into colloidal $Ce(OH)_3$. A study of the physicochemical behavior of solutions of different cerium salts at "trace" concentrations (10^{-8} to 10^{-10} M) has shown that solutions of cerium chloride are practically completely ionized at a pH range of 5 to 7, but are nearly in completely colloidal form at pH 11. On the other hand, carrier-free solutions of cerium (nitrate) are ionized at a pH less than 4 and are colloidal when the pH is 7. At the pH range of our experiments, the physicochemical state of the cerium salts is alkaline. Thus in the solution of $CeCl_3$ at pH 11 and that of $Ce(NO_3)_3$ at pH 8, the cerium is colloidal. Under these conditions fixation by adsorption may occur. This hypothesis is supported by the observation that washing under these conditions removed an appreciable fraction of the activity initially found on the leukocytes.

When whole blood is used, its other constituents compete with the leukocytes to take up cerium. Cerium in the ionic state becomes bound by the proteins of the plasma and the white blood cells. However, the latter appear to take up slowly a significant proportion of the cerium originally bound by the proteins, equilibrium being achieved only after some time of contact. This was demonstrated by the uptake of cerium by leukocytes suspended in a labeled plasma medium and also by the role played by the length of the incubation period when plasma proteins are present in the incubation medium. In this way binding by white blood cells was selective after 1½ hours incubation.

CLINICAL APPLICATIONS

Heretofore white blood cells have been labeled with radioisotopes by one of the following methods:

(i) *In vivo*, by the injection of either P^{32} (Ref 2) or S^{35} (Ref 3) into animals. These two elements are incorporated into either the nucleic acids or the amino acids of the cells by metabolic action.

(ii) *In vitro*, by incubation of leukocyte suspensions with either P^{32} (Ref 4) or Cr^{51} (sodium chromate).[5]

The capacity of the white blood cells to take up ce-

Table 3. *In Vitro* **Distribution of Cerium in Whole Rabbit Blood (cerium salt solutions made up in 0.9% physiological saline)**

Conditions of incubation				*Distribution of radioactivity (per cent total)*				
Salt	*pH*	*Duration min*	*Temp °C*	*WBC*	*Plasma*	*RBC*	*Washings of WBC* 1	2
$CeCl_3$	5–6	30	37	5	95	1	1	1
$CeCl_3$	5–6	60	37	10	90	1	1–2	1
$CeCl_3$	5–6	90	37	15–25	73–85	1–2	1–2	1
$CeCl_3$	5–6	150	37	15–25	70–85	1–5	1–2	1
$CeCl_3$	4	90	37	20–30	30–60	20–40	1–3	1
$CeCl_3$	11	90	37	40–50	variable	variable	1	5
$Ce(NO_3)_3$	4	0	—	10	90	1–2	1–2	1
$Ce(NO_3)_3$	4	90	37	20–25	75–80	1–8	1–4	1
$Ce(NO_3)_3$	8	90	37	30	variable	variable	5–10	1–2

rium raises the possibility of a new method of labeling white blood cells *in vitro*. Such a possibility has a number of advantages over existing methods.

Actually, leukocytes take up only a small quantity of P^{32} (1 to 6 per cent of the initial activity) and a very variable quantity of Cr^{51} (5 to 85%). Furthermore, in both cases the fixation is of very short duration. Maupin[6] reports that the mean period of experimentation available to workers using P^{32}-labeled white blood cells amounts to only 20 min.

These facts can be contrasted with the significant, stable and constant uptake of cerium by isolated leukocytes, which can be obtained either by *in vitro* incubation in physiological saline or by incubation with donor plasma which has previously been labeled. After gentle centrifugation the labeled plasma can, in the latter case, be replaced by nonlabeled homologous plasma. With such a procedure the period spent by the white blood corpuscles in an artificial medium is reduced to a minimum, thus minimizing any changes these very fragile cells may undergo.

Conversely, it is possible to obtain a sample of donor's blood where only the white cells are labeled.

The simultaneous use of the method for the isolation of the white blood cells and labeling with radioactive cerium makes it possible to study in the experimental animal the period spent by the white blood cells in the intravascular bed and their ultimate fate in the organism. Such a study would be done under better conditions than heretofore possible. Studies now in progress have confirmed that in the rabbit labeled white blood cells disappear rapidly from the circulation, and that within seven minutes of intravenous reinjection of the labeled white cells an appreciable amount of activity is found in the lungs.

Such studies in man may yield important information, particularly in the leukemic diseases. Here one would be interested in labeling the patient's own white blood cells by removing a small quantity of blood and reinjecting these cells after they have remained only a short period outside of the body and under conditions of minimum trauma for the cells.

Nevertheless, Ce^{144} cannot be used in man without risk. Its long half-life (290 days), the relatively high energy of the beta rays (2.98 Mev) emitted by its descendant Pr^{144}, its localization in the liver and the skeletal system, along with its long biological half-life all combine to prevent its use in clinical medicine. However, two other cerium radioisotopes (Ce^{141} and Ce^{143}) can apparently be used for humans without danger since their periods are 32 days and 32 hours, respectively, and their beta-ray energy is low—0.57 Mev.

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The Ante-partum Assessment of Placental Function Using Radioactive Sodium

By C. G. Clayton* and G. T. Johnson†

The loss of foetal life due to placental failure assumes greater importance as other major causes of still birth are brought under control by steady improvement in obstetric and paediatric techniques.

The mortality attributable to placental failure is difficult to assess with accuracy because of the inaccessibility of this structure and its decidual environment, and the consequent difficulty of clinical and biochemical study during pregnancy and labour. Certain maternal conditions, however, such as pre-eclampsia, essential hypertension and diabetes, and foetal complications such as accidental haemorrhage and postmaturity are recognised associates of placental injury, and are collectively responsible for approximately one quarter of all perinatal mortality.[1] There can thus be no doubt that accurate assessments of placental function would greatly help in the management of these problems and considerably improve the prospects for the foetus. It is with this idea in mind that we have endeavoured to devise a practical method of measuring placental function antenatally.

The ideal requirement in placental study is for a means of investigating the movement of nutrients and metabolites between mother and foetus without physical interference with the placenta itself. An early measure of placental function may thus be obtained before clinical signs of failure become manifest. Tracer quantities of radioisotopes offer an opportunity for such observations with maximal safety to mother and foetus.

The radioisotope is injected into the maternal vascular system and its transfer to the foetus, by the placenta, is studied with apparatus mounted outside the pregnant uterus. A dynamic picture of the functional state of the placenta can thus be derived together with an over-all index of the ability of the foetal cardiovascular system to transfer electrolytes from the placenta into its own body structures.[2]

A suitable isotope must be safe and compatible with the physical processes under investigation, and these requirements severely restrict the choice. A number of substances have been considered and the authors regard sodium-24 as the most suitable. It is nonspecific to the body tissues, readily available as isotonic saline, and correlation between radiosodium and general electrolyte transfer rates has been clearly demonstrated by Flexner,[3] Cox and Chalmers[4] and Johnson and Clayton.[5] In addition, the maximum permissible body burden is 15 microcuries, so that the injection of 20 microcuries used in a single test is well within the tolerance level, because of excretion.

A number of methods of assessing placental function antenatally have been reported. Brown and Veall[6] injected radioactive isotonic saline directly into the placental villi and observed its clearance rate with a Geiger counter located over the site of injection. They showed that sodium-24 was cleared at a substantially slower rate in hypertensive compared with normotensive pregnancies. Though this technique yields valuable information, its use is restricted to patients having a placenta lying on the anterior wall of the uterus and involves the hazard of direct intra-placental injection.

A number of workers[7–10] have studied the capillary bed of the myometrium which supplies the maternal decidua into which the foetal placenta is implanted. All have shown that when a small volume of isotonic sodium chloride is injected directly into the capillary bed in late pregnancy, it is cleared at a constant rate in normotensive subjects, and at a significantly slower rate in patients suffering from hypertension of pre-eclampsia. The clearance rate is further impaired by exercise and postmaturity and temporarily restored by the therapeutic use of certain hypertensive drugs.

It is clear that this approach only yields evidence about the state of the capillary bed within the myometrium and is thus not a direct indication of placental action.

In previous studies[5] it has been shown that in normal cases the transfer of radiosodium to the foetus at the time of delivery follows a specific curve, whereas a significant reduction in transfer rate takes place when there is some clinical evidence of disturbed placental action at the time of delivery.

An elementary consideration of the physical aspects of this problem has shown that care must be taken in choosing the design and position of the detector system so that the relatively small increase in radiation due to the foetus will be most effectively displayed. Some of these aspects are considered here. Results of this investigation have been incorporated into the design of an apparatus modified from that previously described

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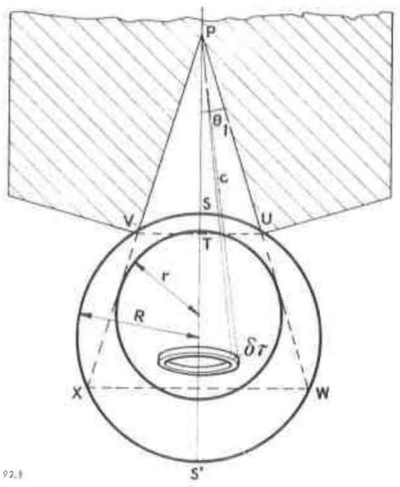

Figure 1. Simple physical model of the pregnant abdomen. The inner sphere represents the foetal sac, the outer sphere the mother. The collimation shown corresponds to a position of P in the second system

and representative records from normotensive and hypertensive pregnancies are included in the text.

These retrospective studies clearly show that the placental transfer of radiosodium gives a practical quantitative measure of over-all placental efficiency. The problem of obtaining the same information before the onset of labour is one with important clinical application.

THEORETICAL CONSIDERATIONS

The size of the mother and foetus, choice of isotope, placental transfer efficiency and the design of the detector are the main factors which influence the ability to discriminate the increasing foetal content of radiosodium against the maternal background.

Furthermore, the maximum dose of radiation which the patient may receive is an overriding consideration, and limits the amount as well as the choice of isotope. For accurate localisation the high-energy gamma radiation from sodium-24 imposes particularly severe problems, but the safe radiation dose given to the patient, and the general compatibility of sodium chloride with the physiological processes under investigation, are considered to outweigh this disadvantage for work with humans.

The very local sodium interchange processes going on in the body concurrently with placental diffusion do not affect significantly the radiation level at a point outside the abdomen, and as far as these processes are concerned, the whole trunk can be considered as a constant source to an external detector.[11]

Though the shape and size of the mother and foetus, and the position of the latter in the maternal abdomen, are outside experimental control it is important to understand how they affect the measurement.[11] The position of the foetus may be modified by abdominal compression provided this does not impair the placental blood supply; the size of the foetus governs the minimum duration of pregnancy at which measurements can be made.

These factors have been investigated by considering a simplified physical model in which the mother is represented by a sphere containing radioisotope of uniform concentration and the foetus by a smaller sphere asymmetrically disposed within the larger sphere, as illustrated in Fig. 1. Elementary measurements of the contour of the pregnant abdomen and consideration of the contribution to the counting rate from the legs and upper end of the trunk and head indicate that the model spheres are a reasonably close approximation to the actual case. In measurements on a model 15% of the background radiation at a point over the abdomen was found to originate in these regions.

The following analysis is intended to define the limit of successful measurement in the ideal case and to give an indication of the significance of the factors which should be considered in the design of a suitable detector.

THE PHYSICAL MODEL

It is assumed that immediately following injection there is uniform radiosodium concentration in the mother but zero concentration in the foetus. The foetal concentration then increases until it becomes ultimately the same as that of the mother, which is assumed to remain constant throughout. This is not unreasonable, since the amount of radiosodium which crosses the placenta compared with the total in the maternal "pool" is small and, on the basis of body weights, less than 5% reduction in maternal radiosodium concentration due to this cause is likely to arise.

Consider now a detector in the form of a small scintillation crystal placed at any point on the central axis and outside the large sphere. Let the radiation intensity (dose rate or counting rate) at this point due to the radioactivity of the large sphere be F_1, and let the corresponding rate for the small sphere when it alone contains radioisotope, at the same concentration as the large sphere, be F_2.

At the time of injection, when $t = 0$, the dose rate at any point on the axis is given by $(F_1 - F_2)$ and at the end of the experiment when $t = \infty$, the dose rate is given by F_1. $(F_1 - F_2)/F_1$ is a figure of merit which describes the relative change in dose rate during the experiment; optimum conditions thus occur when $(F_1 - F_2)/F_1$ is as small as possible. The influence of the separation of the spheres on the magnitude of this ratio has been investigated for a series of positions of the detector along the central axis and three collimating systems. In the first system the detector is uncollimated, in the second system a defined arrangement is employed and in the third system the effect of a very narrow angle beam is demonstrated.

It is assumed that no radiation reaches the detector through the shielding and the consequences of this happening are discussed later. Self-absorption in the source is neglected.

First System. Detector Uncollimated

This case is analogous to the calculation of dose rate at a point outside a sphere uniformly filled

with radioactive material and has been worked out by Mayneord.[12]

If d is the distance of a detector from the surface of a sphere of radius r uniformly filled with radioisotope of concentration ρ, the dose rate D is given by

$$D = \pi k \rho \left\{ 2r - \frac{(r+d)^2 - r^2}{(r+d)} \ln \left(\frac{2r+d}{d} \right) \right\}$$

where K is the gamma-dose rate at 1 cm from a point source of 1 millicurie of the isotope.

By computing this function, F_1 and F_2 have been determined for a number of points on the central axis and three positions of the small sphere within the large sphere, *viz.*, 0.5, 1.0 and 3.0 cm below the surface. Variations in the ratio $(F_1 - F_2)/F_1$ for zero collimation are exhibited as curves (*a*), (*b*) and (*c*) in Fig. 2.

Second System. Partial Collimation

By introducing collimation, F_1 can be reduced and $(F_1 - F_2)/F_1$ made more favourable.

The degree of collimation considered is seen in Fig. 1. Positions of the detector outside the spheres have been chosen to correspond with those in the uncollimated case. For each position there is a tapered collimator which extends to the surface of the large sphere and when projected is tangential to the small sphere.

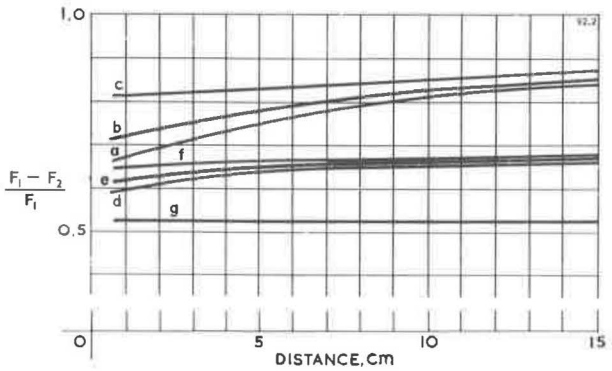

Figure 2. Distance from detector to surface of the large sphere

In this case F_1 no longer relates to the dose rate at a point outside a sphere but to the dose rate at a point outside a solid of the shape $USVXS'W$, Fig. 1. This dose rate is the sum of the dose rates from two end segments of the sphere and a cone. Calculations for these solids are given in the Appendix.

Values of $(F_1 - F_2)/F_1$ computed from Eqs. 1, 2 and 3 are shown in curves (*d*), (*e*) and (*f*) of Fig. 2, for the same positions of the small sphere as before.

Third System. Small-Aperture Collimator

If the angle of the collimator in the above section is greatly reduced, then the curvature of the spheres may be neglected. The radiation intensity at a point detector can thus be calculated from Equation 1, from whence it is easily shown that

$$\frac{F_1 - F_2}{F_1} = \frac{R - r}{R}$$

for all positions of the detector and the foetus.

It may be noted that this relation is also relevant to a crystal detector of finite size at the end of a cylindrical collimator of small aperture, since the radiation reaching points at any given plane in the crystal transverse to the central ray is derived from equal volumes of the source.

For the case considered, $R = 15$ cm, $r = 7$ cm, $(F_1 - F_2)/F_1 = 0.533$ and is shown as a straight line (*g*) in Fig. 2. It represents the least value of $(F_1 - F_2)/F_1$ which can be achieved with these diameter spheres. If the radius of the inner sphere is increased to 8 cm then the value of the parameter is reduced to 0.467.

The above results show that if the absorbing walls of the collimators are perfect and the quantity of isotope unrestricted, then the small-aperture collimator gives the optimum result.

In practice a limit to the aperture size is imposed by two factors. First, the amount of isotope which may be given to a patient is clearly not unlimited and for the "safe" amount the minimum aperture diameter which can be used is that giving an intensity of radiation at the detector compatible with its natural background. In addition, the leakage of radiation through the shielding further restricts the use of a small collimator aperture, and this is of particular importance when a high-energy gamma-emitter such as sodium-24 is employed.

For a given isotope and design of detector, this latter restriction can be allowed for by measuring the count rate corresponding to leakage through the absorber, and in actual tests on humans this was done by inserting a solid plug in the aperture. The preferred arrangement is thus seen to be the minimum aperture which will give the least counting error with the maximum isotope concentration it is safe to permit.

The high radiation sensitivity required of the detector clearly indicates a scintillation counter and the methods of obtaining maximum sensitivity from this instrument have been well dealt with in the literature.[13,14] It may be noted that the crystal and photomultiplier cathode diameters should be the same as the collimator aperture so that there is maximum acceptance of useful radiation, and background due to cosmic rays, or thermal noise, is reduced to a minimum.

Compared to one detector optimally placed, any number distributed around the surface of the large sphere do not improve the sensitivity of measurement but tend to an inefficient system. Thus, if one detector is on the central axis, then any other must be unfavourably disposed since it is in a position where the distance between small and large spheres is increased. An over-all ratio $\Sigma(F_1 - F_2)/F_1$ for the system would thus be greater than the value of $(F_1 - F_2)/F_1$ for the optimum positioned detector.

To substantiate the above results a simple model consisting of a thin-walled glass sphere having a similar but smaller sphere eccentrically mounted within it was constructed. Because of the difficulty of readjusting the smaller sphere within the larger, investigation was confined to a single separation of 3 cm. On oppo-

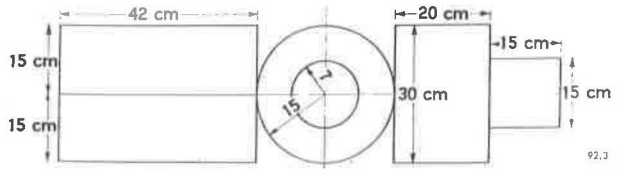

Figure 3. Plan of the model used to substantiate the results which are given in Fig. 2. Each rectangular container is 16 cm high

site sides of the sphere rectangular tanks were arranged to simulate the legs, upper part of the trunk and head. The layout and dimensions of the arrangment are given in Fig. 3. The containers were filled with saline containing sodium-24 at a concentration of 0.01 microcurie/ml, and measurement of $(F_1 - F_2)/F_1$ was made at a number of points using an uncollimated detector and at a single point using two collimated systems. The results are given in Table 1 and it is seen that they substantiate appreciably the curves shown in Fig. 2.

Table 1

Distance from detector to surface of sphere, cm	*Collimator system*	$(F_1 - F_2)/F_1$
3	Uncollimated	0.85
5	Uncollimated	0.87
7	Uncollimated	0.89
9	Uncollimated	0.90
15	Uncollimated	0.93
20	Uncollimated	0.96
10	Cylindrical; 1 cm diam, contained in a 12.5 cm diam lead cylinder	0.40
10	Tapered; min diam 1.4 cm, max diam. 5 cm, contained in a 12.5 cm diam lead cylinder	0.51

APPARATUS AND TECHNIQUE

The complete apparatus mounted over a model of a patient is shown in Fig. 4. The design of the directional scintillation counter is based on the considerations mentioned in the previous section. It consists essentially of a tapered collimator 12 cm in length having an aperture 4 cm in diameter decreasing to 1.4 cm at the crystal. The collimator is formed in a lead cylinder 14 cm diameter and 40 cm long. The crystal, photomultiplier, and inter-dynode resistance chain are built into the same cylinder, but the preamplifier is mounted in an adjacent position on the supporting bracket.

The directional counter assembly is supported from a horizontal arm attached to a vertical pillar which is free to move on floor and ceiling rails. The horizontal arm and attachments are counterpoised so that they can be moved vertically, and also horizontally, about an axis through the centre of the vertical pillar. The counter is free to rotate about an axis through its centre of gravity and parallel with the horizontal arm. In addition the position of the counter along the horizontal arm is also capable of adjustment. With these facilities it is a simple matter to position the directional head over the abdomen, and the counter-balanced system overcomes the anxiety of a patient when confronted with a large bulk poised over the foetus.

The patient rests on a couch in the supine position, and in the experience of the authors this is the only one which enables consistent measurements to be made for a prolonged period. We have tried other methods, including a horizontally mounted counter with the patient standing against the aperture exerting a constant force,[11] but although this enables counts to be taken over a long period, some movement of the foetus inevitably results. In our present technique the counter is first positioned over the abdomen and then an injection made in the antecubital vein; 20 to 25 microcuries of sodium-24 contained in 5 ml isotonic saline is injected. The counter is left in position for 45 minutes or longer if the patient is tolerant. Counts for ½ minute are taken every 40 seconds during this period. At the end of this time the counter is lifted, and returned to position every 5 minutes when another ½-minute count is taken. The patient can relax but is asked to keep still. Sedatives are not used.

To allow for the background counting rate resulting from radiation transmitted through the lead walls of the collimator, a solid plug is inserted into the aperture, as previously mentioned, and a count taken at some time after the continuous period of counting has been completed. This reading is deducted from each observation following correction for radiosodium decay.

Some records from normal and hypertensive patients are illustrated and discussed in the next section.

CLINICAL RESULTS

Placental function, as determined by the above method, is assessed by comparative rates of uptake of labelled sodium ions by the foetal sac, in normal and

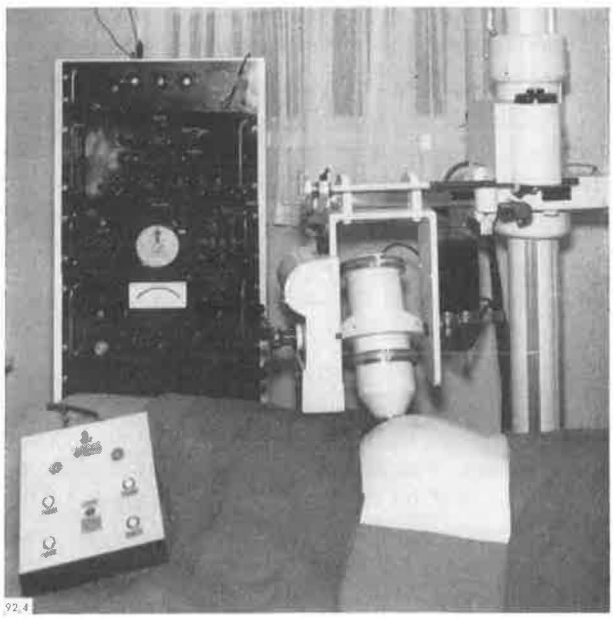

Figure 4. The apparatus mounted over a model abdomen

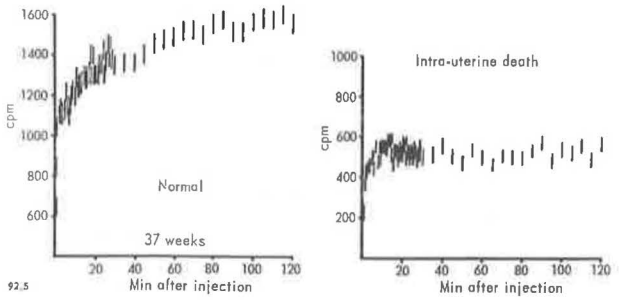

Figure 5. Comparison between normal placental function and foetal death

abnormal pregnancies, and Fig. 5 illustrates the wide variation between normal placental function and foetal death. The first curve shows a steady increase in the total radiosodium content of the foetal sac over a period of two hours, and the latter, no significant alteration in the same period of time, beyond an initial accumulation of radiosodium in maternal tissues.

Figures 6 and 7 are examples from two separate pregnancies complicated by maternal hypertension. The first is prepared from a young primigravida with both hypertension and early renal failure, which were first recognised at the 16th week of pregnancy. The advisability of terminating the pregnancy at this time was unacceptable to her, and the only course was to prescribe a prolonged period of rest in bed, during which time there was no further deterioration in maternal condition, and the foetus grew in proportion to the length of gestation.

Placental function was assessed at weekly intervals from the 30th week of pregnancy—10 weeks before the anticipated date for delivery. An early deterioration in placental adequacy at the 36th week of pregnancy became more prominent at the 37th week, and on this account an elective Caesarean section was carried out. A living female infant weighing 6 lb 6 oz was delivered successfully and it subsequently thrived. Venous cord blood samples collected at birth revealed a haemoglobin concentration elevated to 124% and an oxygen saturation level reduced to 40.1%, figures which are compatible with the antenatal diagnosis of foetal anoxia from early placental failure.[15]

The second record (Fig. 7) is from a multipara with a blood pressure fluctuating in the region of 160/110

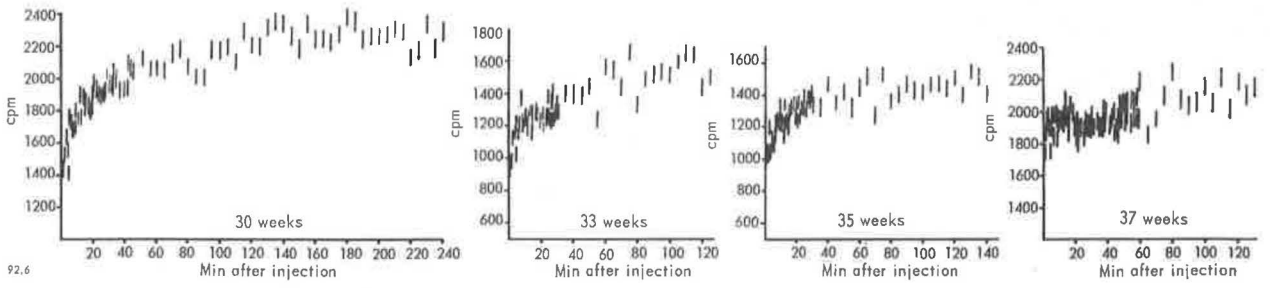

Figure 6. A young primigravida having both hypertension and early renal failure, which were first recognised at 16 weeks. Prolonged rest in bed followed and placental function was assessed at weekly intervals from the 30th week. Deterioration at the 36th week became more pronounced at the 37th week

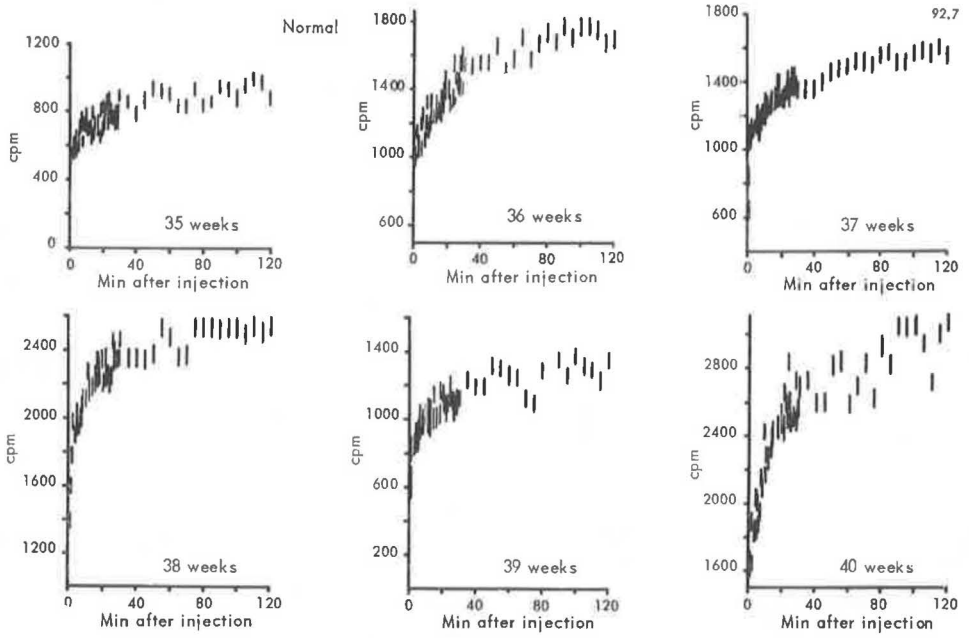

Figure 7. Normal records taken on successive weeks from a multipara with fluctuating blood pressure. Spontaneous delivery occurred at the 40th week of pregnancy

mm Hg throughout the whole course of pregnancy, and who had lost a previous infant from hypertensive disease. She remained in hospital for the last 6 weeks of her pregnancy, and during this time weekly assessments of placental efficiency revealed no deterioration. She was therefore left alone until spontaneous delivery occurred at the 40th week of pregnancy, and the child was spared the need for unnecessary premature delivery with the attendant risks more recently emphasised by F. J. Browne.[16] The infant weighed 8 lb 13 oz and its cord haemoglobin of 123% was compatible with the normal findings at full term.

The clinical aspects of this study have been presented in greater detail elsewhere.[17]

APPENDIX

Calculation of Central Axis Intensities for the System with Partial Collimation

The dose rate at P due to the volume $USVXS'W$, Fig. 1, is made up of the dose rates from the spherical segments USV and WSX and the frustum $UVWX$. It should be noted, however, that since the distance of P from the surface of the large sphere and the position of the small sphere determine the sides of the cone, P is always at the apex of the cone. The radioisotope concentration in both spheres is uniform and equal to ρ mc per cc.

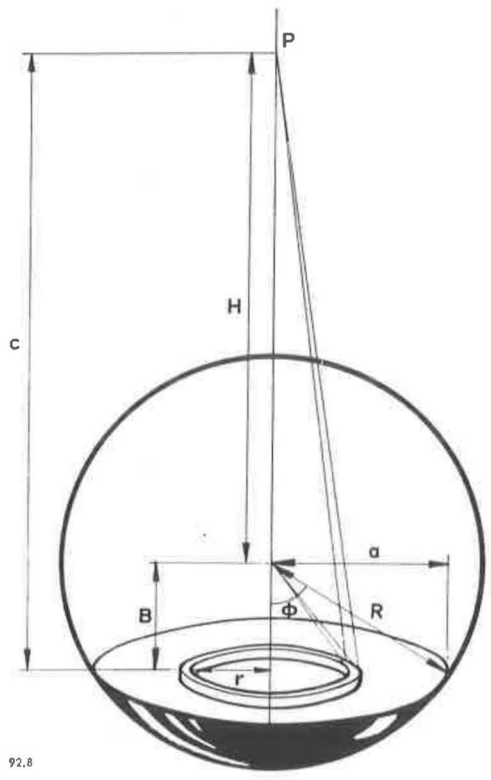

Figure 8

(a) Dose Rate at P from the Cone $UVWX$

The dose rate at P due to the volume element $\delta\tau$ is

$$k\rho\ \delta\tau/c^2$$

where

$$\delta\tau = 2\pi c^2 \sin\theta\ \delta c\ \delta\theta.$$

Hence, the dose rate at P due to the whole cone is

$$2\pi\kappa\rho \int_0^{\theta} \int_0^{PT'/\cos\theta_1} \sin\theta\ dc\ d\theta = 2\pi\kappa\rho\ PT' \ln(\sec\theta_1),$$

and the dose rate from the frustum $UVWX$ is

$$2\pi\kappa\rho \ln(\sec\theta_1)[PT' - PT]. \qquad (1)$$

(b) Dose Rate at P from a Spherical Segment

The dose rate at P, Fig. 8, due to the ring element is given by

$$\frac{\kappa\rho\ 2\pi r\ \delta r\ \delta c}{r^2 + c^2}.$$

And the dose rate at P due to the disc of thickness dc and radius a is given by

$$2\pi\kappa\rho \int_{r=0}^{r=a} \frac{r}{r^2 + c^2}\, dr\, dc = \pi\kappa\rho[\ln(r^2 + c^2)]_0^a\, dc.$$

In the sphere,

$$\begin{aligned} a &= R \sin\phi, \\ c &= H + B \\ &= H + R\cos\phi; \\ \text{therefore} \quad dc &= -R\sin\phi\, d\phi. \end{aligned}$$

Hence, the dose rate at P due to the entire segment is

$$-\pi\kappa\rho \int_0^{\phi} \ln \frac{R^2\sin^2\phi + [H + R\cos\phi]^2}{[H + R\cos\phi]^2} [-R\sin\phi]\, d\phi.$$

Simplifying and writing

$$\alpha = H/R,$$

we have

$$\begin{aligned} &-\pi\kappa\rho R \int_1^{\cos\phi} \ln \frac{1 + \alpha^2 + 2\alpha\cos\phi}{[\alpha + \cos\phi]^2}\, d(\cos\phi) \\ &\quad = \pi\kappa\rho R \left[2\int_1^{\cos\phi} \ln(\alpha + \cos\phi)\, d(\cos\phi) \right. \\ &\qquad \left. - \int_1^{\cos\phi} \ln(1 + \alpha^2 + 2\alpha\cos\phi)\, d(\cos\phi) \right]. \end{aligned}$$

Evaluating the integrals and simplifying, we get

$$\begin{aligned} &\int \ln(\alpha + \cos\phi)\, d(\cos\phi) \\ &\qquad = (\alpha + \cos\phi)[\ln(\alpha + \cos\phi) - 1] \\ &\int \ln(1 + \alpha^2 + 2\alpha\cos\phi)\, d(\cos\phi) \\ &\quad = \frac{1 + \alpha^2 + 2\alpha\cos\phi}{2\alpha} [\ln(1 + \alpha^2 + 2\alpha\cos\phi) - 1]. \end{aligned}$$

The dose rate at P due to the furthermost spherical segment is thus

$$\pi\kappa\rho R\left\{\left[\frac{(1+\alpha)^2}{2\alpha}[2\ln(1+\alpha)-1]-\left(\frac{1+\alpha^2+2\alpha\cos\phi}{2\alpha}[\ln(1+\alpha^2+2\alpha\cos\phi)-1]\right)\right]-2[\{(1+\alpha)\ln(1+\alpha)-(1+\alpha)\}-\{(\cos\phi+\alpha)\ln(\cos\phi+\alpha)-(\cos\phi+\alpha)\}]\right\}. \quad (2)$$

If ψ is the half-angle subtended at the centre of the circle by the nearer segment, then the corresponding dose rate at P can be similarly shown to be

$$\pi\kappa\rho R\left\{2[\{(\alpha-\cos\psi)-(\alpha-\cos\psi)\ln(\alpha-\cos\psi)\}-\{(\alpha-1)-(\alpha-1)\ln(\alpha-1)\}]-\left[\left(\frac{1+\alpha^2-2\alpha\cos\psi}{2\alpha}[1-\ln(1+\alpha^2-2\alpha\cos\psi)]\right)-\left(\frac{(\alpha-1)^2}{2\alpha}[1-2\ln(\alpha-1)]\right)\right]\right\}. \quad (3)$$

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Methods for the Study of Cerebral Blood Flow Kinetics with Gamma-emitting Radioisotopes

By Paul Crandall* and Benedict Cassen†

A simple, conveniently practical method for the study of cerebral blood flow has been developed with the use of gamma-emitting radioisotopes using an external counting technique. The technique is somewhat analogous to and was first suggested by that of externally estimating cardiac-output volume rate.

The aim of these studies is to provide methods for determination of total cerebral blood flow as well as that of parts of the cerebrovascular system. The cerebrovascular system may be physiologically divided into two carotid and one vertebral systems. The success of determining blood flow in the circulatory periphery depends on being able to measure radioactivity in the vascular structure without interference from neighboring structures. Fortunately the torcular Herophili and the jugular veins are sufficiently large and close to the surface of the body that relatively complete "isolation" by radioisotope measurement can be predicated as will be explained below. We have thus far concentrated our efforts on the blood flow values for the carotid–torcular system which is a measure of supratentorial blood flow. We expect at a later time to determine the same for the bilateral carotid–jugular systems which will be a measure of total cerebral blood flow. The differences will be accountable by infratentorial and basilar venous drainage. We believe that information about these subdivisions as well as the total cerebrovascular blood flow will contribute valuable physiological as well as pathological data.

In this method, I^{131}-labeled human serum albumin is pulse-injected into a carotid artery of the patient. The pulse of gamma-ray activity is recorded externally as it passes through the torcular Herophili, a venous sinus near the skull that normally drains a large fraction of the total cerebral blood flow. The record obtained, along with information of the total blood volume of the patient and the final equilibrium value of the blood level, enables the calculation in absolute value of the blood flow through this sinus.

Also further useful information is obtainable from the record, such as carotid–torcular circulation time, and from the shape of the pulse, certain pathological conditions can be detected. The method has been used as a supplement to regular contrast angiogram studies. It is convenient, requiring only one venous sample; it makes use of readily available materials; requires few personnel, and is not dangerous for the patient.

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METHOD

All patients chosen for this study were undergoing preliminary diagnostic carotid angiograms for various clinical reasons. To locate accurately the torcular Herophili, a small metal disc was placed on the patient's scalp, either on the inion or at the juncture of the external occipital crests with the sagittal suture. When the radiographic seriographic record was made, the late venous phases allowed the torcular position to be determined in relation to the disc after correction for radiographic magnification on the films.

About 10–15 minutes after the contrast study was completed, the radioactive blood-flow measurement was made. The necessary equipment consists of a well-collimated, shielded scintillation counter which records on a scintiscaler and Sanborn visocardiette, mounted as a portable unit with the counter on a movable arm, so that the entire unit may be adapted to many locations and positions (Fig. 1).

The patient's head was placed in a lateral position. The counter head with a round aperture, 1 inch in diameter, was applied directly to the scalp in the midline so that its long axis coincided with the long axis of the head. Knowing the position of the torcular from its relation to the metal scalp disc, the counter aperture was then located 3 cm above the lower edge of the torcular and faced it at an angle of 30° downward to the Frankfort plane. The angulation was determined by using a long-armed goniometer, one arm of which was on a line between the lateral limbus of the eye and the external auditory meatus, and the other arm parallel with the long axis of the counter.

After a background activity of 10 sec or more was recorded, the 19- or 20-gauge spinal needle which had been left in place from the contrast angiogram was checked for patency and about 2 cc of saline solution was used to insure that an intramural or extravascular injection would not occur. Usually a dose of 10 to 20 microcuries of RISA was injected in the common carotid artery. The exact amount was determined by weighing the syringe before and after an injection as

well as subtracting the amount left in the needle (this was a constant amount). The amount of RISA used gave a high sharp curve well above the background but did not exceed the ability of the Sanborn visocardiette scale to follow. In most cases a dose of 20 microcuries has been found most suitable.

The dose of RISA was usually in a volume of 1 cc and was injected with one rapid thrust in a fraction of a second as recorded on the moving strip. On the record there was a small burst of activity during the first two seconds, a drop, then a prolonged intense burst of activity through the succeeding 8–10 seconds. Five minutes or more after injection, an equilibrium was reached. After 10 or more seconds of recording, a venous blood sample was drawn from an extremity. The blood sample was subsequently used to determine total blood volume and the microcuries per cc of blood at equilibrium. Following completion of the test, the activity rate on the ECG strip was divided into counts per 2-second interval and the dilution curve was then plotted on semilogarithmic graph paper. Torcular blood flow was calculated by an equation:[1]

$$\text{Flow (cc/min)} = \frac{\text{Equilibrium value} \times \text{Total blood volume} \times 60}{\text{Total count of curve}} \qquad (1)$$

The equilibrium value is in counts per second and total blood volume in cubic centimeters.

This procedure differs from that used in cardiac volume flow in that the equilibrium value cannot be obtained directly by external counting for reasons discussed below.

The equilibrium value in counts per second was obtained by relating it to that obtained from a phantom model of the torcular containing 1 microcurie per cc. The particular circumstances of the phantom model gave 382 counts per 1 microcurie per cc, so the count rate of the equilibrium blood (already known in microcuries per cc) was determined as a proportion of this. The total count of the curve was obtained as is usually done in cardiac output measurements by extrapolating the terminal portion of the curve, which is assumed to be a simple exponential. This extrapolated portion of the total count was found to be only a very small portion of the total.

Circulation time for the carotid–torcular system was measured (1) from the beginning of the injection to the maximum of the curve, and also (2) for the longest circulation time from the injection to the time when the activity reached the equilibrium level.

The general shape of the curve gave some interesting variations under pathological circumstances.

THEORY OF THE METHOD

The scintillation counter subtends an effective sensitive angle of 26°. When placed in the specified anatomical position it "sees" the following large blood vessels in order of distance: the torcular Herophili, the vertebral artery and basilar venous plexus, and the carotid arteries and cervical veins. Considering the RISA as a bolus of material passing through the system immediately after injection, the carotid arteries, the torcular and the cervical veins are "seen" in sequence. Figure 2 illustrates right and left carotid injections separately in the same patient. Since RISA in the venous phase mixes with blood from the opposite hemisphere, the quantity flow is nearly the same. Examination of the ECG strip portion of the record shows that the initial burst of activity in the first two seconds can be attributed to the arterial flow and can be easily separated from the main curve, as has been true in all of our records. The main dilution curve can be attributed to the torcular Herophili and not to other distant veins for the following reason. In considering a point source in front of the counter, the value for radiation falls off as the inverse of the square of the distance. Since the torcular Herophili, the largest venous sinus, is closely applied to the skull and therefore very near the counter, the "inverse square law" indicates that its contribution far overbalances any other distant and smaller venous source.

During the equilibrium phase a different situation exists, however. Here the radioisotope solution is now extremely dilute and fills all arteries, capillaries and veins "seen" by the counter. Because the activity recorded in the equilibrium phase was little above the background level and did not represent the torcular blood in relative isolation, we have resorted to deriving the equilibrium by the use of phantom models.

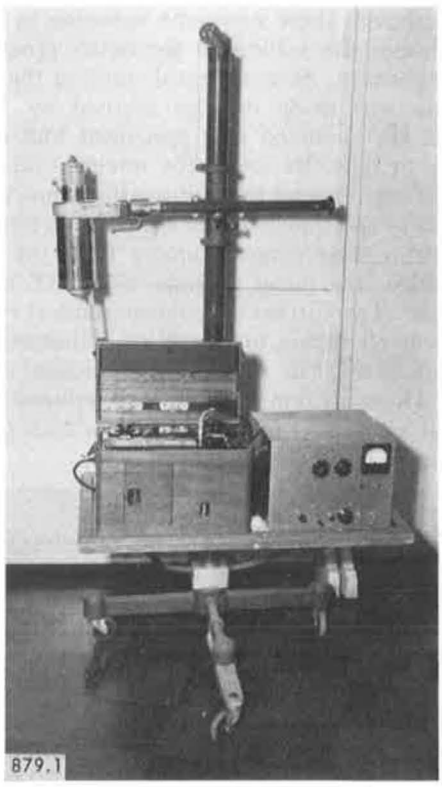

Figure 1. The recording unit consisting of a scintillation counter, scintiscaler and visocardiette

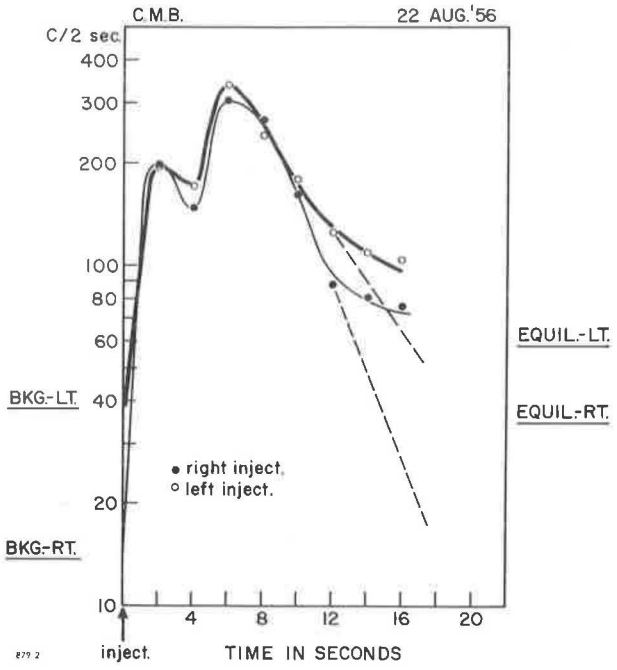

Figure 2. Semi-logarithmic plot of typical pulse record obtained over the torcular Herophili

Ten adult torculars were obtained at post-mortem examination of persons dead from disease elsewhere in the body. Warm wax was pressed into these venous sinuses and allowed to harden. The extremities of the torcular were cut at one inch from the center. The volume of fluid displaced by the solid models was measured. Although there was some variation in shape of three sinuses the volume of the entire group varied only 10 per cent. An anatomical study of the torcular Herophili was made by this method by Edwards in 1931. He examined fifty specimens and classified them as to type. He found the torcular was either a true *confluens sinuum* or a bifurcating sinus in 60 per cent of fifty specimens. When the cross sectional areas of the transverse sinuses coming from the torcular were added, the mean average was 100.8 mm² and 106.4 mm². Two further unusual anatomical variations that occurred were a unilateral deviation sending all the blood to one side (5%) and an unequal deviation (36%). These anatomical anomalies reduced the cross sectional areas to 71 and 78.2 mm² for each group.

Examination of the radiographs of our contrast studies have shown that the torcular Herophili is fairly constant in volume, although the transverse sinuses may differ in diameter, except in cases of unusual anomalies of the torcular. These would be detected on the seriographic angiogram.

A phantom model was then constructed using average dimensions for the torcular Herophili. It was fastened within a dried skull and surrounded by rice. When filled with a solution of RISA of 1 microcurie per cc, the activity corrected for background was 382 counts per second when recorded at the anatomical site mentioned previously, namely, the center of the aperture placed 2.5 cm above the torcular's lower margin. The opportunity was also taken to measure the activity with the counter aperture placed at varying distances from this particular point. The activity fell sharply at any position below or lateral to this, but there was little change when moved in the midline and above, at least within limits of 3 cm above this point. It is therefore imperative to place the counter aperture very accurately as determined by the external scalp marker and its relation to the torcular on the angiographic film.

The scintillation counter consists of a 2 × 2-inch sodium iodide (thallium-activated) Harshaw crystal. The crystal and photomultiplier are protected by 0.5 inches of lead. The lead shutter was perforated by an aperture 1 inch in diameter in lead 2 inches in thickness and surrounded laterally by ¾ inches of lead. Collimation of the detector was entirely sufficient, as checked, to delimit the area to be investigated.

The effect of puncture and the injection of materials intravascularly have been investigated by Greitz.[2] He found a fleeting fall in blood pressure and that a decreased heart rate may be initiated by puncture of the carotid artery, attributable to the carotid sinus reflex. Injection of 1 ml of I^{131} in saline caused no change in ECG or intra-arterial blood pressure during the injection.

We have no indication (Fig. 3) that passage of some of the RISA through the external carotid artery influences the torcular blood flow. Figure 4 illustrates a case with thrombotic occlusion of an internal carotid artery. A small initial rise is followed by a drop to the pre-existing background level; a second rise occurs which is beyond the torcular venous phase as usually

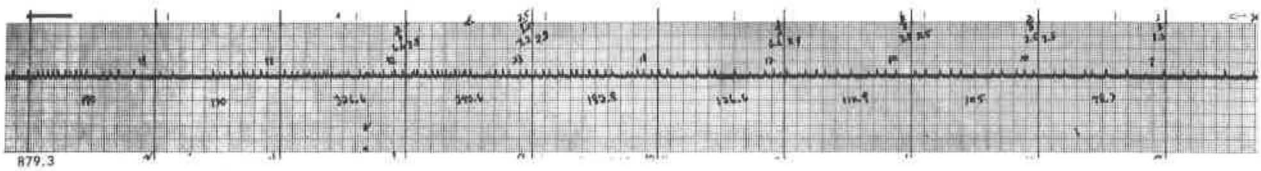

Figure 3. Typical ECG record obtained immediately following RISA injection in the common carotid

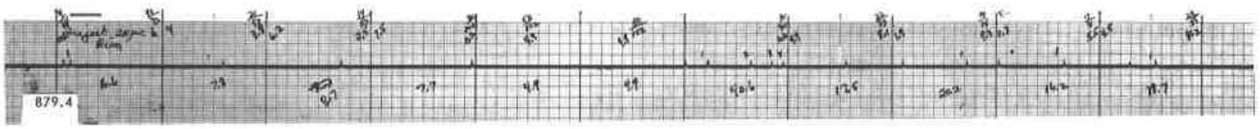

Figure 4. An ECG record obtained from a patient with thrombotic occlusion of an internal carotid artery

Table 1

Name	Age	Diagnosis	Total blood volume	Total count curve	μc injected	Circulation time (sec)		Flow cc/min
						Maximal	Longest	
E.B.	39	Epilepsy	3130	1848	22	6.6	16.6	270
W.C.	35	Parkinsonism	3503	1122	10	6.8	14.0	317
J.R.	34	Epilepsy	6246	693	10	6.2	15.0	330
J.M.	59	Glioma	4572	2036	25	11.0	24.0+	241
H.T.	25	Glioma	4841	1240	10	6.6	15.5	302
E.F.	38	Glioma	6500	902	12	5.6	18.3	293
J.C.	47	Frontal meningioma	4279	1317	15	5.8	16	—
P.S.	30	Intraventricular meningioma	4740	1000	15	6.8	12.3	340
P.T.S.	65	Acute subdural hematoma	5025	1562	15	6.8	18	—
J.L.	45	Old trauma, decerebrate	4279	967	15	8.2	18.4	319
W.Sc.	32	Old trauma, decerebrate	5025	1707	10	8.8	18.6	265
V.A.L.	42	Old trauma, frontal	4359	1205	10	6.9	20.3	351
W.T.	22	Av malformation—basal ganglia	3570	1769	25	5.2	22.0	278
W.Sm.	44	Subarachnoid hemorrhage	4210	1401	27	6.1	12.5	270
F.L.	24	Subarachnoid hemorrhage	3606	717	10	6.0	15.4	477
C.B.	45	Subarachnoid hemorrhage						
		Rt. side	5412	1087	20	5.2	14.6	554
		Lt. side		1000	20	5.4	16.2	505
D.G.	34	Diagnosis uncertain	6060	1093	26	5.8	14.4	300

recorded at 12 seconds. Two other patients showed similar curves. Greitz also found that injection into the external carotid artery did not produce significant activity in measurements of parietal veins for circulation time.

The 1 ml of solution injected did not significantly alter the viscosity of the blood flowing through the carotid artery nor was there ever evidence of any vascular reaction to the material.

DISCUSSION

The principal methods for estimation of human cerebral blood flow have been intravascular gas exchange measurements based on the Fick principle and evaluation of the serial contrast angiogram in time.

Since 1948, the Kety-Schmidt[3] nitrous oxide technique has been the main investigative clinical research tool and it has provided information on cerebral blood flow in relative values quoted for the normal young adult as 54 cc (±12)/100 g brain/min and also information concerning cerebral metabolism and vascular resistance. Assuming a normal adult brain of 1200 g, the Kety-Schmidt value for total cerebral blood flow would be about 650 cc/min. Because of difficulties in complexity of technique it has not been used widely in practice. A recent variation using krypton gas inhalation (Lassen and Munck[4]), but similar in other respects, has recorded normal cerebral blood flow varying from 33–67 cc/100g/min. The necessity of percutaneous needle sampling at several sites and the extensive laboratory work involved do not make the methods appealing for routine clinical application. A recent method reported by Nylin and Blomer,[5] using thorium-B-labeled erythrocytes and recording the dilution curve in multiple jugular blood samples, has given cerebral blood flow in absolute values. Such values have been obtained from only three patients so that the normal range has not yet been determined.

Rapid serial angiography with measurement of the contrast medium at the filling of the carotid siphon and at the emptying of parietal veins has been advocated by Greitz[2] to record circulation time. However no values for quantitative flow have been obtained. Its validity for measuring circulation time has been brought into question in view of the fact that the 4 ml of contrast medium used fills almost the entire unilateral carotid distribution with a fluid different in character from normal blood, that changes commonly occurred even in systemic–cardiovascular kinetics, and that differences may occur in the interpretation of the films. It is undoubtedly of use, however, in assessing the relative changes in flow time in local areas of pathological alteration as compared with normal areas on the same films. From this type of study, Greitz concluded that normal values of circulation time from the carotid artery to the parietal veins were as high as 6.0 seconds. Nylin and Blomer[5] measured carotid–jugular time during the maximum of activity as 8 seconds. From Table 1 of our heterogeneous clinical material the majority of our carotid–torcular circulation times at maximum were between these two values.

Approximately 30 successful examinations in 24 patients have been performed. No adverse or unfavorable reaction has occurred in these patients. Several repeat studies of the same patients have shown values close to the original and several bilateral examinations have shown nearly equal flow rates. Our clinical material has been varied and too small to be significant numerically, but in the abnormal instances the shifts have been in the direction consistent with current ideas of cerebrovascular kinetics.

CONCLUSION

The present method does not measure the total cerebral blood flow but certainly measures a major fraction of it and gives normal flow values consistent with the 650 cc/min determined by the Kety-Schmidt[3] method. This is indicative of the validity of the phantom calibration method as here described.

The results relative to transit or circulation time are also consistent with those obtained by Greitz on rapid serial angiographic studies of the carotid–parietal vein circulation time. No adverse or undesirable reaction has occurred in patients.

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Application of Isotope Encephalography and Electroencephaloscopy for Localization of Brain Tumours

By V. N. Shamov, C. N. Badmayev and N. P. Bekhtereva

Diagnosis and localization of brain tumours frequently present great difficulties. The more usual methods of investigation such as pneumography, angiography, etc., quite often fail to give the desired results or cannot be performed because the patient is gravely ill and the danger of provoking complications is feared.

In such cases the application of tracer techniques may prove to be of great service as it has several obvious advantages such as safety, painlessness, nontraumatism, absence of side effects, relative simplicity and accuracy of results.

The problems connected with the methods and procedures of isotope encephalography in cases of brain tumours are widely discussed in the world's literature. The opinions of investigators differ, however, as to the diagnostic accuracy of this tool. For example, American workers hold that in 95 per cent of cases this method proves to be a valuable tool for correctly diagnosing cases of brain tumours, while according to British authors the accuracy of this method for diagnosis hardly reaches 40 per cent. (Ashkenasy, Davis and Martin,[1] Belcher, Evans and De Winter,[2] De Winter,[3] etc.)

In the Soviet Union investigations dealing with the localization of brain tumours in patients have been systematically carried out for several years using radioactive iodine (I^{131}) and diiodine-131–fluorescein (DIF).

The present communication deals with the results of clinical observations of 150 patients with varied brain tumours who were treated at the Leningrad Neurosurgical Institute by application of the usual tracer technique together with scintillation gamma encephalometry.

Among the patients were 52 males and 98 females, the age range being from 5 to 57 years. Localization and type of brain tumour are represented in Table 1.

Analysis of the data showed that the accuracy of the isotope method for brain tumour diagnosis varies and depends upon the concentration of the labelled substance taken up by the tumour and the depth of the tumour site.

The data also show that superficially located tumours are more accessible to diagnosis due to the intensive radiation which appears above the tumour localization zone. This fact accounts for the high percentage of correct diagnosis (up to 81 per cent) of convex and parasagittal meningiomas and superficial gliomas. The diagnosis of tumours located in the so-called "silent zones" can be made by the use of the isotope method where other methods of diagnosis frequently fail to yield positive results.

Isotopic encephalography is of considerable help in the diagnosis of recurrence of brain tumour, other methods of investigation frequently leading to faulty conclusions. For example, surgical intervention often results in deformation of the ventricular system of the brain due to the development of secondary gliosis and the formation of a defect which is revealed by pneumography. Angiography discloses breakdowns in the vascular system and electroencephalography (EEG) reveals pathological activity which is difficult to differentiate from the symptoms of early relapse of a tumour. In many cases the application of isotope encephalography will enable us to determine whether the epilepsia which develops is associated with gliovascular changes following operation or is caused by the growth of a recurring tumour.

Isotope encephalographic data obtained in studying superficial extracerebral tumours have proved to be more informative than the results of electroencephalographic investigations. The importance of isotope encephalography is especially great in cases of minute extracerebral tumours where the electroencephalographic method of diagnosis is difficult to carry out. A 50-channel electroencephaloscope constructed in the Soviet Union by M. N. Livanov and V. M. Ananyev[4] made it possible to delimit "silent zones" and to detect tumours of this kind by a more definite registration of the bioelectrical brain picture. The electroencephaloscopy data obtained in this way confirmed the results of the isotope encephalography and made the diagnosis certain.

In cases of deep seated tumours when the radiation from the tumour is overlapped by the background radiation of the brain itself, conditions differ. The deeper the tumour, the more difficult it is to demonstrate. In cases of deep intracerebral glioma, ventricular tumours, brain-axis and hypophyseal tumours the accuracy of the method does not exceed 50 per cent. The diagnosis of posterior cranial fossa tumours (neurinoma of the acoustic nerve, tumours of the cerebellum, 4th ventricle and brain-axis) is especially diffi-

Original language: Russian.

cult. Tumours of medium size of the posterior fossa set deeply under a thick layer of occipital muscles near the midline are localized by the isotope method only in 31 per cent of cases. It should be noted that when tumours are located in these areas electrophysiological methods of diagnosis give no better results.

Summarized data on isotope diagnosis of various brain tumours are represented in Table 2.

Observations show that the selective accumulation of diiodine-131–fluorescein (DIF) in the tumour zone depends on conditions of blood supply and the specificity of the histological structure of the tumour. For example, neoplasms of the meningovascular type, meningiomas in particular, accumulate the labelled substance in its highly vascular system, which accounts for a definite temporary focus of gamma irradiation at the tumour epicentrum and, consequently, a high percentage of diagnostic accuracy of meningiomas (up to 80 per cent). The high rate of the DIF accumulation is observed also in tumours with infiltrative growth: glioblastomas, brain carcinomas and metastases.

On the other hand, nonmalignant gliomas with a more restricted type of growth and having a less well-developed vascular network (oligodendrogliomas, astrocytomas, cystic tumours) accumulate radioiodine to a lesser degree and as a consequence it is more difficult to demonstrate them (the diagnosis is confirmed in 42 per cent of cases). For the same reason the isotope diagnosis of the neurinomas of the acoustic nerve and of the adenomas of the hypophysis is not very successful.

Summarized data on isotope diagnosis of brain tumours of various histogenesis are presented in Table 3.

According to our data, isotope encephalography permits localization of brain tumours in approximately 68 per cent of cases. It is interesting to compare the results of our investigations with those of other authors (see Table 4).

The great diversity of results obtained from isotope encephalography data may be attributed to the fact that some investigators in arriving at a diagnosis consider exclusively the data of the isotope method, whereas other authors take into account the data from clinical observations, pneumography, electroencephalography, etc., in making a diagnosis. In other words, they assess the complex of total diagnostic information.

It must also be borne in mind that various investigators employed quite different methods for measuring radiation intensity (single and multichannel, rectangular and normal systems), used different labelled complexes (DIF, labelled albumin and sodium iodine) and counting devices of diverse sensibility (Geiger counters, scintillation counters with and without collimators and scanners). In addition, the observations of different authors are based on varying clinical material.

The isotope method of investigation, like the others, has its advantages and limitations; therefore, when assessing the results of clinical studies, one should bear in mind that negative findings by no means exclude the existence of a tumour.

Table 1. Localization and Type of Brain Tumour

Tumour type	*Localization*			
	Cerebral hemisphere	*Hypophysis*	*Posterior cranial fossa*	*Total*
Meningovascular	52	—	—	52
Glioma	69	—	—	69
Neurinoma	—	—	6	6
Adenoma	—	10	—	10
Other tumours (metastatic osteoma) and parasitic brain diseases	10	—	3	13
Total	131	10	9	150

Table 2. Isotope Diagnosis of Brain Tumours

Location and depth of tumour	*% Accuracy of diagnosis by tumour site*			
	Accuracy	*Approximation*	*Errors*	*Not revealed*
Superficial tumours (extracerebral and cortex)	81	6	4	9
Deep seated tumours (subcortical, intraventricular, brain-axis, hypophyseal)	50	13	10	27
Posterior cranial fossa tumours	31	8	8	53

Table 3. Diagnosis of Brain Tumours of Varying Histological Structure

Kind of tumour	*% Accuracy of diagnosis by tumour site*			
	Accuracy	*Approximation*	*Errors*	*Not revealed*
Meningovascular	80	5	5	10
Infiltrative gliomas	82	9	—	9
Gliomas of restricted type (neurinoma, adenoma, cysts)	42	12	7	39

Table 4. Accuracy of Brain Tumour Diagnosis with the Use of Isotope Encephalography (from various authors)

Investigators	*% Diagnosis accuracy*
Moore, Kohl, Marvin, Wang and Caudille[11]	95
Davis, Martin, Ashkenasy *et al.*[12]	95
Ashkenasy, Davis and Martin[1]	95
Yuhl, Stirret and Libby[13]	90
Chou and French[14]	87
Dunbar and Ray[15]	76
Kohl, Moore and Chou[16]	71
Peyton, Moore, French and Chou[17]	70
Badmayev[18]	68
Davis and Craigmile[19]	61
Svien and Johnson[20]	40
De Winter,[3] Sjögren,[21] Belcher, Evans and De Winter,[2] Rushton, Svien and Baldes[22]	below 40

For the neurosurgeon, it is necessary to use the methods of diagnosis which are more likely to ensure (with the least likelihood of error) the opening up of the cranium immediately above the tumour site. The isotope method possesses this degree of accuracy only in relation to superficially located brain tumours. For tumours of the posterior cranial fossa, base of the brain or lesions of the midline, the diagnostic value of isotope encephalography, at its present stage of development, is doubtful.

It should always be borne in mind that application of the isotope encephalography technique in combination with electrophysiological methods is very profitable. If the first is advantageous in the diagnosis of superficially located tumours, electroencephalography and electroencephaloscopy are especially valuable in detecting intracerebral and brain-axis tumours.

Thus, the diagnosis of subcortical glioma is successfully accomplished by electroencephaloscopy. The subcortical tumour causes significant metabolic and neurodynamic shifts and is, therefore, correspondingly marked by definite slow delta waves within the area of its localization. The diagnosis of extra- and intracerebral tumours located in the midline area of the brain is best achieved by isotope encephalography in conjunction with electroencephalography and electroencephaloscopy.

The use of the Livanov–Ananyev electroencephaloscope for studying the bioelectrical brain picture has demonstrated in the norm general summary shifts of biopotentials. These oscillations are characterized by negative intensification in extensive areas of the brain, positive intensification in other areas and by reversal of electrical charge to the opposite sign in succeeding phases of observation. Similar phase ratios are usually noted between the anterior and posterior parts of the brain. For example, if negativity intensification was initially noticed in the frontal part and positivity intensification in the parieto-occipital part of the brain, then in the next phase the frontal lobe will have an electrical positivity while the parieto-occipital part will demonstrate an intensification of electronegativity. In normal conditions these oscillations will proceed in a rhythmic way and, according to the amplitude and duration, are close to the alpha-potential characteristics. They reflect the periodic synchronization of these wave forms.

Quite a different picture is observed in cases of extracerebral tumours at the base of the brain, i.e., large hypophyseal adenomas or meningiomas of the tubercle of the sella turcica, where an increase of amplitude of oscillations up to 100 mv and a disruption of their regular periodicity are noted. The oscillation period usually remains within the alpha-waves duration. In the electroencephalogram the changes are less clearly demonstrated. The episodic and disseminated synchronization and an alpha-wave amplitude increase were registered.

In the case of intracerebral localization of tumours within the area of the median line, irregularities are clearly demonstrated. Their amplitude reaches 200 mv; they are grouped together making up 8–10 and more successive oscillations, and each wave period of the negative and positive phase slows down to the duration of the delta EEG wave. If the tumour is located centrally in relation to the midline, the groups of oscillation are bilaterally synchronous, but where the tumour localization is eccentric to the midline the oscillations appear to be more distinct on the affected side. The amplitude of oscillations is highest in the frontal areas (Fig. 1). In the EEG these oscillations are represented as outbursts of widespread synchronous high-voltage delta waves (Bekhtereva, Zimkin and Usov[5]).

The changes described above are observed in the form of a synthetic picture on a 50-channel electroencephaloscopy screen and is considered, in conformity with the known data in the literature on the reticular system function of the axis of the brain, as an electrophysiologic expression of the influence of the tumour. (Morrison and Dempsey,[6] Moruzzi and Magoun,[7] Magoun,[8] Jasper,[9] Jasper, 1949; Young, 1954; Gastaut.[10])

The isotope electroencephalographic and the electrophysiologic methods of brain tumour diagnosis supplement each other and the combined application of these two diagnostic tools at the patient's bedside deserve special attention and further development. The combination of these two diagnostic methods should free the physician—and spare the patient—of the necessity of using the traumatic and dangerous methods of pneumo- and angio-graphy.

The limits of clinical application of isotope encephalography have not been defined up to the present in the literature of the world.

SUMMARY

The authors consider isotope encephalography applicable:

1. In all cases where localization is obscure and the nature of the process in the cranial cavity is uncertain,
2. In cases of superficial and extracerebral tumours (convex and parasagittal),
3. When tumour localization in "silent areas" is suspected,
4. For the differential diagnosis of fronto-temporal and posterior cranial fossa tumours,
5. For the detection of tumour metastases in the cranial cavity,
6. For the diagnosis of recurrence of brain tumours,
7. For the differential diagnosis of tumours and inflammatory processes and
8. When pneumography (encephalo- or ventriculo-) and angio-graphy have failed to clarify contradictory and unconvincing data.

Application of isotope encephalography is subject to limitations in the following conditions:

1. Pronounced insufficiency of thyroid gland function.
2. Conditions requiring decompression where an urgent decision is needed as to the location and nature

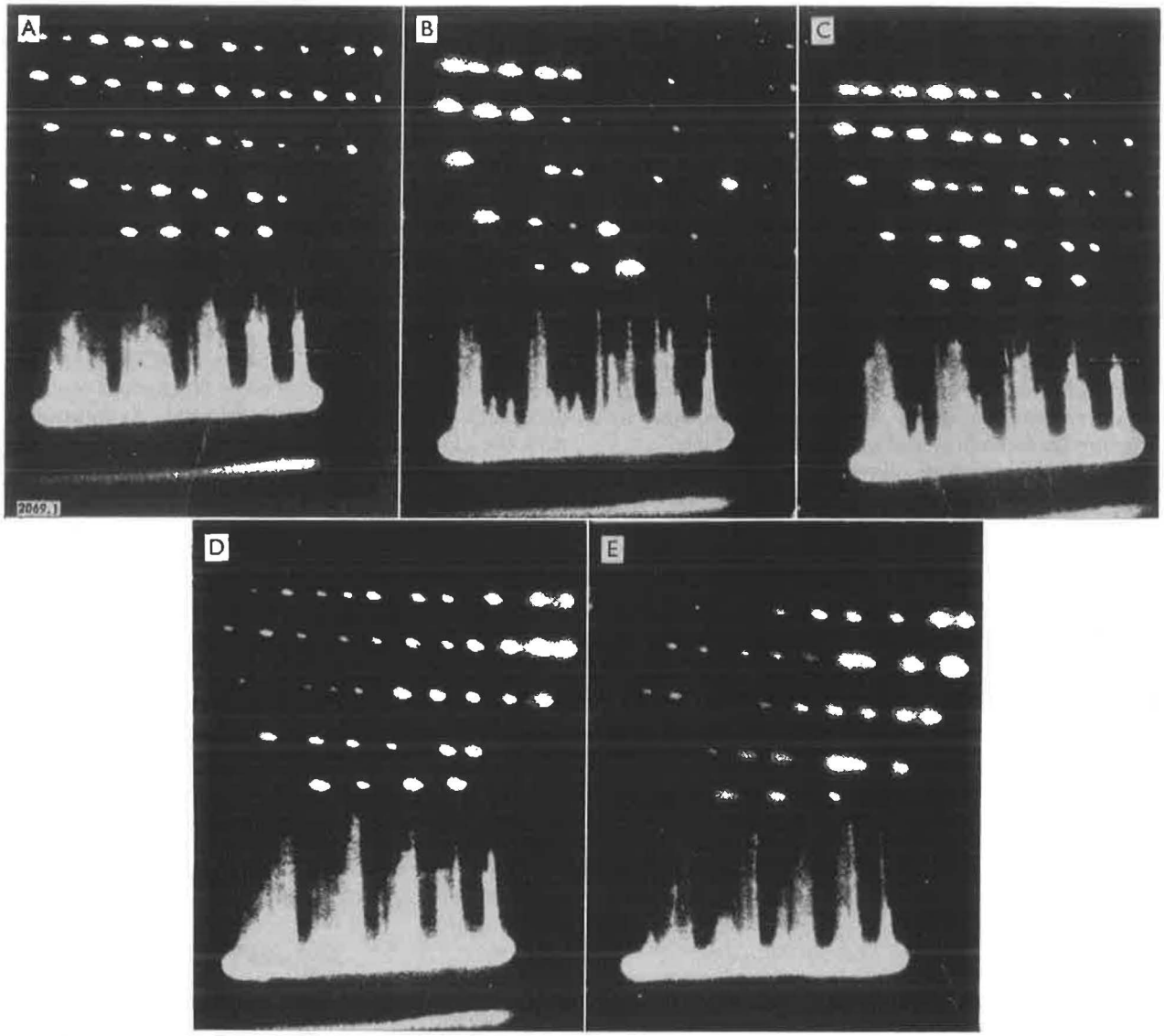

Figure 1. Film-stills of oscillating dynamics observed on the screen of the electroencephaloscope. Increase in negativity is emphasized by intensification of brightness of dots and an increase of amplitude of columns. (For the right hemisphere, 42 leads out of 50 were used. The image in D shows the biopotentials of the occipital area to the right frontal area.) Every horizontal row of dots conforms with the electrodes arranged in a row along the sagittal line. The upper row of dots represents bioelectric potentials led off from electrodes set up along the midline of the head, and the lower row represents the area of the temporal lobe. The left column represents the biopotentials of the upper line, the right column represents the lower line and the remaining 3 columns represent intermediate lines. (A) usual mosaic seen on the screen, midposition. (B and C) sequence of film-stills reflecting the phase of negativity increase in the posterior brain sections and positivity increase in the forebrain sections. (D and E) second phase of oscillations—sequence of stills reflecting negativity increase in forebrain sections and corresponding positivity increase in the posterior brain sections. The negativity increase reaches sufficient amplitude in the forebrain sections and is clearly seen

of the lesion and the immediate therapeutic action to be applied.

Isotope encephalography is a valuable and highly promising diagnostic method which plays a significant role in the complex study of neuro-oncologic patients.

At present the problem is to find labelled substances that have a more complete and preferential isotope concentration in tumour tissue. This depends to a great extent on obtaining the so-called antitumour serum whose antibodies have a selective tumour localization.

The foregoing indicates that the possibilities of isotope encephalography have by no means been exhausted and that scientists face vast prospects of working out practical and theoretical problems in the further development of this valuable method.

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Studies of Body Composition in Normal and Pathological States Using Isotope Dilution Techniques

By E. J. Wayne,* M. M. Bluhm† and J. Crooks*

In our work in Glasgow we have been interested in the application of isotope dilution techniques to the study of body composition. We became particularly interested in the measurement of total exchangeable electrolytes since the assessment of electrolyte disturbance by means of serum concentration has been shown to be fallacious in so far as it does not necessarily reflect changes in total body content.[1]

Physiologists have long appreciated that comparisons of the electrolyte content of various tissues are invalidated by variations in the proportion of lipid since the latter is poor in electrolytes.[2] For this reason they expressed their measurements of electrolytes on a fat-free weight rather than a tissue weight basis. Clinical workers, on the other hand, have in the main continued to use body weight as a standard of reference for exchangeable electrolytes in man.[3,4] Because of this, exchangeable potassium (K_e) in females[5] has been found to have a lower value per kilogram of body weight than in males,[4] presumably because of the greater fat content of the former. Because of the fallacy produced by the contribution of fat to body weight it seemed likely that the established mean values for the exchangeable sodium (Na_e),[6] exchangeable chloride (Cl_e),[3] and K_e might be rendered less useful by the varying fat component of the subjects studied and that the ranges of these values might be made unnecessarily wide.

We therefore felt that the substitution of fat-free weight or lean body mass as the reference standard for the exchangeable electrolytes might result in a narrowing of the ranges of these normal values. This study has been carried out in a group of normal subjects.

We also took the opportunity of studying the relationships between the three electrolytes, particularly that of Na_e with Cl_e.

Thyroid hyperfunction results in a varying loss of lean tissue and fat.[7] For this reason we studied a number of subjects with thyrotoxicosis and observed the relationship between the three electrolytes and lean body mass.

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STUDY OF NORMAL SUBJECTS

Na_e measurements were made in 21 normal males and 17 normal females. We also measured K_e in 21 males and 17 females, and Cl_e in 22 males and 19 females. In 24 of the subjects studied all three electrolytes were measured. The subjects covered a wide range of age and body weight (Tables 1 and 2).

TECHNIQUES

We measured Na_e by the method of Miller and Wilson,[6] giving 30 μc of Na^{24} orally and allowing an equilibration period of 24 hours. K_e measurements were performed by the method of Corsa and his colleagues,[4] four spot urine specimens being collected between 22 and 26 hours after injection of 150 μc of K^{42} (KCl irradiated as K_2CO_3) using a calibrated syringe. We also made simultaneous measurements of Na_e and K_e by the method of Munro and colleagues.[8] In this procedure 100 μc of K^{42} and 50 μc of Na^{24} were given intravenously from a calibrated syringe, and an equilibration period of 22 hours was allowed, after which a plasma sample was obtained followed by two spot urine specimens one and two hours later. Each spot urine specimen was divided into two portions and potassium separated from sodium by precipitation of the former with sodium tetraphenylboron. Potassium and sodium concentrations in plasma and processed urine were estimated by flame photometry. We carried out the measurements of Cl_e by the method of Bradley and colleagues;[9] 20 μc of Br^{82} (NaBr irradiated as NH_4Br) was administered orally and an equilibration period of 22 to 26 hours was allowed. We did not give Br^{82} until at least three days after the administration of Na^{24} and K^{42}, to ensure that Br^{82} plasma counts required no correction for residual Na^{24}. Plasma chloride concentration was estimated by the method of Van Slyke.[10]

To derive total exchangeable electrolyte we used the following equation:

Total exchangeable electrolyte (meq)
= Electrolyte space (litres)
× plasma electrolyte (meq/litre).

In the case of sodium, the electrolyte space and plasma concentration did not require correction by

Table 1. Normal Males

Case No.	Age	Ht., cm	Body wt., kg	Lean body mass, kg	Na_e, meq	K_e, meq	Cl_e, meq	Na space / Cl space
1	18	176	65.9	51.7	3070	3710	1970	1.192
2	33	165	63.6	51.1	2410	3140	1780	1.166
3	29	168	55.5	53.0	2360	2860	1800	1.096
4	36	175	97.4	61.6	3020	3520	2270	1.057
5	27	183	72.7	58.5	2910	3900	2000	1.083
6	22	177	65.4	48.6	2740	3210	1850	1.167
7	27	175	57.3	49.8	2760	2690	1950	1.086
8	35	184	83.0	66.0	3180	3020	2100	1.201
9	25	163	100.5	63.0	2790	3600	1880	1.240
10	21	174	69.0	51.5	3480	3280	2590	1.374
11	24	174	63.2	50.7	2840	3100	1710	1.324
12	18	175	79.5	67.0	3480	3580	2280	1.279
13	21	179	58.6	52.0	3080	3280	1790	1.320
14	28	182	71.8	61.1	2970	3740	2160	1.101
15	22	192	81.0	66.0	3320	—	—	—
16	24	179	92.0	57.0	2470	—	—	—
17	74	159	61.4	47.2	2590	—	—	—
18	31	182	80.0	60.5	3090	4130	—	—
19	67	165	57.3	52.5	2910	—	—	—
20	46	178	118.0	74.6	3530	—	—	—
21	65	165	55.5	44.7	2370	—	—	—
22	22	168	61.3	48.8	—	3140	1710	—
23	22	177	68.2	56.2	—	3240	2020	—
24	22	192	82.0	71.7	—	4500	3010	—
25	22	169	65.0	52.0	—	3080	1930	—
26	23	178	65.5	58.2	—	—	2190	—
27	25	183	87.2	72.6	—	—	2450	—
28	33	178	77.2	59.5	—	3600	—	—
29	43	165	61.0	57.5	—	—	1980	—
30	59	183	82.7	55.1	—	2880	1930	—

Table 2. Normal Females

Case No.	Age	Ht., cm	Body wt., kg	Lean body mass, kg	Na_e, meq	K_e, meq	Cl_e, meq	Na space / Cl space
31	56	140	83.7	48.0	2600	1950	1580	1.260
32	31	159	65.0	41.5	2300	2480	1530	1.239
33	45	154	80.5	45.2	2490	2830	1730	1.159
34	51	161	84.3	46.0	2360	2580	1680	1.143
35	19	168	130.0	65.0	3510	3540	2210	1.295
36	68	154	89.1	58.0	2760	2730	1910	1.084
37	17	165	95.5	55.0	3500	3220	2270	1.223
38	21	157	49.4	34.5	2070	2470	1540	1.078
39	26	165	56.4	42.0	2040	2390	1650	0.972
40	57	151	104.0	62.5	3370	3530	2460	1.166
41	30	163	67.2	41.9	2200	—	—	—
42	71	142	72.2	46.5	2490	—	—	—
43	58	154	72.4	49.0	2290	—	—	—
44	34	160	59.5	40.7	2200	—	—	—
45	22	168	56.4	43.6	2530	—	—	—
46	21	165	65.0	47.7	2360	—	—	—
47	22	168	48.1	38.6	2090	—	—	—
48	55	157	82.7	48.5	—	—	1830	—
49	57	158	93.6	52.0	—	2540	1980	—
50	38	155	70.5	45.9	—	2220	—	—
51	81	152	44.5	33.3	—	1260	1250	—
52	55	156	66.0	45.3	—	—	1680	—
53	18	173	100.2	61.5	—	3080	2440	—
54	50	178	57.2	45.2	—	—	1730	—
55	51	151	50.0	36.7	—	1910	—	—
56	52	152	63.6	47.0	—	2160	1720	—
57	37	170	55.0	45.8	—	—	1830	—
58	66	163	54.0	42.1	—	1700	1370	—

the Donnan factor since this is cancelled by the correction for plasma proteins. In deriving the chloride space, however, it is necessary to correct for the Donnan equilibrium and for plasma proteins since they are additive for cations, and a factor of 0.91 was therefore used. In these cases where K_e was measured alone by the method of Corsa and his colleagues,[4] we found it necessary to increase the values obtained by 6 per cent in order to make them comparable to the values given by the simultaneous Na_e and K_e technique. The *in vitro* experiment by which this correction was obtained will be described elsewhere.

The radiation dose for a person of 70 kg weight did not exceed 0.07 rad due to 50 μc of Na^{24}, 0.07 rad due to 100 μc of K^{42}, and 0.05 rad due to 20 μc of Br^{82}, i.e., the radiation dose due to the combined technique lies considerably below the weekly tolerance dose of 0.3 rad.

Lean body mass was estimated from the Pace-Rathbun formula[11]

$$\text{Lean body mass} = \text{Total body water} \times \tfrac{100}{73}.$$

Total body water was measured by the antipyrine dilution technique of Brodie and associates,[12] the plasma concentration of antipyrine being corrected for plasma proteins. In a few subjects values of lean body mass were derived from measurements of red cell mass employing the correlation established by Muldowney.[13] In future we hope to measure total body water by tritium dilution using an internal liquid scintillation counter to estimate tritium in urine samples.

EXCHANGEABLE ELECTROLYTES IN NORMAL SUBJECTS

The complete data obtained for the normal subjects are given in Tables 1 and 2, and the statistical analysis is given in Table 3. We tested the reproducibility of the measurements of exchangeable electrolytes by carrying out two successive estimations in a number of subjects. The standard deviations were ± 2.3 per cent for Na_e (8 subjects), ± 3.5 per cent for K_e (5 subjects), and ± 3.5 per cent for Cl_e (5 subjects).

The relationship between Na_e and body weight is shown in Fig. 1. The coefficient of correlation was 0.62 and the 95 per cent confidence limits ± 27 per cent. We found that the majority of the points representing males lay above the regression line while the converse was true of the females. When we correlated Na_e with lean body mass, however, in the same subjects (Fig. 1), both the correlation coefficient ($r = 0.82$) and the 95 per cent confidence limits (± 20 per cent) were improved. The points for both males and females were also more uniformly distributed about the regression line (Fig. 1). When we correlated K_e with body weight a very wide range of normal values was found (Fig. 2). Once again most of the males lay above the regression line and the females below. When lean body mass, on the other hand, was used as the reference standard, the normal range narrowed and the male and female values were distributed on either side of the regression line. The effect of using lean body mass instead of body weight as a reference standard for Cl_e was similar to that observed in the case of Na_e and K_e (Fig. 3).

In 14 males and 10 females the correlation between Na_e and Cl_e was highly significant ($r = 0.88$) and the 95 per cent confidence limits (± 17 per cent) were narrower than those for Na_e when either body weight or lean body mass was used as a reference standard (Table 3). Because of the primarily extracellular location of both these ions, this finding was not unexpected. Of greater interest, however, was the observation that in this group of subjects the Na_e could not be wholly accounted for by that present in the extracellular fluid, as represented by the chloride space, since the mean ratio of the sodium space to the chloride space, 1.179, was significantly greater than unity ($p < 0.01$, standard deviation of the mean = 0.024).

Table 3. Statistical Analysis

Electrolyte y	Reference standard x	Number of: Males	Females	All subjects	r	95 % confidence limits: meq	% of mean	Equation of regression line
1. Electrolytes and Reference Standards								
Na_e	B.W.[a]	21	17	38	0.62	± 740	± 27	$y - 2750 = 15.02(x - 74.41)$
Na_e	L.B.M.[b]	21	17	38	0.82	± 560	± 20	$y - 2750 = 40.72(x - 52.48)$
K_e	B.W.	21	17	38	0.45	± 1250	± 41	$y - 3018 = 16.58(x - 74.48)$
K_e	L.B.M.	21	17	38	0.83	± 790	± 26	$y - 3018 = 61.76(x - 52.77)$
Cl_e	B.W.	22	19	41	0.55	± 600	± 31	$y - 1942 = 10.68(x - 73.95)$
Cl_e	L.B.M.	22	19	41	0.84	± 390	± 20	$y - 1942 = 31.84(x - 52.96)$
2. Relation between Electrolytes								
Na_e	K_e	15	10	25	0.66	± 700	± 25	$y - 2845 = 0.544(x - 3139)$
Na_e	Cl_e	14	10	24	0.88	± 470	± 17	$y - 2837 = 1.316(x - 1942)$
K_e	Cl_e	14	10	24	0.67	± 820	± 26	$y - 3098 = 1.143(x - 1942)$

[a] B.W. = body weight.
[b] L.B.M. = lean body mass.

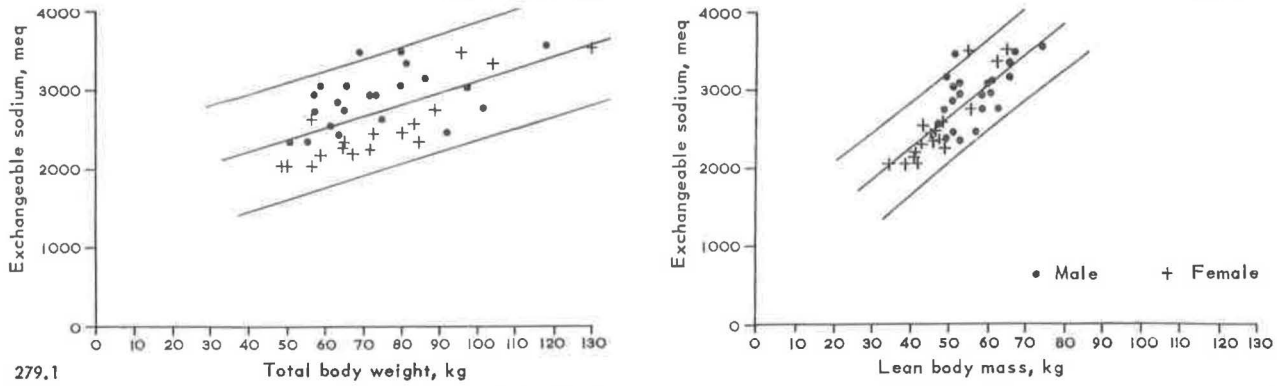


Figure 1. The correlations of total exchangeable sodium with total body weight and lean body mass showing the regression lines and their 95 per cent confidence limits

From the available data we also calculated regression lines for Na_e on K_e, and K_e on Cl_e (Table 3).

SIMULTANEOUS MEASUREMENT OF Na_e, K_e AND Cl_e

We felt that it would be advantageous to devise a method of measuring all three electrolytes simultaneously in order to eliminate the effects of any biological changes which might occur in the interval before Cl_e was measured as in our present techniques. This procedure should be of particular value in evaluating electrolyte changes in pathological states. To obtain these measurements we used a γ-ray spectrometer to count the 0.55 Mev peak of Br^{82} with some contribution from Na^{24}, and the 2.76 Mev peak of Na^{24} with no contribution from Br^{82}. Na_e and Cl_e were estimated by this technique from plasma where the counts from K^{42} were negligible. The same method was used to measure the 24-hour urinary excretion of Na^{24} and Br^{82}. K_e was estimated from spot urine samples after separation of potassium by precipitation with sodium tetraphenylboron. The 24-hour urinary excretion of K^{42} was obtained by processing an aliquot of the 24-hour collection of urine with sodium tetraphenylboron.

This method was compared with that used to measure Na_e and K_e simultaneously, and Cl_e separately. To do this the exchangeable electrolytes were measured in three subjects by both methods. For all three electrolytes the mean standard deviation was ± 3.4 per cent.

EXCHANGEABLE ELECTROLYTES IN THYROTOXICOSIS

In this study we selected 20 subjects (19 females, 1 male) with unequivocal clinical evidence of thyrotoxicosis; the complete data are given in Table 4. The diagnosis in each case was confirmed by measurement of the 4-hour uptake of I^{131} and the 48-hour plasma protein bound radioactivity. In all cases the basal metabolic rate was above the upper limit of the normal range.[14]

We measured Na_e and K_e simultaneously and Cl_e three days later. Lean body mass was measured by the antipyrine dilution technique as in the normal subjects.

We found that all but two of the values for Na_e and all but four of those for Cl_e lay above the regression line for the normal group (Figs. 4 and 6). In the case of K_e, however, there was a more even distribution of values about the regression line (Fig. 5). The

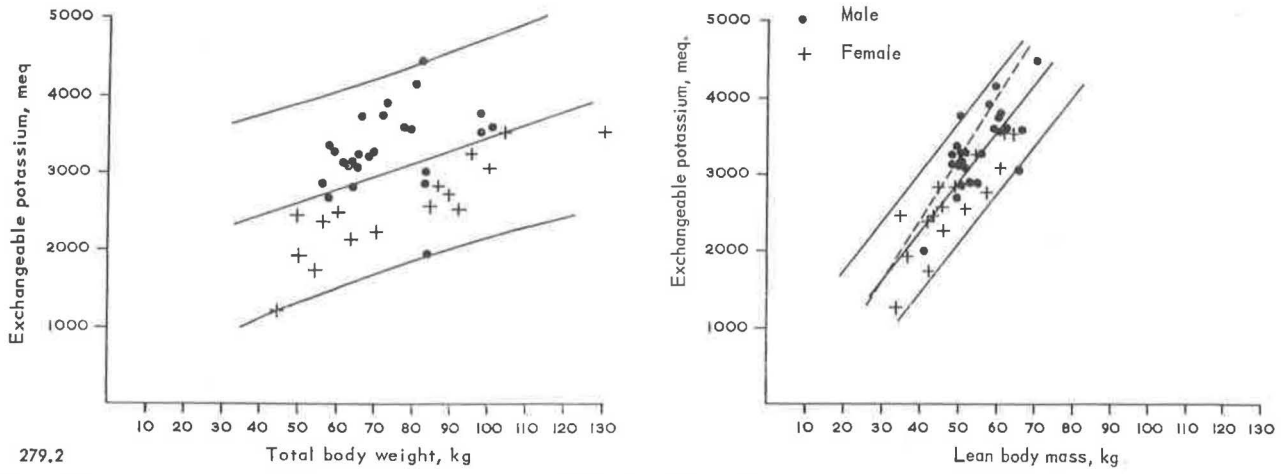


Figure 2. The correlations of total exchangeable potassium with total body weight and lean body mass showing the regression lines and their 95 per cent confidence limits. The interrupted line is the regression line derived from the data of Ikkos and his associates[18]

Table 4. Subjects with Thyrotoxicosis

Case No.	Age	Height, cm	Body weight, kg	Lean body mass, kg	Na_e, meq	K_e, meq	Cl_e, meq	$\frac{Na\ space}{Cl\ space}$
1	44	166	70.2	43.2	2670	2580	1720	1.15
2	51	166	65.3	47.6	2900	2050	1920	1.17
3	41	164	50.8	41.2	2650	1910	1390	1.46
4	24	168	45.4	35.4	1880	1780	1580	0.97
5	48	147	45.7	30.8	1980	1500	1520	1.07
6	34	163	54.3	39.8	2550	1990	1590	1.20
7	49	150	55.9	36.1	2780	2500	1560	1.33
8	45	163	60.2	40.0	2430	2430	1890	0.99
9	54	163	47.2	39.8	2330	2500	1510	1.10
10	41	152	52.4	44.1	2940	2350	1520	1.38
11	37	168	47.3	43.3	2090	2800	1450	1.06
12	38	165	55.0	46.2	2790	2440	1940	0.97
13	19	150	38.2	25.9	1620	1720	1280	0.97
14	48	155	36.8	30.3	1810	1470	1440	0.96
15	45	157	59.3	39.6	2270	2590	1810	0.94
16	28	160	52.6	43.6	2840	2780	1950	1.13
17	66	169	57.0	41.0	2400	2060	1380	1.53
18	42	179	63.4	45.3	2550	3030	2030	1.08
19	40	174	46.4	37.1	2100	2340	1630	1.01
20	46	163	61.7	35.8	2400	2300	1590	1.23

observed values of the exchangeable electrolytes were reduced to a common value of lean body mass in both thyrotoxic and normal subjects by using the regression line for each group. In the case of Na_e the difference between the mean values of the thyrotoxic and normal subjects was found to be statistically significant ($p < 0.05$). No statistically significant difference was found for K_e ($F = 5.87$, $p < 0.05$) and Cl_e ($F = 3.92$, $p < 0.05$).

We calculated the ratio of sodium space to chloride space in these subjects and found it to be 1.135. This value is just within twice the standard deviation of the mean value we obtained in the normal group.

In 10 of the 20 subjects the measurements of exchangeable electrolytes and lean body mass were repeated as soon as the patients had become euthyroid. The changes in Na_e and Cl_e showed no consistent pattern and in all but one case K_e rose. We suspect that the patients will have to remain euthyroid for a prolonged period before a final evaluation of the electrolyte changes can be reached.

DISCUSSION

Exchangeable Sodium

Miller and Wilson,[6] Forbes and Perley,[15] and Edelman and colleagues[16] found no statistically significant difference in Na_e per kilogram of body weight between males and females. Our series, however, shows a striking sex difference (Fig. 1) which is accounted for by the many obese females included in our group. Forbes and Lewis[17] have shown by direct analysis that the sodium content of adipose tissue is low compared with that of the fat-free tissue. Hastings and Eichelberger[2] also found that it was necessary to analyse fat-free muscle before consistent results could be obtained for the sodium content of different muscle samples. It might be expected, therefore, that

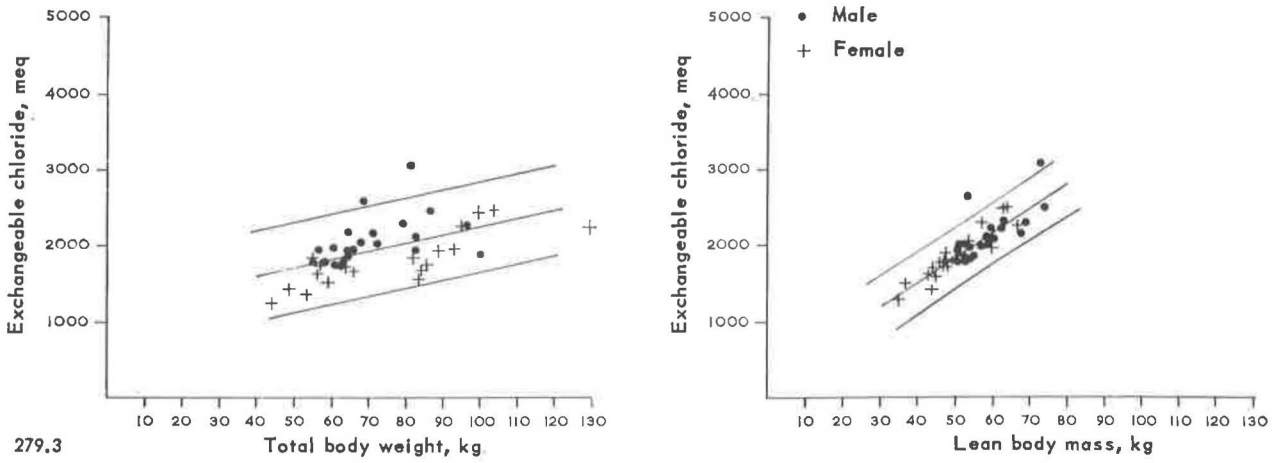


Figure 3. The correlations of total exchangeable chloride with total body weight and lean body mass showing the regression lines and their 95 per cent confidence limits

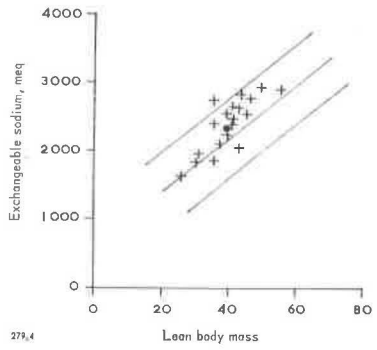


Figure 4. Total exchangeable sodium plotted against lean body mass in thyrotoxic subjects, also showing the regression line and its 95 per cent confidence limits for normal subjects

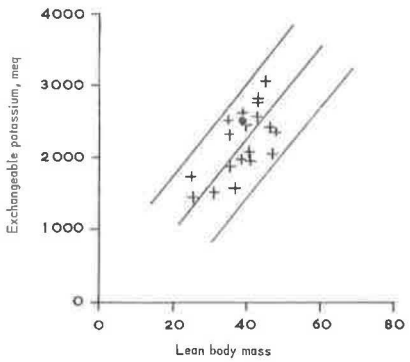


Figure 5. Total exchangeable potassium plotted against lean body mass in thyrotoxic subjects, also showing the regression line and its 95 per cent confidence limits for normal subjects

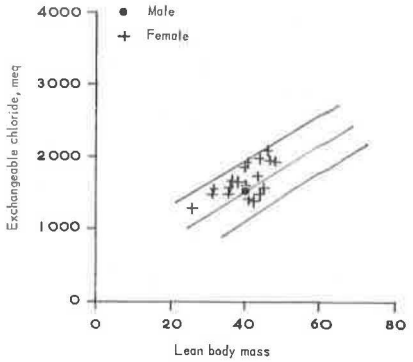


Figure 6. Total exchangeable chloride plotted against lean body mass in thyrotoxic subjects, also showing the regression line and its 95 per cent confidence limits for normal subjects

Na_e per kilogram of body weight would decrease as the proportion of depot fat increased. This effect is well illustrated by two of our subjects. One was a grossly obese female, with an Na_e of 27 meq/kg body weight, this figure being lower than any of the published values for females. The other, a male subject, had an Na_e of 41 meq/kg body weight. When expressed per kg lean body mass, the difference between these values was considerably reduced, the values becoming 54 meq/kg and 50 meq/kg respectively. Our findings, therefore, in conjunction with the evidence of direct tissue analysis, show that it is more accurate to predict Na_e from lean body mass than from body weight especially in subjects with a high fat content. The ease with which lean body mass can be estimated by the tritium dilution technique should add to the value of this reference standard.

Exchangeable Potassium and Chloride

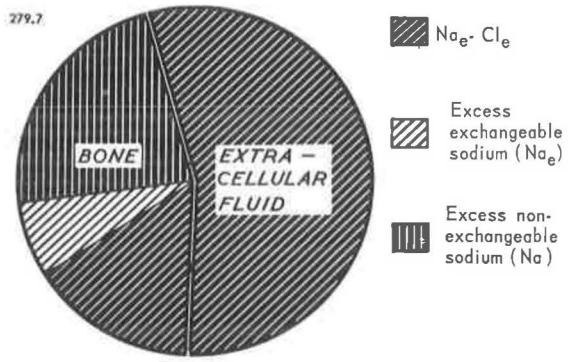
The correlation we have obtained between K_e and lean body mass is supported by experiments of other workers both in human subjects and in animals. Thus, Ikkos, Ljunggren and Luft[18] in Sweden, as part of an investigation into the relation between extracellular and intracellular water in acromegaly, measured total body water and K_e in a control group of 33 normal subjects. From their data we derived antipyrine space measurements and, after correcting for the water content of plasma, estimated lean body mass by means of the Pace-Rathbun formula.[11] When this was done a regression line of K_e on lean body mass was obtained, and it has been included in Fig. 2, the coefficient of the correlation being 0.92. This regression line lies within the 95 per cent confidence limits of the present series, although a slight systematic difference is apparent. Data for K_e, Cl_e and total body water given by Corsa and colleagues[4] and Ikkos, Ljunggren, Luft and Sjögren in another paper[3] are consistent with our results when lean body mass is derived from their values for total body water.

Carcass analysis in rats provides direct evidence of a close correlation of total body potassium and total body chloride with lean body mass[19] while Weir[20] had previously demonstrated that total exchangeable chloride was directly related to the lean carcass in dogs. This evidence suggests, therefore, that chloride is confined to lean tissue and is not present in depot fat. Forbes and Lewis,[17] however, have analysed two human cadavers and found an appreciable chloride content in adipose tissue. This appears to conflict with our results and with the data from animal studies quoted above. The discrepancy is, however, one of definition since the term depot fat, as used in the present study, refers only to the lipid content of adipose tissue. Keys and Brozek[21] estimate that lipids form 62 per cent, water 31 per cent and cell solids 7 per cent of adipose tissue. These relative proportions of water and cell solids are similar to those obtained in muscle, and the nonlipid portion of adipose tissue is therefore included in the estimate of lean body mass derived from total body water.

One would expect, therefore, that adipose tissue as a whole should contain a percentage of chloride and potassium in proportion to its nonlipid content.

Excess Exchangeable Sodium of Bone

We have shown that the ratio of sodium space to chloride space is significantly greater than unity. This finding must be interpreted in the light of the available evidence on the distribution of sodium and chloride in body fluids and tissues (Fig. 7). The sodium content of bone may be regarded as divided into two parts, that contained in the extracellular fluid of bone, and that incorporated into the bone crystal itself.[22] The bone chloride, on the other hand, is confined to the extracellular fluid where it is present along with sodium in the same ratio as in serum. Both ions in this compartment of bone are exchangeable. Bauer[23] has shown by direct radioisotope studies of rat bones that part of the sodium incorporated into the bone crystal is also rapidly exchangeable, and that it is in excess of the exchangeable chloride in bone. This excess of exchangeable sodium in bone is likely to lie at the surface of the bone crystal where it would be in close contact with the extracellular fluid.



$$\frac{\text{Mean Na space}}{\text{Mean Cl space}} = 1.179 \pm 0.024 > 1.0 \ (P<0.01)$$

Figure 7. The distribution of sodium and chloride in bone and extracellular fluid in 24 normal subjects

Our finding that the ratio of sodium space to chloride space is significantly greater than unity therefore means that there is a pool of exchangeable sodium in excess of exchangeable chloride which is large enough to be detected by isotope dilution techniques. It seems probable from Bauer's work that the greater part of this excess is localised in bone although it is possible that a contribution is made by other tissue such as muscle.[24] Harrison[25] has shown that the molar ratio of calcium to sodium in bone is the same in normal, rachitic and osteoporotic rats. It follows that disturbances in calcium metabolism might be associated with changes in the sodium of bone which might be demonstrable by an alteration in the ratio of sodium to chloride spaces.

The relationship between Na_e and K_e is not sufficiently close to be of value for prediction purposes. Na_e in the subjects studied is generally slightly smaller than K_e, and this corresponds with the pattern of results obtained by Moore and colleagues.[26] It was hoped that the data obtained on the relationships between Na_e, K_e, Cl_e and lean body mass might be of help in the study of pathological problems in electrolyte metabolism, particularly in conditions which produce associated changes in lean and fat tissue. For this reason we decided to study the body composition of a group of thyrotoxic subjects using the techniques we had already applied to normal subjects.

Exchangeable Electrolytes in Thyrotoxicosis

Our finding that in thyrotoxicosis there is an increase in Na_e relative to lean body mass could be accounted for by the increase in plasma volume in this condition found by Gibson and Harris.[27] Although inspection of Fig. 6 suggested that there was also an increase in Cl_e, which might be expected if the plasma volume increased, the changes were not statistically significant. This may be due to the small number of cases studied. The fact that serum concentrations of sodium and chloride are normal in hyperthyroidism[28] does not, of course, preclude an increase in the total body content of these electrolytes.

Our results also suggest that the diminution in the potassium content of thyrotoxic patients shown by Danowski and Elkinton[23] can be accounted for by a corresponding loss of lean tissue. It is noteworthy that the mean value of the lean body mass in our thyrotoxic subjects was approximately 39 kg compared with a corresponding figure of 53 kg in our normal group. This finding accords well with the recognised negative nitrogen balance found in this condition.

CONCLUSION

Measurements of total exchangeable electrolytes have become increasingly desirable in studies of electrolyte metabolism. Before the maximum information can be obtained from such measurements it is necessary first to know the relationship between the various electrolytes in normal subjects—the sodium-chloride relationship is an example of this. Secondly, a satisfactory reference standard has to be provided. The conventional one of body weight is unsatisfactory especially in conditions where varying degrees of obesity are present or where changes in the amount of lean tissue occur. In such circumstances lean body mass derived from total body water should be used.

SUMMARY

1. The correlation of total exchangeable sodium (Na_e), potassium (K_e) and chloride (Cl_e) with lean body mass is better than with body weight. In normal subjects it is the same for both males and females.

2. A technique of measuring Na_e, K_e and Cl_e simultaneously is described.

3. The ratio between sodium space and chloride space in normal subjects is significantly greater than unity and it is suggested that this is due to the excess of Na_e over Cl_e in bone.

4. In thyrotoxicosis Na_e increases relative to lean body mass whereas K_e remains unchanged. The relationship between sodium space and chloride space is undisturbed.

ACKNOWLEDGEMENTS

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A Comparison of the Distribution of Magnesium-28 with that of Potassium-42 and Calcium-45

By B. A. Barnes* and G. L. Brownell†

The importance of magnesium in mammalian physiology has been well established. The activation of enzyme systems,[1] the control of neuromuscular function,[2] and the essential role played in animal nutrition[3] and in human nutrition[4] by magnesium have been established in the past. More recently abnormalities of magnesium metabolism have been reported in chronic alcoholics,[5] in patients with cirrhosis of the liver[6] and in parathyroid disease.[7] In spite of the undoubted importance of this mineral few facts are available to permit a clearer understanding of its role in clinical medicine. Data based on direct tissue analysis[8] record the approximate content of magnesium in the tissues of the human body. In a 70 kg adult of normal body composition there are 2100 meq of magnesium of which 45 per cent are located in the skeleton, and the remainder is in the soft tissues. In the soft tissues the largest portion appears in the skeletal muscle where 25 per cent of the total magnesium is located. Per kilogram of body weight there are 30 meq of magnesium of which approximately 17 meq per kilogram of body weight are located in the soft tissues.

The fraction of magnesium in the skeleton shares with calcium an anatomical space where more than 99.5 per cent of the calcium in the body is held. The fraction of magnesium in the soft tissues shares with potassium an anatomical space where 95 per cent of the potassium in the body is found. In the cells of soft tissue magnesium and potassium coexist in a ratio of 1 atom of magnesium to 3 of potassium. In bone the atomic ratio of magnesium to calcium is approximately 1 to 30. The possible interchange of magnesium between the skeleton and the soft tissues is poorly understood. Estimates of the internal metabolic flux of this mineral have been made in young growing rats,[9] but it is difficult to extend the conclusions to humans in view of the artificial nature of these animal experiments. Metabolic studies on patients suffering from severe burns[10] demonstrate that excessive amounts of magnesium have been lost or retained by the body in relation to other minerals suggesting that skeletal magnesium may have been released or deposited to account for the unusual ratios of the mineral flux in these balance studies. Nothing has been established concerning the fixation of magnesium in the soft tissues or concerning its availability for meeting acute deficiencies.

The purpose of this paper is threefold: (1) a comparison of certain features of the dynamics of the transcapillary and tissue distribution of magnesium, potassium and calcium; (2) a determination of the exchangeable magnesium in health and certain diseased states; and (3) an evaluation of the exchangeability of magnesium in the tissues.

MATERIALS AND METHODS

Radioisotopes

Magnesium-28, produced by Mg^{26} (t, p) Mg^{28} in the nuclear reactor of the Brookhaven National Laboratory was available with a specific activity of approximately 500 μc of magnesium-28–aluminum-28 equilibrium mixture in not more than 1 gm of stable magnesium. This isotope with a half-life of 21.3 hr has aluminum-28 as a daughter with a half-life of 2.3 min. Both emit beta and gamma radiations[11] as follows (in Mev):

	Beta	*Gamma*
Mg^{28}	0.459	0.032 (100%)
		1.335 (70%)
		0.393 (30%)
		0.942 (30%)
Al^{28}	2.865	1.782

Potassium-42 with a half-life of 12.4 hr was obtained in a range of 40 to 50 mc per gm of stable potassium. This isotope emits a more highly energized beta radiation (3.58 Mev) and a somewhat weaker gamma radiation (1.51 Mev) than the magnesium isotope.

Calcium-45 was obtained with a specific activity in excess of 15 mc per gm of stable calcium. This isotope with a half-life of 163 days emits only a weak beta radiation (0.254 Mev).

Determination of Isotopes

The determination of the concentrations in the samples of the coexisting isotopes of magnesium and potassium was performed in beta- and gamma-well scintillation detectors of sodium iodide crystals. The effective volume of the wells was 4 cc and the detector crystals were connected to appropriate apparatus to record the disintegrations. The sensitivity of the beta-radiation detection was increased by placing the

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samples in lucite tubes with a negligible absorption at the above beta-ray energies. The tubes were screened to assure uniformity of their absorption characteristics. Each sample was counted in the beta-well and gamma-well detectors successively so that essentially two simultaneous and independent measurements of the beta and gamma radiations were made. By comparison with standards of magnesium-28 and potassium-42 related to the injected dose a calculation could be completed separating the amounts of the two isotopes coexisting in a single sample. The weak beta emission of the calcium-45 did not interfere with the analysis for the radiomagnesium or radiopotassium because these low energy radiations were absorbed in the aqueous medium of the sample.

In 18 analyses of prepared solutions containing the three isotopes of magnesium, potassium and calcium it was possible to compare the known composition with that determined by simultaneous isotope analysis as above. The magnesium content as analyzed was found to be 102 per cent of the known composition with a standard deviation of 7.6 per cent. The potassium as analyzed was found to be 104 per cent of the known composition with a standard deviation of 8.9 per cent.

After a suitable delay to take advantage of the decay of magnesium-28 and potassium-42, the analysis for calcium-45 was completed. In the method used[12] a standard amount of stable calcium is added to the aqueous sample, and all the calcium is precipitated with oxalate so that the calcium-45 precipitate is occluded in a constant mass of stable calcium. Thus self-absorption is standardized. In 62 replicate analyses of a standard solution the coefficient of variation (standard deviation $\times$ 100/mean) was 8.0 per cent.

The analyses of the stable magnesium, potassium and calcium were completed by methods reported from this hospital.[13]

Expression of Results

In presenting the data on the isotope concentrations in tissue, the results are normalized for the amount of radioactivity injected, for the body weight of the patient and for the size of the sample analyzed. Thus the concentrations are expressed as a per cent of the injected dose per kg of body weight per kg of tissue (serum, muscle or bone). In this manner the data from different patients have been corrected for any irrelevant variations caused by the amount of radioactivity injected, the weight of the patient or the size of the tissue sample. The normalization is described by the following formula:

$$\text{Concentration} = \frac{\text{Cpm, Sample}}{\text{Cpm, Injected}} \times \frac{\text{Body Wt}}{\text{Sample Wt}} \times 100. \quad (1)$$

The corresponding specific activity is obtained by dividing the above concentration by the amount of the stable element in a kilogram of tissue.

Experimental Methods

Patients were injected early in the morning (or the previous afternoon) of the day the samples were to be collected to permit sufficient time for mixing of the isotopes in the body. A calibrated syringe was employed and the dosage of the isotopes was approximately 1 μc of magnesium-28, 1 μc of potassium-42 and 0.15 μc of calcium-45 per kg of body weight. The three isotopes were prepared for injection in a common hypertonic solution with the pH adjusted to approximately 5, which is distinctly acid, to minimize the occasional problem of a faint flocculent precipitation of the carrier magnesium. Following the injection of the isotopes the blood was collected at suitable intervals to provide data on the declining concentration in the serum over the ensuing 24 hours. The serum was separated promptly from the blood and the same sample was used in all the subsequent determinations of the radioactive and stable elements. Where specimens of bone and muscle were to be obtained at an operation, the radioactive magnesium was injected at appropriate times prior to the operation so that the tissue specimens could be obtained at varying intervals following the isotope injections. Thus data were obtained concerning the uptake of magnesium-28 by these tissues in relation to time.

During the experimental period urine was collected to determine the renal excretion of the radioisotopes from the body. The losses of the isotopes by this route were generally less than 5 per cent of the injected dose although in a few studies they were twice this value. The minor loss of these components in the urine was presumably related to the urinary excretion of the stable components at the time of the injection and was sufficiently small so that correction of the data was unnecessary. The modest loss of magnesium-28 in the urine may have been partly stimulated by the carrier magnesium present. However, the presence of the carrier did not lead to excessive losses.

Selection of Patients

The studies to be reported were performed on six patients suffering from acute focal nervous system disorders and on one normal individual. These subjects were used for the triple-isotope study. For the determination of the uptake of magnesium in bone and muscle, patients undergoing rib resections at thoracotomy and others requiring amputations for peripheral vascular disease were selected. In the latter condition the bone and muscle analyzed were at the proximal end of the amputated specimen. These tissues were adjacent to those judged by the surgeon to be grossly normal and to have an adequate blood supply to ensure healing. Consequently, although some specimens were obtained from patients with peripheral vascular disease, it is safe to assume that the bone and muscle studied were essentially normal. In addition to these patients in whom there was no major metabolic disorder, 5 patients with cirrhosis of the liver and 4 alcoholics have been studied to determine the total exchangeable magnesium 18 to 24 hours following the

injection of the isotope. The results in these patients suffering from advanced metabolic disorders have been compared with the data from the more normal group to evaluate possible effects of liver disease and chronic alcoholism on magnesium metabolism.

RESULTS

The data of the simultaneous distribution of calcium-45, magnesium-28 and potassium-42 are displayed in Fig. 1. These typical results are from a patient admitted to the hospital for treatment of a recent focal lesion of the central nervous system. There were no gross physiologic disturbances other than those consequent to a stuporous condition and immobilization. The points represent experimental data, and the curves running through them are calculated on the assumption of there being three major rates of

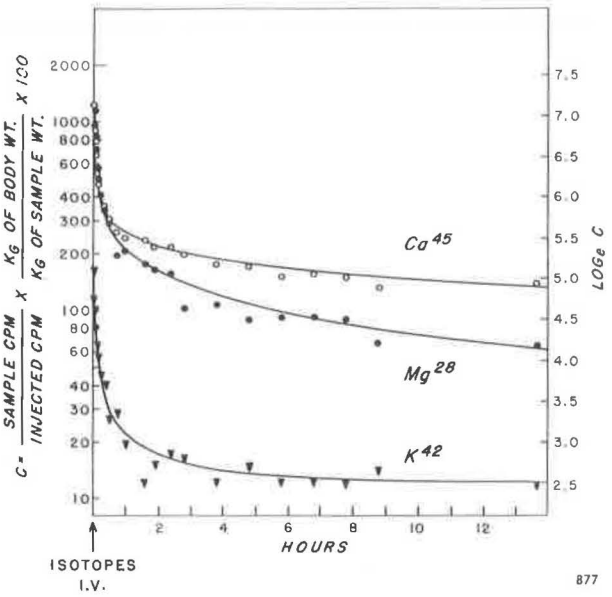

Figure 1. Concentration (following simultaneous injection) of radioisotopes of calcium, magnesium and potassium in man

distribution. The curve synthesis utilizes standard techniques in breaking the data into three groups by inspection and in calculating for each group by the method of least squares a representative linear, logarithmic function. The summation of the effect of three exponential rates of distribution is presented in the following three equations of the curves representing the calcium-45, magnesium-28 and potassium-42 data. C is defined in Fig. 1, and t equals hours:

$$Ca^{45}: \quad C = 840e^{-8.7t} + 130e^{-0.69t} + 190e^{-0.025t} \quad (2)$$

$$Mg^{28}: \quad C = 850e^{-7.1t} + 170e^{-0.55t} + 120e^{-0.046t} \quad (3)$$

$$K^{42}: \quad C = 107e^{-6.6t} + 18e^{-0.69t} + 13e^{-0.0027t}. \quad (4)$$

From these equations by evaluating the first derivatives at $t = 0$ the initial rate of transfer of the isotopes from the serum may be estimated.[14] This estimate is a crude minimum approximation of the actual rate of transfer of the stable mineral components in the human across the capillary membrane for two reasons: (1) there is the minimizing effect of the appreciable duration of the injection, and (2) there is the similar influence of the imperfect mixing of the isotope in the vascular compartment occurring simultaneously with the earliest transfers. Such calculations indicate that more than 100 per cent per minute of the injected dose of magnesium-28 and calcium-45 are leaving the serum at $t = 0$. This enormous loss of isotope from the serum confirms the well-known rapid exchange between the capillary bed and the extracellular space and extends our knowledge in this regard to include another ion. Furthermore, it may be seen that the initial loss of tracer from the serum is approximately equal for calcium and magnesium. Because of the experimental errors minimizing the magnitude of the initial transfer rates, the potassium rate by similar calculation gives an erroneously low value, less than that for the divalent cations.

The serum specific activities of these three isotopes between the fourteenth and twenty-fifth hours following the intravenous injection provide information as to whether or not equilibrium between the isotope and its stable form in the body has been reached. The potassium specific activities of the serum are essentially constant during this interval, and the magnesium and calcium specific activities decrease approximately 30 per cent due to the continuing distribution of these minerals throughout the body. In spite of the fact that equilibrium has not been reached with magnesium or calcium, calculations based on the mean specific activity of the serum in this interval may give an estimate of a *virtual* mass of the stable minerals with which the isotope has exchanged. This represents the mass that could have exchanged with the isotope and be in equilibrium to produce the particular specific activity in the serum. Values for the mean exchangeable masses of magnesium, calcium and potassium between the fourteenth and twenty-fifth hours are given in Table 1 where data from studies on nine individuals are presented. Of the nine subjects, five had acute focal central nervous system lesions; one had Hodgkins lymphoma of the retroperitoneum; two had localized peripheral vascular disease; and one was a normal volunteer.

Additional data from patients suffering from chronic alcoholism and from patients with cirrhosis of the liver have not revealed any alteration in the exchangeable magnesium or other minerals that is significantly different from the data in Table 1. In the future observations may disclose a significant difference that is not

Table 1. Exchangeable[a] Mineral per Kilogram of Body Weight at 18 Hours following Injection of Isotopes

Mineral	*Determinations*	*Mean ± SD[b] meq*
Mg	10	3.1 ± 0.3
Ca	8	3.4 ± 0.5
K	5	45 ± 11

[a] Consult text for discussion of "exchangeable mineral" for magnesium and calcium.
[b] S D—Standard deviation.

now apparent because of the limited number of cases. In four other patients the specific activity of muscle in an eighteen-hour period following the injection of magnesium-28 increased to a value approximately one-fourth that of the serum. This adds to the evidence (to be considered below) that the soft tissue magnesium throughout the body is not available for exchange as is the case with potassium.

DISCUSSION

The data in Fig. 1 recording the simultaneous distribution of calcium-45, magnesium-28 and potassium-42 based on falling serum concentrations indicate that magnesium and calcium leave the blood stream at almost equal rates. These rates are considerably slower than the rate at which potassium leaves the blood stream. It is not surprising that magnesium and calcium behave alike considering their chemical similarities. The relative concentrations of the three isotopes with the passage of time followed a definite pattern in all subjects, of which the data in Fig. 1 are characteristic. In reviewing the data it is pertinent to consider the size of the stable pool of mineral with which the isotope has exchanged.

The exchangeable mineral per kilogram of body weight at 18 hours following the injection of the isotopes is given in Table 1. The small size of the calcium pool has been interpreted[15] to be due to a very gradual exchange of the isotope with the relatively fixed calcium in bone. The value of 45 meq for potassium agrees with previous reports[16] and is in harmony with the total body potassium determined by direct analysis.[8] In contrast the value of 3.1 meq for the exchangeable magnesium is less than a fifth of the amount of stable magnesium known by direct analysis to exist in the soft tissues (see introduction). It is to be emphasized that 3.1 meq represents a *virtual* amount of magnesium with the necessary mass to produce the determined serum specific activity at equilibrium conditions. In so far as equilibrium conditions are *not* achieved and in so far as a portion of the magnesium-28 is picked up by the skeleton, an even smaller fraction than one-fifth of the soft tissue magnesium appears to be available for prompt exchange. Here we have a clear distinction between the intracellular magnesium and potassium in regard to exchangeability. It is tempting to explain the fixation of magnesium in the tissues by its double charge with the consequent possibilities for a more permanent chemical bonding. If subsequent studies demonstrate that magnesium is a rather fixed component of the tissues, it will confirm our impression that alcoholics and patients with cirrhosis do not have an altered mass of exchangeable magnesium.

Additional evidence for the minimal uptake of magnesium-28 by the soft tissues is seen in the four studies to determine the specific activity of skeletal muscle. At a time when serum and tissue specific activities are equal for radiopotassium, the specific activity of skeletal muscle for radiomagnesium is one-fourth that of the serum. Further tissue analyses are required to complete our understanding of the delayed distribution of magnesium-28 to other organs.

SUMMARY

A technique of studying the simultaneous distribution of magnesium-28, calcium-45 and potassium-42 is presented to clarify the physiologic role of magnesium. The rates of transfer of magnesium and calcium from the serum were found to be approximately equal. The minimum virtual mass of magnesium with which the isotope had exchanged at 18 hours was found to be only a small fraction of the stable soft-tissue magnesium. Direct measurements on skeletal muscle confirmed this interpretation. Intracellular magnesium, unlike potassium, is not available for prompt exchange.

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Autoradiography in Biology and Medicine

By P. J. Fitzgerald*

The availability of radioactive isotopes and progress in physics has led to the development of a technique of considerable promise to the biologist in his investigations of tissue and cellular metabolism. By this technique, isotopes may be localized to an organ, to part of an organ or even to individual cells. The radioactive object is placed against, or covered with, photographic emulsion and the rays or particles from the isotope produce an image of the radioactive area of the object in the emulsion. After photographic processing the emulsion areas containing the image produced by radioactivity may be examined visually or after magnification by the visible-light microscope. The method makes possible at the cellular level a correlation between the presence or absence of an isotope label and the normal or pathologic features of the object being studied. This complements the study of organ concentration of isotope by standard counting techniques where a population of cell types occurs. The processed photographic emulsion is called a radioautograph, an autoradiograph or, more conveniently, an autograph. The technique is reliable, simple and relatively inexpensive.

In one respect a radioautograph initiated the atomic era. It was Becquerel's accidental observation in 1896 that a fragment of uranium ore lying on a photographic plate caused darkening of the plate emulsion which led to the discovery of the natural radioactivity of uranium and its momentous sequelae.[1,2] Apparently the first application of radioautography in biology was in 1904 when London exposed a frog in a bottle to the emanations from radium, then placed the frog on photographic emulsion and obtained an image of the amphibian after processing the emulsion. The first autograph of artificial radioisotopes was made by Groven in 1938. Hamilton and his colleagues revived interest in the method in 1940 when they demonstrated I^{131} in the thyroid gland. Subsequent progress has been rapid, particularly with the development of nuclear track emulsions.

TECHNIQUES OF METHOD[3–5]

Track Autography

Individual alpha and beta particles and gamma rays produce tracks in photographic emulsions if the particle traverses an emulsion sensitive to its energy. An unstained histologic section of liver which had been removed at surgical operation from a patient with jaundice was covered with a thin strip of photographic emulsion, exposed and processed. The alpha-particle tracks are apparent as shown in Fig. 1 and come from thorotrast granules that were picked up by the liver 25 years before operation.[1] Figure 2 shows beta particles from a thyroid cancer in a patient who had been given radioactive iodine (I^{131}).[1] Gamma rays encountered in biology do not produce tracks. Up to now track autography has not been extensively used.

Topographical Autography

Autoradiography is usually employed to record only a fraction of the path of a few to thousands of tracks of particles, as illustrated by the thyroid gland which concentrates radioiodine in the colloid of its spherical follicles (see Fig. 3).

Emulsions

X-ray emulsions used in clinical roentgenology, lantern slide emulsion and, recently, the nuclear track emulsions of the physicist have been adapted to the method. X-ray emulsion may localize an isotope to a zone of approximately 25–50 microns, i.e., to an organ or to a group of cells. The nuclear track emulsions permit localization of an isotope to a zone of about 10–15 microns with most isotopes. By using thin strips of emulsion and carbon (C^{14}) or tritium (H^3) it is possible to obtain intracellular localization.[6] Even chromosomal differentiation has been achieved with tritium.[7]

Specimen Contiguity

A large specimen, e.g., bone, may be placed in a cassette against X-ray emulsion[3] and a good gross image of the radioactive area in the specimen obtained (see Fig. 4).

Histologic sections containing isotope may also be floated onto emulsion, both becoming bonded together so that after photographic processing the microscopist may focus on either the emulsion or the tissue (Fig. 5).

For cytologic studies a thin strip of film may be placed over a preparation of tissue culture cells, or over small organisms to achieve very fine localization (see Fig. 6).

Counting Procedures[2,8] and Sensitivity[9]

Alpha-particle track counting is fairly reliable and practical. Beta-particle counting is much less reliable

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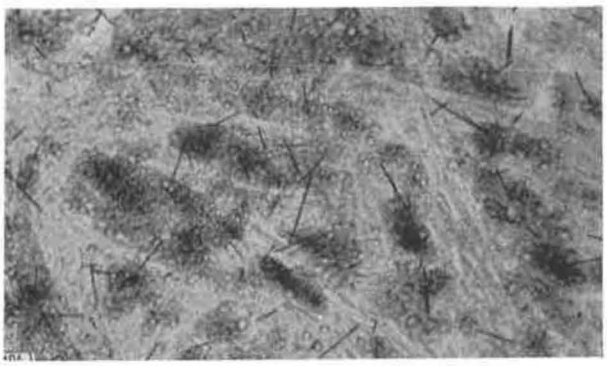

Figure 1. Autograph showing alpha-particle tracks (thin straight lines) from thorotrast granules in the liver; patient given thorotrast 25 years before

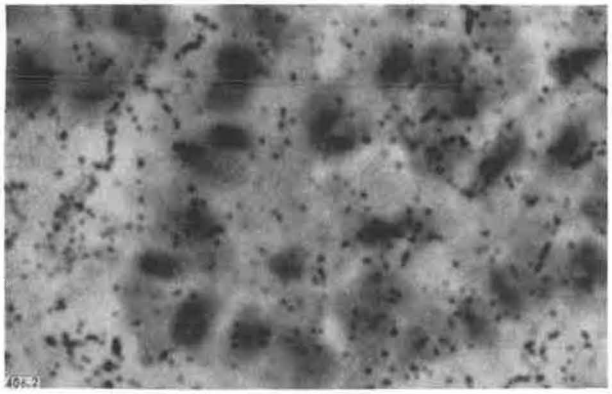

Figure 2. Autograph showing beta-particle tracks from an underlying thyroid cancer tissue (faint outline of tissue seen)

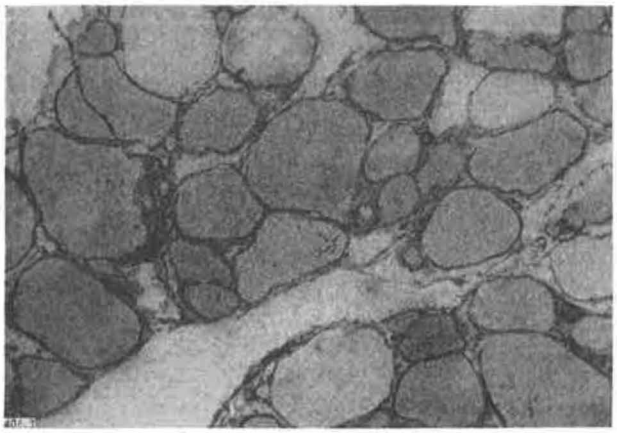

Figure 3. Normal thyroid gland autograph. Isotope concentrated in the spheres (follicles) containing radiocolloid; varying concentration from follicle to follicle

because of the randomness of the track. With many problems, densitometry has been employed after the emulsion response has been determined. Grain counting of cellular concentrations of isotopes has been extensively employed and is very reliable.[2,8]

The technique cannot be used with any high degree of sensitivity for very small amounts of radioactivity in large specimens. However, it may detect very small amounts of radioactivity in very small specimens. As

Figure 4. Bone autograph after I^{131} administration. Image probably reflects high blood concentration and bone vascularity

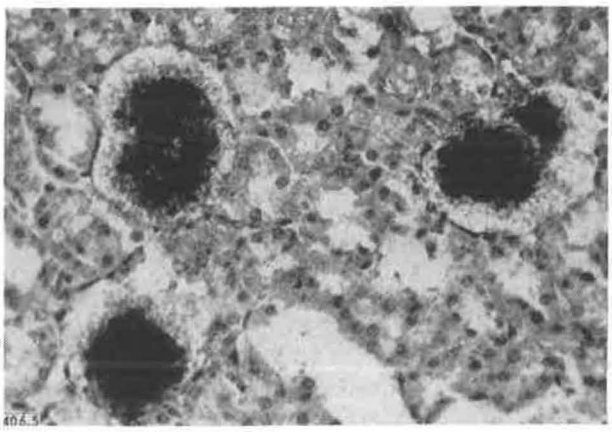

Figure 5. Autograph of mouse kidney with glomerular localization of a labeled antiglomerular antibody (S^{35})

little as 1×10^{-9} μc of carbon (C^{14}) per cell nucleus, or 1×10^{-17} g of polonium might be recognized by autography. It has been stated that as few as 50–100 atoms of phosphorus (P^{32}) or sulfur (S^{35}) might be discerned by autography. Many clinical autographic studies may be carried out with doses of I^{131}, P^{32} and other isotopes that are well tolerated by humans. The technique has been employed more extensively in animal studies.

APPLICATION OF METHOD

The following examples illustrate the ways in which autoradiography has been used.[1,2,4,5]

Diagnosis of Thyroid Diseases

We have studied 261 patients with thyroid disease as shown in Table 1. In the cases of thyroid cancer it was demonstrated that the concentration of radioiodine paralleled the amount of colloid present in the cancer—the more colloid formed the greater the amount of isotope concentrated. In no case did the

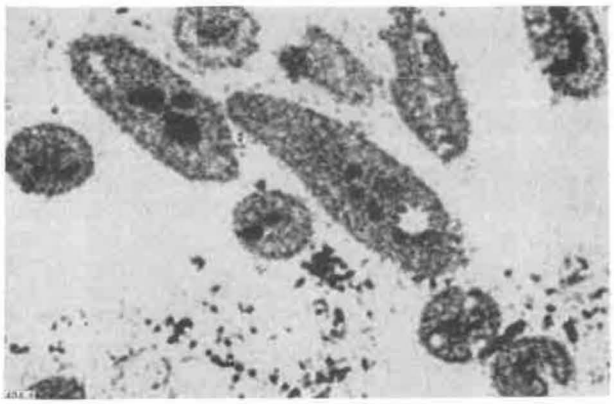

Figure 6. Autograph of thin sections of paramecia incubated in a medium containing tritium (H^3). Radioactive image of intracellular concentrations in nuclei, micro-nuclei, and in the extracellular bacteria appears as small black dots

thyroid cancer take up as much isotope as the normal thyroid tissue. This fact may be used clinically inasmuch as relatively inactive or "cold" nodules are more likely to be cancerous than the more radioactive or "hot" nodules and demand serious clinical attention. About three-fourths of the cases of one type of thyroid cancer—the follicular type seen in Fig. 7—showed concentration of the isotope and it is in this type of cancer that the best results from therapy might be anticipated.

Some nodules in the nodular type of goiter took up more radioiodine than the normal thyroid (Fig. 8), whereas other nodules showed less concentration.

Demonstration of Isotopes in Other Parts of the Body

Bone

Many heavy elements have been shown to concentrate in bone.[1] The tragedy of the radium watch dial painters has been recalled by recent autographs of the preserved bones of some of the victims who died 30 years ago. Radioactive calcium and strontium rapidly accumulated in growing bone and a similar concentration of strontium was noted at the periphery of an osteogenic sarcoma. Phosphorus in mice was deposited both in marrow and bone. Calcium, strontium and phorphorus all concentrate to a greater extent in the epiphysis of growing bones than in the diaphysis. The

Table 1. Concentration of I^{131} in Connection with Diseases of the Thyroid Demonstrated by Radioautography

Diagnosis	*No. cases*	*No. positive cases*	*% Positive*
Carcinoma	150	60	40
Nodular goiter	69	60	85
Chronic thyroiditis	13	12	92
Hyperthyroidism	12	12	100
Adenomas	9	9	100
Metastatic carcinomas	3	0	0
Aspiration biopsy	3	1	
Aberrant thyroid (lingual)	1	1	
Calcified thyroid nodule	1	1	
Total	261	156	60

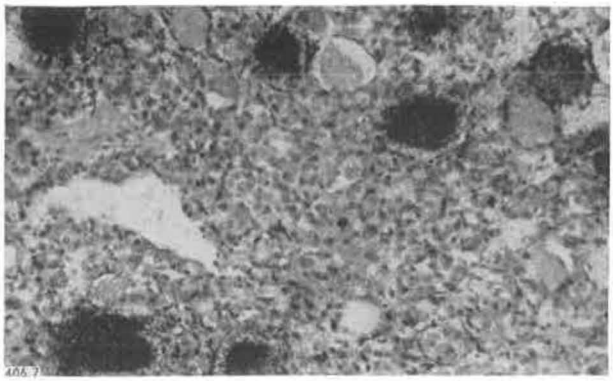

Figure 7. Autograph of thyroid cancer. Black areas indicate presence of I^{131} in some cancer tissue

production of osteogenic sarcomas in animals by feeding them Sr^{89}, Y^{91}, Ce^{144} and Pu^{239} has been accompanied by a demonstration of the isotope in the lesions by autography.

Thorium, uranium, polonium, lead, thallium, fission products and actinide elements have all been demonstrated in bone by autography. The long half-life of some of these isotopes subjected to such monumental retention poses serious problems in health protection.

Skin

Mustard gas labeled with S^{35} penetrated deeper into the dermis of human skin than did lewisite labeled with As^{74}. Thorium penetration in human skin has also been studied.

Brain

Radiocopper showed heavy concentration in the most anterior brain structures in the early embryo and later revealed accumulation in the eye and in the auditory and olfactory placodes. Potassium accumulated in the cerebral and cerebellar cortex, in the basal ganglia and roof of the fourth ventricle of rat brains.

Reticulo-endothelial System

Because of the phagocytic properties of the reticulo-endothelial system, many substances may be expected

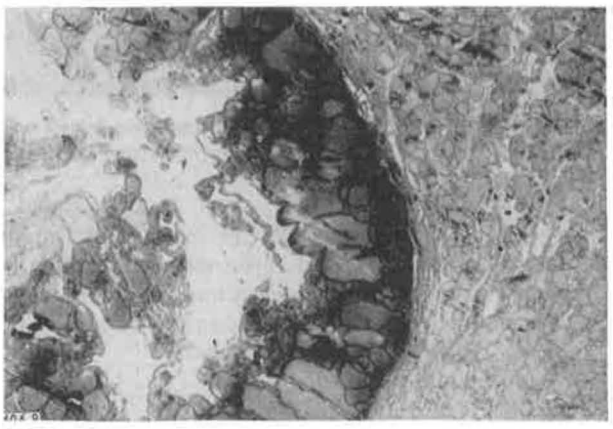

Figure 8. Nodular goiter with more I^{131} in the goiter (left) than in the normal thyroid tissue (right)

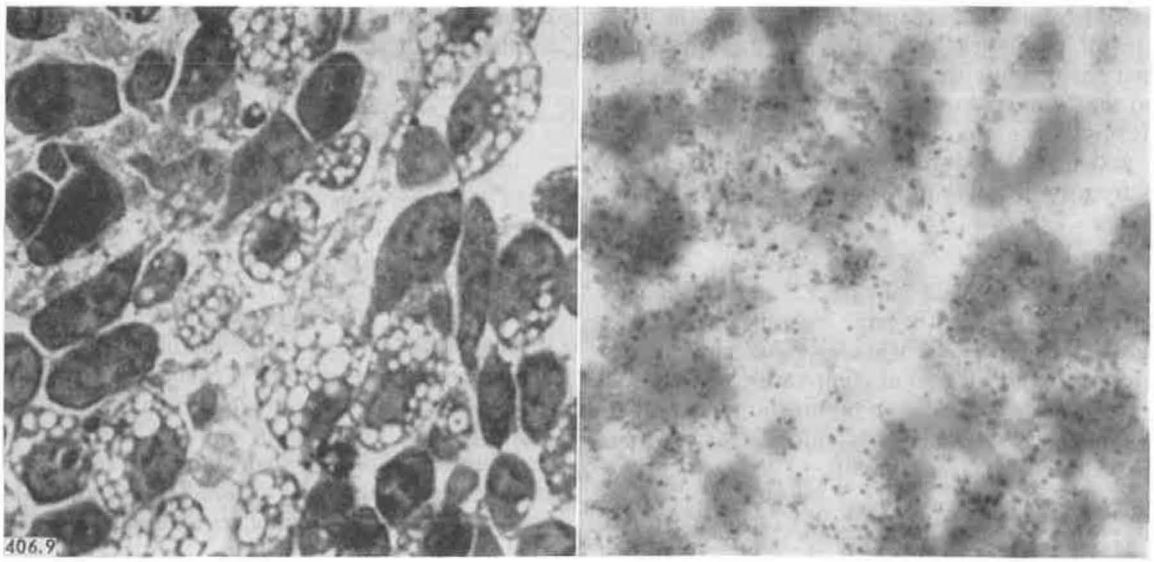

Figure 9. Left, sarcoma cells (180) in focus; right, the autograph with the reduced emulsion grains in focus. Emulsion grains indicate that radioactivity had been present in underlying sarcoma cells, some definitely in the nucleus, some in the cytoplasm. Cells grown in C^{14}-adenine

to concentrate in its cells, particularly if they are particulate or colloidal. Autography has shown that polonium, colloidal chromate phosphate, colloidal uranium, gold, thorotrast and many other substances accumulate in the system.

Blood and Bone Marrow

Individual peripheral blood cells and marrow cells picked up enough C^{14}, administered to rats as glycine, to give autographs of the individual cells. The youngest erythropoietic and granulopoietic marrow cells gave the most intense autographs with P^{32}.

Genito-urinary System

Autographs of human bladder and kidney stones using P^{32}, and corpora amylacea of the prostate after I^{131} injection have been recorded.

Immunology

Radioactive antibodies produced by a glomerular antigen are localized in glomeruli.

Endocrinology

Pituitary hormones labeled with I^{131} have consistently shown localization of the isotope in the proximal convoluted tubules of the kidney as well as in other organs. Prolactin has been found in the ovary. The maturation of spermatozoa in the mouse testis has been timed by radioautography.

Gastrointestinal Tract

The demonstration of P^{32} in radioautographs of the intestinal mucosa after histologic processing and ribonuclease digestion has led to the belief that the isotope was in the desoxyribonucleic acid fraction of the nuclei. Lead has been shown to concentrate in the glandular epithelium, and more so in the small intestine than elsewhere.

Tissue Culture

P^{32} has been demonstrated in the cytoplasm and nuclei of chick fibroblasts growing in tissue culture. We have demonstrated C^{14}-labeled adenine in sarcoma cells and in the basal cells of normal skin which was grown in the tissue culture containing the radioactive adenine. Adenine was intranuclear in some sarcoma cells (see Fig. 9).

Insects

I^{131} fed to larvae, pupae, and adult drosophila flies concentrated in the larval skeleton and tracheal trunks. Extraction studies suggested that the isotope was present in the protein of the chitinous portion of the skin. P^{32} was concentrated in the epithelium of the midintestine of the larvae and pupae of the wax moth, meal worm, cockroach, and firebrat.

Protozoa

Autography with paramecia demonstrated that C^{14}

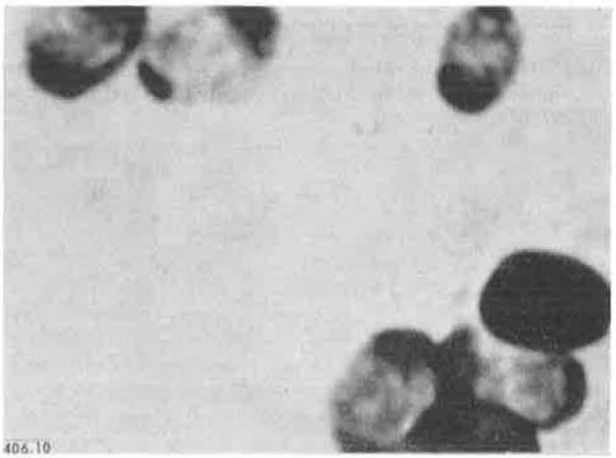

Figure 10. Yeast, *Torula utilis*, autograph. Yeast grown in medium containing tritium (H^3)

originally given to algae appeared early in the food vacuoles of paramecia and later was uniformly distributed throughout the organism. We have demonstrated that some paramecia absorbed C^{14}-labeled glycine, formate, acetate, nucleic acid precursors, methionine and S^{35}-labeled methionine. P^{32} beta-particle tracks from radioactive protozoa have been counted.

Bacteria and Fungi

Fungi and bacteria labeled with P^{32} and I^{131} showed by autography that pathogenic organisms remained in dogs for long periods, whereas the nonpathogens could not be demonstrated at comparable periods. We have grown *Torula utilis* in a medium containing tritium (H^3) and demonstrated cytoplasmic incorporation of the isotope (see Fig. 10).

Plants

Tomato plants grown with the roots submerged in nutrient solutions containing P^{32} revealed that young plants absorbed more isotope than older ones and concentrated more isotope in the seed and pulp of the fruit. S^{35} was localized in the leaf and kernel, regions of high protein content, of spring wheat plants.

Other Uses of Autography

Autography has been used in studies of protein metabolism, immunity, phosphorus metabolism, paper chromatography, membrane permeability, and in the localization of krypton, tellurium, sulfur, iron, hafnium, beryllium, cobalt and other elements.

TRITIUM AUTOGRAPHY

In 1951 we suggested the use of tritium (H^3) for intracellular localization of labeled compounds and demonstrated its use with paramecium and yeast (see Figs. 6 and 10). Recently Taylor *et al.* have shown with tritium-labeled thymidine that there is chromosomal incorporation of the isotope in the desoxyribonucleic acid of bean root seedlings.[7] From their autographs the authors draw important conclusions concerning mitotic division, replication, and the structure of this very important nucleic acid. The use of similar tritium-labeled compounds and autoradiography should give rise to significant, possibly revolutionary, data in the field of cellular metabolism.

SUMMARY

A survey of the autoradiographic technique and its applications is given. It is pointed out that cellular function may be studied by this method as a supplement to the organ concentration of standard counting techniques. The merits of intracellular and even intrachromosomal localization of tritium-labeled compounds in such studies are emphasized.

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Total and Partial Body Radioactivity Measurements for Metabolic Tracer Studies*

By G. J. Hine and B. A. Burrows

The metabolic behaviour of radioactive elements and compounds in man has been studied chiefly by measuring the radioactivity of biological samples, such as serum or other body fluid, tissue or excreta. The turnover rate of I^{131} in the thyroid gland has been determined routinely by an external counting system. Recently, attempts have been made to study the accumulation and discharge of radioactive elements (Fe^{59} and Cr^{51}) or tagged compounds (I^{131}–rose bengal, I^{131}–Diodrast) by spleen, liver or kidney using external counting procedures.

If the radioactivity is not concentrated in a single organ, it becomes difficult to determine the exchange rates in the various body compartments. Recently, large sodium iodide crystals and multichannel analyzers which allow an accurate measurement of the body radioactivity have become available. The exchange rates of the various body compartments, however, will differ considerably from that of the body as a whole, especially during the first twenty-four hours after the administration of a tracer dose. Smaller sodium iodide counters may be placed at various body sites to compare their counting rates with that of the body.

The combination of total and partial body counting appears to be useful for equilibration studies. Some details concerning the experimental methods and a few early results are given.

COUNTING SYSTEM

Several methods have been described recently for body radioactivity measurements.[1] Of these, the technique of Marinelli using a large single sodium iodide crystal appeared promising for clinical tracer studies. Although the problem of reducing the background counting rate to an absolute minimum is of the greatest importance for the measurement of the natural body radioactivity in human subjects, for clinical tracer studies employing doses from a few to several hundred microcuries, the reduction of the background to a useful level is a minor problem. In constructing a body counter our main concern has been to build a flexible device which can be used for total as well as partial body counting (see Fig. 1). Instead of enclosing patient and scintillation counter in an iron room,[2] the sodium iodide crystal is shielded by 5 inches of steel on all sides except the one facing the patient. This reduces the background counting rate of the 4×4 inch NaI (Tl) crystal from 40,000 counts per minute (above 70 kev) for the unshielded crystal to 4000 counts per minute for the crystal in the iron shield. The background would be further reduced to less than 1000 counts per minute if the patient were placed in a bathtub-shaped iron shield. However, as mentioned above, for our clinical tracer studies such a shield is not required.

The mounting of the 1200-pound shield is shown in Fig. 1. By motor drive it can be raised and lowered or moved from right to left, and the whole unit runs back and forth on tracks (not shown in the figure). Finally, the steel shield rotates around an horizontal axis so that it can be directed at any angle. For body counting the patient is seated comfortably in a "contour" chair (Fig. 2) and the axis of the sodium iodide crystal is positioned vertically. The front face of the crystal is placed at 50 cm from the midline of the patient.

For the body measurements the pulses from the large sodium iodide crystal are counted as a function of their pulse height with a RCL 256-channel pulse height analyzer. The ratio of the scattered to the unabsorbed γ rays depends on the patient's size and weight and varies with the distribution of the radioisotope throughout the body. Therefore, by recording the pulse energy spectrum these factors can be taken into consideration. At present, the photoelectric peak corresponding to the high energy γ rays emitted from the administered radioisotope is taken as a measure of the body radioactivity.

In addition to this large sodium iodide crystal, several smaller (2×2 in.) crystals are used to measure simultaneously the turnover rates at a few selected body sites. These counters are well shielded and set up in such a way that they receive little radiation from other parts of the body. (A counter on which the patient's heel is resting is shown in Fig. 2.) Finally, these counters are made insensitive to scattered radiation by counting only pulses above a selected discriminator level.

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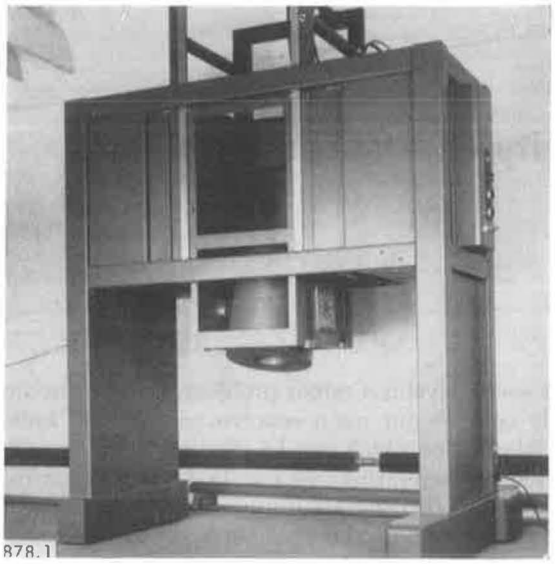

Figure 1. Body counter

Figure 2. Patient positioned beneath body counter, heel resting on small scintillation counter, the lead shielding of which is partially removed. Counter for head counts is not shown

TRACER STUDIES

For the first application of the counting techniques described above, a study of body electrolytes seemed to be of interest. As shown in Table 1, no difference between "exchangeable" body sodium and potassium in a group of normal subjects and in a similar group of patients with essential hypertension could be detected, although there was a marked increase in body sodium content in patients with cardiac failure. Even though the total body sodium and potassium may not be significantly changed in a chronic disease such as hypertension, it is still conceivable that the amounts or the exchange of the electrolytes in different body compartments may be altered.

The radioisotopes of sodium and potassium (Na^{24} and K^{42}) are suitable for studies which require *in vivo* counting. Due to their short half-lives (15.0 and 12.4 hours respectively), amounts up to 150 μc can be given without exceeding the weekly permissible dose. Both radioisotopes emit rather energetic γ rays (1.38, 2.76 and 1.51 Mev), therefore their absorption in the body is minimal.

Although in the study the counting was continued at different intervals for 60 hours following the intravenous injection of the tracer dose, the curves for the first 6 hours only are shown in Fig. 3. All data have been corrected for the physical decay of the radioisotopes. Examples of the information which can be obtained from such measurements are discussed below.

Table 1. "Exchangeable" Body Sodium and Potassium

	No. of cases	Na^{24} *meq/kg*[a]	K^{42} *meq/kg*[a]
Normal subjects	30	38.5	40.2
Essential hypertension	20	37.8	37.0
Cardiac failure without peripheral edema	15	51.8	35.9
Hyperadrenalism	4	35.9	23.9

[a] Oral tracer doses of Na^{24} and K^{42} were administered 18–24 hours before serum and urine samples were obtained for determination of the isotope dilution. The Na^{24} and K^{42} content of each sample was determined by a multiple counting method.[3]

Body Counts

The counting rate of the body counter described above depends on two factors: (*a*) the fraction of the administered dose retained by the body and (*b*) the actual distribution of the radioisotope within the body. In the case of radiosodium and radiopotassium only a small percentage of the dose is excreted during the first 24 hours. For the normal subject whose body radiosodium counts are shown in Fig. 3, the urinary radiosodium excretion was 3% of the dose during the first 6 hours and 7% for the first 24 hours. His body counts however, had dropped to 79% within 6 hours and to 71% within 24 hours.

Immediately after the injections of the tracer dose a spectral pulse distribution is obtained within two minutes, and the observed intensity of the high-energy γ-ray line is plotted as 100%. Since the 4 × 4-inch sodium iodide crystal is positioned directly above the patient's abdomen its efficiency for counting radioactivity in the head or legs is considerably less than that for the trunk. Therefore, before the tracer dose has been completely distributed throughout all body compartments, the body counts decrease more rapidly than the body radiosodium retention curve obtained from urinary excretion. According to our measurements about 8 hours are required for the radiosodium activity over the patient's heel to reach a flat maximum, and the radiosodium counts from the patient's head increase for about 30 hours. It takes several days for the exchange of radiosodium in the bones to reach equilibrium.[4] The body radiopotassium counts also decrease more rapidly than can be accounted for by urinary excretion during the first 8 to 10 hours. After this period the body radiopotassium counts decrease by only 3% per day, in good agreement with the

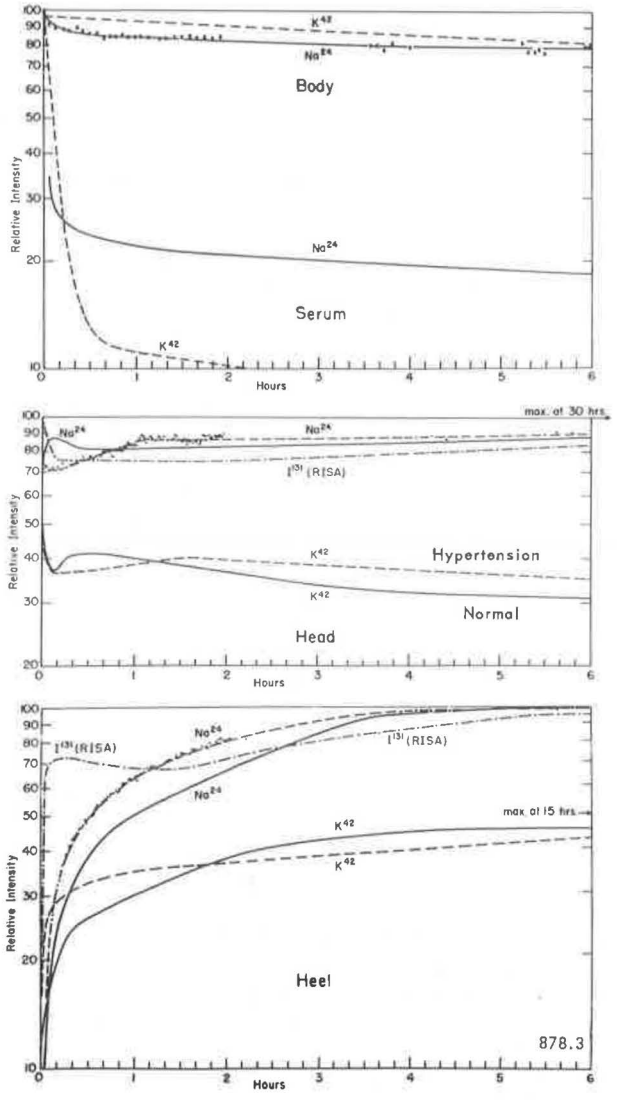

Figure 3. Examples of body, serum, head and heel counting rates during the first six hours after administration of a tracer dose. At the right hand margin the times when the Na^{24} counts in the head and the K^{42} counts in the heel reach a maximum are indicated. The counting rates have been normalized where they reach a maximum. The actual measurements are indicated only on three curves

urinary excretion rate. The body radiopotassium reaches equilibrium in less than half a day; radiosodium requires more than 3 days.

In summary, with our single crystal set-up two kinds of information can be obtained: (*a*) the rate of exchange between different body compartments and (*b*) the per cent body retention after completion of the mixing phase. The second type of information will be of value especially in the case of long-life radioisotopes, such as Na^{22}, Fe^{59}, Co^{60}–labeled vitamin B_{12}, and Cs^{137}. Body retention can then be followed for several months, whereas urinary collections over long periods of time are always questionable.

Head Counts

The rates of uptake of radioactive sodium, potassium, chlorine, bromine, and iodine in the hand of a fasting subject were measured by Hamilton twenty years ago. Since then a variety of measurements have been made of different body sites. The exchange of radiosodium in the foot has been given special attention. However, we have no knowledge of any reports of measurements of the exchange rates of any radioisotope in the human head. The foot and the head are sites which can be investigated without much interference from the radioactivity in the patient's body. While the body counts are being obtained, foot and head counts can be taken individually and blood samples can be drawn from a vein in the patient's arm.

A sodium iodide crystal is placed at about 5 inches behind the patient's head, well shielded and collimated by lead bricks (not shown in Fig. 2). The results obtained with this head counter were checked with a second shielded sodium iodide crystal placed in close contact with the patient's temple for the Na^{24} studies. Though the counting rate near the temple was much higher, the relative changes of the two counting rates with time were found to be in excellent agreement, showing that the radiosodium turnover rates in the head can be accurately observed with the counter in either position.

Two examples for the Na^{24} and K^{42} exchange rates in the head are given in Fig. 3. The solid line curves are those for a normal subject and the dashed curves for a patient with progressive severe hypertension. The Na^{24} and K^{42} data were taken on the same individual in two successive weeks. In addition, the head counting rate after the intravenous injection of I^{131}-labeled human serum albumin (RISA) and the Na^{24} and K^{42} serum radioactivity curves for the normal subject are shown.

If K^{42} or RISA are given, the counting rate observed from the head has its highest value in the first minute. In the case of RISA the counting rate decreases rapidly during the first half hour and after that it stays practically constant for 24 hours, showing that the initial mixing phase is completed in about half an hour. After K^{42} administrations there is also an initial decrease in counting rate. During the first 10 minutes the counting rate from the head drops to about 75% of its first-minute value; during the same time the serum radiopotassium decreases to about 30% of its initial level. This shows that the radiopotassium clears the serum rather rapidly as it is taken up by the tissues. The head counts show a subsequent rise for half an hour (about 2 hours for the hypertensive), and this early uptake phase seems to be completed in a rather short time.

In the case of Na^{24} the situation is somewhat different. The serum level does not drop as rapidly as that of radiopotassium, and for the hypertensive it decreases by only 15% during the first 6 hours (not shown in Fig. 3). While the serum radioactivity decreases, the head counts increase for about 30 hours, indicating that the radiosodium uptake in tissues and other compartments is a slow one. Besides this slow radiosodium uptake there seems to be a fast early uptake phase. The counting rate from the heads of nor-

mal individuals increases by about 15–25% during the first 8–10 minutes, though the serum radioactivity decreases by about 30% during that time. In the case of the hypertensives, this early uptake phase seems to be considerably delayed. The head counts are either constant or decrease during the first 10–30 minutes and then increase rather slowly (Fig. 3, "dashed" head curve for Na^{24}).

In summary it may be stated that counting of the head seems to be of considerable interest for studying distribution rates. Much more information must be collected on normal subjects and patients with a variety of diseases, such as hypertension, cardiac failure, hyperadrenalism, etc.

Heel Counts

As shown in Fig. 2, the patient's heel rests on a shielded sodium iodide counter. Since the foot is rather inflexible the counting geometry is constant and reproducible. Though the heel is in close contact with the counter, a certain fraction of the counts results from the radioactivity in foot and ankle. The change in counting rate over the heel when either Na^{24}, K^{42} or RISA were administered to a normal subject is given in Fig. 3.

The I^{131} radioactivity over the heel increases rather rapidly within the first 10 minutes while the head counts decrease, perhaps a reflection of the blood supply in the head as compared with that of the foot. After completion of the initial mixing of the RISA there is a marked decrease of the heel counts for about one hour before the start of a 30% rise during the next several hours.

The K^{42} heel counts also increase rather rapidly for the first 10–20 minutes, while the K^{42} serum level drops markedly during this time. After this initial fast uptake, the rate of uptake decreases and a flat maximum is reached within 8–14 hours. When Na^{24} is administered, the initial increase of the heel counts is somewhat slower than for K^{42}, whereas the Na^{24} serum level decreases less rapidly. This shows again that the radiopotassium is more rapidly incorporated in the tissues than radiosodium.

The marked difference between the Na^{24} uptake in the head for the first 1–2 hours in normals and hypertensives was not observed in the heel curves (dashed Na^{24} and K^{42} heel curves), probably because the initial uptake at this site is rather slow in any case.

No detailed information can be expected from measurements of radioactivity over the patient's heel because the initial mixing phase and the early tissue uptake cannot readily be separated. However, heel counts might be useful for the study of tissue retention over longer periods.

CONCLUSION

By counting the radioactivity from an injected tracer dose in the patient's body, head and foot, the exchange rates between different body compartments can be estimated. This method gives more information than can be obtained from serum samples and urine collections alone. The rapid changes occurring during the first few hours after the administration of the tracer dose can be followed in detail. Certain differences of the exchange rates in normal subjects and patients with essential hypertension become apparent from the head radiosodium measurements. Observations during the first two hours seem to be of particular value, and measurements can be repeated within a few days interval to investigate the effect of therapy on these exchange rates.

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Study of Radioactive Phosphorus (P^{32}) Distribution in Man by External Bremsstrahlung Measurements

By M. Tubiana, P. Albarede and H. Nahum*

Investigations of the distribution and metabolism of radioactive phosphorus in the human or animal organism have already proved of great value. Practical methods of investigation, however, have been limited by the characteristics of P^{32} which, when it decays, emits only beta particles with a maximum energy of 1.7 Mev, and a penetrating power in tissues of 8 mm at most (average, 1.4 mm). Despite the fact that these trajectories are very short, external detection methods have been used to locate their hyperconcentration in superficial tumors (skin[1] and breast[2]). Such methods, however, are not practical for deep-seated tumors, because when measurements are made in a medium in which P^{32} is uniformly distributed, more than 50% of the beta rays that reach the detector come from phosphorus located in the 1 mm thick superficial layer.[3] For these reasons it seemed important to study the potentialities of techniques based on detection of bremsstrahlung.

PRINCIPLES

Emission and slowing down of beta particles in matter cause the formation of electromagnetic radiation. The origin of this radiation is twofold: (1) an "internal" bremsstrahlung that accompanies ejection of the beta particle from the atom.[4,5] and (2) an "external" bremsstrahlung produced by the slowing down of the beta particle in the electrical field of the nuclei close to which the trajectory of the particle passes.[6] The intensity of internal bremsstrahlung at the beginning is independent of the atomic composition of the surrounding medium; the energy spectrum is continuous, and in the case of P^{32}, is rather closely similar to that of the external bremsstrahlung. The intensity of external bremsstrahlung, on the other hand, is proportional to the atomic number Z of atoms of the medium and to the square of the kinetic energy of the electrons, but the energy spectrum of photons is almost totally independent of the atomic composition of the medium.

When P^{32} is distributed in carbon or water, the number of photons emitted with an energy greater than 50 kev is about 2 photons for every 100 disintegrations and all the photons carry approximately 0.5% of the energy of the beta particles.

APPARATUS FOR MEASURING

We used a scintillation counter made of a sodium iodide crystal, a Dumont 6292 photomultiplier, a linear amplifier passing a 2-megacycle band and having a gain of 25, and an amplitude selector with a 2-v or 5-v channel which could be used also as a single-threshold discriminator and pulse numerator. The pulse amplitude was calibrated in energy units using the gamma rays emitted by Tm^{170}, Ce^{144}, Hg^{203} and I^{131} as well as the X rays emitted by leaves of Au, Pb, W and U excited by an electron beam. The crystal was surrounded by a lead collimator 5 cm thick with a cylindrical opening 5 cm in diameter and the source consisted of a few mm^3 of a concentrated solution of P^{32} sealed in the center of a plexiglass sphere with a radius of 1 cm.

STUDIES ON MEASURING CONDITIONS

Spectral Distribution of Pulse Energy

The pulse spectrum recovered at the photomultiplier outlet has been investigated with a 2-v channel:

(*a*) When the source was in the open air, theoretically and according to the results obtained by other workers (Liden, Kellershohn, Tubiana), the number of pulses decreases rapidly as a function of the energy (Fig. 1, Curve 1A). The spectrum has been investigated with two crystals mounted serially in the same photomultiplier. One was 3.7 cm in thickness and 3.7 cm in diameter, the second 2.5 cm thick and 3 cm in diameter. The number of pulses collected with the first (Fig. 1, Curve 1A) is greater than with the second (Curve 1B), particularly in the field of the higher energies. The number of pulses measured was under 35% when the threshold of the selector was 3 v; under 42% when it was 9 v; and less than 50% when 20 v. These three thresholds correspond to energies of about 80 kev, 125 kev, and 280 kev.

(*b*) Since the source in a diffusing volume was surrounded in all directions except that of the detector by a medium having a specific gravity of one (water and plexiglass—inset Diagram A), the diffuse photons created at the outlet resulted in an increase in the

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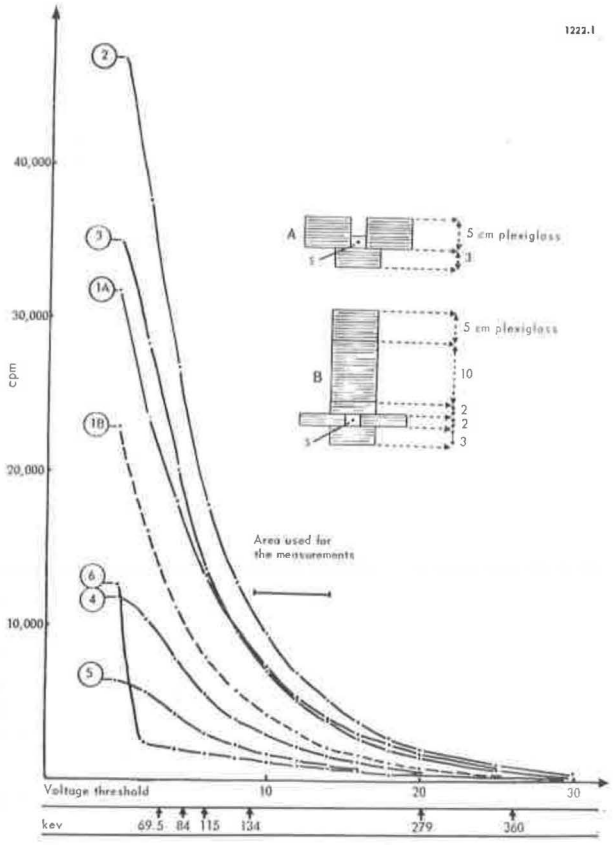

Figure 1. Spectra obtained with a 2-v channel, showing counts per minute (cpm) relative to selector voltage threshold, arrows indicating corresponding energies (kev) obtained by calibration with monoenergetic sources of X rays or gamma rays; Curve 1-A was obtained when the radiation source (S) was in open air (inset Diagram A) using a crystal 3.7 cm thick and 3.7 cm in diameter; Curve 1-B the same except using a crystal 2.5 cm in thickness and 3 cm in diameter; Curves 2 through 5 were obtained with the source in a diffusing medium and with differing thicknesses of plexiglass above the source (inset Diagram B); Curve 2: none; Curve 3: 2 cm; Curve 4: 10 cm; and Curve 5: 15 cm. Curve 6 was obtained for natural background (× 10)

number of low-energy pulses (Curve 2). The number of pulses thus increases by 50% for a 3-v threshold, 32% for 9-v, and 10% for a 20-v threshold.

(*c*) If one places above the source—the source–crystal distance remaining constant—increasing thicknesses of plexiglass or of water (inset Diagram B), there is both an increase in diffuse radiation and an increase in filtration of the direct radiation caused by a growing thickness of water or plexiglass. This appears to be the reason why the spectral distribution following filtration through 8 or 10 cm of water or plexiglass, is not very different from that found with a small source in the open air.

Measurement of Pulses

A 5-cm-thick lead collimator with a canal 1 cm in diameter defines a narrow beam whose attenuation curve was to be studied. By measuring all the pulses, regardless of their energies (threshold–discriminator position at 0), we found that they could be broken down, with copper filtration, into several components. The first corresponds to a radiation with an attenuation coefficient of 1.2 cm^2/g, and a mean energy of about 70 kev. By measuring only pulses of amplitudes ranging from 2.5 to 7.50 v, the attenuation coefficient for the first component was 0.31 cm^2/g in copper, and 0.150 cm^2/g in aluminum, corresponding to photons with an energy of 120 kev. When measuring amplitude pulses between 9 v and 14 v (the measuring condition in man), the attenuation coefficient in copper is 0.16 cm^2/g (HVL = 4.7 mm Cu), corresponding to photons with an energy of about 200 kev.

The difference in anatomical composition of bone and soft tissues modifies slightly the bremsstrahlung emission. When P^{32} is located in a medium equivalent to bone the number of pulses counted, using a 2-v channel, is greater by 12.5% for a zero threshold, 5% greater for a 5 v threshold and less than 1% greater for a 9-v threshold.

The choice of practical measuring conditions must rest on several considerations. Statistically, it is advantageous when the ratio R_s/R_{mp}, the number of pulses due to the source (R_s) to the number of pulses due to the background (R_{mp}), is as large as possible. The number of pulses due to the background decreases rapidly when the threshold advances from 0 to 5 v, and then continues to fall at a slower rate. The R_s^2/R_{mp} ratio, which is a criterion of statistical quality of the counter,[7] is maximum for a 2-v threshold, and decreases rapidly thereafter by a factor of 5 between 2 and 10 v, and by a factor of 10 between 10 and 20 v.

It is important to find conditions for which the influence of scattering and attenuation by filtration is in minimum. The requirements, however, are contradictory and it seemed preferable to measure a fairly high-energy radiation using a rather high threshold and a 5-v channel. (With a 5-v threshold, passing from a channel of 2 v to one of 5 v, the number of pulses goes from 144 to 283 and the ratio from 4.9 to 8). It seemed preferable also to use a thick crystal. A 5-v channel with a 5-v threshold can then be selected for measuring since under these conditions, 6000 cpm/mc P^{32} with a background level of 105 are registered. With the same geometric and electronic conditions, 75,000 cpm/mc I^{131} are counted.

Phantom Measurements

The conditions for measuring radiation from internal sources in man are obviously different from artificial conditions, particularly since phosphorus is diffusely distributed in the organism with areas of hyper- and hypo-concentration. The conditions in man however can be simulated for experimental purposes using a vessel filled with 20 liters of a slightly radioactive solution, in which one or several ampoules containing a more concentrated solution are arranged. To assess the existence and importance of hyper concentration zones, it is necessary to determine the conditions in which the number of pulses due to the whole arrangement is lowest, and at the same time the conditions for which the number of pulses due to the most active source is greatest. The requirements raise several problems.

In particular, beta particles that come from the most superficial layers of the solution must be eliminated. This of course could be done by deflecting the particles with an intense magnetic field, but this technique would disturb operation of the photomultiplier which is very sensitive to the existence of such a field. As already indicated, the beta particles may also be eliminated by stopping them with a plexiglass filter. Such a filter can be arranged so that it is in contact with the crystal, with the opening of the collimator, or with the surface of the vessel. Table 1 below shows the ratio K (the apparent activity of a source placed about 5 cm deep in a vessel full of water and the activity measured when the vessel is full of a P^{32} solution) for these three arrangements.

Table 1. K when Beta Particles Are Eliminated by Filter Placed in Different Locations

Filter thickness	*Surface of vessel*	*Opening of collimator*	*Lower face of crystal*
5 mm	2	1.92	1.92
10 mm	2.04	1.86	1.92

The ratio is most favorable when a 10-mm thick filter is in contact at the surface of the vessel for then the smallest possible proportion of bremsstrahlung caused by the beta particles in the filter actually reaches the detector. However, the advantage derived when compared with results obtained with the other two positions, is not great.

The spectrum was analyzed again for three conditions (see Fig. 2): (*a*) a vessel filled with radioactive solution (Curve a), (*b*) an ampoule filled with a more concentrated solution but placed outside the field of vision of the crystal (Curve b), and (*c*) the ampoule placed in the axis of the collimator at a depth of 5 cm in the vessel (Curve c). These positions are shown in the inset diagram (Fig. 2).

The results obtained are similar to those of Kellershohn.[8] They show that the spectral intensity passes through a maximum, which is doubtless related to degree of auto-absorption of the lowest energy radiation. In addition, there is very substantial scattering, as shown by Curve b and by comparing the three curves with that obtained when the source is in the open air (Curve d), in which the role of auto-absorption is much less.

In order to determine the optimum counting conditions in such cases, it was necessary to consider the pulses due to the whole of the vessel (Curve a) as the background (R_{mp}), and the difference between Curve c and Curve a for each point of the spectrum as the activity of source R_s. The ratio R_s^2/R_{mp} goes through a maximum for a threshold located at 4 volts, then decreases rapidly. If we call the maximum value 100%, it drops to 45% for 9 v, 21% for 14 v and 7.5% for 20 v.

Therefore, from a purely statistical viewpoint, it was of interest to carry out measurements between 4 and

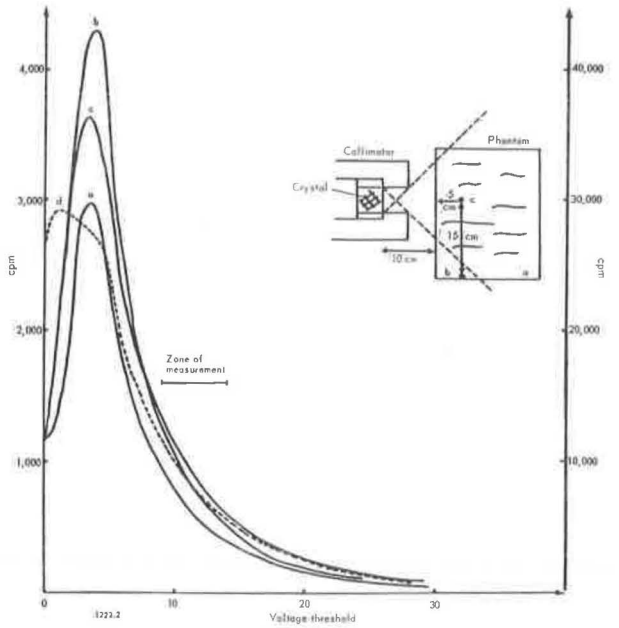

Figure 2. Spectra obtained with a 2-v channel, showing counts per minute (cpm) relative to selector voltage threshold. Curve *a* obtained when vessel was filled with radioactive solution only; Curve *b* same as (a) but including an ampoule with more concentrated radioactive solution in the field of "vision" of the crystal; Curve *c* same as (a) but with the ampoule in the axis of the collimator; and Curve *d* with the ampoule in open air; electrical characteristics: operating voltage 1700, gain 100, megacycle band 2, threshold 0 to 30; I^{131}: threshold 26 v, selector channel 1 v

9 v, but this is a range in which auto-absorption and scattering are important factors. The additional radiation due to scattering (Curve b) was found to be 50% at 5 v, 33% at 8 v and 25% at 10 v. For this reason it seemed preferable to us to use the relatively high threshold of 9 v.

The role of the lead collimator is very important because it stops radiations which come from regions other than those being studied. We have compared the results obtained with the crystal in two positions in the same collimator. The greater the distance between the collimator opening and the lower surface of the crystal, the smaller is the vessel volume "seen" by the crystal. The greater distance reduces the apparent activity of the vessel. Values of the ratio of source activity (i.e., total activity minus vessel activity) to vessel activity (Fig. 3) is more favorable when $d = 10$ cm than when $d = 5$ cm. Results stress the fact that good collimation increases the precision of measurements.

The number of pulses was counted when an ampoule filled with 2 mc of solution was in the axis of the collimator or more than 10 cm outside it. With a crystal–surface distance of 10 cm, the quantity of P^{32} that must be contained in the ampoule in order that the number of pulses counted when the ampoule is in the axis of the collimator be greater by 25% than the number counted when the ampoule is placed more than 10 cm outside the axis is shown in Table 2.

From these results we calculate that for the activity to be higher by 25% when an ampoule with a volume of 50 cc is placed in the vessel in the axis of the

Table 2. Amount of Radioactivity the Concentrated Source Must Contain

	Cm depth of source (in axis of collimator)				
	2	*6*	*10*	*14*	*20*
Ml of the diluted solution equivalent	120	250	600	1250	2500

collimator, the ratio of concentration of solution in the ampoule and vessel respectively should increase from 2.5 for a depth of 2 cm to 50 for a depth of 20 cm. With a 10-ml ampoule, this ratio should increase from 12 to 250 for the same increase of depth.

To verify these results, measurements were made using 3 ampoules: (*a*) one of 120 ml filled with a solution four times more concentrated than that used for the vessel; (*b*) the second of 10 ml filled with a solution 10 times more concentrated than that of the vessel, and (*c*) a third of 50 ml with a concentration twice that of the vessel. The results of these measurements (Fig. 4) showed that to obtain a difference of 25%, still higher concentrations than those employed must be used. This appears to be due to the fact that the larger the size of the source, the less satisfactory are the geometric conditions of the measurements and the efficiency of the source.

The various results suggest that in the human organism where the ratio of concentrations rarely exceeds a factor of 5, differences are revealed only if tumors are relatively shallow. However, even in these cases, the measurements must be lengthy if they are to be significant, and the area being investigated must be compared with a presumably healthy symmetrical one. The theoretical possibilities of these methods of measurement, therefore, are limited. They can be increased only by raising instrument sensitivity and reducing background radiation. The use of long measuring periods (10 minutes at least), of stable counters detecting a low natural background, and of good collimation are the conditions needed for obtaining results that can be interpreted meaningfully by counting *in vivo*.

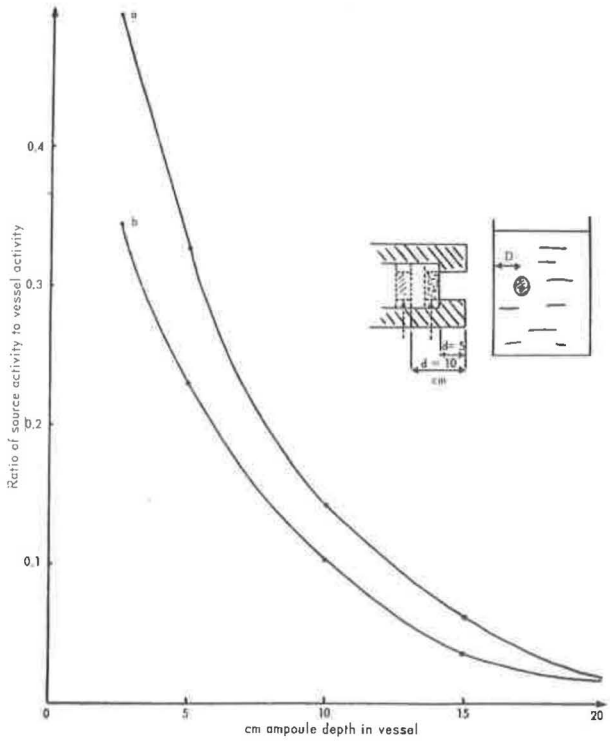

Figure 3. Ratio of the source activity to vessel activity as a function of ampoule depth in the vessel; Curve *a*, surface of the crystal 10 cm from the collimator opening, and Curve *b* 5 cm; electrical characteristics: operating voltage 1700, gain 100, megacycle band 2; selector threshold 9 v, selector channel 5; I^{131}: threshold 26 v, selector channel 1; filter: 1 cm plexiglass

Measurements in Man

Since 1957, thirty-three subjects have been investigated and classified according to their clinical condition.

Radioactive phosphorus was injected intravenously in the form of a sterile solution of sodium radiophosphate. Prior to administration, landmarks were drawn on the patient's skin over the areas of the liver, spleen, sacrum and all other areas that might be studied. The first measurements were made at these various levels a few minutes after the injection of P^{32}

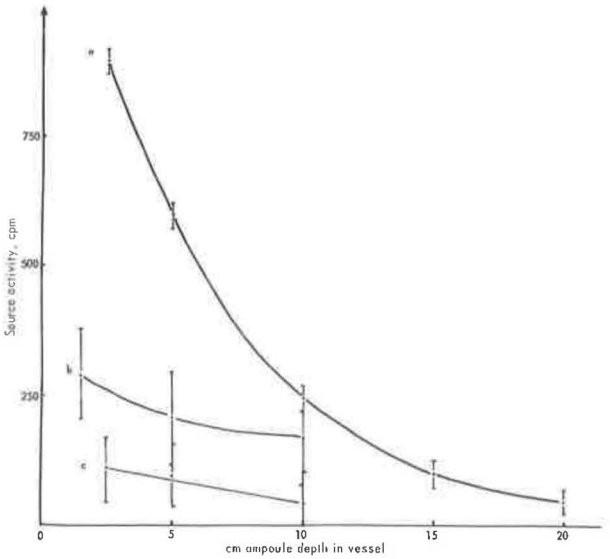

Figure 4. Source activity (total activity minus vessel activity) as a function of ampoule depth in the vessel (vessel activity alone, with distance from the surface of the crystal to collimator opening 5 cm, was 2600 cpm, with background 2753 additional); Curve *a*, 120 ml ampoule, concentration × 4; Curve *b*, 10 ml ampoule, concentration × 10; and Curve *c* 50 ml ampoule, concentration × 2; electrical conditions: operating voltage 1700, gain 100, megacycle band 2, threshold 9 v, selector channel 5; I^{131}: threshold 26 v, selector channel 1; filter: 1 cm plexiglass

and then at 4, 6 and 24 hours, and thereafter daily for one week. The scintillation counter, described above, was installed on a radiology-type tripod equipped with a luminous centering device. Distance from the lower face of the crystal to the skin was 10 cm. Measurements were reproducible within $\pm 5\%$ and prior to each measurement, the spectrum was recalibrated. The natural background and a standard sample were measured.

A fixed amount (200 mc) of P^{32}, producing a uniform distribution of P^{32} corresponding to an anion dose of 3 r in the body, was used for injecting.

Breast Cancer

Six injections were given to five patients. In all cases the radioactivity was found to be greater over the diseased breast. The ratio (number of pulses over the diseased breast to the number of pulses over the normal breast) was always greater than one and oscillated, depending on the patient, between 1.15 and 1.8. The ratio did not vary much as a function of time.

The relative increase in activity did not appear to be a function of the volume of the tumor. It was as marked for a small tumor (Fig. 5) as for a very large

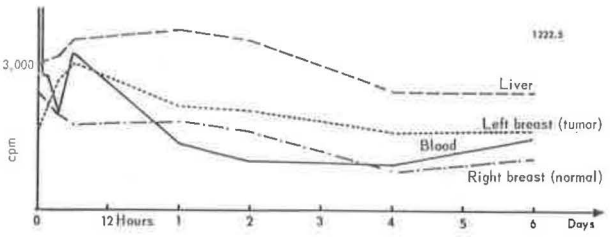

Figure 5. Activity (cpm) measured at different times (days) for different body parts (patient Cha)

one where the whole breast is increased in volume and is tense and edematous.

Measurements were made in one case before and after radiotherapy, a 4000-r tumor-dose being applied to the breast, before the second examination. The two curves are similar and since the uptake was slightly greater following radiotherapy, uptake does not appear to have been inhibited by irradiation in this case.

The increase in radioactivity at the level of the cancerous breast appeared to be less marked than that which had been found when counting beta particles with a G-M counter[2] even though in this case, only the P^{32} contained in the most superficial tissue layers was measured. This seems to be due to the fact that radioactivity of the whole thickness of the thorax is measured at the same time as that of the breast, and that the mass of the tumor volume represents only a small fraction of the tissues "seen" by the counter. Against these weaknesses of the method there is the great advantage of its not being subject, as in case of measurements of beta particles, to the difficulties relating to shape and size variations of the tumor, and to thickness of the superficial tissue. Time will reveal whether the method will be of value in prognosis and in determining the action of various therapeutic agents, particularly the hormonal ones involving phosphorus metabolism, which, from certain recent experiments on mice, seem possible.

Reticulosarcoma

The radioactivities of healthy and affected extremities were compared in four subjects with reticulosarcomas (Fig. 6). Two cases (Vis and Jar) were patients with untreated bone tumors. The most significant differences were noted in those cases where the ratio reached values of 3 or 4. Two other cases (Tou with a reticulosarcoma of the small muscles of the leg and Tro with a sarcoma of the lower extremity of the femur) had already been irradiated and had received, respectively, 4200 r at the time of the test. In these two cases, activities of the diseased areas after 24 hours were very close to those of the symmetrical healthy areas.

Other Cancers

A case with mediastinal tumor and one with lymphosarcoma of the tonsil have been investigated. The differences found between healthy and tumor areas were very small and not significant. In a case of Hodgkin's disease, the activity measured over a mass of nodes was lower than that over the liver and spleen at first, but the activity over the nodes decreased less rapidly than in the other two areas and it became greater after a month.

Malignant Hemopathies

Two cases of polycythemia vera, two cases of myeloid leukosis and three cases of lymphoid leukemia were investigated. The results of measurements over the liver, spleen and sacrum, are shown in Figs. 7, 8 and 9. It would seem that, to the extent that external counts permit valid comparisons between subjects of different morphologies, in cases of polycythemia the activities are greatest over the liver, spleen and sacrum. Studies by other investigators on patients with polycythemia produced similar curves.[8,9]

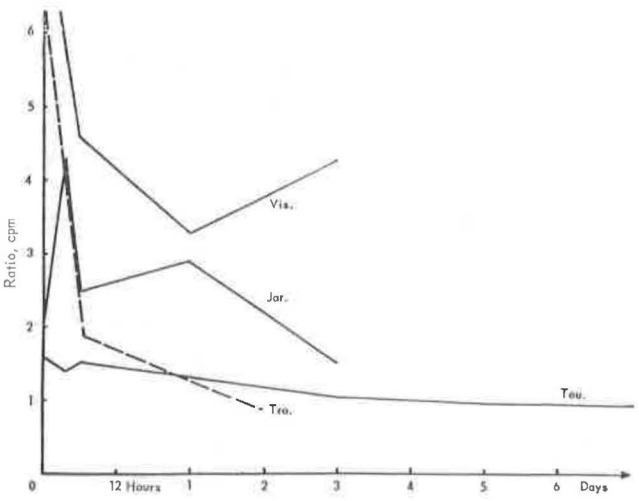

Figure 6. Ratio of counts per minute from diseased tissue over counts per minute from symmetrically healthy tissue as a function of time in days—four patients with reticulosarcomas

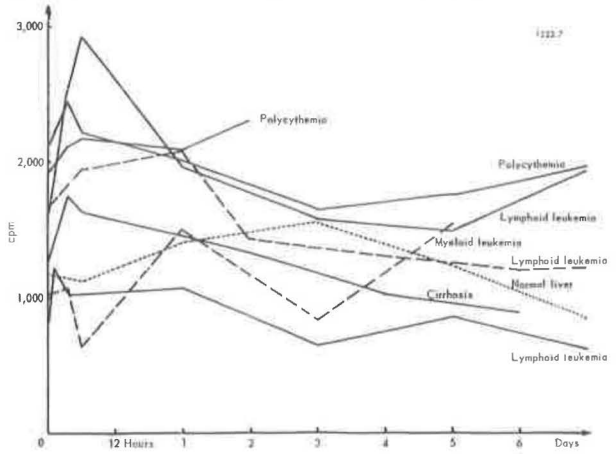

Figure 7. Radioactivity over the area of the liver in eight subjects showing various hemopathies

In the case of lymphoid leukemia, the radioactivity over lymph node areas was not found to be markedly increased even when the nodes were swollen.

Alcoholic Cirrhosis

In one case of cirrhosis, radioactivity over the liver area decreased more rapidly than in the other subjects (Fig. 10). Conversely, blood radioactivity appeared to reach an earlier maximum.

Fractures

Six cases of recent fractures of the radius or of the tibia have been studied. For those into which P^{32} was injected less than 20 minutes after the accident, the radioactivity measured over healthy and over injured limbs was similar. On the other hand, a clear-cut and persistent difference (Fig. 11) was found in the three cases which were examined 25 to 40 days after the accident. In these patients, phosphorus uptake was distinctly greater over the site of fracture (Fig. 12).

There was no hyperfixation of P^{32} in the affected limbs of 2 cases of old fractures with pseudoarthrosis. This test may provide a valuable guide in prognosis in fractures where faulty union is suspected.

Osteopathies

An increased and persistent uptake was found over the tumor in a case of eosinophilic granuloma. Four cases of Paget's disease have been studied. In two of

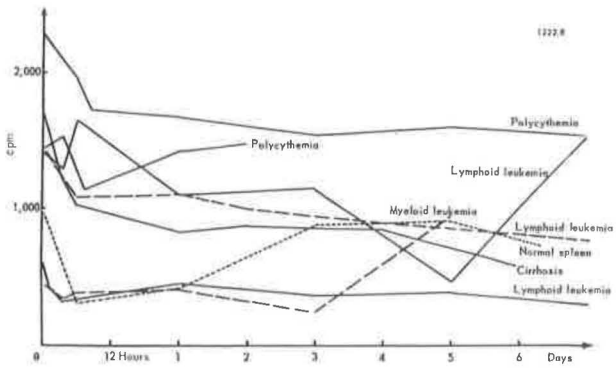

Figure 8. Radioactivity of the splenic area in eight subjects showing various hemopathies

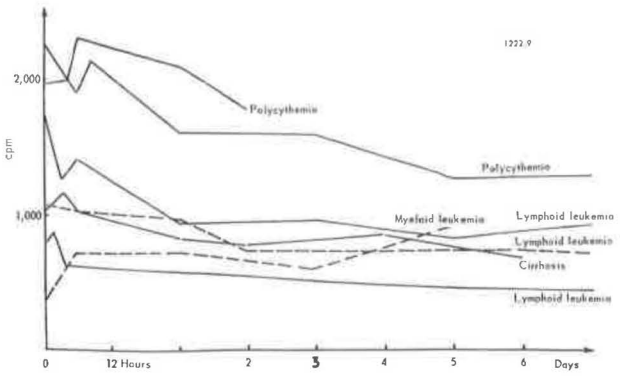

Figure 9. Radioactivity over the sacral region in seven subjects showing various hemopathies

these (Fig. 11) the difference in uptake between the diseased and unaffected extremities was very marked. In the other 2 cases, the radioactivity over the two areas was analagous. It is possible, although it has not yet been proved, that the lesions which take up phosphorus are the ones undergoing changes. These results must be compared with those of Desgrez and Guerin[10] who also observed substantial hyperconcentration of radioactive calcium in Paget-diseased bone. Additional investigations are needed to determine whether these findings are caused by vascular or metabolic changes in the area.

DISCUSSION

Interpretation of the curves obtained by measurements made over the visceral areas is difficult because it is impossible to establish the proportion of radioactivity due to circulating blood, that due to the phosphate of the extracellular liquids, and that belonging to intracellular phosphorus.

In addition, the over-all curve is a composite of complex significance inasmuch as phosphorus takes

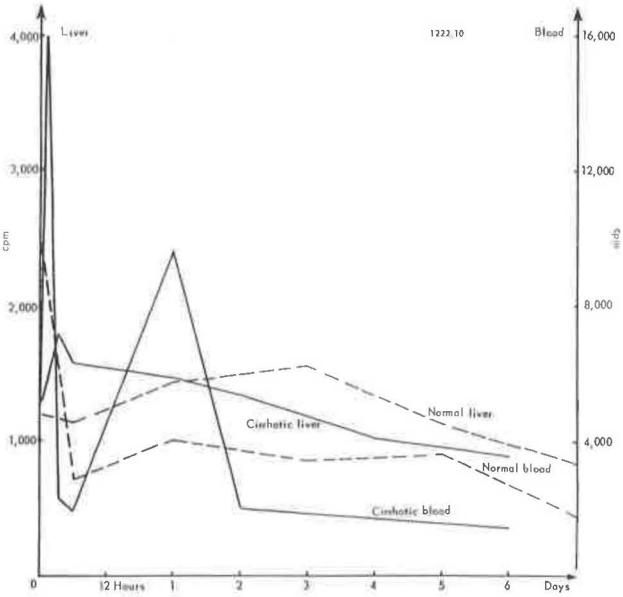

Figure 10. Radioactivity over the liver for two subjects (left ordinate) and 1 ml of blood (right ordinate)

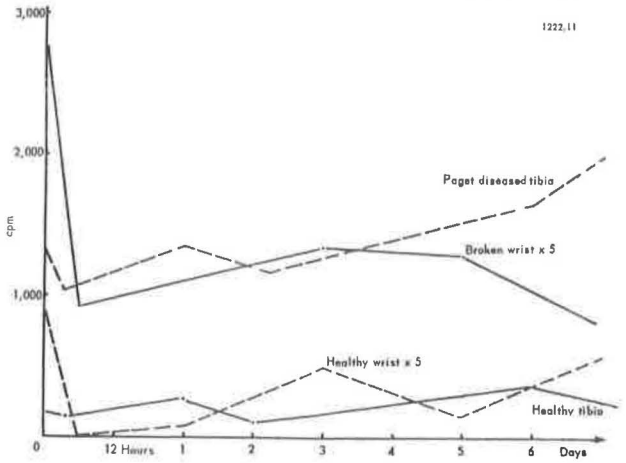

Figure 11. Radioactivity over healthy and injured limbs of two subjects, one having a fracture of the lower end of the radius and the other Paget's disease of the tibia

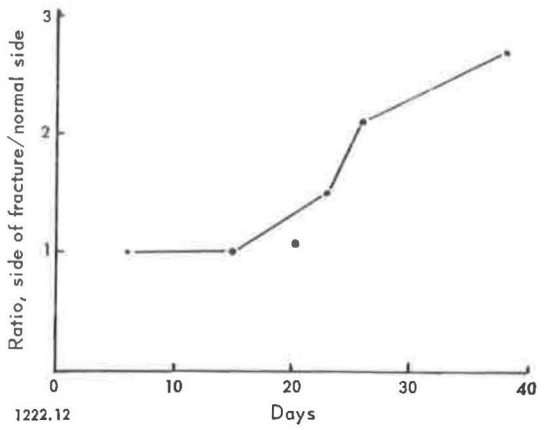

Figure 12. Radioactivity over healthy and injured limbs of two subjects; ordinate: ratio of the radioactivity of the side of fractures over the radioactivity of the normal side; abscissa: time in days after the day of fracture when the injection was given

part in the metabolism of phospholipids, nucleic acids and glucides, and exists in a multiplicity of chemical forms which have different rates of renewal. More studies are needed to learn in what specific kinds of cases these measurements may be clinically useful.

Hyperfixation at the level of tumors (carcinoma of the breast and sarcoma of the limbs) may be demonstrated objectively despite technical difficulties. Investigation requires, however, some precautions and we cannot minimize the small differences between normal and tumor-bearing areas, particularly if the tumor is deep seated.

The ratio of activity of areas with tumor to the activity of corresponding healthy areas seems to vary but little with time. It would be worth while to investigate the factors which might influence it.

In cases of bone lesions, fractures, or osteopathies, relative hyperfixation appears to be much more marked. This may have possibilities for clinical use.

CONCLUSIONS AND SUMMARY

After an intravenous injection in man of 200 mc of P^{32}, the course of radiophosphorus can be followed. However, the conditions under which the measurements are made permit demonstration of zones of hyperfixation, particularly if they are deep, only if the volume of these zones, and hyperconcentration, are great. Hyperfixation has been demonstrated over the areas of breast cancers and of reticulosarcomas. This hyperfixation is much more marked in bone lesions, such as those of fractures or Paget's disease.

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Kinetics and Distribution of P^{32} as Measured by Bremsstrahlung Intensity in Diagnosis and Therapy

By H. G. Mehl*

For the *in vivo* study of P^{32} activities in deeply lying organs, bremsstrahlung measurements alone are promising. Relevant observations on this subject were published as early as 1942 by Marinelli and Goldschmidt[1] in relation to the determination of radiostrontium in human skeletons. Since that time Wyard,[2] Kellershohn,[3] Liden[4] and Mehl[5–7] have studied the metabolism of P^{32} by means of bremsstrahlung measurements. Further investigations into the following questions seem important:

(i) What is the extent of P^{32} accumulation in solid tissues, in organs of the reticulo-endothelial system and in the other shoft tissues?

(ii) What information can be obtained about the kinetics of phosphate metabolism from determinations of the half-life of the activity in certain organs?

(iii) Are measurements of P^{32} bremsstrahlung useful for tumour localization in diagnosis?

The basic concepts and the preliminary results of our investigations are summarized in this paper.

PHOTON EMISSION OF P^{32}

The isotope P^{32} is commonly regarded as a "pure" β emitter, since no accompanying γ or K radiation can be observed with the β decay. In more recent studies by Siegbahn and Slatis,[8] Bainbridge[9] and Weinzierl,[10] earlier results[11,12] based on cloud chamber investigations suggesting a relatively strong positron intensity could not be confirmed. As a maximum for the ratio β^+/β^-, however, a value greater than 10^{-6} cannot at present be accepted.

The theoretical result of Knipp and Uhlenbeck[13] as well as those of Bloch[14] on the causation of the emission of the internal bremsstrahlung (IBS) and those of Bethe and Heitler[15] for the external bremsstrahlung (EBS) could largely be confirmed experimentally for P^{32}.[16–27] The photon yields of IBS and EBS (kev/disintegration) can be found in Table 1. The IBS is not dependent on the external media. For IBS it can be assumed that for every 100 β disintegrations about 0.21 photons with an energy of more than 90 kev are emitted ($X_{IB}:\beta = 2 \times 10^{-3}$). The shape of the photon spectra of IBS and EBS respectively show a striking similarity. Therefore the value X_{IB}/β can provisionally be accepted for estimation of the total intensity. As far as can be ascertained the orthophosphate solutions of P^{32} used are not contaminated by other photon-emitting radionuclides, therefore the measured photon intensity can be ascribed solely to the IBS and EBS of the P^{32}. Information on this question of noncontamination is essential since any other process of photon emission will seriously interfere with the results and interpretations of the relatively small photon yields from P^{32} bremsstrahlung. The spectrometric controls of the radioactive material received from Amersham have given us no suggestion so far of the presence of any such contamination.

PHOTON YIELD AND RELATIVE SPECIFIC PHOTON EMISSION IN DIFFERENT TISSUES

The P^{32} yields from different tissues can be determined if the effective atomic numbers are interpolated from Table 1, as demonstrated in Fig. 1. The following values can be established:

Fat	2.6 kev/disintegration
Water-equivalent tissue	3.3 kev/disintegration
Bone	4.8 kev/disintegration.

The photon intensity in bone, at an equal level of specific activity, will amount to 1.8 of the intensity in fat. An estimation of the relative specific photon emission (photon emission/wet tissue, liver = 100) must take account of the specific P^{32} activity of the organs studied. The values for specific organ activities are taken from the post-mortem investigations done by Lawrence,[28] Erf,[29,30] Warren,[31] Forssberg,[32] Reinhard *et al.*[33] and Platt.[34] In these estimations, however, the fact had to be considered that the majority of cases investigated were deaths from leukemia or other malignant disease.

Therefore the excessively high values found in neoplastic tissues—as far as they could be recognized as such—had to be disregarded in our measurements on nontumour patients. Notwithstanding these precautions some of the values given may not be representative of normal. The relative specific organ activities (liver = 100) have been calculated (Table 2).

In the measurements which we have made, high photon intensity yields can be expected from ribs, sternum, thoracic and lumbar vertebrae as well as from liver and spleen.

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Table 1. Photon Yield from IBS and EBS Given as in Photons Converted Disintegration Energy (kev/disintegration)

IBS		*EBS*			
Theor.	*Expti.*	*Element or material*	*Z*	*Theor.*	*Expti.*
1.22[24]	1.05[16]	Plexiglass	5.97		1.59[27]
	1.18[22]	$(C_6H_{10}O_3)^n$			
	1.64[23]	C	13	4.81[24]	4.2[16]
	1.47[24]				4.55[24]
		Fe	26	9.375[24]	8.85[24]
		Sn	50	21.6[24]	24.2[24]
		Pb	82	22.0[24]	28.6[24]

SPECIFIC ORGAN ACTIVITY IN *IN VIVO* MEASUREMENTS OF P^{32} BREMSSTRAHLUNG

As can be seen from the photon spectra of IBS and EBS (Figs. 2 and 3), the proportion of photons of low energy is extremely high. By self absorption, however, the proportion of photons of low energy will be reduced selectively depending on the depth within the organism of the radiation source. Therefore, *in vivo* measurements require precautions to exclude an excessive contribution from radiation sources lying close to the surface; such may be accomplished in three different ways. We may use either (1) a 1 mm Cu filter in scintillation counting, (2) a 1 mm Cu filter in measurements of photo current, or (3) scintillation counting within a preselected range of energy from 80 to 300 kev.

Figures 2 and 3 demonstrate the effects on the photon spectra of filtration by 1 mm Cu + 30 mm H_2O as well as by 1 mm Cu. Measurements of photo current are convenient in so far as the scintillations enter into the measurements proportionally to the photon energy. Thus, unlike scintillation counting, photons of high energy are registered more effectively than photons of low energy. For this procedure a collimator of high effectivity is required. Scintillation counting in the third procedure probably will give the best results. It is, however, dependent on the constancy of the single channel discriminator and its high voltage setting, especially for investigations over longer intervals.

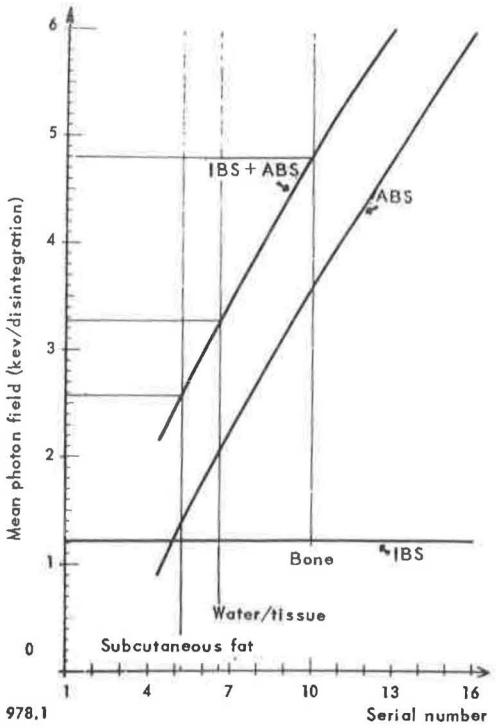

Figure 1. IBS and EBS photon yield in different tissues

In vivo determinations of the total activity of a single organ are handicapped by the fact that no single organ, expected to show a definitely increased photon emission, can be shielded sufficiently from the influence of the activity of the neighbouring tissues. On the other hand, systematic scanning of the total body with a collimator having a relatively small spatial angle will probably produce the most useful results. Mayneord,[35] Colliez *et al.*,[36] Folichon and Gandy[37] and Mehl[38] in comparable investigations on radionuclides emitting γ rays have found as a first approximation that the measured radiation intensity is independent of the distance between measurement system and object, and proportional only to the specific activity and to the diameter of the object along the "visual" axis provided the objects measured are large in relation to the aperture of the collimator. This is formulated as:

$$I = c \cdot a \cdot d \neq f(D)$$

where c = proportionality factor (standard factor)
a = specific activity
d = diameter of organ
D = distance of measurement system from object measured.

We have investigated the limitations of this relation in the case of P^{32} bremsstrahlung.[7] From Fig. 4 the condition of measurement and the results showing the relation $I \sim d$ can be seen. It was also possible to confirm the observation that the measured intensity is reasonably independent of the distance between measurement system and object.

The horizontal expanse of the object, however, was found to influence the validity of the relation just given. Using our measurement system in phantoms, a minimum horizontal expansion of at least 8 cm was required to arrive at constant results. For this reason,

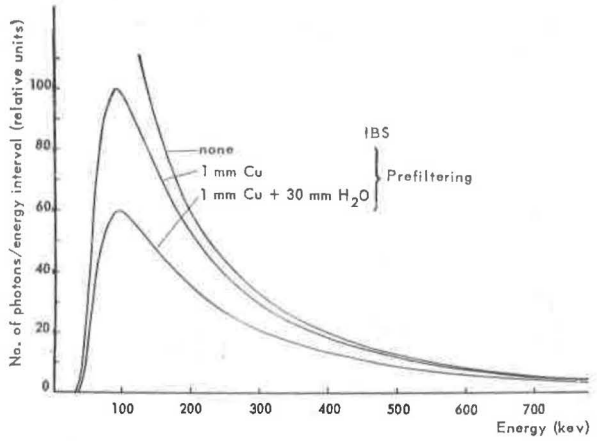

Figure 2. IBS photon spectrum under different filtration conditions

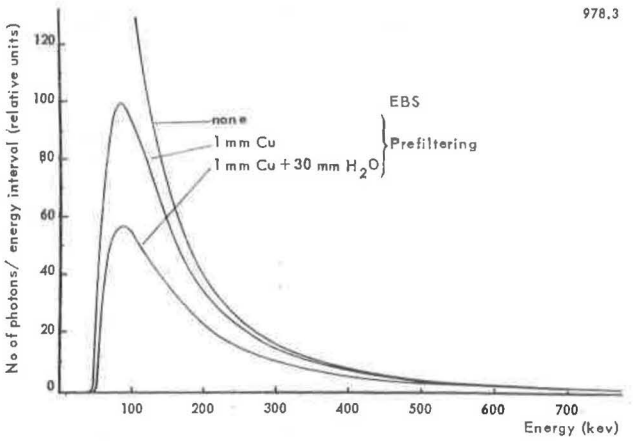

Figure 3. EBS photon spectrum under different filtration conditions

the determination of the specific activity has so far been limited to relatively large organs. Fortunately the large expanse of the liver permits the isolated determination of the specific activity of the liver tissue, and consequently the irradiation dose received by the liver in P^{32} therapy can be estimated. By postmortem determinations of the mean diameter of the liver and standardization of the arrangement of measurement, we were able to establish a basis for quantitative determinations of the liver activity. In further experiments on phantoms, we are now studying the conditions for estimating the specific activities of other organs.

Our investigations were at first limited to intensity measurements in the median section of the body of patients treated for polycythemia or leukemia with therapeutic doses P^{32}. In the course of time we were induced to extend the measurements of the intensity distribution to cover the total body of the patients. By this means the difficulty of reproducing an identical position of the patient in comparative intensity measurements over certain localizations at different dates was removed. For this technique a distance of 2 cm with equal collimation was chosen. This results in a sufficient overlap of the areas "spotted."

Table 2. Specific Activity and Photonemission, Different Organs

Organ	*Rel. spec. activity*	*Rel. spec. photonemission*
Liver	100	100
Spleen	70–90	70–90
Kidney	60–75	60–75
Lung	40–50	40–50
Muscle	20–45	20–45
Tongue	66	66
Brain stem	30–40	24–32
Thyroid	25–45	25–45
Fat	20	16
Skin	10	8
Rib	57–175	85–255
Sternum	90–140	130–200
Vertebrae	60–100	90–145
Tibia (diaphysis)	20–35	29–52
Femur (diaphysis)	10–45	15–67
Femur (epiphysis)	20–45	29–67
Skull	10–30	15–44
Teeth	40	58

RESULTS OF MEASUREMENT

Distribution of Intensity of P^{32} Bremsstrahlung over the Median Line of the Body

Figure 5 shows the typical distribution of the P^{32} bremsstrahlung intensity within the 9-day period following intravenous injection of 5 mc P^{32}. Liver and urinary bladder can be definitely recognized by increased intensities immediately after administration of P^{32}. A further intensity maximum, not yet very prominent, can be seen over the mandible. These maxima were more striking in a patient studied 24 hours after intravenous application of 6 mc P^{32} (Fig. 6). Here, for the first time, two maxima can be discerned over the head, one at the base of the cranium and the other over the mandible. A small increase of the bremsstrahlung intensity could also be found over the sternal area. In the first 10 days after application the highest maximum was regularly found at the site of the liver. The intensity at this localization over the

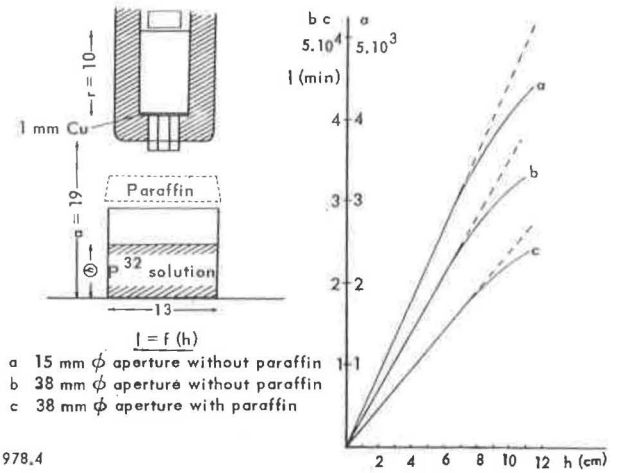

Figure 4. Arrangements and results of measurements showing the relation $I \sim d$

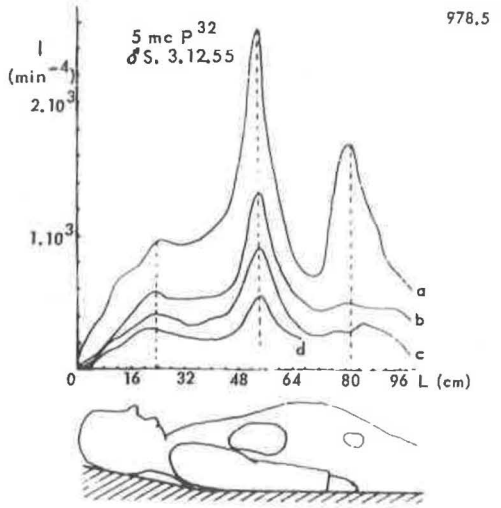

Figure 5. Distribution of bremsstrahlung intensity over the median line of the body during the 9-day period after the I.V. administration of 5 mc P^{32}. a, at ½h; b, at 2 d; c, at 5 d; and d, at 9 d, respectively

first few days was three times that measured over the calves.

We have once seen a remarkable shift of the intensity distribution in the course of studies over a longer period of time. Figure 7, after the oral application of 5.5 mc P^{32}, demonstrates this observation. Thirty two days after incorporation, the intensity over the head is definitely higher than that over the liver. Again the two maxima over the base of the cranium and the mandible can be seen. The relatively high intensity found over the lower abdomen on the first day can be explained by a quantity of P^{32} not yet resorbed from the intestine. Obviously even over this area the bremsstrahlung intensity relative to that over the liver again increases in the course of time. This led us to a systematic investigation of the intensity distribution over the total body area.

Intensity Distribution of P^{32} Bremsstrahlung over the Total Body Area

Figure 8 (A to E) presents the intensity distribution over the total body on the first, fifth, tenth, twenty-fifth and thirty-second day after oral application of 5.5 mc P^{32} (case 1). The values in these figures (corrected for zero effect) have been joined to form isointensity curves which decline exponentially. The 9th curve thus corresponds to about one half and the 30th curve to $\frac{1}{10}$ of the original intensity. Also in these figures the intensity values of local maxima are indicated as percent of the peak value simultaneously found over the liver. The intensity distributions on the 25th and 32nd days markedly differ from that initially found on the first day. With later measurements new intensity peaks are recognized over sternum, clavicles, left lung and heart (weak because of partial overlapping by the liver), right lung, vertebral column, pelvic region including femur and—symmetrically to the median axis—two pairs of weak maxima corresponding possibly to the ovaries and kidneys. In this case the spleen could not be definitely delimited, probably because of overlapping by the liver. This is the first case in which we have observed P^{32} uptake in the skull in this manner. Figure 9 (A to H) shows distributions of measured intensities in another case of polycythemia (case 2). Higher intensities could be recognized only over the femur, vertebral column and ribs.

Determination of the Half-life of Bremsstrahlung Intensities over Different Organs

Intensity distribution measurements over the total body enhance the accuracy of determinations of the half-life of bremsstrahlung intensities over different organs. Minor shifts of the body within the coordinate

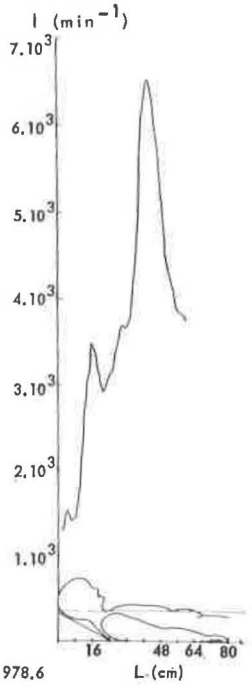

Figure 6. Distribution of bremsstrahlung intensity over the median line of the body 24 hr after the I.V. injection of 6 mc P^{32}

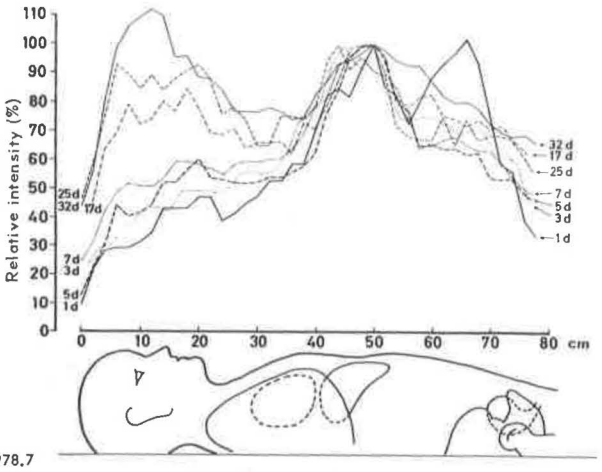

Figure 7. Distribution of bremsstrahlung intensity over the median line of the body (liver = 100) within the 32-day period after oral administration 5.5 mc P^{32} (case 1)

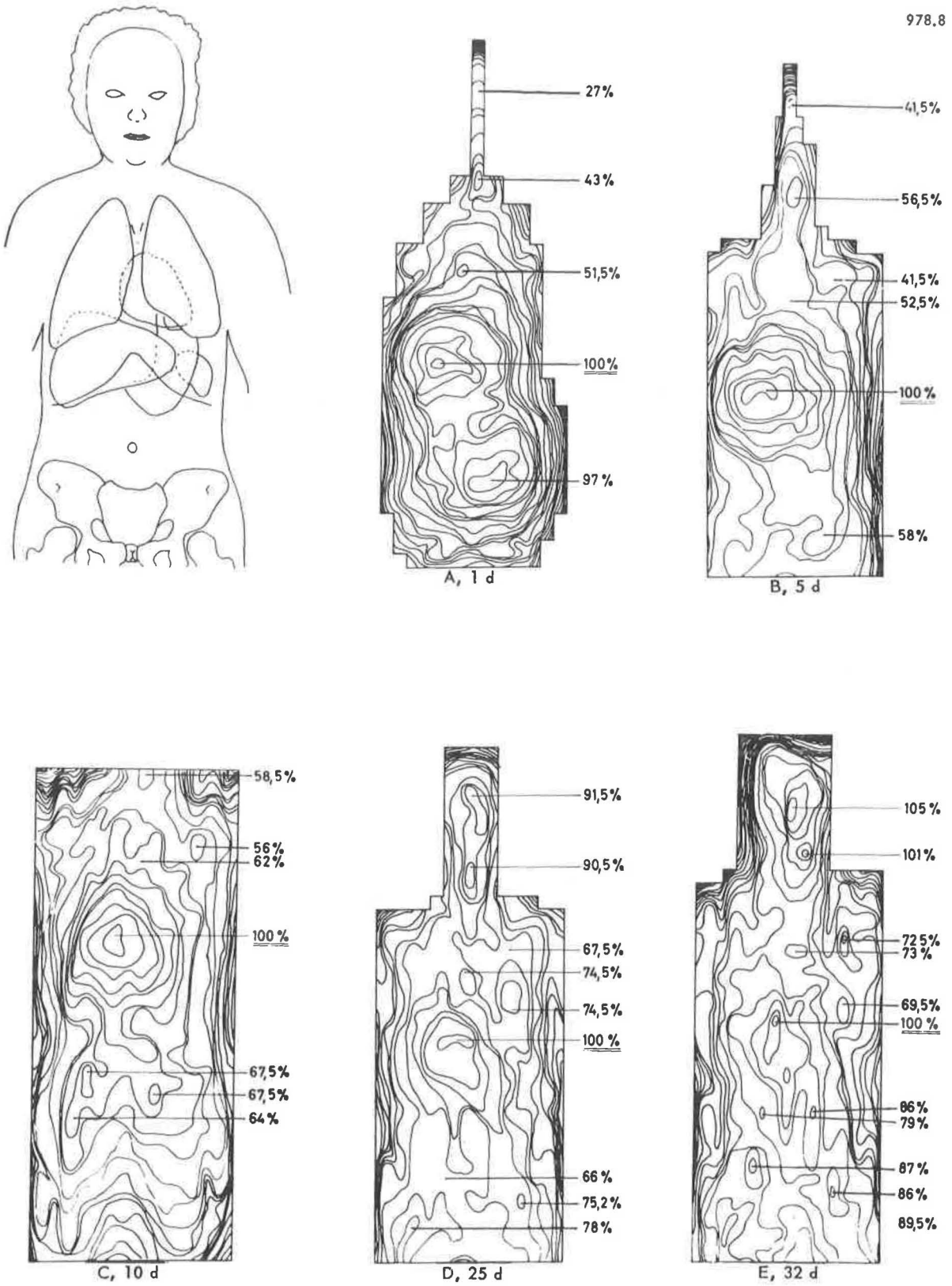

Figure 8 (A to E). Distribution of bremsstrahlung intensity over the total body within the 32-day period after oral administration of 5.5 mc P^{32} (case 1)

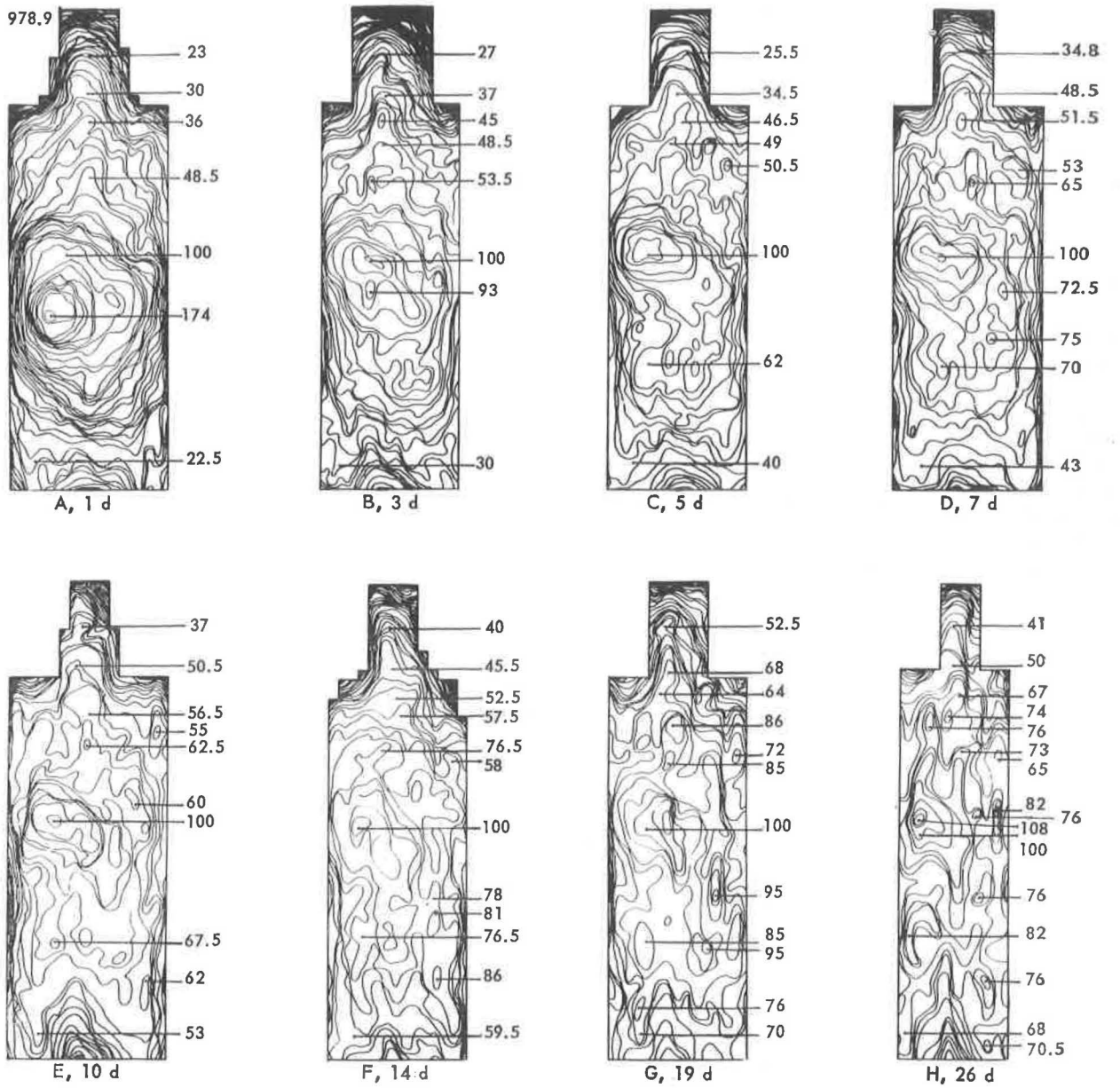

Figure 9 (A to H). Distribution of bremsstrahlung intensity over the total body in a 26-day period after the administration of P^{32} (case 2)

system become unimportant since the site of single intensity peaks can be precisely determined. In Fig. 10 the decline of intensity of the maxima over liver, left lung and heart as well as base of skull and mandible of the case shown in Figs. 7 and 8 is represented on a semilogarithmic curve. With the exception of the liver peak showing a complex decay function (T_e = 4.4 d to 10.8 d), at all other sites and approximately purely exponential decay is found. The intensity at the base of the skull declines with $T_e = T_p = 14.3$ d, the intensity over the mandible with $T_e = 15.2$ d and the intensity over lung and heart with $T_e = 9.6$ d (disregarding the inaccurate first values which lead to $T_e = 8.7$ d). The shift in direction towards the median line of the body as shown by the liver peak indicates that the intensity at this site represents not only liver activity but probably also includes activity of the vertebral column. Therefore, the final value measured for liver uptake may well have been influenced by the bone intensity and should actually be assumed as lower. Figure 11 shows corresponding half-life determinations for the case shown in Fig. 9. The effective half-life of P^{32} in the organs at various times of measurement never reaches the physical half-life of the phosphorus. In observations up to twenty days the most frequent value of T_e has been found with 8.2 d. Measurements of the decay function of total blood resulted in values identical with that of the liver intensity. Further determinations of half-life of corresponding intensity peaks in other patients gave essentially the same results. A full review of these findings awaits results of recent investigations.

Estimation of the Specific Activity of Organs

At present we can determine only the specific activity of the liver with any confidence. In these determinations it must be borne in mind that over a time interval of more than ten days the sources of error already mentioned become important. Notwithstanding this, a rough estimation of the dose absorbed by the liver is possible by an evaluation of the first measurements taken after the administration of P^{32}. In our measurements at 30 minutes after injection, the specific liver activity was found to be three to five times greater than the mean specific activity over the total body, calculated from incorporated dose and body weight.

The specific organ activities of all other organs except the liver can be estimated at present only in a very rough way since the geometry of the measurements for quantitative estimation is too complex. However, with our collimator arrangements even in the first days after the P^{32} incorporation, an accumulation of the isotope in bone is strongly suggested—in spite of the limitations stated above for small structures. This makes an accumulation factor 5 or even more for solid tissues a possibility.

CONCLUSIONS

Bremsstrahlung measurements can well be utilized for metabolic studies of the behaviour of P^{32}. The results of *in vivo* measurements may soon permit a definite answer to the controversial question of P^{32} accumulation in bones. Even now, in individual cases, qualitative information on the distribution of this radionuclide can be obtained from bremsstrahlung measurements. From half-life values for certain tissues it has already been possible to draw useful conclusions on its metabolic kinetics. With these investigations the first basic concepts for qualitative diagnostic examinations are also given. Kellershohn,[27] from his investigations on phantoms, has shown the applicability of this technique to tumour localization studies. Similarly Liden[4]—with a dose of 5 mc P^{32}—was able to localize the bone metastasis (humerus) of a gynecological carcinoma. Our own efforts in this diagnostic field will be reported later.

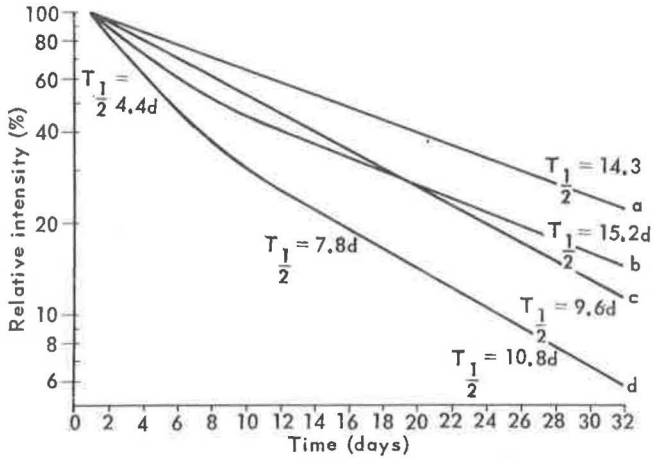

Figure 10. Decay functions of bremsstrahlung intensity as measured over: a, the base of the skull; b, the mandible; c, the left lung + heart; and d, the liver (case 1)

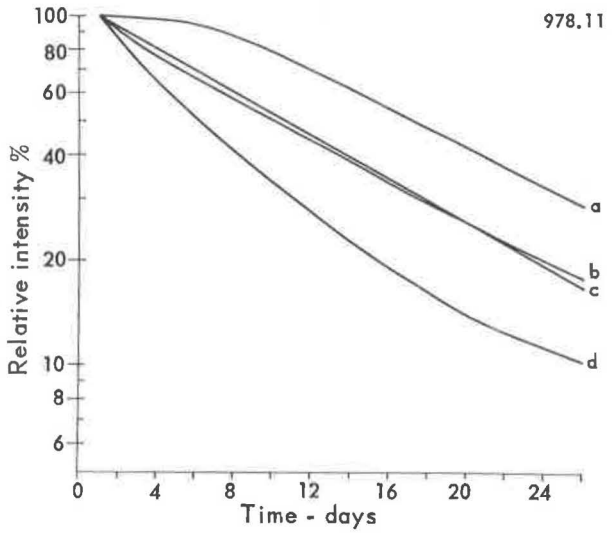

Figure 11. Decay functions of bremsstrahlung intensity as measured over: a, the femur; b, the mandible and maxilla; c, the base of skull; and d, the liver (case 2)

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Study of Digestion and Absorption with Radioactive Isotopes Following Gastrointestinal Surgery

By Komei Nakayama, Atsushi Ohtsuka, Teruo Kuraishi, Masaaki Koshibu, Michio Arima, Michio Fukushima, Tsuneo Nakagami and Shizuka Fuse*

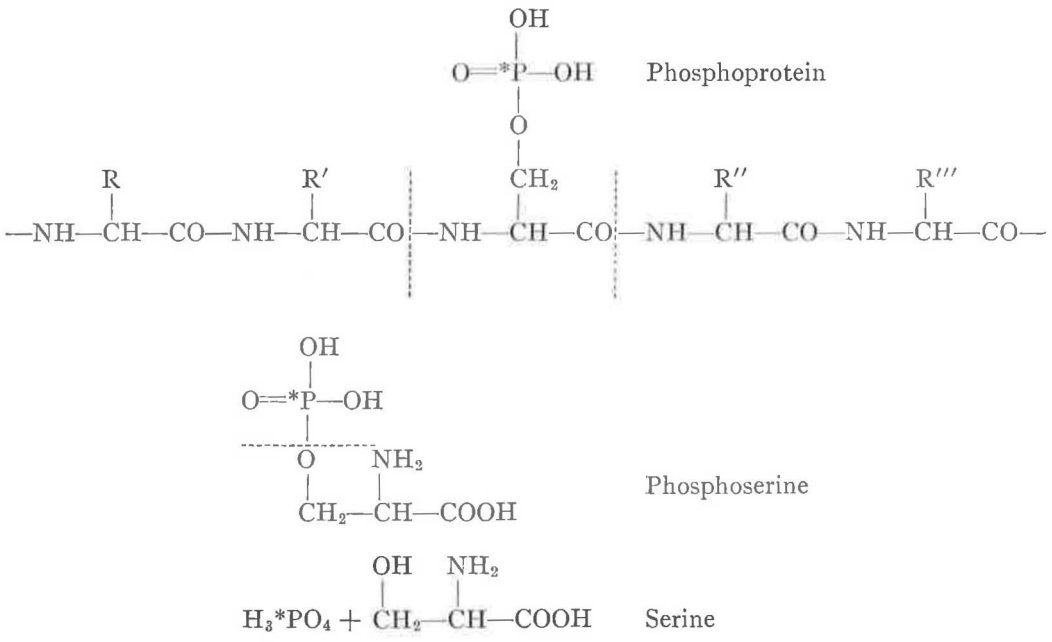
There are many carcinomas of the digestive tract among Japanese, especially of the stomach. Carcinoma of the stomach can not be treated successfully at this time without radical surgery, including complete resection of all lymph nodes that contain metastases. During the past ten years we have performed major operations for carcinoma which have included subtotal gastrectomy, total gastrectomy, and combined resections of stomach, spleen, pancreas, liver and colon. With the progress made in surgery the procedures now available are much safer.

There are, however, many unknown conditions that exist following the extensive operations, especially those which involve pathological physiology. It is in this field that we are making studies, using radioactive isotopes. The work to be reported has pertained mainly to the digestion and absorption of ingested radioactive protein and fat following various types of gastric surgery. The methods of labeling materials with radioactive isotopes for use as indicators are outlined and all the work done has been according to our original methods.

PROTEIN INDICATOR

Preparation of P^{32}-Phosphoprotein

We have used P^{32} as a marker for the phosphoprotein involved in digestion and absorption since it is the isotope most readily available in Japan. Phosphoprotein separates into the various amino acids during the process of digestion as follows, the labeled P^{32} in each case being indicated with an asterisk:



The action of phosphatase is to separate phosphoric acid so that inorganic P^{32} can be absorbed from the intestinal tract. P^{32}-phosphoprotein does not separate into the inorganic P^{32} until the last process of digestion.

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We have made P^{32}-phosphoprotein *in vivo* by a method obtaining P^{32}-casein from goat's milk:

Intravenous injection (2 μc P^{32} each 2 hr for 8 hr)
↓
Lactating goat
↓
Milked (after 9 and 18 hr)
↓
Goat's milk (10 cc water 70 to 80 cc)
+
10% Acetic acid (mix)
+
Sodium acetate (mix and let settle)
↓
Precipitated casein filtration
↓
Removal of fat with ether
↓
*P^{32}-casein

One microcurie of inorganic P^{32} was injected into the superficial vein of a lactating goat every two hours for four doses. Samples of milk were taken 9 and 18 hours after giving the first injection and P^{32}-casein was obtained in a relatively pure form from the fresh milk. We got approximately 500 cc of milk a day from one goat, and from this we were able to obtain about 15 g, or 50 μc of P^{32}-casein.

We obtained P^{32}-vitellin from hen's eggs by injecting 100 μc of P^{32} intramuscularly into White Leghorn hens daily for three days. The eggs used were collected the second through ninth day after the first injection. From yolks of these eggs we prepared the P^{32}-vitellin as indicated by the following general procedure:

P^{32} (100 μc per day injected for 3 days)
↓
White Leghorn hen
↓
Egg
↓
Yolk (add 10% saline + ether)
↓
Filtration
↓
Dilute the filtrated solution to $\frac{1}{20}$
↓
Filtration (boil the sediment with alcohol-ether)
↓
Filtrate, collect the sediment
↓
*P^{32}-vitellin

The amount of P^{32} obtainable from each egg shows a marked increase in the second egg from any given hen and reaches a maximum in the fourth egg; the amount then decreases gradually in the eggs collected sequentially. The total quantity of P^{32} contained in seven eggs produced during the first ten days was only about 8% of the amount injected. Furthermore, the amount of P^{32}-vitellin contained in each yolk decreases daily after laying, though the decrease was only about 1.5 mc.

Acquisition of P^{32}-protein from the liver and mucous membrane of the digestive tract of a dog was accomplished by giving a mature dog food containing high protein and guronsan for several days in order to improve the function of the liver and then giving P^{32} by intramuscular injection. Dosage of the injection was at the rate of 500 μc/kg of body weight. The first injection was given 24 hours before sacrifice and the second three hours after the first, using the same dosage. The liver and mucous membrane of the digestive tract were minced and the P^{32}-protein was obtained by the Fiske-Subbarow method:

P^{32} (500 μc/kg, 2 intramuscular injections 3 hours apart)
↓
Mature dog
↓
Sacrificed (after 24 hr)
↙ ↘
Liver Mucous membrane
↓ ↓
Minced Scrape
↘ ↙
Fiske-Subbarow's method
↓
Protein (containing *P^{32})

From a 10 kg mature dog we were able to obtain 125 or 300 μc of P^{32}-protein from the liver, and 25 g or 200 μc from the mucous membrane.

Preparation of S^{35}-Protein

We have used S^{35} as an indicator in such a way that it is not lost even when the protein is broken down into amino acids in the digestive tract. Yeast was cultured in a modified Naegeli's medium and S^{35} was added as shown:

Glucose	5.0%
Tartaric ammon	1.0
KH_2PO_4	0.1
$CaCl_2$	0.01
$MgCl_2$	0.02
K_2SO_4	<0.005
$*SO_4$	1000 μc
pH	5.8

The yeast formed S^{35} amino acids of methionine and cystine contained in the body of the yeast cells. Figure 1 shows the uptake rate of S^{35} in yeast, which reaches a peak at about 48 hours and then gradually decreases. This peak represents 77 per cent of the 1 μc used in the culture. Ninety nine per cent of the attached S^{35} is in the methionine and cystine. When these indicators were used, the S^{35} containing amino acids appeared in the blood, thus indicating by means of radioactivity the degree of digestion and absorption of protein.

Preparation of C^{14}-Glycine

In order to study the absorption of protein apart from digestion, we selected the radioactive amino acids $*C^{14}$-glycine and $NH_2—CH_2—*COOH$ for experimental animal research.

FAT INDICATOR

There are only a few reports available on diagnoses of diseases of the pancreas and on clinical case studies after gastrectomy. Up to the present time the study of digestion and absorption of fat was done by using I^{131}-triolein catalyzed by Dichloramine T., but we have been unable to obtain any of this material. Accordingly, we originated the idea of using I^{131}-labeled sesame oil. This oil contains many different fatty acids, the main ones being oleic and linoleic which halogenize at their double bonds. We have been successful in labeling sesame oil with I^{131} as shown, the yield of fat containing I^{131} being 25% which is relatively high.

Solution 1:

10 mc NaI^{131} + 1 drop dil. HCl + 1 drop 3% H_2O_2 + 2cc 0.1*N* I + 2 cc 0.1*N* Br + ether (let stand 24 hr in cool dark place; wash 5 or 6 times with $\frac{1}{500}$ *M* KI; dehydrate by ventilation with underpressure) → I^{131}-sesame oil.

Solution 2:

10 g sesame oil + 50 cc ether.

The labeled sesame oil is stable in 1% HCl and 10% trichloracetic acid, and as shown in Table 1, it does not separate after a trial digestion *in vitro* at 37°C. The I^{131}-labeled material therefore is satisfactory for the study of digestion and absorption of fat.

METHOD OF ADMINISTRATION

An attempt was made to standardize and maintain control conditions as much as possible both in patients and experimental animals. Nothing was permitted by mouth after the evening meal until the test meal was given the following morning. Content of the test meal for patients is outlined in Table 2. To the test meal was added labeled radioactive protein (2 μc/kg of body weight) or labeled radioactive fat (1 μc/kg of body weight). No other food was given for the next six to eight hours. In order to prevent an accumulation of I^{131} in the thyroid gland, it was necessary to give 100 cc of 2% sodium iodine solution orally each day for three days before the test meal.

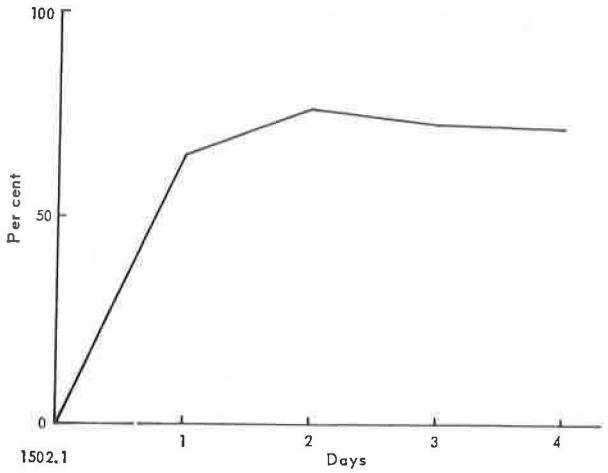

Figure 1. S^{35} uptake in yeast as a function of time in days

MEASUREMENT AND ANALYSIS OF RESULTS

A sample of peripheral blood was taken hourly for six to eight hours after the test meal had been given and the counts per minute (cpm) per gram of blood were determined by means of a radiation counter. The rate of absorption is shown (Fig. 2) where cpm/g is plotted as a function of time. It was found that most of the labeled fats and proteins were excreted within three days; accordingly, fecal materials and urine were collected for this interval and analyzed in order to determine both the rate and amount of absorption more accurately. Table 3 shows the activity excreted by different patients. We found that 0.6% of the in-

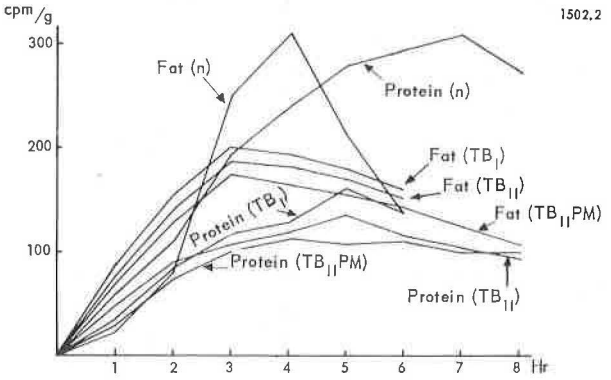

Figure 2. Counts per minute per gram of peripheral blood at different times after a test meal, showing the amount of protein and fat in normal (n), esophago-duodenal anastomosis (TB_I), esophago-jejunal anastomosis (TB_{II}), and esophago-jejunal anastomosis combined with resection of pancreas and spleen ($TB_{II}PM$) patients

Table 1. Artificial Digestion Test
Sample: I^{131}-sesame oil, 0.01 cc, 54,260 counts per minute (cpm)

Hr	*Gastric Juice Water layer, cpm*	*Free-HCl Total activity, %*	*Bile Water layer, cpm*	*Menlengracht Total activity, %*	*Pancreatic juice Water layer, cpm*	*Diastase Total activity, %*
1	246	0.45	286	0.53	566	1.04
2	297	0.55	627	1.54	572	1.05
3	385	0.71	1116	2.06	848	1.56
4	374	0.69	924	1.70	1046	1.93
5			1246	2.29	1232	2.27
6			1131	2.08	1254	2.28

jected dosage of I^{131} and 0.2% of injected dosage of P^{32} was all that could be recovered from the fecal matter. Absorption then was determined by calculations as follows:

$$\text{Per cent absorption} = \frac{\text{Ingested dosage (cpm)-fecal excreted dosage (cpm)}}{\text{Ingested dosage (cpm)}} \times 100$$

$$\text{Per cent urinary excretion} = \frac{\text{Urinary excreted dosage (cpm)}}{\text{Ingested dosage (cpm)}} \times 100$$

The urinary excretion for three days was collected in order that fat and protein metabolism as well as kidney function could be determined. The fecal material was mixed and homogenized, and one gram of the mixture was used for testing. Urine was collected and the total amount measured. Counts per minute per cubic centimeter were determined and on the basis of figures obtained, activity of the total volume was calculated. Sample specimens were placed in a special container and converted to dry form, then counted three times (two minutes required for each) and an average taken. Our effort was to show the physiology and the pathological-physiology of digestion and absorption by comparing results on cases following various surgical procedures.

FINDINGS

Figure 2 shows the blood level of both protein and fat averaged for 10 normal cases. As may be seen, the protein level reaches a maximum in six to seven hours and the fat level in four hours after administration of the test meal. Absorption of orally administered protein and fat was 95 and 96 per cent, respectively, and excretion in the urine was high during the first day (Fig. 3). Figures 2 and 3 also show results obtained on 10 cases three to four weeks after surgery which included total gastrectomies such as esophageal-duodenostomy and esophageal-jejunostomy illustrated in Fig. 4. It is of interest that the blood level of protein rises slowly in the operated cases despite the fact that food reaches the intestine as soon as ingested. The curves show that maximum absorption is reached five hours after ingestion and that it is 50 and 47% of normal in each case, which, it would appear, is caused mainly by absence of the gastric mechanism for hydrolysis of protein. Protein absorption and urinary excretion rates are low but are parallel to normal. Fat absorption reaches a maximum level in the blood in three hours after ingestion but it is only 62 and 56% of normal.

We have compared digestion and absorption of protein and fat following two types of total gastrectomies, esophageal-duodenostomy and esophageal-jejunostomy. Esophageal-duodenostomy showed slightly better passage of food through the duodenum, and thus that the action of secretin and pancreatin aided the process of digestion. The 10 cases of total gastrectomy with combined resection of pancreas and spleen were checked three to four weeks following surgery. These results are also represented in Figs. 2 and 3. As might have been expected, they show a lower level of absorption and digestion of protein and fat than those for the cases of simple gastrectomy. Possibly such resections may have a deleterious effect on metabolism over a longer period of time, but, as is known, resection of half to two-thirds of a parenchymatous organ like the pancreas causes no serious immediate difficulty.

There are many hypotheses about the mechanism of fat digestion and absorption; accordingly, we shall not try to discuss this subject apart from the general

Table 2. Test Meal

	Protein, g	*Fat, g*	*Carbohydrate, g*	*Water, g*	*Total, g*
Bread	15.5	0.9	79.0	54.6	150
Hens' egg	7.2	6.6		41.2	55
Cows' milk	3.2	5.6	7.4	163.6	180
Total	26.1	13.1	86.4	259.4	385

Table 3. Fecal Excretion
(Total amount for 3 days following injection)

P^{32}		I^{131}	
Patient	*Activity (%)*	*Patient*	*Activity (%)*
M. O.	0.42	F. Y.	0.10
S. A.	0.40	R. U.	0.01
S. T.	0.60	Y. H.	0.18
R. H.	0.33	K. M.	0.15
K. K.	0.57	Y. O.	0.04

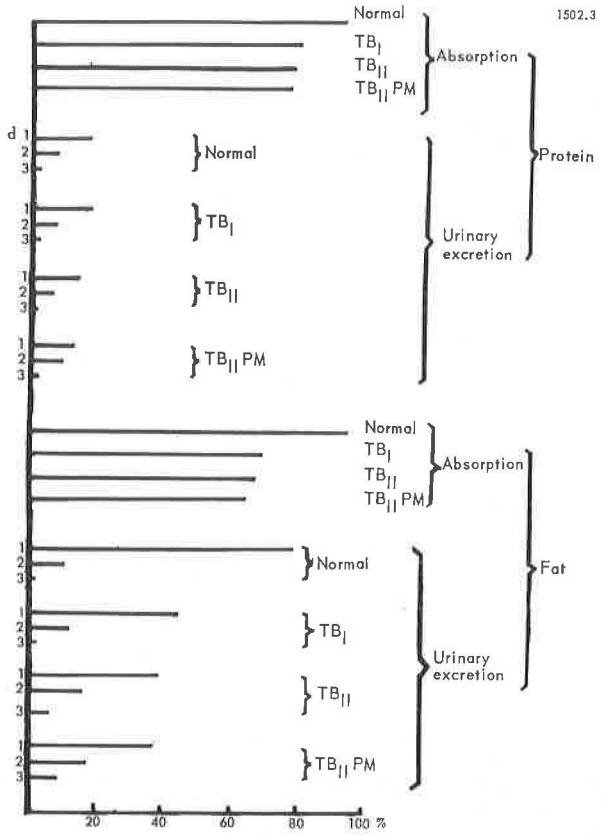

Figure 3. Per cent of radioactive materials absorbed and excreted relative to amounts administered taken as 100 per cent (identification the same as for Fig. 2)

problem. Much has been learned, however, about protein metabolism from experimental work including our own. Inorganic P^{32}, P^{32}-protein, S^{35}-protein and C^{14}-glycine have been administered to five mature dogs. The results are shown in Fig. 5 where the curves for P^{32}-protein, and S^{35}-protein indicate a similar and almost equal absorption rate. The same materials were also given to five mature dogs after total gastrectomies and the results are shown in Fig. 6 where the curves for P^{32}-protein and S^{35}-protein are again similar and show almost equal absorption rates. Since C^{14}-glycine does not need to be digested, it seems necessary to conclude that the movement of P^{32} radioactivity in the blood following administration of P^{32}-protein shows the correct absorption rate of protein. Although the absorption curve for C^{14}-glycine is different from that of P^{32} after total gastrectomy, this is also to some extent true for non-gastrectomized animals, though the amount of absorption is essentially the same. In all our experiments, administration of P^{32}, either as inorganic P^{32} or P^{32}-protein, has proven to be the most satisfactory means of studying digestion and absorption of protein. This is fortunate inasmuch as P^{32} has been the easiest for us to obtain and inasmuch as its radiations are the easiest for us to count.

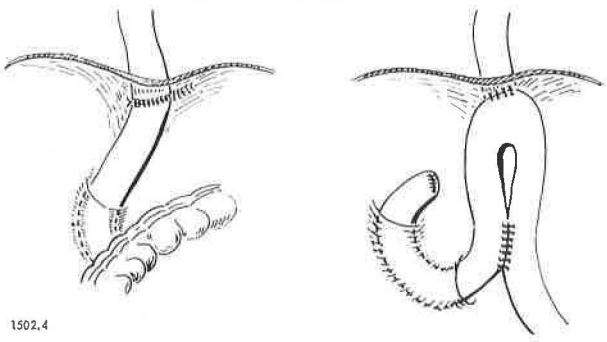

Figure 4. Esophageal-duodenostomy and esophageal-jejunostomy

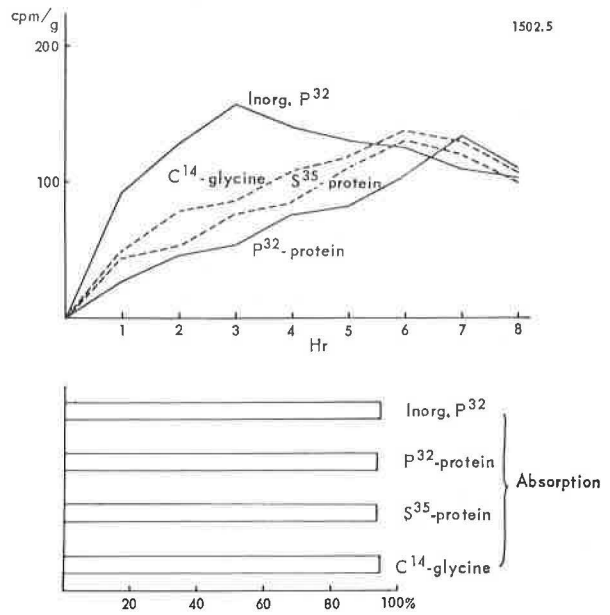

Figure 5. Absorption of inorganic P^{32}, P^{32}-protein, S^{35}-protein and C^{14}-glycine in normal dogs (average of five cases)

Figure 7 shows clinical results comparing the absorption of inorganic P^{32} in normal cases with that in cases following total gastrectomy and esophageal-jejunostomy. Here definite differences in rates and amounts of absorption are seen. Next we compared the absorption of total gastrectomies using inorganic P^{32} and P^{32}-protein. This investigation revealed a definite differ-

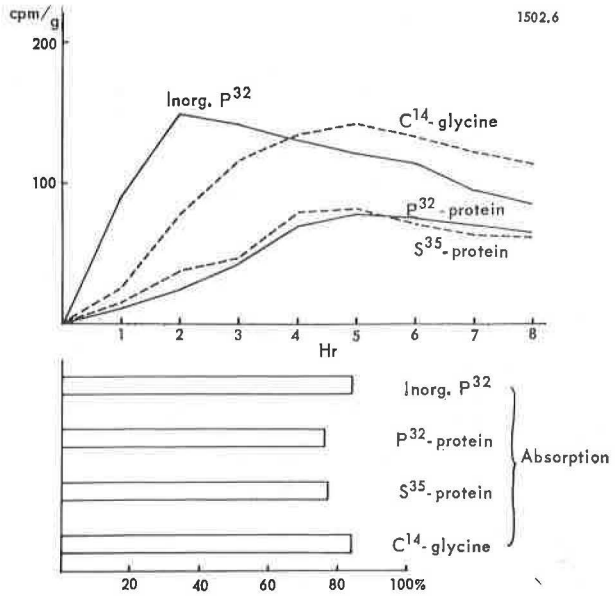

Figure 6. Absorption of inorganic P^{32}, P^{32}-protein, S^{35}-protein and C^{14}-glycine in dogs after total gastrectomy (average of five cases)

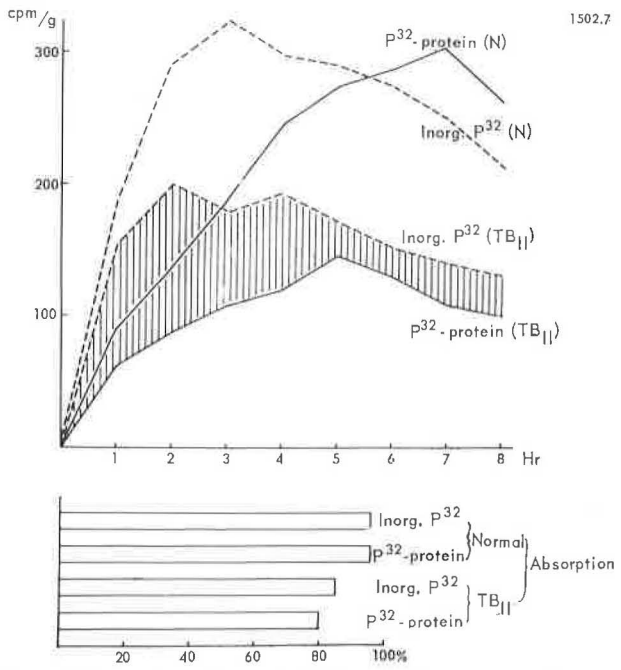

Figure 7. Comparison of inorganic P^{32} in normal human cases with cases following total gastrectomy (average of ten cases)

ence, the ability of digestion being much lower than the ability of absorption.

SUMMARY

Recent developments in surgical techniques for removal of gastrointestinal carcinoma have provided the means for removal of vital organs such as the stomach, pancreas, spleen, part of the liver and large intestine. Nutritional management of patients experiencing such removals thus has become an important problem.

Studies have been made of the nutritional complications created by certain of the newer surgical practices, using radioisotopes as a means for analyzing protein and fat metabolism. The labeled protein and fat materials used were synthesized *in vitro* and extracted from products such as goat's milk, hen's eggs, and dog's intestinal membranes and livers. S^{35}-protein from yeast and C^{14}-labeled amino acid were also used, and I^{131} attached to sesame oil was used to follow fat absorption. The various indicators were given orally in test meals. Blood level, and fecal and urinary excretion were then measured at various times after the oral administration.

The results obtained were as follows:

1. In human cases of simple total gastrectomy, curves showing the rate of absorption of protein and fat in the blood were lower than those obtained for normal individuals, and the total absorption as measured by fecal excretion was as low as 70 to 80% of normal.
2. Among the cases of total gastrectomy, absorption was superior in the case of esophageal-duodenal anastomosis as compared with esophageal-jejunal anastomosis.
3. Digestion was disturbed more than absorption by total gastrectomy.
4. Poor digestion and poor absorption of protein and fat were observed after total gastrectomy combined with resection of pancreas and spleen; furthermore, no improvement in post-operative recovery was seen to take place as a consequence of treatment.
5. The findings indicate that absorption of amino acids occurs in that part of the intestine where proteins are broken up into amino acids by digestion.

These findings have an important bearing on the problem of control of protein nutrition following surgery of the digestive tract. We have obtained many kinds of interesting results through application of radioactive isotopes in the field of digestion and absorption of the intestinal tract following surgery, only part of which have been reported here.

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Clinical Applications of Activation Analysis

By J. M. A. Lenihan* and Hamilton Smith†

Most of the observable properties of matter depend on the electronic structure of atoms and molecules. The nucleus is a tightly packed assemblage whose properties are not easily demonstrated. The earliest technique in nuclear physics—and still one of the most fruitful—was to study the constitution of a nucleus by examining the fragments and radiations resulting from its disintegration, which might be natural (in radioactive elements) or artificial. In recent years more delicate methods have become available. Nuclear energy levels, in light elements at least, can be charted by excitation experiments with relatively modest equipment. Other properties are elicited by the study of nuclear magnetic resonance. One of the most useful laboratory techniques arising from the development of atomic energy is the method of activation analysis, which has recently been reviewed at length by E. N. Jenkins and A. A. Smales.[1]

Several elements, when bombarded by neutrons inside a nuclear reactor, become radioactive to an extent permitting detection or quantitative estimation with a sensitivity and simplicity beyond the reach of conventional analytical procedures. This paper describes some applications of activation analysis in hospital practice, clinical science and forensic pathology. The work to be discussed does not exploit the full sensitivity or elegance of the activation technique. It was undertaken rather to provide a useful service for hospitals and other organisations out of modest resources in equipment and staff.

Arsenic, the element on which we have so far concentrated our efforts, is particularly suitable for analytical investigation by neutron activation. Its only stable isotope, As^{75}, has a large cross section for neutron capture giving the radioactive isotope As^{76} which decays with half-life 27 hours, emitting β rays of maximum energy 3.0 Mev and γ rays of maximum energy 2.0 Mev. The specific activity induced after irradiation to saturation at a thermal neutron flux of 10^{12} n/cm^2/sec is 0.92 c/g.

Small samples (1–5 mg) of hair, skin, nail or other material are weighed, sealed in individual polythene bags, packed into an aluminium can and sent to the Atomic Energy Research Establishment, Harwell, for irradiation; the usual period is one day. About 50 tissue samples, together with a 2 to 3 mg sample of "Analar" arsenious oxide, can be fitted into a standard 30-ml Harwell container. After irradiation the cans are returned by air to Glasgow. Each sample is removed from its polythene bag, transferred to a 25-ml micro-Kjeldahl flask and digested with sulphuric and nitric acids; the digestion method is essentially similar to that described by E. Kahane and M. Pourtoy.[2] The digested sample is transferred to a 200-ml flask, with 10 micrograms of stable arsenic carrier, in the form of arsenious oxide. This arsenic, together with any present in the original sample, is converted to arsine by a modification of the Gutzeit method, described by M. D. Thomas and T. R. Collier.[3] The arsine is collected in mercuric chloride solution, which is made up to a convenient volume and assayed in a Geiger counter (type M6, accepting liquid samples). The arsenious oxide standard is treated in the same way and the arsenic content of each sample is found by comparison of the counting rates.

This analytical procedure has been used in two main ways: (A) for measurement of arsenic levels in normal hair and correlation with smoking habits, and (B) in an activation analysis service.

SMOKING HABITS

Cigarettes contain appreciable amounts of arsenic, presumably from insecticides used to spray the tobacco plant. E. J. Bailey, E. L. Kennaway and M. E. Urquhart[4] analysed cigarettes from many countries and found arsenic concentrations (in parts per million) between 0.0 (Turkey) and 81.0 (Denmark). Some British cigarettes contained more than 50 ppm, though the arsenic content of one popular brand fell from 25 to 100 ppm in 1948 to 1 to 2 ppm in 1956. About 60% of the arsenic in a cigarette is retained in the ash, 25% remains in the unsmoked stump and about 15% appears in the smoke. Arsenic is a known carcinogen, though not a very powerful one. The possibility that its ingestion might contribute to the increased incidence of lung cancer in smokers deserves investigation. If smokers do, indeed, absorb greater amounts of arsenic than nonsmokers, it should be possible to demonstrate higher concentrations in the hair, which is one of the main routes of excretion for this element. With these considerations in mind, the following experiment was made.

Samples of hair from more than 1000 subjects were examined by the activation analysis technique. Infor-

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Table 1. Constitution of the 1000-Subject Group

	Age			Total
	Under 25	*25 to 50*	*Over 50*	
Male smokers	94	117	130	341
Male nonsmokers	165	49	49	263
Female smokers	58	82	16	156
Female nonsmokers	113	70	57	240

	Smokers	*Nonsmokers*	*Total*
Male	341	263	604
Female	156	240	396
	497	503	

mation on the smoking habits of each subject was recorded when the sample was obtained. These data were concealed from the analysts until their work was completed. A summary of the finds on the first 1000 samples and of the information supplied by each subject was transferred to punched cards and analysed.

The subjects were drawn from patients and staff in various hospitals and from members of Glasgow University. Patients known to have been treated with arsenical drugs were excluded but otherwise nothing was done to influence the choice of subjects by the physicians, surgeons and university teachers who obtained the samples. No attempt was made to select a group of subjects representative of the whole population in regard to age, sex or smoking habits; it was desired only to obtain a large number of samples which would include some from smokers and some from nonsmokers.

After the analysis of the 1000 samples had been completed, the individual records were examined to find the constitution of the group. The results are given in Table 1.

A summary of the 1000 results is given in Table 2. From these figures and from the abstract which is presented graphically in Fig. 1, it is clear that there is no difference in the arsenic content of hair between smokers and nonsmokers in the group that we have examined. There is, however, a markedly greater arsenic content in the hair of the men than of the women. Whether this finding will be valid for larger groups, more representative of the population as a whole, is still to be determined by experiment. It is known that arsenic embodied in the hair can be

Table 2

	Arsenic content of hair, ppm				
	0–0.49	*0.5–0.99*	*1.0–1.49*	*1.5–2.49*	*2.5–*
Male smokers					
Age:					
Under 25	29	33	17	8	7
25–50	46	46	12	9	4
Over 50	56	49	12	5	8
Total	131	128	41	22	19
Male nonsmokers					
Under 25	36	65	34	19	11
25–50	33	12	1	2	1
Over 50	19	25	3	1	1
Total	88	102	38	22	13
Female smokers					
Under 25	38	15	4	1	0
25–50	62	11	6	1	2
Over 50	6	6	3	1	0
Total	106	32	13	3	2
Female nonsmokers					
Under 25	66	37	5	5	0
25–50	53	13	4	0	0
Over 50	40	14	3	0	0
Total	159	64	12	5	0

Summary	*Arsenic content of hair, ppm*				
	0–0.49	*0.5–0.99*	*1.0–1.49*	*1.5–2.49*	*2.5–*
Males	219	230	79	44	34
Females	265	96	25	8	2
Smokers	237	160	54	25	21
Nonsmokers	247	166	50	27	13

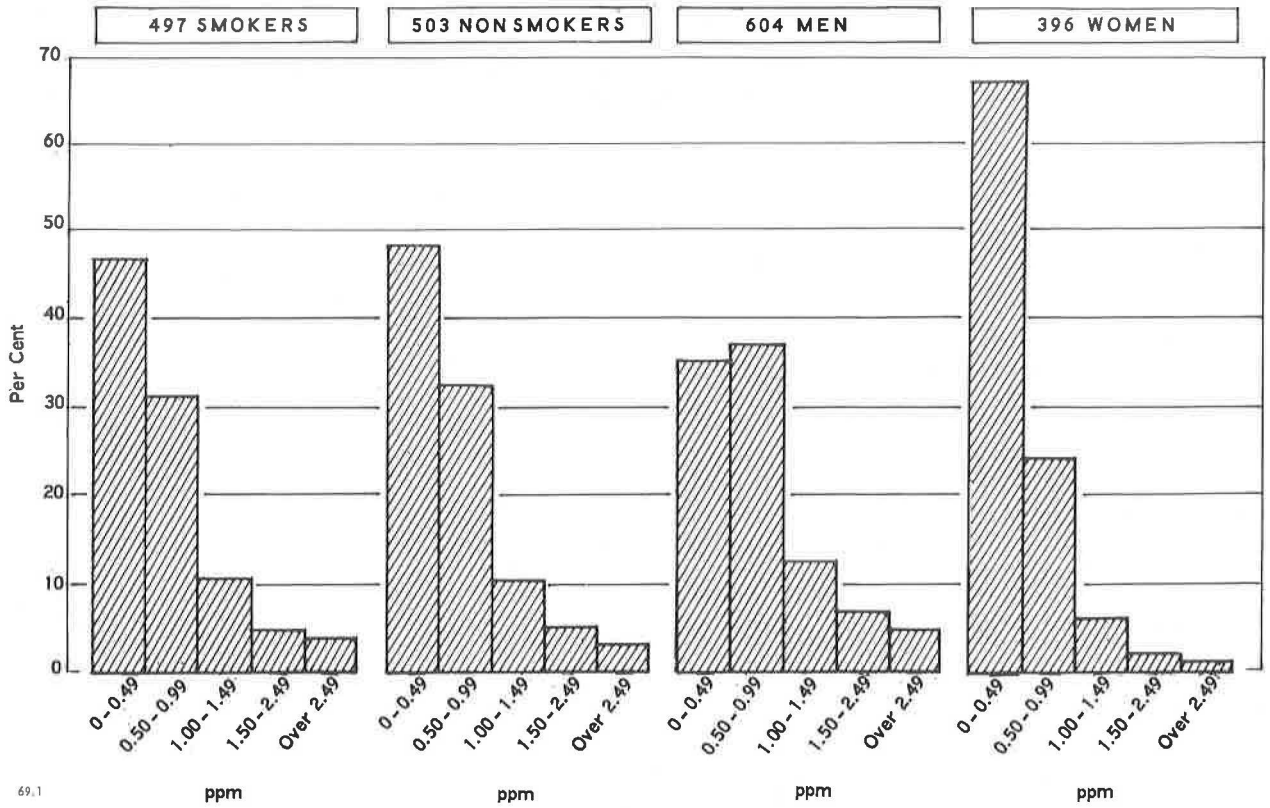

Figure 1. Arsenic content in hair of smokers and nonsmokers

partially removed by washing.[5] Since women wash their hair more often than men, a lower arsenic level is not unexpected.

ACTIVATION ANALYSIS SERVICE

Facilities for the estimation of arsenic by activation analysis are provided for hospitals and government departments in the West of Scotland. Among the investigations carried out recently are the following.

Analysis of Samples in Chronic Arsenical Poisoning

A patient seen in a dermatological clinic bore the hallmarks of arsenical intoxication, though stoutly denying exposure to arsenic or ingestion of this element. Further enquiry revealed that he had for twelve years been consuming daily draughts of a mixture containing heroic quantities of arsenic (and of potassium bromide, which complicated both the clinical investigation and the activation analysis). The following arsenic levels were found by activation analysis:[6]

	ppm
Head hair	65
Finger nail	11
Skin	7
Beard hair (on admission to hospital)	8
Beard hair (8 days later)	2

The patient was discharged from hospital after appropriate treatment and admonition. Further samples obtained from the same patient 18 months later were examined with the following results:

	ppm
Hair	0.89
Nail	0.47
Skin	0.27

Analysis of Samples in Chronic Arsenical Poisoning with Skin Cancer

Arsenic is used in the manufacture of insecticides (lead arsenate), weed killer (sodium arsenite) and sheep dip (arsenious oxide, sodium arsenite). Ingestion and external contamination may be avoided by the use of protective clothing and other simple hygienic measures which are, however, not always observed scrupulously.

A worker in a sheep dip factory was admitted to hospital suffering from squamous carcinoma of the scrotum, attributed to chronic irritation by arsenical dust. Samples of tissue were examined by activation analysis with the following results:

	ppm As
Head hair	329
Nail	117
Skin	1.86

The nail and hair samples were probably contaminated externally with arsenical dust.

Samples of beard hair, obtained with an electric razor at intervals after the patient's admission to

hospital, were found to contain the following amounts of arsenic:

Date of sample	*As content, ppm*
7 June 1957	3.12
14 June	1.79
28 June	0.84
5 July	0.94

The rapid return to a normal level is interesting.

Suspected Criminal Arsenical Poisoning

An elderly person repeatedly became ill after food, with vomiting and abdominal pain. Extensive medical and surgical investigations, including laparotomy, revealed no abnormality. Food was taken without incident in hospital but the illness recurred on the patient's return home. Arsenical poisoning was then suspected. Samples of vomitus were sent to two laboratories for chemical examination by conventional methods. The results were inconclusive, one analyst reporting slight traces of arsenic and the other finding none. Samples examined by activation analysis had the following arsenic contents:

	ppm
Head hair	0.77
Nail	0.20
Vomitus	0.15

On the basis of these findings, which are all within normal limits, inquiries into the possibility of arsenical poisoning were discontinued.

Arsenical Contamination of Mouse Lungs

A cancer research laboratory submitted ten samples of dried mouse lung for examination. Five of the mice had lived since birth in a dust-free atmosphere and the other five had inhaled the normal air of Glasgow, containing about 3×10^{-12} g of arsenic per litre. The diet and other living conditions were the same for both groups. The arsenic contents of the ten samples were found by activation analysis to be as follows.

Mice reared in dust-free atmosphere:

0.18, 0.32, 0.44, 0.42, 0.43 ppm (mean = 0.36).

Mice reared in normal atmosphere:

0.80, 0.72, 0.71, 0.88, 1.01 ppm (mean = 0.82).

The experiments described here have been made with simple chemical and physical apparatus, suitable for the rapid examination of large numbers of samples. The treatment and radioactive assay of 100 samples has been done regularly by one of us, with the help of a junior technician, in two days. Methods are now being developed for the routine estimation by activation analysis of several other elements of industrial or clinical interest (see Table 3). The sensitivities quoted in this table might be much improved by using the higher neutron fluxes now available or, in some instances, by the use of γ-ray spectrometry on the irradiated specimen.

Table 3. Sensitivity of Activation Analysis (with simple apparatus and techniques) for certain Elements of Clinical Interest

Element	*Isotope*	*Half-life*	*Sensitivity of activation analysis, gm*[a]
Antimony	Sb^{122}	2.8 d	4×10^{-9}
Arsenic	As^{76}	27 hr	2×10^{-9}
Copper	Cu^{64}	13 hr	3×10^{-9}
Manganese	Mn^{56}	2.6 hr	5×10^{-10}
Phosphorus	P^{32}	14 d	4×10^{-8} [b]
Mercury	Hg^{197}	23 hr	6×10^{-9}
Zinc	Zn^{69}	51 min	4×10^{-8}

[a] Mass of element required to give 1000 disintegrations/min after irradiation to saturation at a thermal neutron flux of 10^{12} n/cm²/sec and subsequent decay for one half-life or for 3 days, whichever is the shorter.
[b] After irradiation for one week.

ACKNOWLEDGEMENTS

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The Use of Scintillography in Medicine

By A. Gandy and H. Jammet*

Since radioisotopes were first introduced into medicine for diagnosis, their application has been greatly widened as a result of technical improvements. These improvements increase the precision of the method and provide more data from a given test.

Scintillography is a typical example of an improvement over the older method of localizing radioactive iodine in thyroid tissue point by point. The enormous gain in time and, particularly, the extraordinary increase in precision suggested the possibility of a more general application of the method.

We shall describe the method and discuss its possibilities and limitations before citing the specific cases to which it has been applied at the Curie Foundation.

PRINCIPLES

A suitably protected scintillation counter equipped with a narrow-angle diaphragm moves in a horizontal plane above the area being studied. The counter scans the area while describing, at a constant speed, a series of equidistant parallel lines.

The impulses from the counter are selected by a discriminator and only those with an amplitude greater than an adjustable threshold are let through. These impulses are transmitted to a recording device that is mechanically connected to the counter and each pulse is indicated on a sheet of paper by a line perpendicular to that of the displacement.

When the counter passes above an inactive region it delivers a very small number of impulses that correspond to its own activity. This produces only a few strokes distributed at random above the lines scanned. On the other hand, when the counter passes over an active region the frequency of the pulses increases and the strokes are closer together.

Thus, the device will give for a given distribution of a γ-radioactive substance a series of cross-hatched strips that are darker as the activity of the region being studied increases.

PROPERTIES OF THE SCINTILLOGRAM

The image which is produced by the device just described is called a "scintillogram." Like a picture, it is only an imperfect expression of the reality. In the discussion which follows we shall clarify the relationship between the scintillogram and the objects it represents.

Original language: French.

* Curie Foundation.

Since the scintillogram expresses a physical phenomenon by a picture, we shall employ the vocabulary used in photography, adapting definitions where needed. We shall also show that the two techniques are remarkably similar.

Darkening

For a scintillogram, we can define the mean darkening on a unit of line by the ratio $N = n/l$, in which n is the number of strokes on the unit of line with a length l.

Brightness

The definition of "brightness" of the object examined presents greater difficulties. Indeed, in ordinary photography brightness is a surface property. In our case, the emission of the radiation comes from within the volume (as is the case, for example, when light is emitted during electrical discharge in a gas). Therefore, we must replace the tridimensional object being examined by a bidimensional object, defined as a "superficial activity," which corresponds to brightness. The apparatus we use produces a plane scintillogram of this equivalent object.

We shall examine more closely this concept of an equivalent object for it plays an important part in the interpretation of the results. Let us consider a volume containing a radioactive substance distributed according to specific activity m. Above this volume is the counter C in its lead shield. The shield is perforated by a channel d, the diaphragm (see Fig. 1). The counter receives, as a first approximation, only the radiation emitted by the small conical volume comprised between distances h_1 and h_2. It can be shown that the radiation received by the counter is equivalent to that which would be emitted by a small surface S located at a distance h intermediate between h_1 and h_2 with a superficial activity $\bar{m}(h_2 h_1)$, in which the term $\bar{m}$ represents the mean value of the specific activity in the volume unit under consideration.

However, there are many other ways of replacing the volume-unit by a surface-unit to produce the same image. For each object having a given volume and activity there is a corresponding infinity of equivalent bidimensional objects—this equivalence is clear from the standpoint of scintillography. Reciprocally, a bidimensional object has an infinity of corresponding tridimensional objects with different volumes and activities.

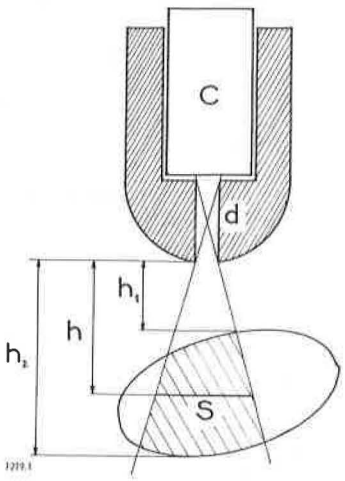

Figure 1. Diagram of counter

However, in most instances in applying this method, there is no ambiguity because scintillography is principally used to examine objects of which the shapes and location are approximately known. Nevertheless, these factors must be borne in mind when interpreting a scintillogram.

The Law of Darkening

We have just defined two magnitudes that allow us to characterize a part of the picture and the corresponding part of the object that it represents. The relationship between "brightness" of the object and "blackening" of the image will be discussed.

To simplify the explanation we shall replace the real object by an equivalent plane object—it is always possible to find one.

If we now consider a plane object with uniform superficial activity A, computation will show that when the counter is moved above this object, the number of pulses delivered by the counter during the unit of time is given by the formula $n = KA\Phi$ in which K is the sensitivity coefficient for the counter and Φ is the size of the radiation beam circumscribed by the diaphragm.

Since the stylus moves with a velocity V, the blackening is $N = KA\Phi/V$. Thus, for plane objects with a uniform superficial activity, the blackening is proportional to this activity.

Unfortunately, the shield does not keep out all the radiation and the "background" limits the area of linearity in the lower range by creating a halo. On the other hand, the thickness of the lines traced by the stylus limits this area in the upper range by creating a saturation phenomenon. Indeed, from the point where the strokes become very close and lie side by side, there is actually no increase in apparent blackening by having the strokes overlap each other.

It is interesting to compare the blackening formula obtained above to the corresponding photographic law,

$$N = kEt$$

in which k represents the sensitivity of the film; E, the amount of light; and t, the duration of exposure.

The counter sensitivity, therefore, corresponds to the film sensitivity. The light E corresponds to $A\Phi$ of the superficial activity according to the size of the effective beam and finally, the exposure time t corresponds to the reciprocal of the scanning velocity V, or the total scanning time T.

Allowing for the phenomena that limit linearity, it is possible to establish for the instrument some characteristic curves that are similar to the characteristic curves of photographic films.

Definition of the Image

Within the limits where the relationship between the blackening of the picture and the superficial activity of the object is linear, we shall see what takes place when we go beyond the boundary between two areas of the object with superficial activities of A_1 and A_2. Blackening does not suddenly jump from value N_1 to value N_2. Since the diaphragm of the instrument has a diameter d, there is a time during which the counter "sees" both a part of A_1 and a part of A_2. The blackening varies progressively (Fig. 2) over a distance that is of the same order of magnitude as the diameter of the diaphragm.

We can compare this phenomenon to that which takes place when a photograph is made with a simple *camera obscura* without the lens: the sharpness of the image is limited by a fuzziness due to the finite dimensions of the diaphragm. The sharpness of the picture taken with a *camera obscura* is increased by reducing the dimensions of the aperture but, then, brightness is lost. We also can increase the sharpness of the scintillogram by reducing the dimensions of the diaphragm, but in that case blackening is reduced. Because of the halo caused by the "background" of the counter we go beyond the limits of linearity and reduce the contrast between the image of the active area and that of the inactive area.

It is interesting to carry this comparison somewhat further. If we try again to increase the sharpness of the picture made with the *camera obscura* by reducing the dimensions of the aperture as much as possible,

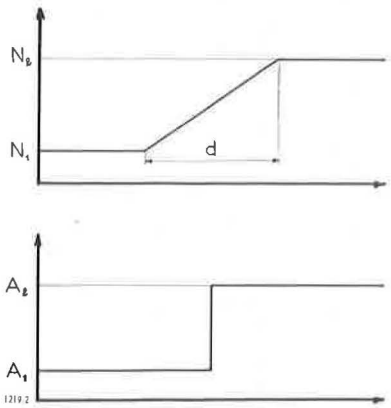

Figure 2. Upper diagram: object with two areas of superficial activities A_1 and A_2. Lower diagram: relation between blackening of the image and superficial activity of the object. Blackening varies progressively over a distance d that is the same order of magnitude as the diameter of the diaphragm

diffraction phenomena that increase the lack of sharpness appear. Similarly, if the dimensions of the diaphragm of the counter are reduced, a very important phenomenon which greatly limits the sharpness of the image becomes evident. This is called "statistical lack of sharpness."

To understand the reason for this phenomenon, we must remember that the pulses delivered by the counter are distributed at random. If the number of pulses that appear during a unit of time has the mean value n there is a certain probability that the number observed has a value n', different from n. The probability of a given relative deviation is greater as n is smaller. Therefore it is possible to observe local inversions in the blackening, the most marked corresponding to the lowest activity. The probability of an inversion is greater as the blackenings become closer and smaller. By reducing the diaphragm, the blackenings are reduced by a precise amount. A point is finally reached where it is no longer possible to discern clearly the images of two areas with different activities.

This phenomenon of "statistical lack of sharpness" was worth mentioning for it always occurs, even with very marked blackenings. When the contrast is weak, the lack of sharpness of "statistical origin" becomes particularly noticeable, and this greatly reduces the resolving power of the device. Indeed, if the object examined has an area where superficial activity has a value greatly different from that of the region surrounding it, the relevant blackening will not reach its theoretical value (by the law of blackening) unless this area is greater than the one the diaphragm circumscribes on the object. (For example, Fig. 3 shows the variations which occur in blackening when the counter goes over three strips differing in width.) This is due to the transition phenomenon called "geometrical lack of definition." It causes a reduction in contrast for images of small objects which has, as a corollary, an increase in the "statistical lack of sharpness" which makes the image illegible.

In practice, the involved area must have dimensions equal, at the least, to once or twice the diameter of the diaphragm in order to give an image suitable for interpretation.

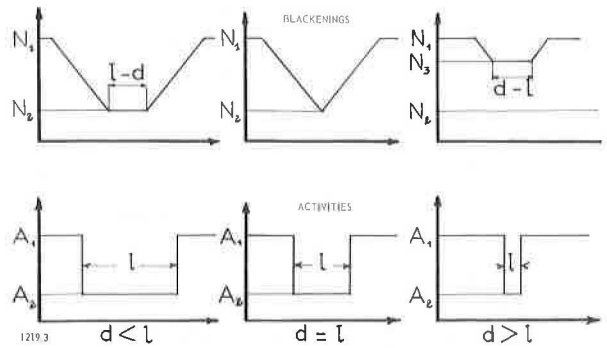

Figure 3. Variation in blackening when the counter equipped with a diaphragm having diameter d passes over a strip of length l having activity A_2, located in an area where the activity can be expressed by A_1 (examining distance $h = 0$)

PREPARATION OF A SCINTILLOGRAM

The parallelism just established between photography and scintillography is exceedingly useful when determining the conditions for obtaining a good image of a given object and is summarized in Table 1.

Table 1. Equivalences between Photography and Scintillography

Photography	*Scintillography*
Brightness	Superficial activity
Exposure time	Scanning time
Light	Product of superficial activity by the size of the beam used
Blackening	Blackening
Film sensitivity	Sensitivity of the counter (this varies with the voltage and the threshold of the pulse discriminator)

To obtain a good picture the photographer measures the mean brightness of the subject with an exposure meter, and, having chosen a film of a given sensitivity, he adjusts the diaphragm opening and the exposure. In the same way, the mean superficial activity of the object of which a scintillogram is to be made is first measured. This is done with the instrument itself, without operating the scanning device. After this the sensitivity of the counter (namely, the voltage and the discriminator threshold), the diaphragm and the scanning speed are adjusted, bearing in mind that (*a*) sharpness of the image is better as the diaphragm is smaller and the distance of observation shorter and (*b*) duration of a given scan must not be too long, lest the patient tires.

If the dimensions of the diaphragm are reduced, scanning time will increase and will be much faster than the separating power of the device. It therefore becomes necessary to compromise on an acceptable sharpness while retaining a reasonable scanning time.

The device built at the Curie Foundation has a constant scanning speed and from experience it is known that merely by adjusting the high voltage and discriminator threshold it is possible to obtain, without a change in the diaphragm opening, true pictures of objects having very different superficial activities.

The same examinations conducted under the same conditions (for example, examination of the thyroid body) do not always produce images with the maximum clarity, but, on the other hand, they permit classification of the scintillograms as a function of their mean blackening which then is related to the functional condition of the organ.

INTERPRETATION OF THE SCINTILLOGRAM

Neither the scintillographic image nor the radiological image permits direct immediate interpretation. It is only through knowing the conditions under which the scintillograms are made and understanding the properties that have been reviewed briefly above that valid conclusions can be drawn.

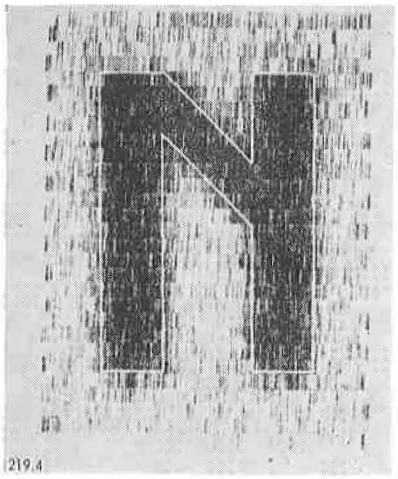

Figure 4

We have seen how a radioactive source gives a scintillographic image and we will now see how information on the object being studied may be obtained from a scintillographic image.

The interpretation of the scintillograms can be made in two stages. Firstly, the scintillographic image enables us to define a plane object. It gives a picture of its superficial activity, but the accuracy with which this object is visualized is poor due to imperfections in the method: (*a*) the contours may be inaccurately defined and, moreover, (*b*) since the law of blackening is a statistical law that involves small numbers, the values of superficial activity deduced from it contain serious errors. For example, in the reproduction of the scintillogram as a plane object with uniform superficial activity (see Fig. 4), the contour of the object is shown as an overprint and the lack of definition of the image's contour and the unevenness of the blackening can be seen.

Secondly, having defined the plane object, we have shown that in volume it could represent an infinity of objects. Theoretically, this indefiniteness can be eliminated by making scintillograms in three mutually perpendicular planes, but actually, as in radiology, this is in most instances unnecessary. Nevertheless in some cases (for example, a study of thyroid metastases), it is worthwhile to carry out at least two scintillograms at two different incidences to determine the shape and size of the tumour.

We shall see below that despite its imperfections, the scintillographic method can be very useful in medicine provided we do not use it for information it cannot supply. The method has been applied at the Curie Foundation in a study of thyroid and liver diseases and for following certain cases being treated with radioisotopes.

CLINICAL APPLICATIONS

Thyroid Scintillography

The scintillographic method was first applied for the observation of thyroid tissue loaded with I^{131}.

Method

The scintillographic examination of thyroid tissue is relatively simple and is done in three stages: (i) administration of I^{131} to the patient; (ii) systematic scanning over normally or abnormally located thyroid tissue; and (iii) automatic topographic analysis of the pertinent zones.

The patient fasts for 3 hours and is then given orally an amount of I^{131} sufficient to produce a superficial activity equivalent to about 1 $\mu c/cm^2$. The dose is determined as a function of the apparent weight and mean iodine-fixation rate, and generally a dose of 100 μc I^{131} is adequate.

A systematic search for thyroid tissue precedes all scintillographic examination. This is done very easily with the scintillograph before starting the scanning device or the stylus. It makes possible a rapid estimation of location, size and mean I^{131} uptake rate of the thyroid gland or of the abnormally located heterotopic or metastatic thyroid tissue.

An automatic analysis of the iodine-capturing zones is made using the same apparatus, but this time with the recorder and the recording stylus and the scanning device in operation. Perfect centring is necessary for accurate anatomic localization, and framing should be

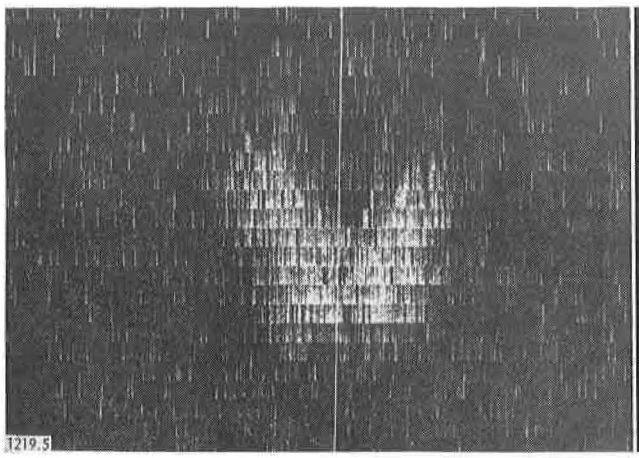

Figure 5. Normal thyroidogram

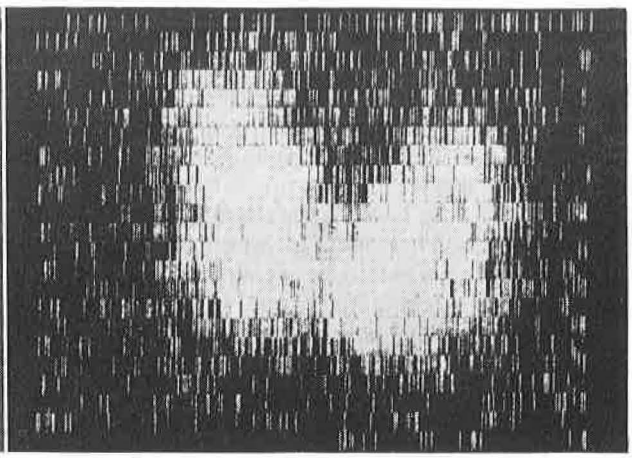

Figure 6. Thyroidogram in Graves' disease

adapted to the size of the zones to be explored. The utilization constants of the device are set, according to the general rules described above, for each case.

Analysis of the Thyroidograms

The normal thyroidogram shown in Fig. 5 has the form of two ovoid masses in which the wider shadow represents the lower pole. These two masses are separated by a variable distance and connected by the less dense isthmus. The lower pole is more or less elongated depending on the case. The area of the image varies between 20 and 30 cm^2. The contours are clear and the colour homogeneous.

The abnormal thyroidograms generally show multiple and complex modifications which make their interpretation difficult. For clarity of presentation, we shall distinguish between topographic, functional, dimensional and morphological abnormalities.

The topographic abnormalities can readily be shown, provided the anatomical elements have been correctly located. In most cases, there is a displacement of the organ, for example, anteriorly. Occasionally, this shift is accompanied by a more or less marked distortion of one or the other lobe. A comparison of the scintillographic images and the radiographic images is very interesting. By superimposing one on the other, it is often possible to verify the thyroid origin of a radiological opacity of the nature described here.

The functional abnormalities are related to the modifications of the colour of the scintillographic image. There might be global and homogeneous modifications of the blackening corresponding to a diffused functional disorder which results in either a hyper- or a hypo-fixation, a frequent index of hyper- or hypoactivity. This may be the only abnormality, but in general it is associated with an increase or a decrease in the volume. Figure 6 is a good example of a thyroidogram showing thyroid hyperactivity in Graves' disease. The modification in colour may often be heterogeneous corresponding to hyper- or hypo-fixing nodules.

Modifications in the volume of the thyroid body appear as an increase or decrease of the surface of the thyroidogram. They involve the whole of the organ in the case of diffused hypertrophy or pure thyroid atrophy. More often they are associated with morphological modifications.

The morphological abnormalities are connected with modifications in the contour of the scintillographic images. They present a variety of aspects which can be schematically classed as incomplete or additional images. The incomplete pictures present fairly characteristic aspects in the body of the thyroidogram or at its periphery which enables us to interpret them easily. When they show a particularly sharp edge and a substantial contrast, they are suggestive of cystic formations. On the other hand, the presence of ill-defined and irregular edges suggests a low uptake nodule, which may be benign but is more often malignant. Other pictures range from simple convex distortions of a lobe to voluminous polynodular goitres. Figure 7 shows an elongated goitre.

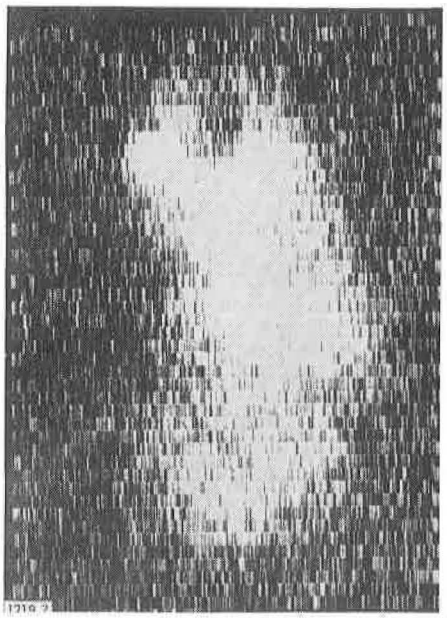

Figure 7. Scintillogram of an elongated goitre

It is interesting to study heterotopic or metastatic thyroid tissue by scintillography. The embryological heterotopes of the thyroid can be accurately located and their shape and activity well defined by this method. When the metastases of thyroid cancer acquire enough iodine, it is possible to make a complete study of them. An image can then be obtained that provides data not only on their contour and dimensions but also on their functional activity. Figure 8 shows a case of a metastatic thyroid-neoplasm invasion of the pelvis in which a number of details appear.

Indications for Thyroid Scintillography

Thyroid scintillography is indicated either to confirm a diagnosis or to follow the course of treatment of thyroid affections. It is useful in diagnosis to complement the information supplied by clinical, radiological and biological examinations.

During examinations for syndromes of the thyroid showing major hypoactivity or hyperfunctioning, a topographic analysis of the gland is very useful. In cases of hyperthyroid activity, it is possible to distin-

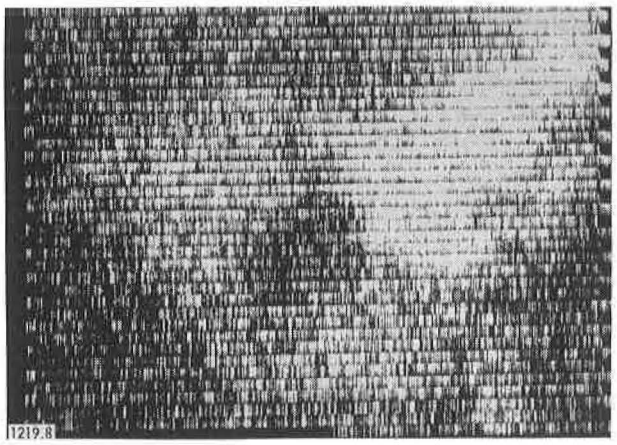

Figure 8. Metastatic thyroid carcinoma in the pelvis

guish cases of diffuse hypertrophy from those with only hyperactive nodules. This may be important therapeutically because of the different indications for medical or surgical treatment.

It is quite obvious that in making the diagnosis of benign or malignant thyroid tumours, scintillography is extremely useful. The thyroidogram makes it possible to determine the localization, volume and shape of the lesions. It also furnishes information on how functional activity is distributed in the gland. The method may be extended to the iodine-capturing metastases and is valuable in considering indications for therapy.

In the therapeutic field, besides making it possible to determine better the indications for treatment, scintillography also makes it possible to modify and adapt techniques and to verify the results of thyroid treatment, whether medical, surgical or radiotherapeutic. For medical treatment, it is particularly helpful for determining indications and for following the efficacy of thyroid extracts, of synthetic antithyroid compounds and of stimulants of thyroid function.

Prior to surgery, it is possible to make an accurate diagnosis of the lesions and to foresee the difficulties that may develop. Scintillography makes it possible to evaluate postoperative results and particularly to evaluate the success of the excision of the lesions.

Scintillographic analysis has the same advantages in external radiotherapy as it has in surgical treatment. It is useful especially for a better determination of the irradiation beams. However, it is particularly for cases where radioiodine is employed in treatment that it is most useful. Whether dealing with functional syndromes of goitres or thyroid cancers with or without metastases, radioiodine therapy, if it is to be correctly carried out, requires prior to its administration a highly accurate determination of the irradiation dose for the irradiated tissue. The scintillographic image gives information on the size of the lesions and their rate of iodine fixation, and provides data for computing the therapeutic dose. Finally, it is possible to assess the anatomic and functional effects of the radioiodine during treatment.

Liver Scintillography

Scintillography of the liver is not possible by administering a radioelement in the form of a simple substance. Taking advantage of the detoxifying function of the liver, a substance is administered which is essentially or exclusively eliminated by the liver. The substance used is Rose Bengal tagged with I^{131}. This contains 4 iodine atoms of tetrachlorofluorescein. Rose Bengal labelled with I^{131} can be followed within the organism because of the γ rays emitted.

Scintillographic analysis gives a picture of the liver, or a hepatogram, when it is done at the time of maximal concentration of the Rose Bengal in that organ.

Method

The method is similar to that applied in the study of the thyroid. It consists of three stages: (i) administration of tagged Rose Bengal; (ii) functional liver investigation, and (iii) analysis of the scintillographic image.

An amount of labelled Rose Bengal in isotonic solution is injected intravenously. The equivalent superficial activity of the dose injected corresponds to 1 $\mu c/cm^2$. The amount depends on the apparent weight of the liver and the assumed rate of uptake. For a normal liver weighing approximately 1500 g which fixes 30% under ideal conditions, a dose of 500 to 1000 μc is adequate. This amount seems large when compared with the dose used for thyroid examination, but it represents only a small amount of irradiation for the body and a moderate one for the liver. The tagged Rose Bengal is very rapidly extracted from the blood so that the irradiation received by the whole organism is about $\frac{1}{10}$ rad. Passage through the liver lasts only a few hours and the resulting irradiation is assumed to be less than 5 rad. The subsequent irradiation of the digestive tract is certainly less than this.

Functional investigation of the liver of itself has the advantages of a biological study of chromagogue function. However, its use here is for determining the ideal conditions for obtaining a good scintillographic image. It includes a study of blood clearance as well as liver concentration. After the intravenous injection, blood samples of 0.05 or 0.1 ml are taken during the first 2 hours and are used to measure radioactivity of the blood. Normally after a half-hour only 10% of the substance is left in the body (see Fig. 9, curve 1). The activity of the liver tissue is recorded simultaneously and this activity increases progressively because there is a marked uptake of the Rose Bengal. The curve then reaches a maximum which corresponds to the equilibrium between fixation and elimination by the liver. The maximum is relatively high and is normally reached a half-hour after intravenous injection (see Fig. 9, curve 2). Thus the best time for carrying out scintillographic examination for a patient with normal liver function is approximately one-half hour after the intravenous injection of tagged Rose Bengal.

The patient is placed in a supine position for the scintillographic examination. The position of the thorax, umbilicus and breasts are carefully noted. Scanning of the area can be carried out moving from the lower to the upper part, or in the reverse direction. In the former case, the gall bladder has not had time to concentrate the drug. If the latter method is used, it is possible not only to obtain a hepatogram but also a cholecystogram if the patient has fasted. This is the usual and the best method.

Analysis of Hepatograms

For a normal liver, the hepatogram (Fig. 10) gives the picture of a shaded surface entirely located under the ribs with sharp and even contours in the form of a curvilinear triangle. The lower side of this triangle follows the costal margin and the upper side passes through the right breast and is marked by the shape of the heart on the left. The shading of the surface is homogeneous, although slightly darker over the larger

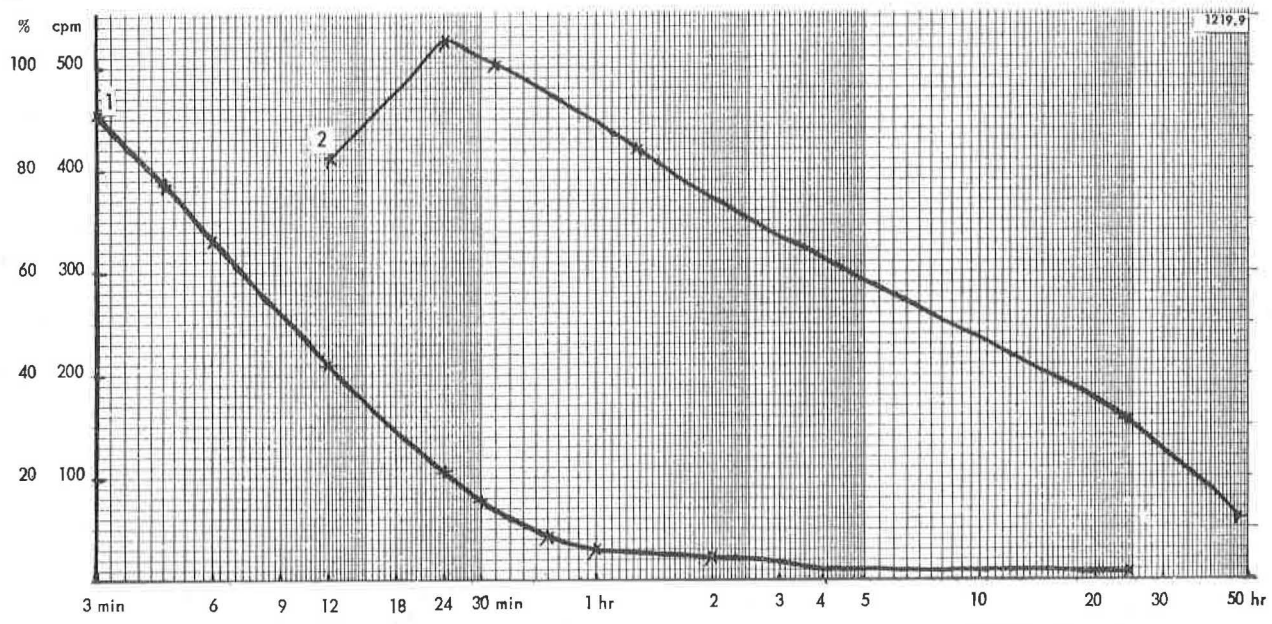

Figure 9. Radioactivity in blood (curve 1) and over liver (curve 2) after intravenous injection of I^{131} Rose Bengal

right lobe. The oscillations over the area are between 200 and 300 cm^2. The image of the gall bladder (or the cholecystogram) appears at the level of the inferior internal edge of the right lobe as a more marked opacity, ovoid in shape and darker in colour.

The analysis of abnormal hepatograms makes it possible to distinguish topographic, functional, dimensional and morphological anomalies.

The topographic modifications are caused by shifts in position of the organ, and are more often due to a juxta- or extra-liver tumour which pushes back or, in some cases, tilts the organ.

The dimensional modifications are the result of changes in the volume of the liver which may have an over-all effect on the organ, but more frequently affects only one of the two lobes. Sometimes there seems to be an equilibrium between partial atrophy and a neighbouring compensatory hypertrophy.

The functional modifications correspond to abnormalities in the shading of the scintillographic image. They may be the result of changes which uniformly affect the whole organ but which are noted only in cases of total functional deficiency. More often localized alterations occur and appear as areas of decreased opacity, rather than an increase in opacity corresponding to an area of functional hyperactivity.

The morphological modifications are characterized by alterations in the contour or the shading of the image. In most cases, the images show lacunae that disturb the hepatogram and these correspond to an area of hypofunction or tumour tissue that is not functional. These lacunal images are infinitely variable in number, size, shape, shading and location. They may be produced by cysts, abscesses, primary or secondary neoplasms, angiomata, etc. Because of its limited power of separation the scintillograph reveals only lesions with a diameter greater than 2 or 3 centimetres, unless they are confluent.

Indications for Liver Scintillography

The indications for liver scintillography are more relevant for the diagnosis than for treatment of liver disorders. Liver scintillography is especially applicable where surgical affections of the liver are involved. A few of the most characteristic examples are shown here.

The images of hydatid cysts of the liver show extremely clear lacunae in the middle of liver tissue (see Fig. 11). Indeed, the total absence of vascularization makes it possible to obtain particularly marked contrasts between the functional tissue and the cysts, and the evenly rounded shape clearly delimits the cyst from surrounding normal liver tissue. These lacunae are generally single, occasionally double and rarely multiple.

Liver abscesses produce lacunal images which are not as clear as the images of cysts. There is a peripheral area of reaction which reduces the contrast of the lacunae. The contours are more regular than in the case of the cysts. Here again, except for rare exceptions, the tumour is usually single (see Fig. 12).

As might be expected, the lacunae that correspond to primary cancer are very irregular due to peripheral neoplastic invasion and they are very often difficult to interpret (Fig. 13). The changes within the tumour mass do not always produce good contrasts and the diagnosis rests in the main on the presence of a single lacuna with very irregular contours.

Only neoplastic metastases formed by nodules having a sufficient volume can be shown by the hepatogram. The image from a secondary liver cancer is characterized by a multiplicity of lacunae with sharp contours, reduced dimensions and marked contrast (Fig. 14). In the case of smaller and very numerous hepatic nodules the image seems to be heterogeneous, although

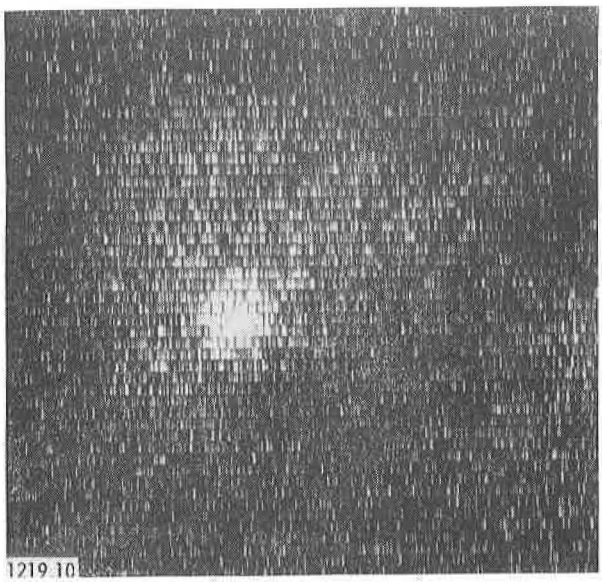

Figure 10. Normal liver

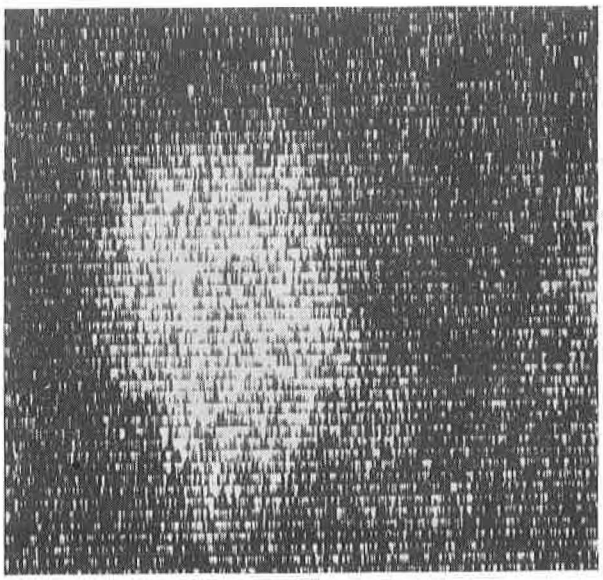

Figure 11. Hydatid cyst

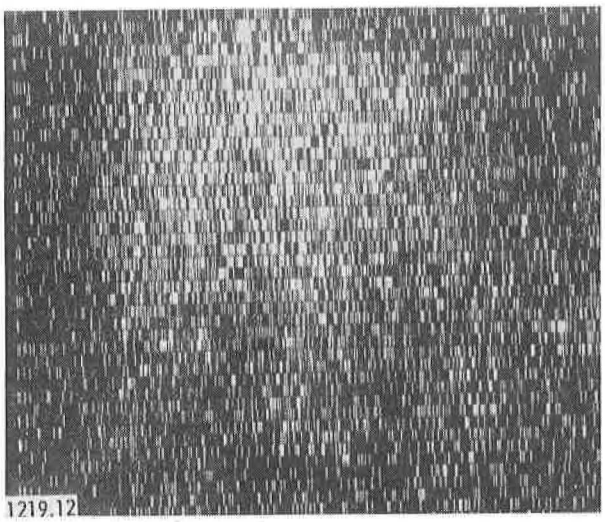

Figure 12. Liver abscess

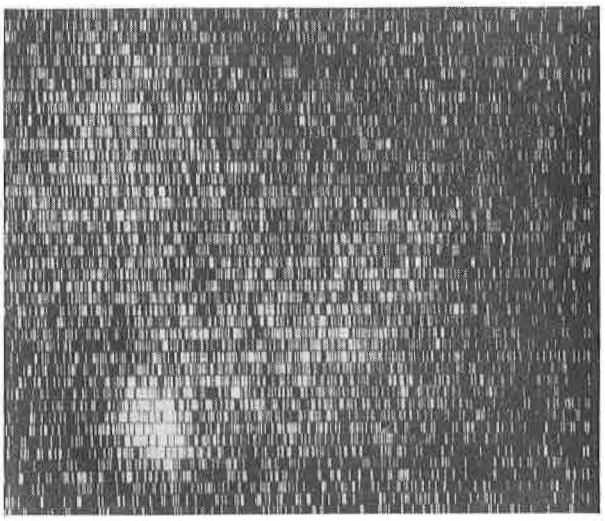

Figure 13. Primary hepatic neoplasm

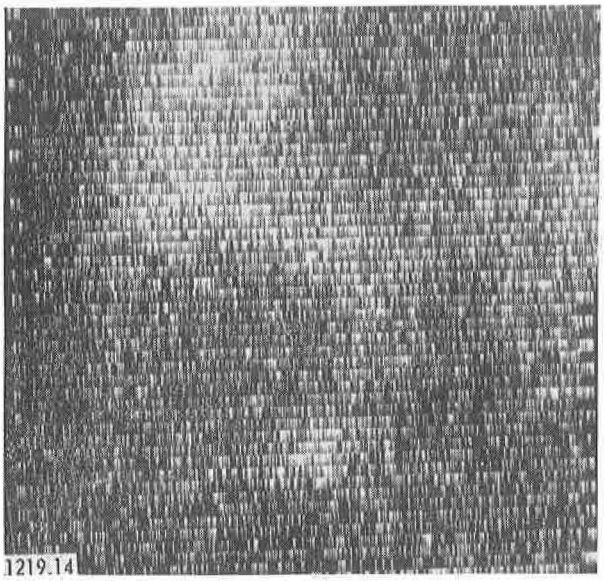

Figure 15. Reticulohemangioma of the liver

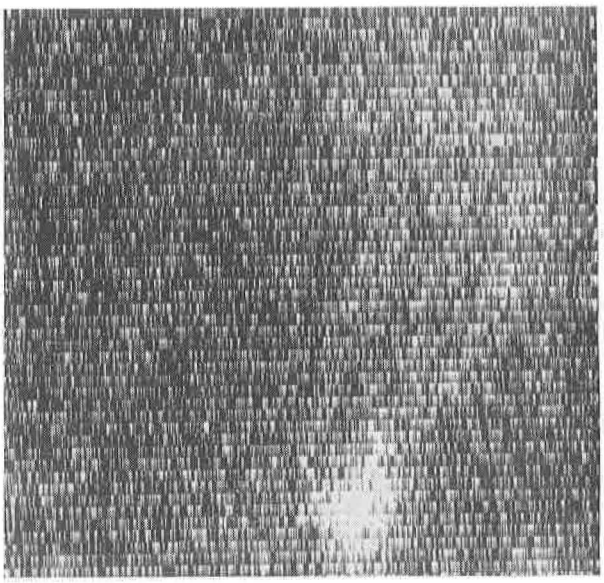

Figure 14. Secondary liver neoplasm

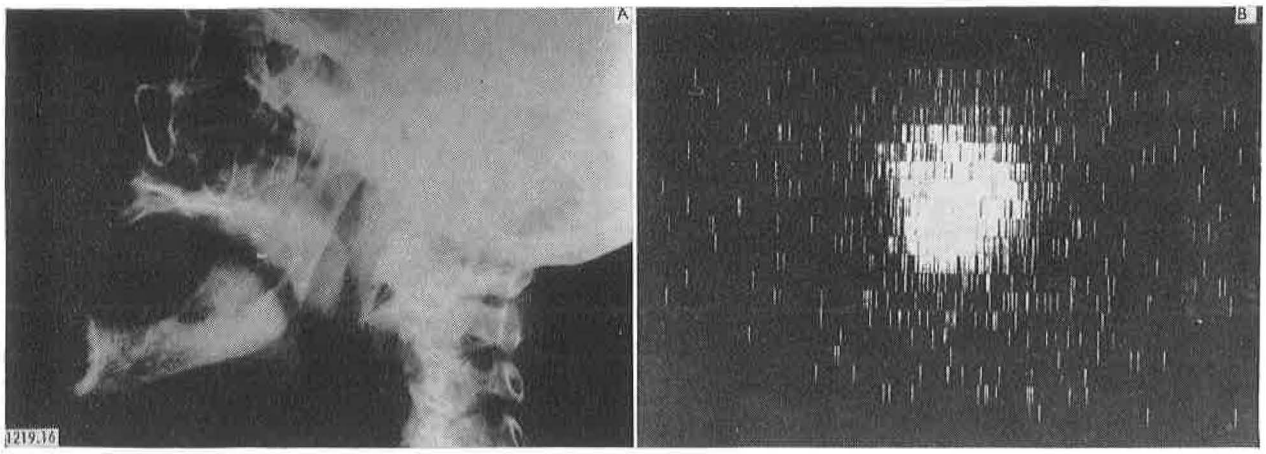

Figure 16 A and B. Scintillograph with radiological confrontation

it is impossible to make a distinction between such an image and that which is obtained from the sclerotic changes caused by, for example, cirrhosis of the liver.

The reticulohemangiomas of the liver are characterized by a marked enlargement of one lobe. The lacunary image represents nearly the entire increase of volume that pushes back the healthy parenchyma. Because it is so highly vascular, it is characterized by a less marked and quite different contrast from that caused by a cystic tumour of similar volume (see Fig. 15).

In medical conditions such as cirrhosis, jaundice, etc., functional study of the liver with labelled Rose Bengal is complemented by scintillographic analysis. The latter makes possible a functional topographic study of the organ from which it is possible to derive data not only on the amount of functional capacity of the liver but also to determine whether functional deficiency is due to a diffuse involvement of the entire liver tissue, to homogeneously distributed islets or to areas localized in either of the lobes. In addition, the hepatogram makes it possible to estimate the extent of functional replacement which often takes the form of a compensatory hyperplasia.

SCINTILLOGRAPHY AS A METHOD OF CONTROL

The scintillographic method is not only indicated for diagnostic use, but it may also be used to follow therapy with radioisotopes. Following the injection or implantation of radioelements, a scintillographic study gives an image that represents the spatial distribution of the irradiation. This is particularly useful if we want to know the limits of therapeutic irradiation and its coincidence with the tumour lesions, and in demonstrating the degree of uniformity of the radiation dis-

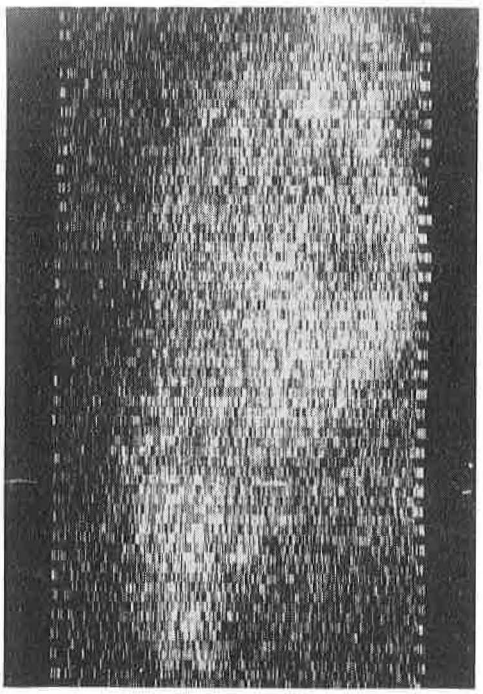

Figure 17. Colloidal radiogold in pleural cavity

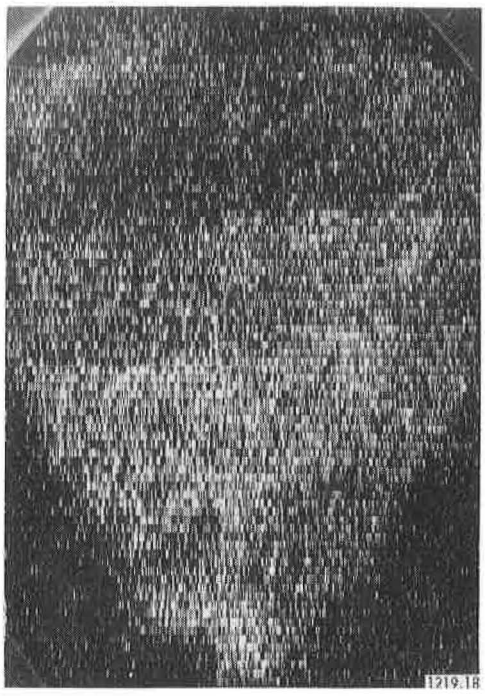

Figure 18. Colloidal radiogold in peritoneal cavity

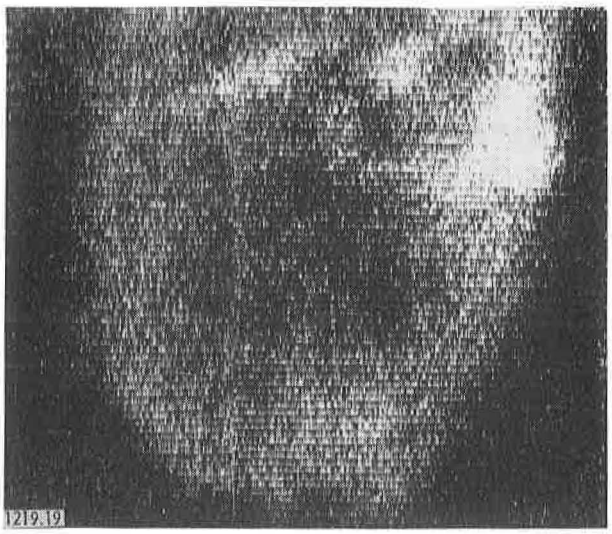

Figure 19. Heterogeneous distribution of colloidal radiogold in pleural cavity

tribution. Scintillographic analysis for monitoring can be applied either when implantations of sealed sources or injections of radioactive substances in colloidal form have been used.

Monitoring after Implantations of Sealed Sources

Implantation of sealed sources can be effected by means of punctures with radium or cobalt needles, by sutures with radioactive substances or by implantations of radioactive gold grains.

In the case of punctures with needles or sutures with threads, direct examination is often sufficient to verify the topographic distribution which can be completed by a radiographic examination under two incidences. The usefulness of this method is limited.

Implants of radioactive gold grains disappear inside the lesions and the radiographic method is used to determine their distribution. Often, the radiographs under two incidences provide only a representation that is difficult to interpret. When carried out under two incidences, the scintillographic images give better information on the distribution of the radioactivity. Figure 16 shows an example of a scintillograph with a radiological confrontation.

Monitoring after Injections of Radiocolloids

The radiocolloidal solutions are being used to infiltrate tumours or are being introduced into serous cavities (pleural and peritoneal). Radiographs, as noted above, do not show whether or not the distribution of the colloidal particles is satisfactory. Scintillographic analysis alone will permit us to determine the extent and uniformity of the colloid diffusion. This method is particularly useful after the infiltration of colloidal

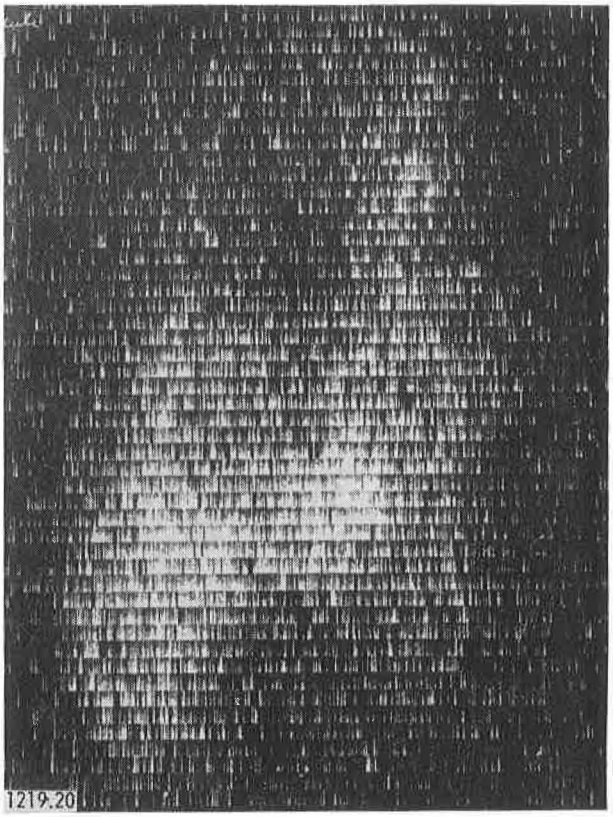

Figure 20. Heterogeneous distribution of colloidal radiogold in peritoneal cavity

radiogold into a variety of tumours. The injections of colloidal radiogold into serous cavities for the symptomatic treatment of pleural or peritoneal effusions can be readily controlled. When these examinations are carried out systematically, the distribution of radioactivity appears to be homogeneous in some cases. Figures 17 and 18 show, respectively, images of pleural and peritoneal cavities in which colloidal gold is diffused fairly homogeneously. However, in many of these cases the diffusion of the radiocolloid may be very irregular. With treatments into the pleural cavity deposits may predominate at the base; in the case of treatments into the peritoneal cavity deposits may predominate around the site of injection. Occasionally adhesions and even septation formation will give a checkerboard type of image. Figures 19 and 20 are images of the heterogeneous distribution of colloidal gold in the pleural and peritoneal cavities. It is obvious that the therapeutic effect may be inadequate with heterogeneous distribution and it is often possible to show a relationship between failure of therapy and lack of uniformity in the distribution of the radiocolloids. In cases where the effect of septation on the adequacy of distribution is doubtful, injection of a small amount of the radiocolloid may determine whether or not the use of this method is indicated.

The Use of Increase of Contrast in Automatic Photoscanning for the Visualization of Organs and Tumors by Means of Radioactive Isotopes

By C. Winkler*

Interest in the determination of the distribution of radioactive materials within the body by external counting of gamma radiation for purposes of clinical diagnosis and for checking therapeutically applied isotopes increases continuously. In 1950 *Allen et al.*[1] developed an automatic scanning device which registered mechanically the counting rates according to their distribution in the working plane by use of a relay-recording system connected to a Geiger counter. Since then, especially after the introduction of the scintillation counter for medical use, several reports have been published suggesting different possibilities for improving the graphical representation of the distribution of isotopes in patients. Progress has resulted mainly from the use of spectrometers to suppress interfering scattered rays and background radiation by pulse height analysis.[2] Another method for eliminating scattered radiation and improving the degree of resolution without loss of radiation intensity is based on coincidence measurements of the annihilation radiation of positron emitters, e.g., in connection with the localization of brain tumors.[3] Further improvements might be achieved with other electronic equipment, for example, by employing a special ratemeter circuit which accelerates the speed of the scanning motors whenever the counting rate falls below a certain critical preset value.[4] The development of focussing collimators[5] has considerably improved spatial resolution, which is particularly important when small areas and minor differences in radioactivity are to be detected.

Finally, for the visualization of small differences in radiation intensity, very essential experiments in the development of photoscanning methods have recently been published.[6,7] By using these procedures, increased contrast in the resulting photographic image could be achieved in two ways; first, by a scanning light beam whose pulse frequency and pulse brightness increase with the counting rate or secondly, by light emission from a tungsten filament with filament current (light intensity) increasing with counting rate.

After a detailed study of the methods mentioned above, we have carried out several experiments with these commonly used scanning devices. However, since in many cases the equipment proved to be unsatisfactory, we have developed a scanning device and procedure which, in our opinion, offer especially favourable conditions for the use of radioactive substances in diagnosis. We assumed that in some cases it might be desirable to have a picture which quantitatively represents the distribution of isotopes. However, it might more often be particularly important to demonstrate accumulations of radioactive isotopes in certain parts of the body, even if the pulse rates are low and the difference of the radioactivity between the location of the accumulation, e.g., a tumor, and the surroundings is small. In addition, we believed it important to construct a device for accurate anatomical localization of isotope distributions with a minimum possibility for error.

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DEVICE AND PROCEDURE

A scintillation counter with a thallium-activated NaI crystal is connected *via* linear amplifier–differential discriminator to a ratemeter in the usual way. The output voltage supplied by the ratemeter is linearly dependent on the pulse rate; it is modified in a modulator which, because of its main function, may best be called "contrast amplifier." Its special qualities will be explained later on. The modulator energizes the light source of a photographic recording system which serves to expose an X-ray film. The output of the count-ratemeter is also fed to a line-drawing graphic recorder (Fig. 1).

The scintillation crystal is housed in a lead collimator which may be provided either with simple cylindrical, simple conical or with focussing aperture insets. This scintillator, fixed on a scanning framework, is driven by motors at constant speed unless the counting rate falls under a preselected minimum value. When this occurs, the scanning motors are accelerated by a special ratemeter circuit.

For the method of photographic recording we have developed, we use a light focussing system with a 3.8 v Osram light source. The scintillator and focussed light source are colinear and rigidly connected with the scintillator above and the light source and film below the patient. Lateral motion of the scintillator is thus perfectly reproduced by the same motion of the light source. The X-ray film Kodak HS is mounted in a light-proof box with the light source introduced through a dark slide. The plateholder is in direct

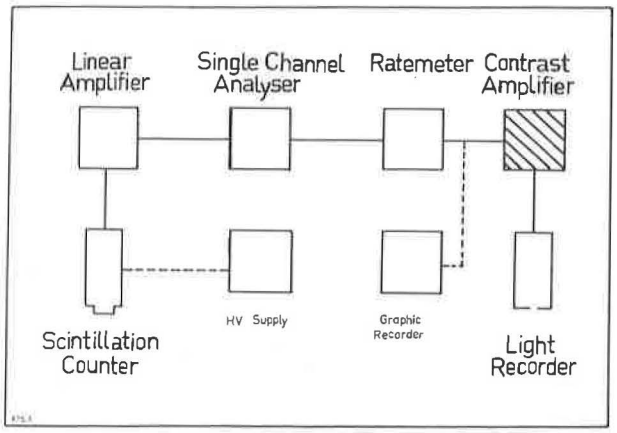

Figure 1

contact with the body, but if necessary a lead shield may be interposed. After finishing the scan and with the position of the film against the body unaltered, an X-ray exposure of the body is made on the same film. For this exposure the scintillator is replaced by an X-ray tube at as great a distance as possible. This double exposure will result in a combined roentgen-photoscintigram in which the distribution of the radioactive isotopes is in correct topographic relation to the section of the body in question.

In placing the film near the body to be scanned the possibility of direct exposure to the isotope must be kept in mind. However, with the use of tracer doses this effect is of no practical importance. In cases where the distribution of therapy doses, e.g., radiogold, is to be determined, the lead screening previously mentioned can be introduced by means of a rail between the film and the patient if necessary. Since in these cases a high scanning speed can be chosen with respect to the high degree of activity, interfering direct exposure can almost always be avoided. If necessary, however, the recording may take place beside the patient on a table that is more effectively screened.

The modulator, or contrast amplifier already mentioned, consists of two independent direct current amplifiers connected in series, and serves to transform linear pulse rate changes into exponential ones. Thus it is possible to achieve an increase of contrast in the recorded image of the isotope distribution whenever there are but small differences of radioactivity. The degree of contrast will be determined by the characteristic calibration adjustment of our amplifier and by the choice of the initial recording point. At a constant scanning speed the combination of the amplifier gain, the qualities of the light source, and the light calibration of the X-ray film will result in reproducible film densities.

Figure 2 shows a set of curves (C_7 to C_6) as they frequently occur in practice. In this instance the curves nearly satisfy the parabolic function $y^2 = 2px$ with various parameters p. For practical purposes the pulse rate has been plotted against film darkening as determined by a photometer.

In cases where an arithmetic relation between the film density and the counting rate is useful, this can be approximately achieved by an appropriate choice of the characteristic curve and the respective initial point, combined with empirical standard films.

In order to choose the most advantageous parameter for maximum contrast, one must consider the differences of radioactivity to be detected, the medium value of the pulse rates and their statistical variations. The latter is given for a RC ratemeter system as[8]

$$\mathfrak{S} = 0.71 \sqrt{\left(\frac{N}{RC}\right)}.$$

Thus the variation is proportional to the square root of the counting rate N and inversely proportional to the square root of the time constant RC. It is obvious that with small pulse rates, $\mathfrak{S}$ determines the lower limit of resolution. A decrease of $\mathfrak{S}$ can always be achieved by increasing RC. This, however, makes the ratemeter more sluggish and requires slower scan speeds with the attendant problem of slow drift. The state of equilibrium of the ratemeter reading is practically achieved after a time of setting of[8]

$$t = RC(0.5 \log 2NRC + 0.394).$$

With time constants $RC > 1$ sec line shiftings due to the inertia of recording can be avoided by an automatic compensating control mechanism.

In practice, we may generally dispense with the mathematical treatment of these relations—which we shall deal with elsewhere—by using the graphic method to be described. With this method, it is nearly always possible to find the best setting for the contrast amplifier.

If only small pulse differences are present in the scintigram, we usually scan the respective area of the body for a first orientation at a medium speed with small ratemeter time constant, and register the pulse rates on the recorder. Areas which suggest increased concentration of radioactivity determined by this scanning will afterwards be examined at a slower speed and perhaps greater time constant. The difference of the average values of the recorded pulse rates as well as the recorded statistical variation around these average values will then be used to find the best suitable char-

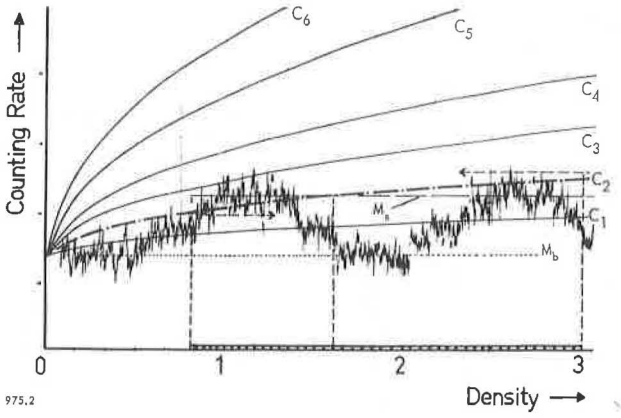

Figure 2

acteristic of the contrast amplifier (Fig. 2). The curves plotted correctly to scale on transparent paper are laid upon the recorded counting rates in such a way that only those pulse rates that are to be represented in the scintigram will fall into the area of the characteristic curve chosen. (See Fig. 2 where such a curve is indicated by the use of a broken line alternating with dots.) It is possible to avoid film darkening from the background counting rate by choosing an appropriate zero point of recording.

The advantage of our scintigraph method when compared with other scanning methods, e.g., with mechanical relay recording systems, can be illustrated by Fig. 3 which represents the result obtained from a neck phantom. Above the right and the left side of the thyroid gland radiation intensities were detected which were respectively about 1.25 and 1.35 times higher than that of the background area. The very small pulse rates are represented on the recorder curves. Such small differences in intensity are not picked up when the thyroid gland is visualized by conventional means and with relatively large doses of iodine-131 (50 to 200 μc). However, from our recent experience,[9,10] small differences are detected when either very small doses of iodine-131, or iodine-132, are administered in order to reduce radiation exposure.[11] Figure 4 shows the scan which was taken from the same phantom by relay recording with one of the conventional methods. Visualization was not achieved by this method.

In Fig. 5 a brain tumor (glioblastoma) is detected by RISA. The accumulation factor was about 1.3 to 1.4. In cases where the accumulation area contains several times the background radioactivity, contrast amplifying is not necessary. This is demonstrated in Figs. 6, 7 and 8 which show scintigrams of an adenoma of the thyroid in the skull, a dystopic thyroid gland in the tongue and a retrosternal goiter after the application of I^{131}. Figure 9 represents the rose bengal scintigram of the right lobe of the liver of a patient whose left lobe was destroyed by metastases from a carcinoma.

To detect the distribution of therapeutically applied isotopes, as, e.g., radiogold, we chose an amplifier increase giving the ratios of distribution in an approximately linear way (Fig. 10).

Finally, we should like to point out that in many cases the quantity of radioactive materials needed for scintigrams may be reduced by using increased contrast. In order to keep the radiation exposure as low as possible—especially where young patients are concerned—we very often use the short-lived I^{132} for tests of thyroid function.[12] Recently we have also carried out thyroid gland scintigraphy with I^{132}, which is al-

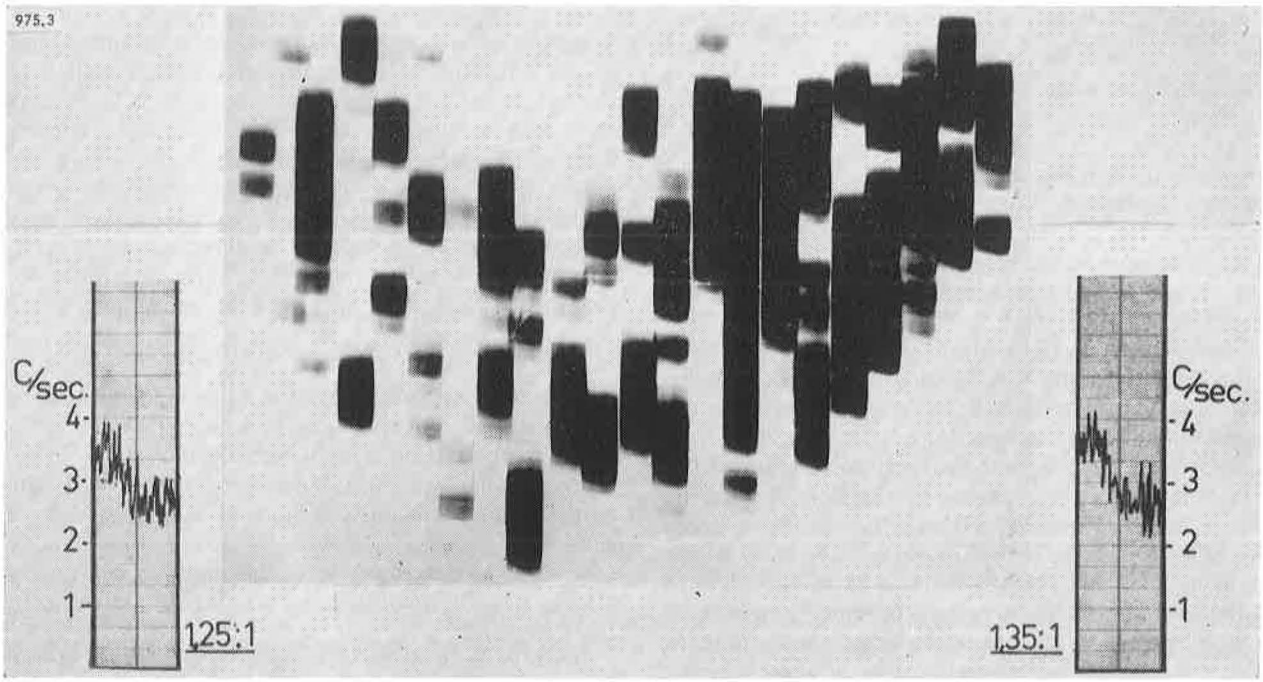

Figure 3

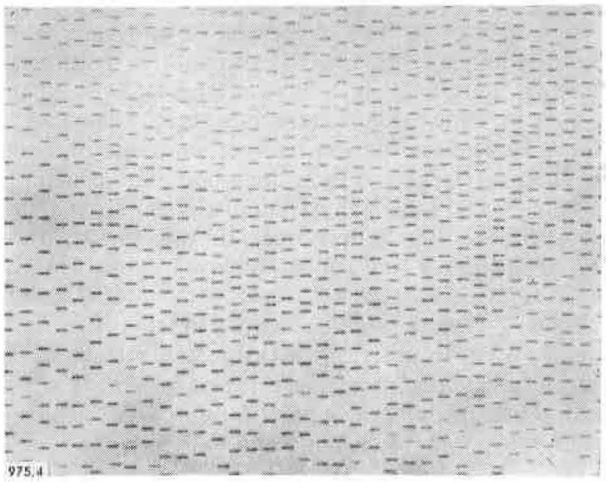

Figure 4

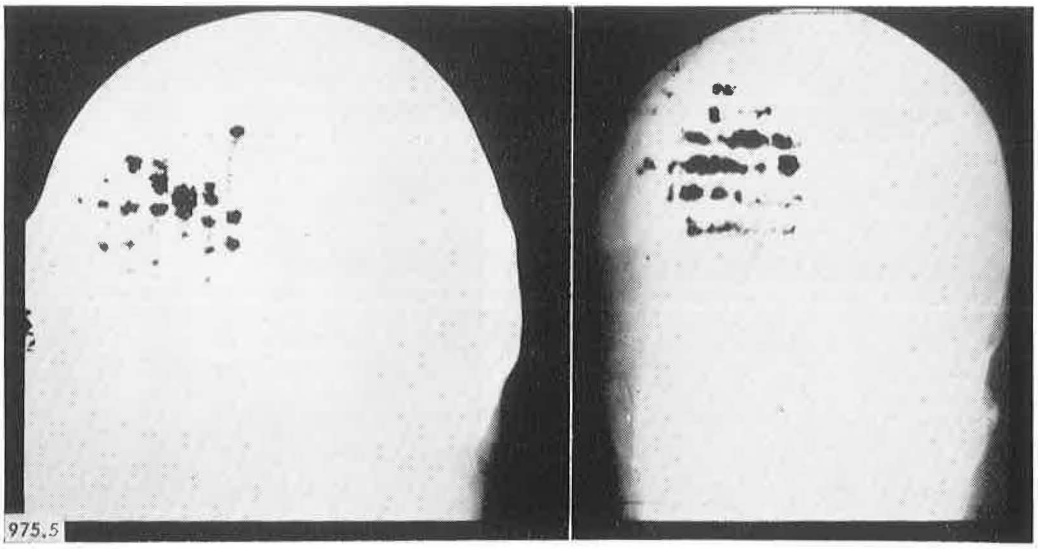

Figure 5

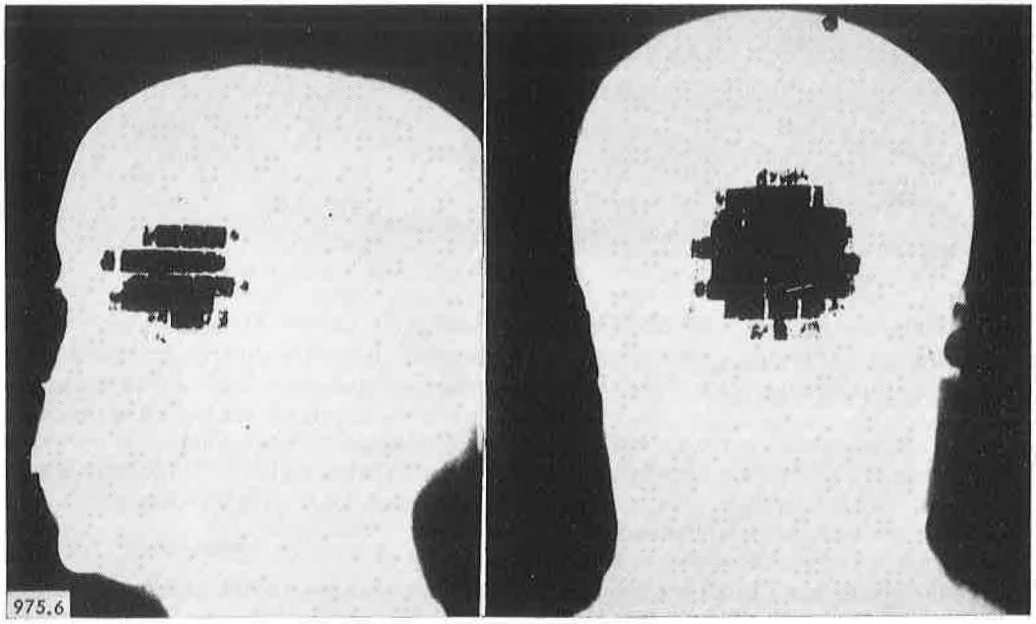

Figure 6

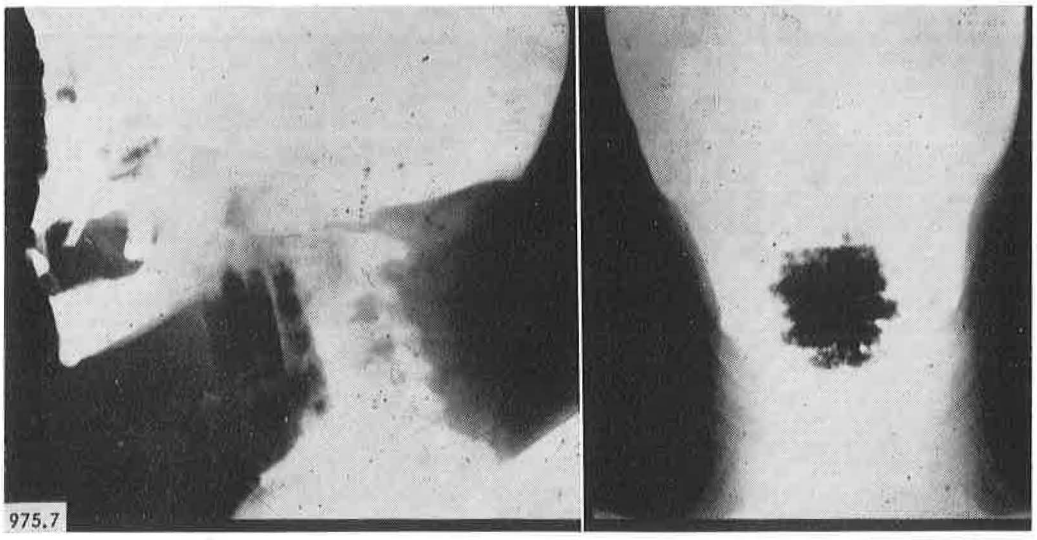

Figure 7

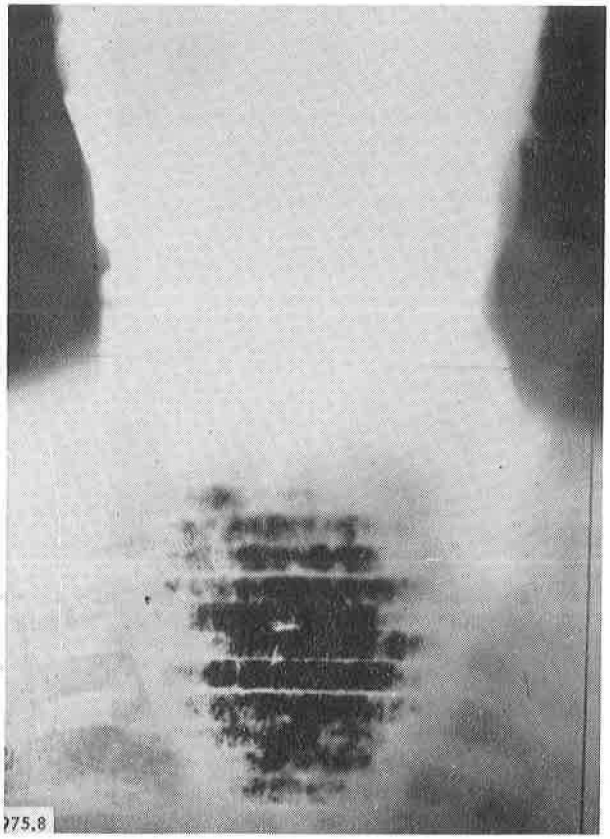

Figure 8

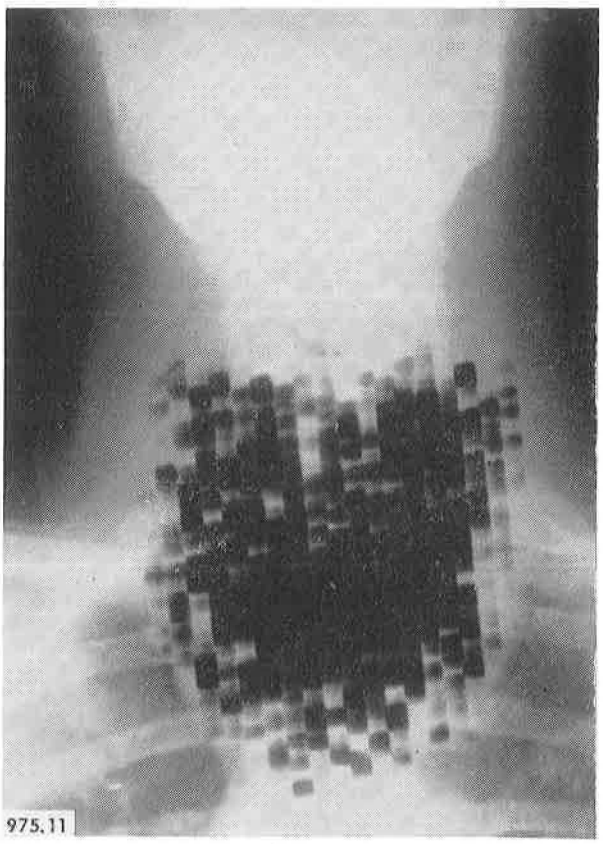

Figure 10

most always possible during the first hours of the iodide phase. The optimum time for taking a scintigram with I^{132} is dependent upon the iodine avidity of the thyroid gland.

Since a decrease of radioactivity occurs within the course of the scanning procedure, because of the short half-life of I^{132} ($T\frac{1}{2}$ = 2.3 hours), it is necessary to attach a compensating device to the ratemeter to make up for the loss of intensity. For measurement of 10 to 20 minutes' duration the loss is 5 to 10 per cent.

The scintigram of a retrosternal goiter in Fig. 11 was taken three hours after the administration of a test dose of 35 μc I^{132}. Location, shape, and extension of thyroid tissue are clearly indicated. In comparison with the test dose of 100 μc I^{131} commonly used for thyroid gland scanning, the radiation exposure of the thyroid is about 120 times less and correspondingly the radiation exposure of the whole body is greatly reduced because of the shorter half-life of I^{132}.

SUMMARY

After detailed studies of the scanning methods reported during recent years, and after clinical and experimental tests with a conventional scanner, the au-

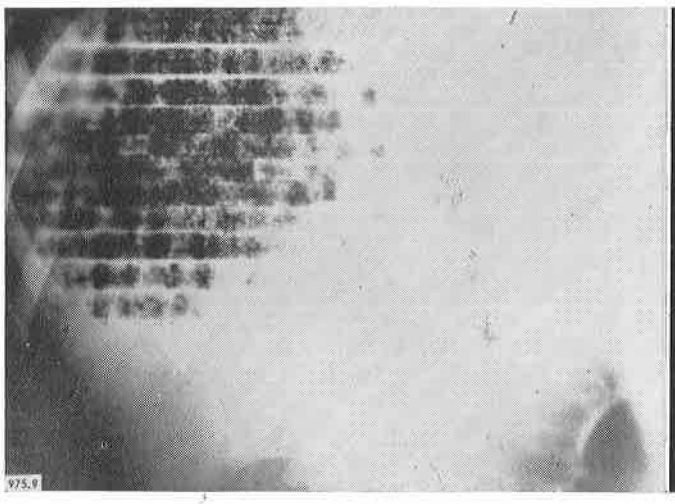

Figure 9

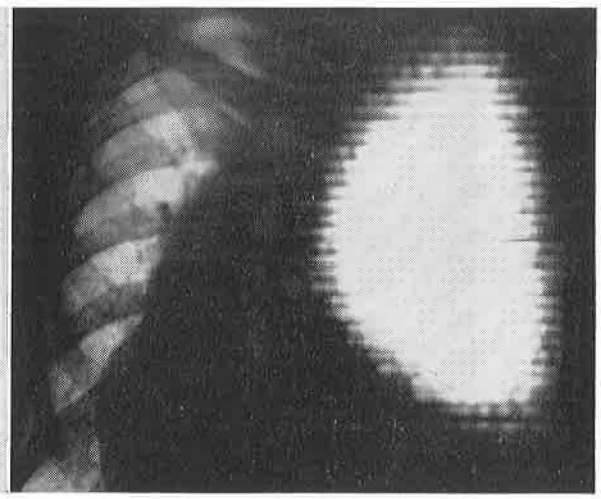

Figure 11

thor developed an apparatus for photoscintigraphy and a method which may be regarded as new in several respects. Thus it is possible to visualize the distribution of gamma-emitting isotopes within the body on an X-ray film whose developed increase of density varies either linearly or in any selected nonlinear way with the detected radioactivity. In this way any degree of differences in radiation intensity can be represented at the greatest contrast possible.

By means of a special device, an anatomically accurate localization of the distribution of isotopes can be achieved when the film used for photoscintigraphy is double-exposed by an X-ray tube.

A series of illustrations show the results of experimental and clinical studies. The possibilities for diminishing the amount of radioisotopes used for diagnostic purposes and thereby of reducing undesirable patient radiation by this method are pointed out.

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Visualization of Some Internal Structures Utilizing Radioisotopes

By Hymer L. Friedell, William J. MacIntyre and Abbas M. Rejali*

It has been recognized for many years that radiation arising from selectively deposited radioelements in tissues may be used to record the geometric deposition of these elements, and thus reflects the general configuration and structure of the organ or tissue under examination.[1,2] Although some concept of the general deposition of radioelements in the body can be established by making static counts of the accumulated radioactivity and recording along some type of grid system, more graphic illustrations can be made with an automatic scanning scintillation counter. This method has been selected for our studies and will be described in a discussion of our techniques.

The most effective visualization of any organ occurs when a radioelement is chosen in which the differential uptake between the organ and the surrounding tissues is very great. However, by suitable handling of the radiation signal, it is possible to accentuate modest differences in the deposition of radioelements which may occur so that the examination of the final record permits ready and easy perception of these differences.

By using techniques which accentuate comparatively small differences in the concentration of radioelements, it has been possible to adapt the scanning techniques to the study of certain organs which have received little attention previously. In our studies we have been able to obtain useful clinical information on the configuration and structure of the liver and to record the configuration and appearance of various blood pools in the body.

The scanning techniques which are to be described involve some special features which require mention. First of all, a special cut-off circuit is introduced which suppresses a certain amount of the radiation. This is so operated as to record fully any radiation reaching the counter above a previously determined level while eliminating completely any radiation below this level. A second innovation is the conversion of the radiation signal into an oscilloscopic record which is then photographed. By varying the intensity of the oscilloscopic beam with counting rate, further accentuation of certain differences may be obtained. Thirdly, the use of a tape recorder has given promise of markedly improving our entire scanning procedure. By utilizing a tape recorder, all the data are stored in the tape. The electromagnetic record, after being synchronized with the scanning movements of the detector, is then fed back into the counting rate meter and recorded by either of the two methods noted above. This has the very important advantage of permitting multiple records at numerous cut-off levels.

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TECHNIQUES

In the inherent problem of accentuating the record of the radiation arising from the site of interest over its surrounding medium, the first approach is one of minimizing the effects of the surrounding radiation. Although improvements in shielding and elimination of scattered radiation have been helpful, they are of no value in differentiating sites that contain radioactivity in varying amounts which still give direct radiation. Therefore, a method was devised to utilize a counting-rate-controlled cut-off circuit which permits the operator to arbitrarily select a counting rate below which no points are recorded. Thus any radiation reaching the counter above this previously determined level is recorded fully, while radiation reaching the counter below this level is completely eliminated. Small variations in counting rate that might formerly have escaped detection may now be more readily visualized. An example of a liver scan made with and without such a cut-off control circuit is shown in Fig. 1. The accuracy to which this control can be set is limited only by the counting rate and the time constant of the counting rate control. This latter must be small enough to keep the memory or lag effects small at the scan speed which has been selected. For large-area scanning, the parameters have shown a standard error of approximately 10 to 20%. The details of the circuit have previously been described.[3]

In the above technique, accentuation of the site under scrutiny has been accomplished by the reduction of surrounding effects rather than increasing the response from the site of interest.

For this latter effect, a system for recording light has been utilized for accentuating small differences in the counting rate. In this technique a simple method of synchronizing a light beam with the position of the detector head has been accomplished by coupling electromechanically the position of the detector head in reference to the x and y deflection axes of an oscilloscope. The z axis is modulated by the output from the detector so as to produce a visible record each time a

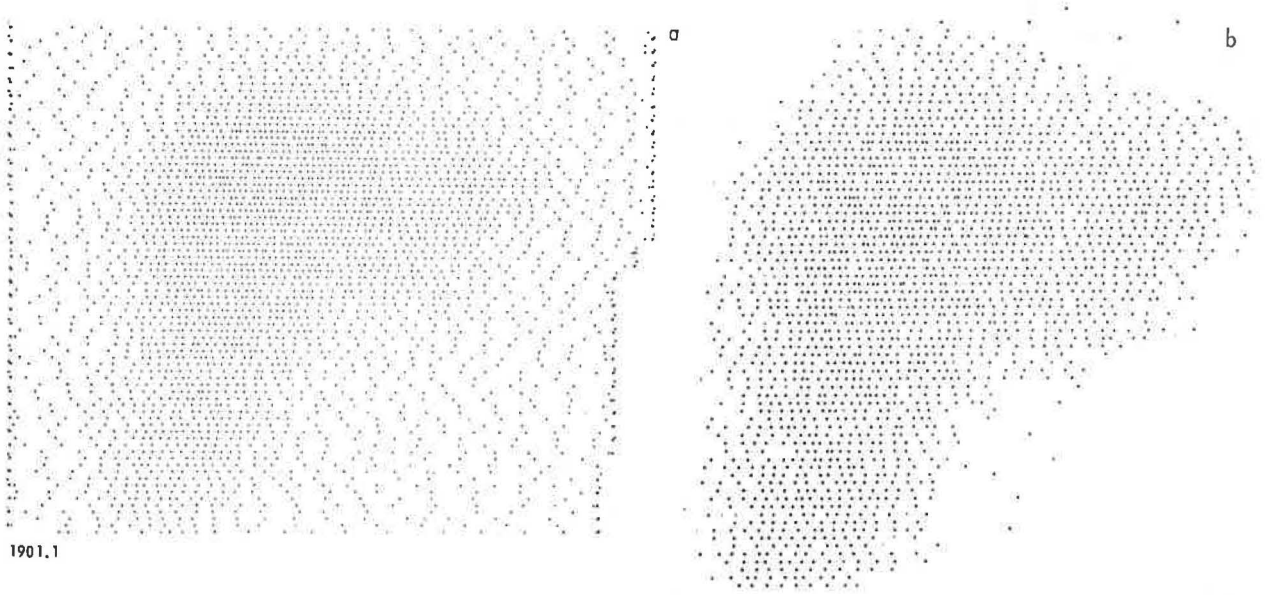

Figure 1. Liver scans made with and without a counting rate cut-off control circuit. (a) without background cut-off; (b) with background cut-off

count or a specified number of counts are recorded. The total effect of the dot distribution over the oscilloscope face is then recorded on film.

In the following system a wide range of accentuation of response may be obtained by modulation of the oscilloscope beam intensity. For a response linear with the counting rate, the oscilloscope beam intensity is constant. The greater exposure of the film at a higher counting rate is due to the greater superposition of dots by the oscilloscope beam per unit time. The intensity of each dot may also be arranged to increase non-linearly with the counting rate so that the increased counting rate produces a greater exposure of the film, not only by the greater superposition of the dots, but also because each dot at the higher counting rate is individually more intense. The schematic of this arrangement is shown in Fig. 2, and the variation of exposure with various settings in Fig. 3.[4]

An additional advantage of recording light is the ability to superimpose the actual scan on the roentgenogram. Because of this, the conventional oscilloscope camera was discarded and a wide-angle lens focused so that the actual size of the scanning area could be duplicated on the film record. It is of interest to note, in this latter respect, that with this technique the size of the oscilloscopic dot may be adjusted to the actual size of the collimated beam so that an exact representation may be obtained of the radioactivity actually subtended by the collimator.

The primary disadvantage of the conventional method of recording light is the narrow range of effectiveness whereby a small increase in the counting rate may quickly saturate the film. This may not be undesirable under certain circumstances where the presence or absence of radioactivity is all that one wishes to record. It is a distinct disadvantage when

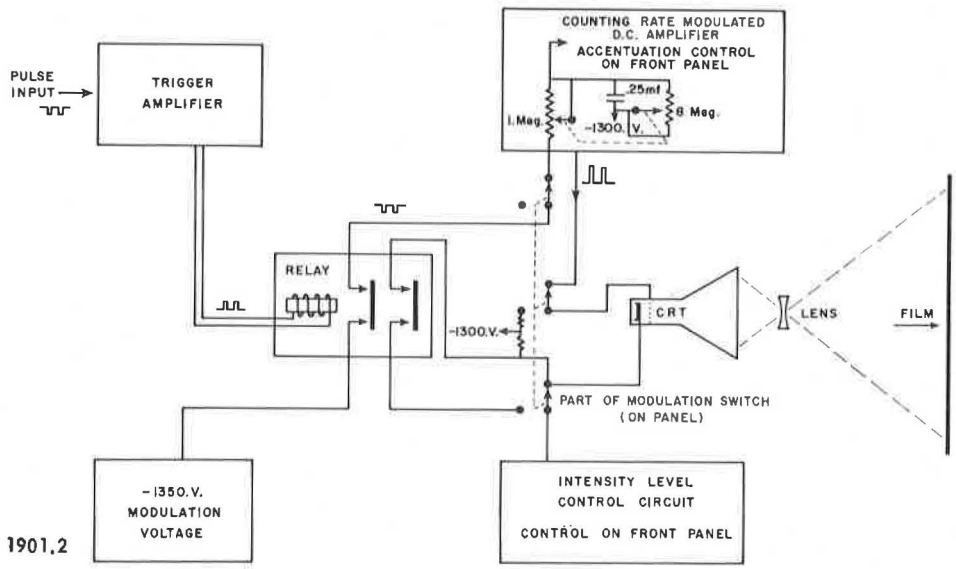

Figure 2. Diagrammatic representation of optical recording system

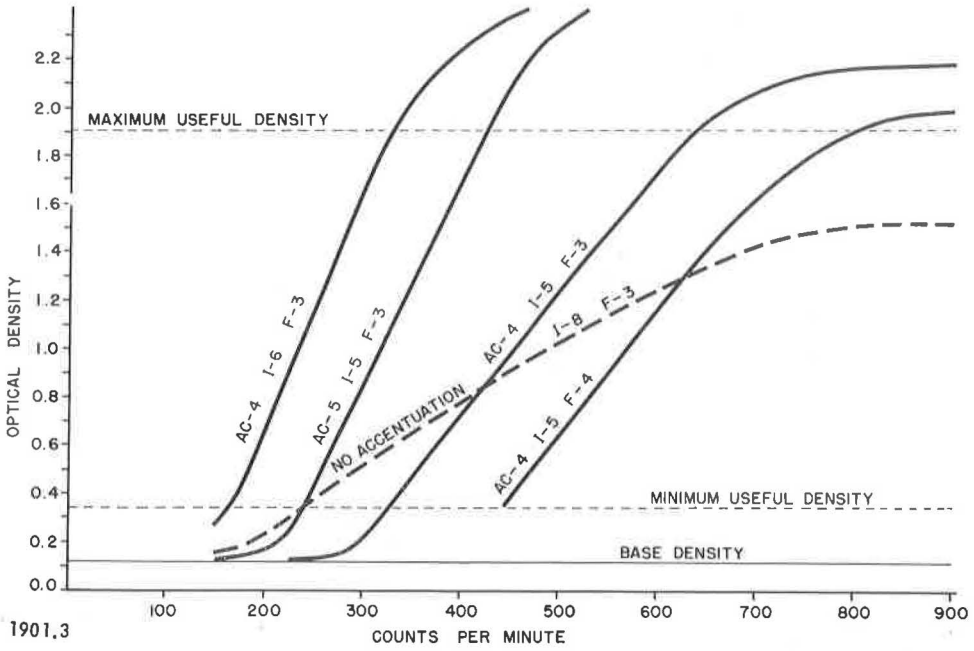

Figure 3. Variation of exposure at different optical settings

one wishes to reproduce on a scan the varying levels of radiation which may be present in a large area or large volume. It is for this latter application that the oscilloscope technique has provided a satisfactory solution. By selection of maximum and minimum counting rates, the optimum accentuation of density with counting rate may be achieved. Without such a choice, a large measure of the advantage of light recording may be lost.

Both the correct accentuation for the photographic response and the operating level of the cut-off circuit may in many cases be difficult to obtain for the optimum record. Choosing a proper level is determined in part by previous experience of the operator as well as by making a careful preliminary survey of counting rates at multiple sites. Even so, it is impossible to predict the entire range of counting rates and for this reason it is sometimes difficult to obtain an optimum setting on the first run. It has, therefore, been found advantageous to record the entire scanning trace on an electromagnetic tape recorder. In this way, the electromagnetic impulse may be fed back into the recording mechanism so that multiple scans at various counting rate cut-off levels and various accentuation slopes may be obtained. In the technique employed here, the tape responds to all the counts received by the detector as well as to the mechanical position of the detector head itself. The play-back is then synchronized so that it is identical in both record and position of the original scanning.

This method has the advantage of permitting inspection of records obtained at multiple accentuation settings and also of providing the opportunity to examine in detail variations which occur at counting levels that are not characteristic of the entire scan and hence would be lost if one over-all set of parameters were employed.

CLINICAL DATA

Visualization of the liver has been attempted since 1924 by various methods.[5–7] This is an important organ system, and determining the exact nature of its configuration and structure will often provide vital information. In our attempts to apply the radioisotope technique for graphic visualization of the liver, we have found that three elements are very useful: radioactive tetraiodophenolphthalein (I^{131}), radioactive rose bengal (I^{131}) and radioactive colloidal gold (Au^{198}). In a previous paper we have recorded the accumulation and retention rate of these compounds in the liver.[8] All three of these elements have been used successfully by us, and generally 2 to 4 microcuries per kilogram of body weight of any of these materials is required. Most of our studies have been made with tagged rose bengal. Recently, however, we have been concentrating on Au^{198} because of one very important special advantage: practically all of the gold is deposited in the liver in a very short time and almost none remains in the circulation after a few hours. This provides a very steep differential uptake between the liver and surrounding structures. In addition, once the radiogold is captured by the liver reticulo-endothelial cells, it remains essentially *in situ* until it disappears by physical decay.

With regard to our studies of the liver, it may be desirable to discuss the manner in which our investigation differed from the usual method. The most important difference was the use of radioactive compounds which were metabolized by the liver tissue proper, thus outlining the liver itself and permitting, secondarily, observation of changes in its general structure. Previous attempts to identify metastatic nodules in the liver, for example, were directed towards choosing a radioelement which would be taken

up by the tumor. Our approach was the reverse. We attempted to outline the metastatic nodule by concentrating a radioelement in the liver proper, and observing alteration in liver structure produced by the tumor nodule. Since these differences were often modest, the techniques for accentuating these differences so that they might become readily observable became very important.

Of considerable interest is an estimate of the minimum size of a lesion that might be detected by this means. With the present method of investigation, in which the background system permits a differentiation of about 20% in the counting range, estimates have been made of the approximate size of a spherical lesion that would displace sufficient volume in the subtended solid angle to permit detection. By calculation and by direct measurement in a phantom, it appears that a space-occupying lesion centrally located in a structure

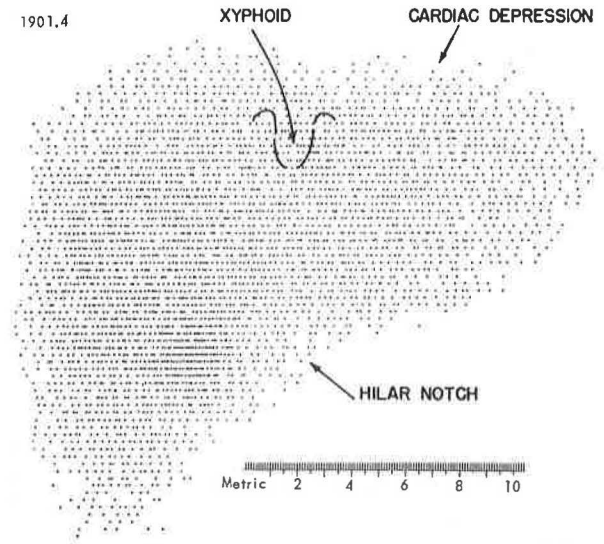

Figure 4. A normal hepatoscan of a patient who received 150 μc of rose bengal. Note slight concentration of rose bengal within the gall bladder

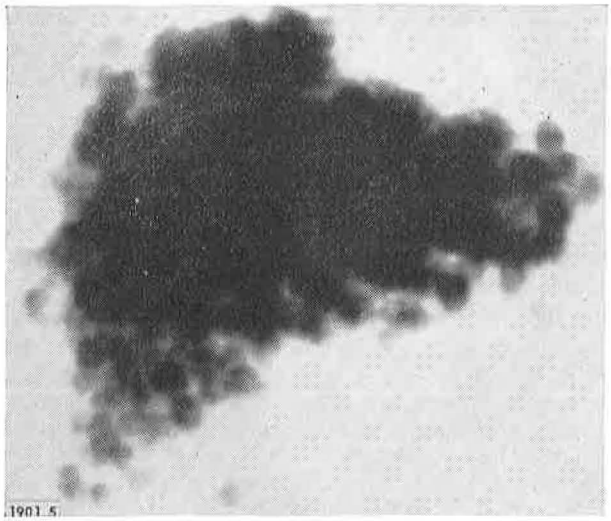

Figure 5. Scan of the liver after the administration of 250 μc of gold. The liver is essentially normal. The scan is produced by the oscilloscopic method

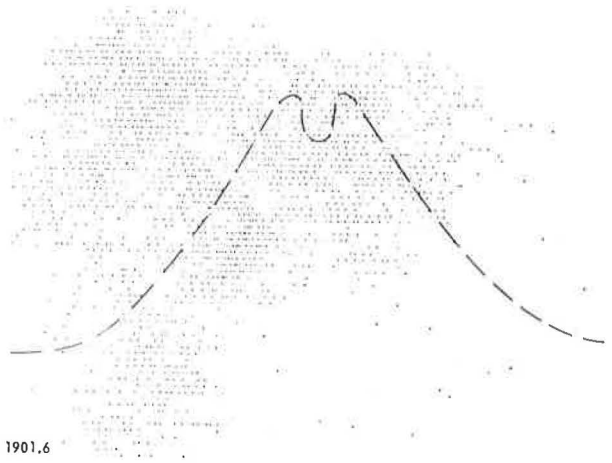

Figure 6. A scan of the liver with 150 μc of rose bengal. The liver was enlarged and there are multiple defects. These proved to be metastases from an adenocarcinoma

10 cm thick must be at least 2.5 cm to be detected, and in a structure 5 cm thick, the lesion must be at least 1.5 cm in size.

Since hepatoscans require approximately one-half hour for completion, motion of the liver should be minimized. This is achieved primarily by getting the patient to remain quietly in the supine position where respiration is generally shallow and slow. Diaphragmatic motion may also be minimized by the use of an abdominal binder. The use of sedation or a respiratory depressant might also be helpful.

In Figs. 4 to 11 a number of representative liver scans have been reproduced. These show the normal configuration of the liver as well as alterations due to various defects.

Another useful application of this method has been in the visualization of blood pools within the body. Here again, modest differences in the differential uptake of radioelements have been accentuated by our techniques and have given good results. The radio-

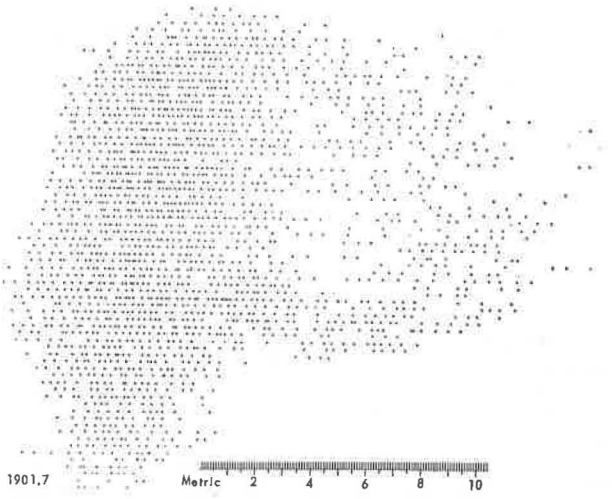

Figure 7. A hepatoscan performed after administration of 200 μc of rose bengal. The multiple defects proved to be due to multiple cysts of the liver

Figure 8. A scan performed after the administration of 250 μc of rose bengal. The numerous defects were the result of metastatic carcinoma arising from the stomach

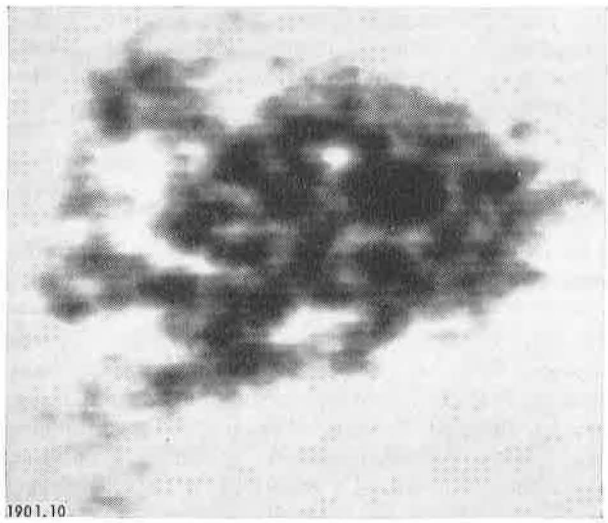

Figure 10. An oscilloscopic scan of the liver performed with 200 μc of rose bengal. The defects were due to metastases to the liver

active compound of choice for this work is tagged human serum albumin (I^{131}). It comes into equilibrium with the blood protein within a few minutes and remains relatively unchanged during the time necessary for carrying out the study. Generally not more than 20% of the tagged albumin is removed from the blood during the first hour.

It was found that good graphic illustration of the cardiac blood pools and other large vascular channels was possible with a dose of 300 to 400 microcuries of tagged radioalbumin. The size and configuration of the cardiac blood pools could be compared with the cardiac shadow on conventional roentgenograms of the chest. The matching of the recorded blood pools and the cardiac silhouette on roentgenograms makes possible certain observations which are helpful clinically. Similarly, aneurysmal dilatation of certain of the great vessels could be easily demonstrated and their diagnostic significance ascertained.

Figures 12 to 15 show illustrative examples of scans of the cardiac pool and of various aneurysmal dilatations.

Additional information is contained in a previous publication.[9]

DISCUSSION AND CONCLUSION

Visualization of the liver and various blood pools has been made possible by utilizing the techniques described here. In essence, the success of these studies has been dependent upon methods which accentuate

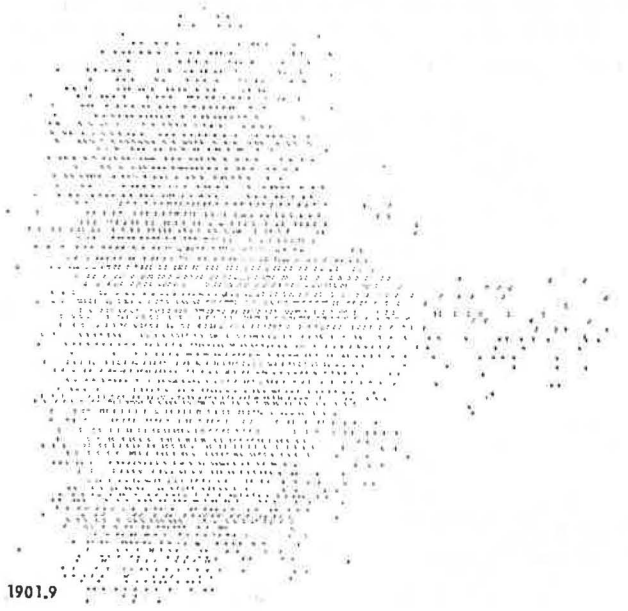

Figure 9. A scan performed after the administration of 200 μc of rose bengal. The defect was proven to be the result of metastases from a primary carcinoma of the pancreas

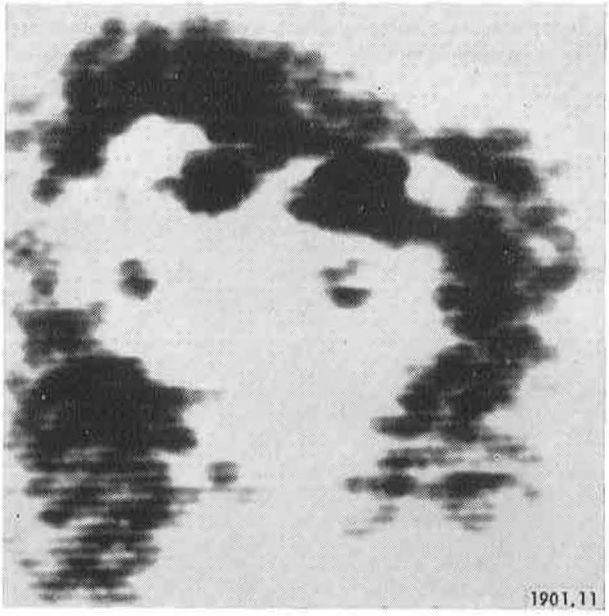

Figure 11. An oscilloscopic scan of the liver after the administration of 250 μc of colloidal gold. The defects were due to extensive carcinomatosis of the liver

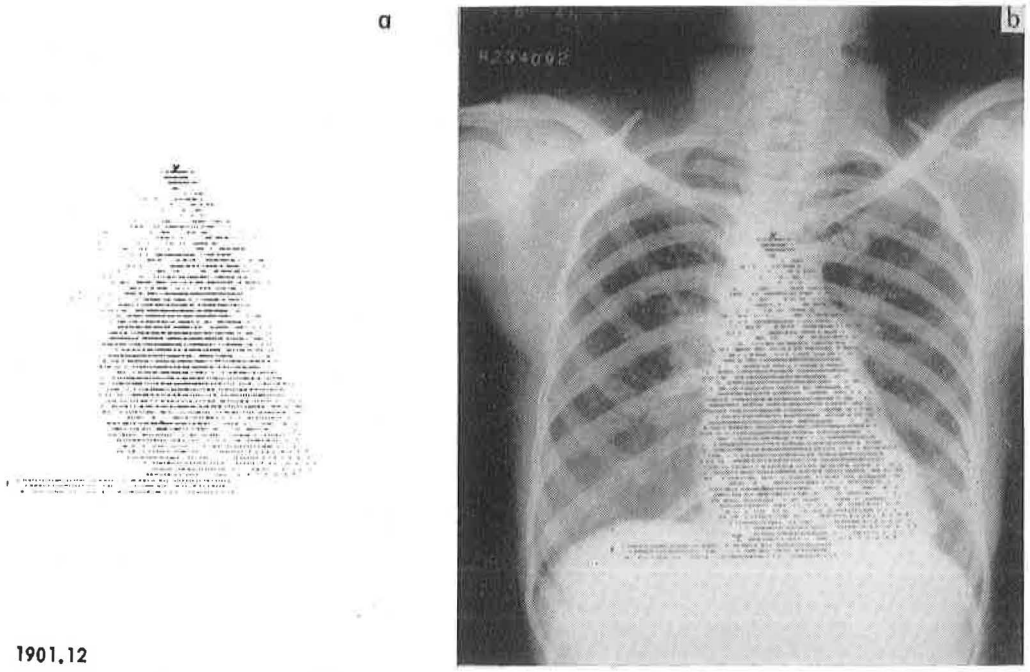

Figure 12. The appearance of a normal cardiac pool by scanning. (a) represents the appearance of the scan itself; (b) represents the scan superimposed upon the cardiac silhouette. Note the satisfactory matching between the size of the blood pool and the size of the heart shadow

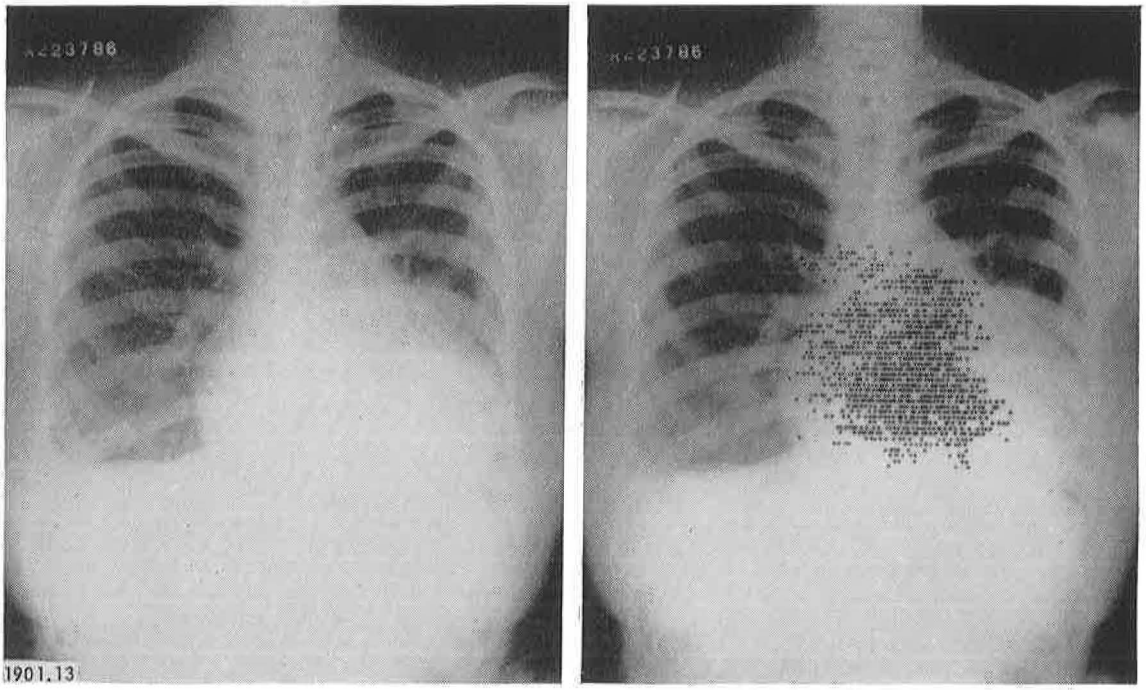

Figure 13. Superimposition of a scan of the cardiac pool upon a roentgenogram of the chest. The marked discrepancy between the two was due to a large amount of fluid in the pericardial sac

modest differences in the relative deposition of the radioelements. The practical application of these scanning techniques for graphic visualization of the liver and of various blood pools has proven useful clinically. The hepatoscans are valuable in separating liver from nonliver masses in the abdomen, in demonstrating metastatic invasion of the liver by neoplastic processes, and distortion of the liver structure by space-occupying masses such as cysts and hemangiomata. Marked displacement or enlargement of the liver may also be observed.

The delineation of blood pools should prove to be helpful in the study of cardiovascular disease. By this method it is possible to establish the presence of marked discrepancies between the size of the cardiac pool and the size of the cardiac silhouette on X ray.

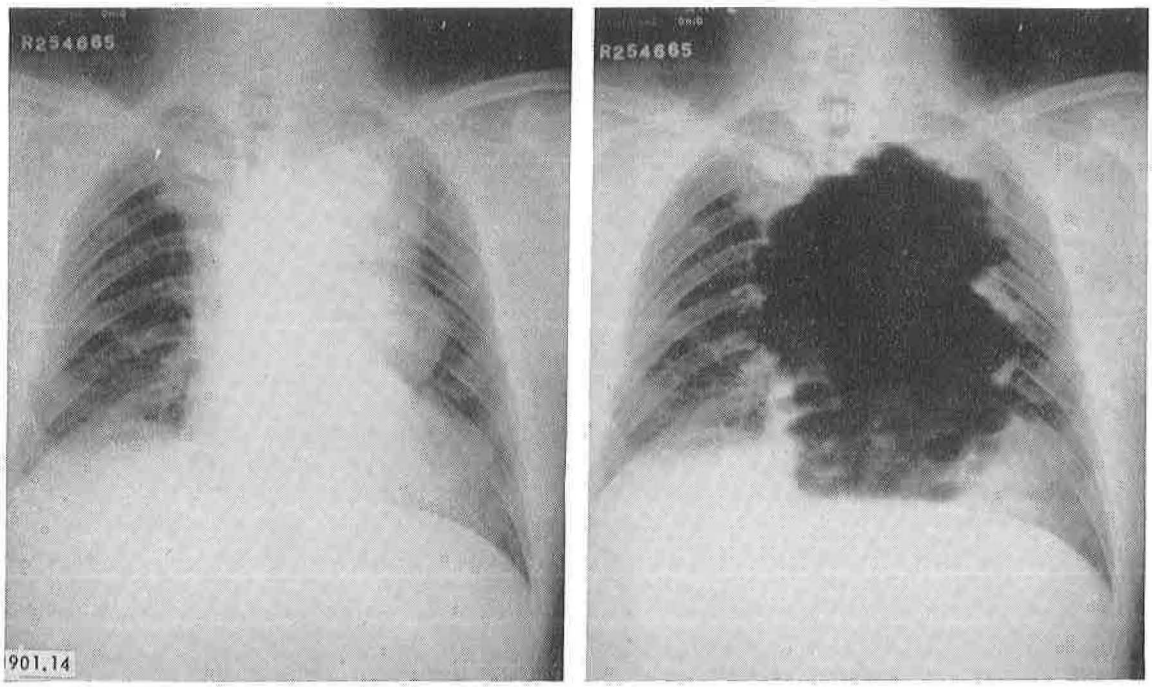

Figure 14. A scan of the blood pools in the heart and aorta performed by the oscilloscopic method is superimposed upon a roentgenogram of the chest. The large mediastinal mass is obviously filled with blood and indicates a large aneurysm of the aorta

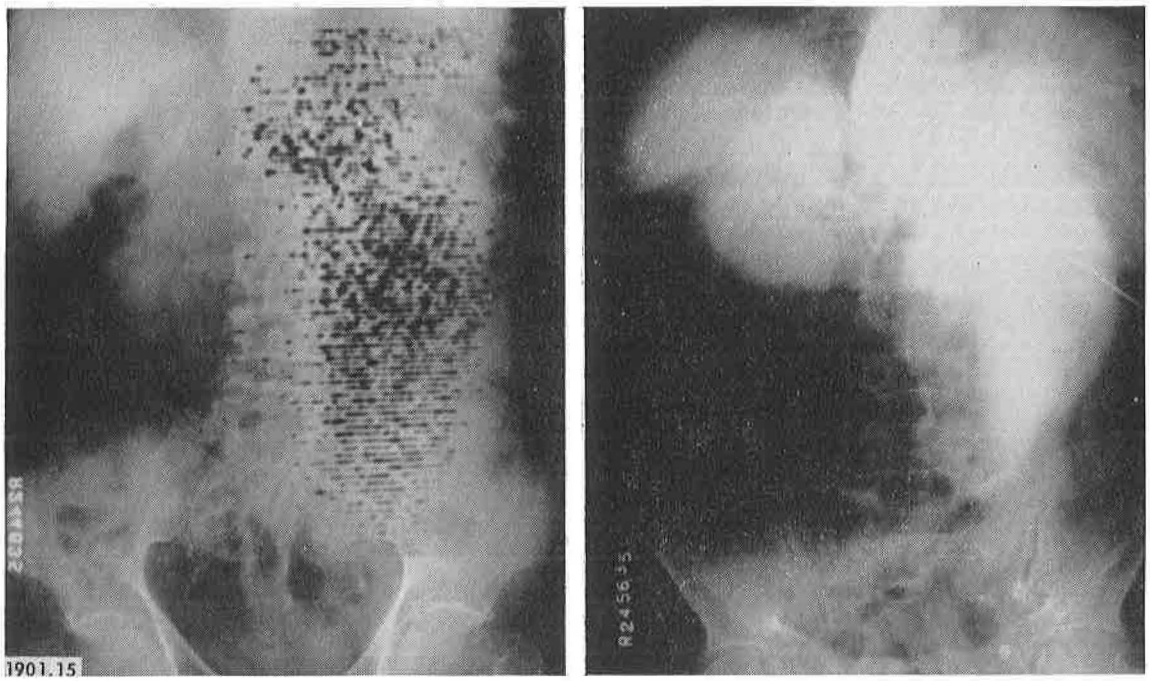

Figure 15. An oscilloscopic scan of the abdomen showing a large blood pool. This compares favorably with the large blood pool visualized on the aortogram (a confirmed aneurysm of the abdominal aorta)

This has proven helpful in establishing the diagnosis of pericardial effusions. Visualization of the size of the cardiac pool has also been useful in the study of other conditions. The presence of large aneurysms in both the thoracic and abdominal aorta has been demonstrated by the visualization of unusually large blood pools in these areas. In the mediastinum this method is particularly helpful in differentiating large mediastinal tumor masses from aneurysmal dilatation of the aorta.

It appears that this method may permit the development of further improvements in resolution. The application of focusing collimators may contribute to this improvement. An increase in scanning speed may be obtained in several ways and may help in improving delineation by minimizing the effects of motion of the

structure under study. It may also be possible to use other radioelements, particularly those having short half-lives, so that more intense radiation may be obtained without increasing the dose to the patient.

There are encouraging possibilities that these techniques may be applicable to other body structures, such as the brain and spinal cord, for visualization of various deformities and obstructions, and possibly to the placenta to determine its position and implantation in the uterus.

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A New Direct Localizing and Measuring Device for Extended Radiation

By K. H. Lauterjung and W. Gruhle*

There are two general methods of recording radiation intensity and distribution of a definite area in time and space. The first method or scintiscanner system uses a scintillation counter which simultaneously records the radiation when moved across the area. By the second, the area under test is "seen" by a number of closely packed detectors which at the same time record the radiation. While the first method has the disadvantage of requiring too long a recording time for rapid changes, the second is rather expensive and has a restricted resolution in the two dimensions.

The new method to be described combines the two principles. The area under observation is covered with detectors and their signals are displayed in a time sequence on a CRO screen.

DETECTORS

The main feature of the system is the use of G-M counters to the spreading discharge in the counter. The propagation speed of the discharge depends solely on counter parameters and is used to measure the place where incoming radiation hits the counter. For this purpose an indicating probe is provided. To avoid the use of a separate electrode or a split cathode, the anode wire is divided by an insulating glass bead near one end of the counter. The short anode wire indicates the arrival of the discharge which has spread along the main anode wire and passed over the bead. The delay between the primary pulse of the main anode and the pulse occurring at the indicating end is in direct proportion to the distance of the bead from the place of the origin of the discharge. Thus localization of all discharging events is possible.

Scanning of the whole area, which is covered by ten counters, is made by electronic gates. The gates are normally closed, but one remains open to allow the counter to deliver its information to the recording device. With a frequency of about 1 kc/s the counter gates are opened in a cyclic manner, each counter being open for 1 msec every 10 msec.

RECORDING DEVICE

Figure 1 shows a block diagram of the whole apparatus. Every counter A in the layer covering the sensitive area immediately produces (at the left side in Fig. 1) a primary pulse when triggered by a discharging event. The right end of the counter delivers the delayed pulse containing the information for localizing. Both pulses are fed through cathode followers B to the gates C which are normally closed. Each counter is connected with a corresponding pair of gates which are opened in a cyclic sequence by gate pulses from the ring counter D, continuously triggered by a pulse oscillator E. The localizing information of each discharging event is now mapped by the XYZ deflection of the cathode ray tube beam CRT. The first pulse coming from the main anode of a counter (left end) passes the gate and triggers with its leading edge the sweep generator F which produces a single X sweep in the CR tube. The beam remains blanked out until the second pulse from the indicating anode of the counter delivers a trigger pulse to the beam intensifying generator G which unblanks the beam to produce a sharp bright dot. The position of the dot along the line is a true reproduction of the "hitting place" of the incoming radiation particle.

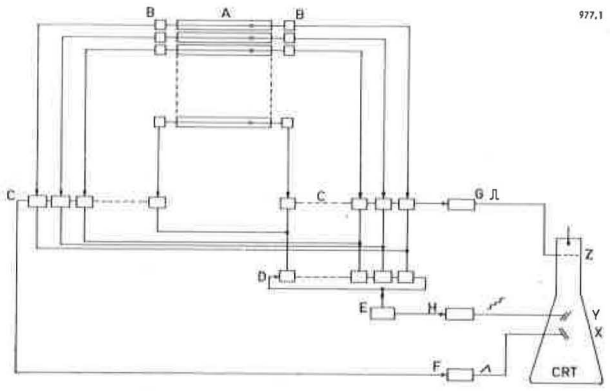

Figure 1

When the gates switch for the next counter, the beam is deflected in the vertical direction to a new level to produce 10 equidistant lines, each corresponding with the position of a single counter. The Y deflection is controlled by a staircase generator H which is triggered by the master oscillator E and returns to zero position (line no. 1) after the complete cycle.

The length of a single line is about 10 μsec, only slightly longer than the maximum discharge spreading-

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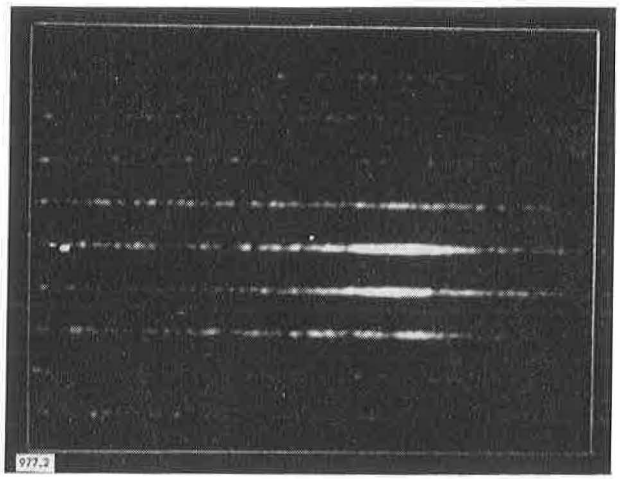

Figure 2

time in the counters. The switching-time from one line to another is less than 0.5 μsec. Individually controlled high tensions are applied to all counters to match the differences in discharge velocity.

The *display* on the CRT screen of the mapping of the radiation distributions shows a pattern of bright dots, varying in space and frequency. Each accumulation of dots represents the location and intensity of a radiation source. The display may be observed visually or by means of photographic recording. Figure 2 gives an example with an exposure time of 1 sec, the source being placed in the upper right corner of the area.

Although the inevitable cosmic ray background is small, dots having no real relation to primary events may appear. They might arise if a line is triggered immediately before the switch to the following line. If the latter happens to be delivering a "brightening" pulse to the CRT beam, a false dot will appear. By blocking the unblanking generator G for the first 10 μsec after each line switching, this difficulty is avoided. The space resolution in the vertical direction is equal to the counter diameter in the horizontal sense and of the same order. The whole device may be extended by introducing additional counters, the expenses increasing every 6 tubes per counter. A conventional oscilloscope may also be used for the sweep generator F and the cathode ray tube.

Europium-155 as a Source in Portable Radiographic Devices

By J. S. Robertson*

In many situations it is desirable to have a method for producing radiographs which does not require a source of electrical power. Among such situations may be mentioned requirements for diagnostic radiographs at scenes of accidents, requirements which may arise during power failures and requirements arising in remote locations. These requirements lead to consideration of the radioisotopes as portable sources of penetrating ionizing radiation. In order for the resulting radiographs to be comparable in quality with those being obtained with X rays, however, the radioisotope to be used must meet many rather stringent specifications.

THE GENERAL PROBLEM

The principal criteria by which the quality of a radiograph is judged are density, definition and contrast. Assuming that the standard films in use in X-ray work are to be used, the isotopic radiation must compare with X rays in energy and intensity in order to meet these criteria.

The standard clinical procedures for obtaining radiographs with X rays involve the use of 30 to 125 kvp beams. In industrial applications high energy gamma rays, such as the 1.17 and the 1.33 Mev gamma rays emitted by cobalt-60, have been used successfully, but these rays are too penetrating to be used in clinical radiography. It is to be expected that the most satisfactory contrast will be obtained with the use of isotopes which emit X rays or gamma rays of 100 kev or lower only. Use of the bremsstrahlung from energetic β emitters, such as Sr–Y^{90}, has also been considered.[1]

The density of a radiograph is the product of the intensity of exposure and the time of exposure. Diagnostic X-ray machines deliver about 5 r/sec at a working distance of 50 cm. In practice, greater distances and exposures of only a fraction of a second are used. About 0.1 r may be taken as being representative of the radiation dose delivered to the film in diagnostic procedures. An isotope emitting a gamma ray of 100 kev delivers[2] only 0.2 r/curie·hour at 50 cm, so to deliver 0.1 r in a minute would require a 30 curie source. A source fully competitive with an X-ray machine would have to contain about 1500 curies.

Sharp definition requires that the isotope be concentrated in a volume sufficiently small to be regarded as a point source. Because multicurie sources are needed, the latter requirement means that very high specific activities or, ideally, carrier-free isotopes are required to keep the mass small.

Another important characteristic is the radioisotope's half-life. Too short a half-life causes the radiation emission rate to diminish rapidly so that frequent replacements of the source are necessary to maintain convenient exposure times. With very long half-lives, however, the mass associated with a given source strength is too large. Because increasing the working distance decreases the intensity of exposure, the use of long working distances does not replace the point-source requirement.

Only a few radioisotopes appear to meet all of the above criteria and of these the use of thulium-170 has been most extensively explored.[3–6] Two other possible radioisotopes, americium-241 and cerium–praesodymium-144 are compared with thulium-170 by Dennis and DeLuca[4] who also briefly discuss the history of the attempts to use radioactive isotopes in medical radiography. Pool[7] and Spangenberg and Pool[8] discuss various X-ray emitters as possible sources. More recently Spangenberg and Pool[9] discuss their efforts to use several radioisotopes, including europium-155, and conclude that there are numerous possibilities, but that the best one has not yet been designated. The author feels that europium-155 deserves more detailed attention than it has been given.

CHARACTERISTICS OF EUROPIUM-155

Europium-155 has a half life of 1.7 years. (Spangenberg and Pool[9] assert that the half-life is approximately 5.5 years). It decays by emission of either a 0.15 or a 0.24 Mev β–particle followed by emission of principally 0.153 Mev and 0.0865 Mev gamma rays, with less intense emission of 0.0600, 0.0453, 0.0265 and 0.0189 Mev gamma rays.[10] The β–energies are sufficiently low that high energy bremsstrahlung is not a problem.

A major advantage of europium-155 over most of the other possible radioisotopes is that it can be produced carrier-free. If the half-life is 1.7 years, a curie of carrier-free europium-155 weighs only 0.74 mg. Therefore, even a 30 curie carrier-free source could be contained in a few cubic millimeters and constitute a point-source for a working distance of 50 cm.

The chief disadvantages of europium-155 occur in its production. Before the difficulties inherent in the production of Eu^{155} can be explained, it is necessary to discuss the theory upon which its production is based.

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Europium-155 is produced from samarium-154 by the reaction, $Sm^{154}(n, \gamma\text{-}\beta^-)Eu^{155}$. The intermediate product, Sm^{155}, has a half-life of only 24 minutes, and so can be ignored in most calculations concerned with the production of Eu^{155}. The reactions of the other samarium isotopes with neutrons are depicted in Fig. 1. The first difficulty is that although the cross section for the Sm^{154} reaction is 5.5 barns, if naturally occurring samarium is used the Sm^{154} competes unfavorably for neutrons with Sm^{149}, which has a cross section of 50,000 barns, for the (n, γ) reaction and with Sm^{152}, which has a cross section of 140 barns, for the (n, γ) reaction. The Sm^{149} acts as a very effective local neutron shield. Therefore, when natural samarium is used, it must be distributed during activation in very thin layers and time must be allowed for "burn-up" of the Eu^{149}. The Sm^{152} (n, γ) reaction yields Sm^{153} with a half-life of 47 hours. The latter is troublesome chiefly during removal of the product from the reactor and for the first few weeks thereafter. Alternatively, electromagnetically separated Sm^{154} can be used. Electromagnetic separation of the Eu^{155} after its activation has also been suggested.[9]

Another complication in the production of europium-155 is that the product, europium-155 itself, also has a rather large neutron capture cross section, variously estimated as being 9,000 to 14,000 barns. This means that after a certain period, which will subsequently be shown to be a function of the ambient neutron flux, the rate of removal of the product by neutron capture is as great as its rate of production. At this time the activity is said to be saturated, and of course the saturation activity is lower than would be the case if there were no "burn-up" of the product. The "burn-up" product, europium-156, decays with a half-time of 15 days and with emission of a 2.0 Mev γ ray. To minimize contamination of the product with europium-156, it is essential that the activation time be kept as short as possible. An undesirably long time is required for the europium-156 to disappear by radioactive decay, if the initial ratio of Eu^{156} to Eu^{155} is several hundred times as great, as may occur with high neutron fluxes.

Because the product, europium-155, is a different element from the target material, samarium, it is at least theoretically possible to separate the product from the target and achieve a carrier-free product.[11–13] The methods for achieving this separation are being studied currently to determine the most practical method for the present purposes. High-yield recoveries of both the samarium and the europium are desired so that the maximum activity of the latter is obtained and so that the former can be reused as a target. Repetition of an activation–separation–activation cycle can be used (again in principle) to build up the europium-155 activity from a given samarium target to a value comparable to that which would be attained if there were no "burn-up." There is some hope that a process permitting continuous cycling of a given target can be developed.

The following calculations constitute the theoretical basis for choosing the activation times to be used at the various neutron fluxes available:

Sm^{154} = number of Sm^{154} atoms/gram Sm
Sm^{155} = number of Sm^{155} atoms/gram Sm
Eu^{155} = number of Eu^{155} atoms/gram Sm
T = Eu^{155} half-time (1.7 years) = 5.36×10^7 sec
λ = Eu^{155} decay constant
$= \dfrac{0.69315}{T} = 1.29 \times 10^{-8}$ sec^{-1}
$R_{Eu^{155}}$ = activity of Eu^{155}
$= \dfrac{\lambda Eu^{155}}{3.7 \times 10^{10}}$ curies/gram Sm
σ_1 = (5.5×10^{-24})
= activation cross section, cm^2/n·atom Sm^{154}
σ_2 = $14{,}000 \times 10^{-24}$
= burn-up cross section, cm^2/n·atom Eu^{155}
A = 150.43
= atomic weight of target Sm, grams/mole Sm
t = activation time, sec
ϕ = thermal neutron flux, n/cm^2 sec.

Assuming constant Sm^{154} (for $\phi = 10^{15}$, "burn-up" of Sm^{154} is only 1% in 21 days) and ignoring the small correction for the lag due to build-up of Sm^{155} (half-time 24 minutes), the rate of build-up of Eu^{155} is the difference between its rate of production and its rate of removal by decay and by "burn-up":

$$\frac{dEu^{155}}{dt} = \phi\sigma_1 Sm^{154} - \lambda Eu^{155} - \phi\sigma_2 Eu^{155},$$

$$Eu^{155} = \phi\sigma_1 Sm^{154}\left(\frac{1}{\lambda + \phi\sigma_2}\right)(1 - e^{-(\lambda+\phi\sigma_2)t}),$$

$$R_{Eu^{155}} = \left(\frac{\phi\sigma_1 Sm^{154}}{3.7 \times 10^{10}}\right)\left(\frac{\lambda}{\lambda + \phi\sigma_2}\right)(1 - e^{-(\lambda+\phi\sigma_2)t}),$$

$$R_{Eu^{155}} = (1.34 \times 10^{-13}\phi)\left(\frac{1.29}{1.29 + 1.44\phi \times 10^{-12}}\right)(1 - e^{-(1.29+1.44\phi\times10^{-12})10^{-8}t}).$$

For activation at $\phi = 3.4 \times 10^{12}$ n/cm^2 sec

$$R_{Eu^{155}} = 0.456\left(\frac{1.29}{6.19}\right)(1 - e^{-6.19\times10^{-8}t}).$$

At saturation

$$R_{Eu^{155}} = 0.095 \text{ curies } Eu^{155}\text{/gram Sm}$$

(saturation activity with no "burn-up" would be 0.456 curies/gram).

Activation half-time

$$= \frac{0.69315}{6.19 \times 10^{-8}} = 1.12 \times 10^7 \text{ sec} = 130 \text{ days}$$

(2.3 years for 99% saturation).

For activation at $\phi = 3 \times 10^{14}$ n/cm^2 sec,

$$R_{Eu^{155}} = 40.2\left(\frac{1.29}{4.33}\right)(1 - e^{-4.33\times10^{-6}t}).$$

822.1 ISOTOPES OF SAMARIUM, EUROPIUM AND GADOLINIUM

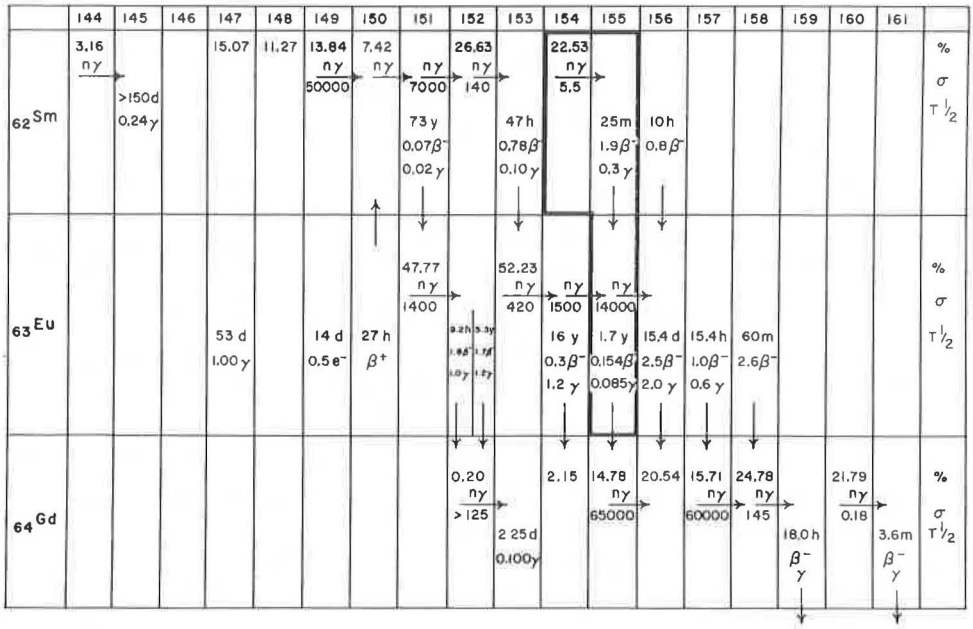


Figure 1. The interrelationships of the isotopes of samarium, europium and gadolinium with respect to neutron capture reactions. The isotopes of principal interest are enclosed in heavy borders

At saturation

$$R_{Eu^{155}} = 0.1197 \text{ curies } Eu^{155}/\text{gram Sm}$$

(saturation activity with no "burn-up" would be 40.2 curies/gram).

Activation half-time

$$= \frac{0.69315}{4.33 \times 10^{-6}} = 0.16008 \times 10^{6} \text{ sec} = 1.85 \text{ days}$$

(12.3 days for 99% saturation).

From the above calculations it is seen that for a given sample little is gained in terms of saturation activity by using a neutron flux greater than 3×10^{12} n/cm^2 sec, but the saturation time does become shorter as the flux is increased. The advantage of a high neutron flux is enhanced if the target material is recycled and higher activities are built up outside of the reactor.

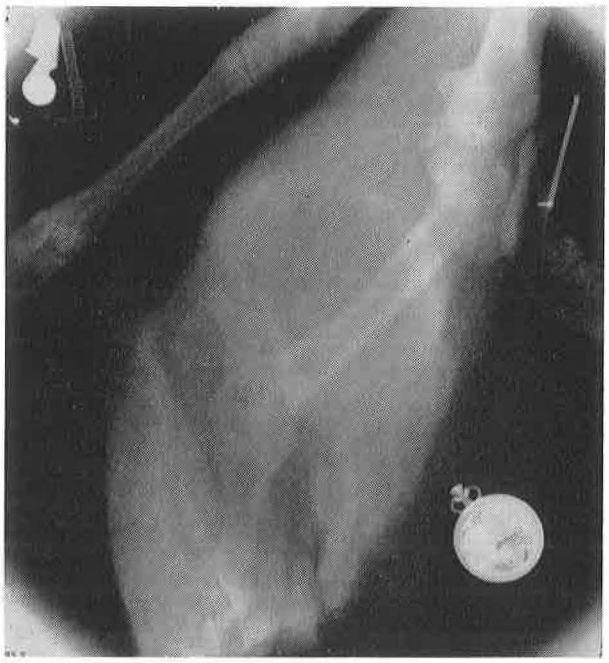
PREPARATION AND USE

Two principal sources suitable for radiography have been prepared. The first was prepared by activating 100 mg of 99 per cent electromagnetically enriched samarium-154 in the Brookhaven Research Reactor at a thermal neutron flux of about 3.5×10^{12} n/cm^2 sec for a net time of 1170 hours, and is a source of about 10 mc. The second was prepared by activating 100 mg of the enriched samarium-154 in the Materials Testing Reactor at a flux of 2.5×10^{14} n/cm^2 sec for 14 days, and this source is about 50 mc. Radiographs have been taken, using these sources and using standard X-ray films and standard developing procedures. The sources were used without separating the europium from the samarium. The mass of these low intensity sources is thus comparable with that of stronger separated sources. The sources were contained in a device designed for use with thulium sources by the Army Medical Research Laboratory, Fort Knox, and constructed by the Development Branch, ASMPA, Fort Totten, to whom we wish to express our gratitude for the loan of the device. Because the sources are relatively weak, prolonged exposures are necessary. The use of more intense sources requires chemical or electromagnetic separation of the europium-155. Several chemical procedures are being tried for this purpose.

RESULTS

Figure 2 is a radiograph of several objects exposed to the 10 mc source for 100 hours. The large object is a leg of lamb. The teeth and mandible are from a skull. The metallic objects include a spring, a stopwatch, and the shutter which was removed from the exposure device. The teeth show good detail of structure, as does the mandible. Although the contrast in the leg of lamb is inferior to that which can be obtained by X ray, the quality of this radiograph would be adequate for diagnosis of fractures and compares favorably with the published results obtained with thulium-170. Some of the lack of contrast may be attributable to the presence of residual contamination with europium-156. If this is indeed the case, some improvement should be noted in future radiographs.

Figure 3 compares an exposure of the mandible to europium-155 with a radiograph made with 50 kvp X rays. The trabecular pattern in the mandible is clearer in the X ray but the teeth are overexposed in the X ray and their structure is shown better in the europium-155 radiograph.



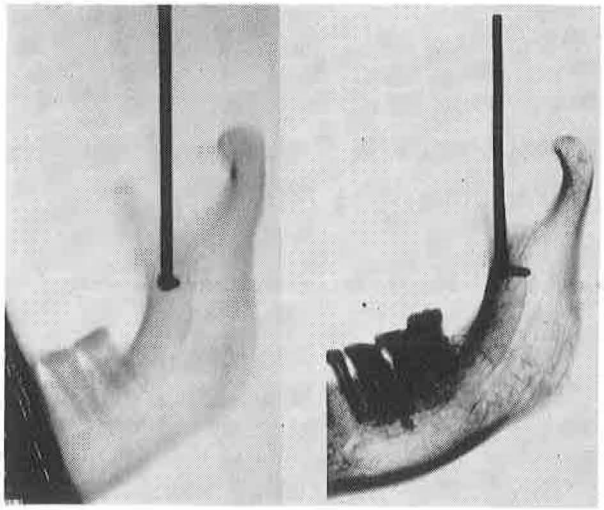


Figure 2 (left). Radiograph of leg of lamb and other objects exposed to a europium-155 source

Figure 3 (above). Comparison of radiographs made with europium-155 (right) and with 50 kvp X ray (left)

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Studies on X Rays and Bremsstrahlen from Source-target Mixture

By E. W. Coleman,* L. E. Brownell† and C. J. Fox†

The X-ray machine has proved an invaluable tool in medicine in the diagnosis of fractures, tumors, tuberculosis, etc. However, because of the high electrical energy requirements and the size and weight of portable gasoline-operated field units, it has not been practicable in the past to use these machines in remote areas. There has thus been a real need for a rugged, portable X-ray facility for field radiography when it is not possible to transport the patient to a hospital where conventional X-ray equipment is available. Gamma radiation or the "bremsstrahlung" from various beta-particle sources provide a solution to this problem in the form of portable radioisotopic sources.

The successful application of radioisotopes in medical radiography requires an abundant supply of source material meeting the exacting requirements of the art. An isotope suitable for medical radiography must have a high specific activity so that sources of small diameter and high radiation intensity can be made. The radioisotope should emit radiation having essentially the same characteristics as the radiation from an X-ray tube used for diagnosis. To obtain a differential absorption between various body tissues, radiation is required with energies in the range of from 30 to 100 kev and preferably from 30 to 80 kev. The half-life of the radioisotope should be long enough to permit use of the source for a reasonable length of time before replacement is required.

Portable X-ray units utilizing radioactive sources of radiation have been reported by the Army Medical Research Laboratory.[1–5] While such units have certain advantages over conventional field radiographic equipment, the quality of radiographs produced is not considered acceptable. The presence of even a small amount of higher-energy radiation results in a loss of radiographic contrast between bone, muscle and fat.

Thulium-170 was found to be a usable radiographic source, but because of high-energy bremsstrahlung originating within the source, the radiographic quality was poor. Radiographic sources using pure beta-emitting radioisotopes and external target foils have been proposed. The disadvantage is the limitation of source thickness to the depth of penetration of the beta particles in the source material, since thicknesses greater than this will result in self-absorption of beta particles in the source rather than in the target material. This is a severe restriction with sources of long half-life such as strontium-90, because the maximum specific activity of such sources is limited by their slow rate of decay. This means that if a small "point" source is used, the exposure times will be very long, and if a source of larger area is used, the X-rays will not be well collimated and a sharp radiograph will not be possible. Another disadvantage is that the electromagnetic radiation produced by self-absorption of beta particles in the source and from back-scatter in the shield may not have the energy spectrum necessary for a good radiograph. Coleman and Brownell[6,7] proposed the elimination of these difficulties by use of source-target mixtures. If the target is intimately mixed with the beta-particle source, the source thickness may be increased significantly because the electromagnetic radiation is more penetrating than the beta particles. Furthermore, if the atoms of the beta-particle source are chemically combined with the target atoms, each source atom will be surrounded by target atoms. This increases the probability of interaction between the beta particles and electrons surrounding the target atoms as compared to electrons surrounding other source atoms.

In view of logistic problems expected in storing, transporting and replacing sources of short half-life, such as thulium-170 (127 days), only those isotopes with a half-life of one year or longer should be considered satisfactory. A "use-life" of three to four half-lives was considered reasonable, based on operating experience with thulium-170. Because of the low specific activity of strontium-90 and americium-241, these radioisotopes were not considered satisfactory, and the authors limited their studies to promethium-147 and thallium-204.

PREPARATION OF PROMETHIUM-147 TUNGSTATE SOURCE

Since the promethium-147 sources were found to be superior to the thallium-204 sources, only the preparation of promethium sources will be described.

The first promethium-147 source was prepared by evaporation on barium tungstate. The spectrum of this source showed tungstate to be a suitable target,

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† Fission Products Laboratory, Engineering Research Institute, The University of Michigan, Ann Arbor, Michigan.

and a promethium–neodymium tungstate source was prepared using a neodymium carrier.

The "cold" runs with neodymium carrier indicated a slight solubility of the tungstate in water. To lower the solubility, an ethanol–water solution was used. The neodymium tungstate prepared in the "cold" runs was found to be a pale pink material easily ground to a fine powder. The precipitate fluoresces soft blue in ultraviolet or white fluorescent light. The material was also used to determine the bulk density of <120-mesh precipitate when compacted in a cast plastic capsule. A bulk density of 0.8 g/cm³ was determined, and 100 mg was chosen as the loading for these capsules. The promethium-147 was obtained from Oak Ridge, Tennessee, as a solution which contained 1.55 (±20%) mc/ml of Pm^{147} in 0.13*N* HCl. The total solids were less than 1 mg/ml with less than 10 ppm of heavy metals.

The neodymium tungstate–promethium-147 tungstate sources were prepared by the following procedure. To a 50-ml beaker containing 1.00 ml of neodymium carrier solution, 3.00 ml of promethium solution and 10 ml of distilled water were added. The solution was neutralized with NaOH until a cloudy precipitate began to form. The precipitate was redissolved by dropwise addition of 0.13*N* HCl and stirring. To the clear solution, 5 ml of absolute ethanol were added. The tungstates were then precipitated by dropwise addition of 1 ml of 0.53*N* Na_2WO_4 solution. After settling for 15 minutes, the clear supernatant liquid was removed by pipette and the precipitate washed by stirring in 5 ml of 1:1 ethanol–water solution. After settling, the supernate was again removed and given a final wash with pure ethanol. As much liquid as possible was removed by decantation and the precipitate was dried in the beaker at 50°C. The precipitate cake was broken up and left to dry overnight at 100°C. The dry precipitate was crushed with a glass rod and transferred to a cast plastic capsule with a 2-mm-thick window. The combined filtrates of all operations were evaporated and the resulting salt mixture was dried and sealed in a similar capsule. The count rate from the filtrate salts was about 12.4% of the count rate from the precipitate.

After evaluation of the millicurie promethium-147 tungstate source, a 1-curie promethium tungstate source was ordered from the Oak Ridge National Laboratory. This source was encapsulated in a modified Standard Oak Ridge capsule.‡ The modification consisted of pressfitting a 4-mm-id aluminum sleeve into the source cavity and machining the stainless steel window to 0.005 in. Aluminum was chosen for the sleeve to minimize bremsstrahlung and characteristic X-ray production in the vertical walls of the source cavity, so that the effective focal spot size would be 4 mm. The capsule was silver-soldered after filling and placed in a larger lucite capsule with an air-path aperture to the window. The plastic capsule was used only to eliminate the possibility of accidental contact with the thin window during handling. The question of mechanical strength in a 0.005-in. stainless steel window, and the relatively high absorption factor for low-energy radiation ($e^{-\mu x} = 0.25$ at 25 kev) suggests that a thicker beryllium metal window would be stronger and should improve the radiographic efficiency by attenuating a smaller part of the low-energy radiation.

‡ The preparation of the tungstate and the encapsulation were performed by R. S. Pressley of the ORNL staff.

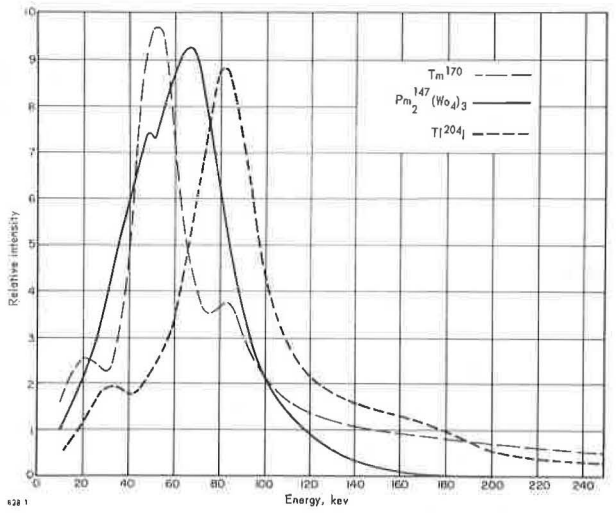

Figure 1. Comparison of the spectra of three radiographic sources

COMPARISON OF SPECTRA FROM EXPERIMENTAL SOURCES

The spectra of three possible radiographic sources (thulium-170, thallium-204 iodide, and promethium-147 tungstate) shown in Fig. 1 may be compared. Although all three sources have peaks in the characteristic X-ray region, the broad, flat, higher-energy bremsstrahlung spectra of the thulium-170 and thallium-204 sources indicate that shielding difficulties and poor radiographic contrast may be expected from these sources. The spectrum of the promethium sources is a definite improvement over thulium-170 with regard to higher-energy components. The major peak is at a higher energy than the thulium, but is still in the diagnostic region. A low-energy peak could be obtained by use of molybdate instead of tungstate as target material.

COMPARISON OF RADIOGRAPHS OF VARIOUS TISSUES USING EXPERIMENTAL SOURCES

Of the three spectra shown in Fig. 1, that of promethium-147 tungstate is most promising with thallium-iodide second. Figure 2 shows radiographs of an eviscerated, preserved mouse sealed in a plastic test tube. These radiographs were taken with the two beta-particle X-ray sources and with a 67-kvp machine X-ray for comparison. A rigorous comparison of the radiographs of Fig. 2 is difficult because of the wide variation in focal spot size and source-film distance used. Nevertheless, the improvement achieved with promethium-147 tungstate over thallium-204 iodide is evident. The higher degree of contrast is even more

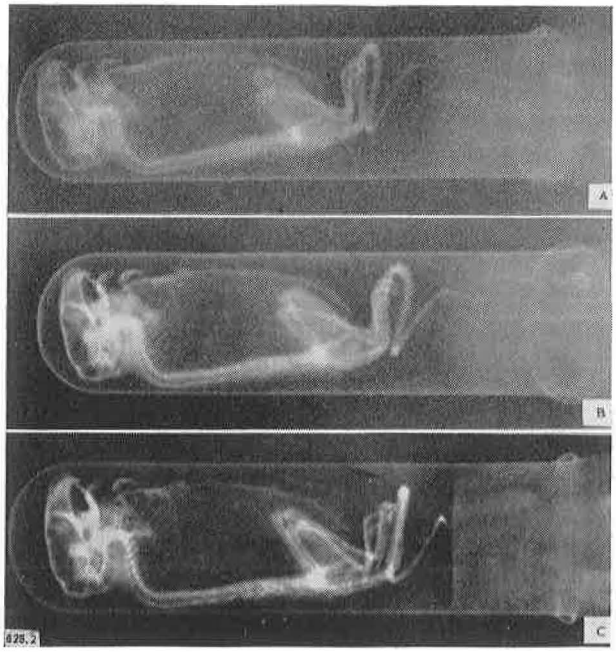

Figure 2. Radiographs of preserved mouse (contact prints). A—Tl^{204} iodide, 4-mc source, 2-mm diam. Exposure, 240 hr at 5 in. B—Pm^{147} tungstate, 1-curie source, 4-mm diam. Exposure, 15 hr at 8 in. C—Machine X-ray, 67 kvp, 1.25 ma at 30 in.

pronounced in the original radiographs. Although the high degree of resolution obtained in Fig. 2 C is reduced in the promethium-147 tungstate radiograph, the contrast is comparable. The definition of the thoracic cage is adequate for gross examination, and the definition of vertebrae is fair. The sutures used in the abdominal wall are also distinguishable.

A further comparison of promethium tungstate with thulium-170 as medical radiography sources is presented in Figs. 3 and 4.

The radiograph of a human hand in Fig. 3 shows good details considering the source diameter of 4 mm and the source-subject distance. The quality of the radiograph is adequate for fracture or foreign-body localization. The wrist detail is good, and the fingernails are easily recognized in the original radiograph. Current technology indicates exposures of less than 1 hour are possible.

The major improvement over similar radiographs produced with thulium-170 is in radiographic contrast. Thulium radiographs exposed for maximum detail are grey and white, instead of the continuous gradation from black to white required for excellent contrast. A typical thulium radiograph is shown in Fig. 4. The promethium radiograph shows improved contrast, probably due to the absence of high-energy bremsstrahlung in the spectrum.

TECHNICAL RADIOGRAPHS USING PROMETHIUM-147 TUNGSTATE SOURCE

The use of promethium-147 sources for technical radiography is well demonstrated in Fig. 5. A variety

Figure 3. Radiograph of human hand, 79-hr exposure at 20 in. from a promethium tungstate source

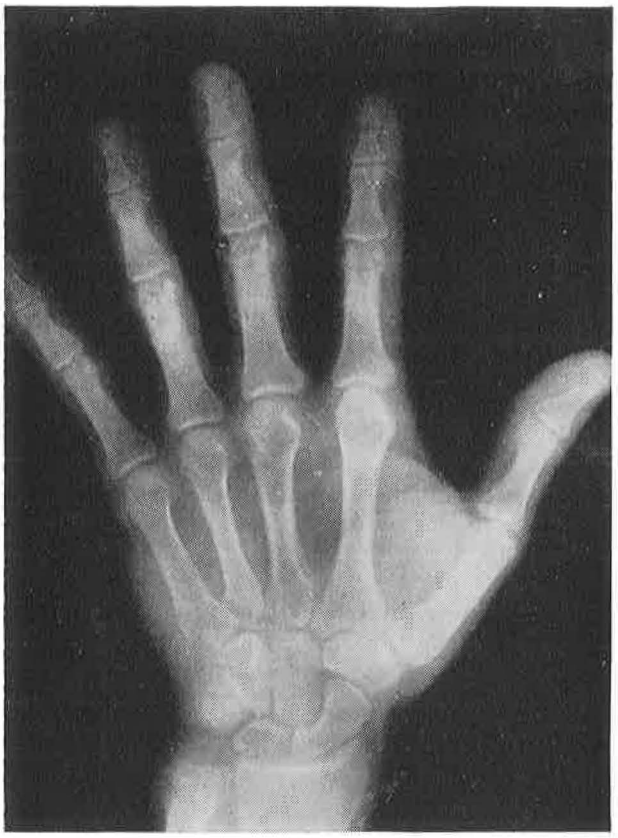

Figure 4. Radiograph of human hand, using thulium-170.[1] (Repr inted by permission of the Office of the Surgeon General, Department cf the Army)

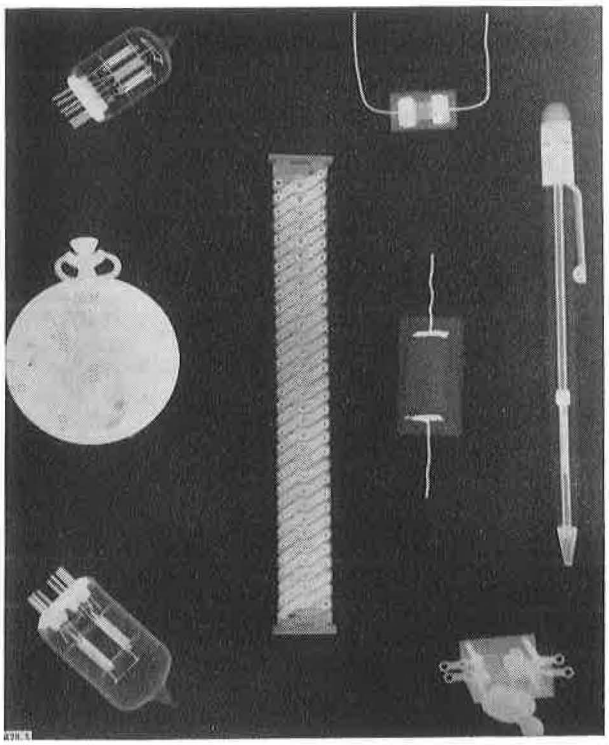

Figure 5. Technical radiograph, 44-hr exposure at 10 in. from a promethium tungstate source

of small objects is shown in varying degrees of detail. The detail in the expandable metal watch band is sufficient to determine the integrity of the small spring in each link. The thin mica standoff insulators and the filaments in the electron tubes are easily visible. The lack of good detail in the stopwatch is perhaps the best example of the improved spectrum of promethium sources relative to thulium sources. Similar radiographs with thulium have shown complete detail of the watch, indicating the presence of a higher-energy spectrum.

CONCLUSIONS

Radiographs made with promethium tungstate source-target mixtures show improved contrast compared to thulium-170 radiographs. Limited tests with radiographs of commercial objects of low mass indicate the possibility of use of promethium tungstate sources for industrial radiography of light-weight products. However, the efficiency of production of the radiographic image must be increased to shorten the required length of exposure before medical application can be realized.

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Record of Proceedings of Session D-17

Uses of Isotopes in Medicine, Part I

WEDNESDAY MORNING, 10 SEPTEMBER 1958

Chairman: Mr. M. A. Patetta-Queirolo (Uruguay)

Vice-Chairman: Mr. A. O. M. Stoppani (Argentina)

Scientific Secretaries: Messrs. D. H. Copp and T. E. F. Carr

PROGRAMME

P/2533 The uses of radioactive isotopes in medicine (UN Survey) ..... R. H. Chamberlain

P/277 Applications of I^{132} to measurements of day-to-day changes in human thyroid functions ..... K. E. Halnan and E. E. Pochin
(Presented by Mr. Halnan)

P/1222 Study of radioactive phosphorus (P^{32}) distribution in man by external bremsstrahlung measurements ..... M. Tubiana *et al.*
(Presented by Mr. Tubiana)

P/1219 The use of scintillography in medicine ..... A. Gandy and H. Jammet
(Presented by Mr. Jammet)

DISCUSSION

P/278 The preparation and use of oxygen-15 with particular reference to its value in the study of pulmonary malfunction ..... N. A. Dyson *et al.*
(Presented by Mr. G. R. Newbery)

P/1385 Investigation of central hemodynamics by means of selective quantitative radiocardiography ..... G. Monasterio and L. Donato
(Presented by Mr. Donato)

P/215 Inhalation radiocardiography ..... C. H. Jaimet *et al.*
(Presented by Mr. Jaimet)

DISCUSSION

P/2069 Application of isotope encephalography and electroencephaloscopy for localization of brain tumours ..... V. N. Shamov *et al.*
(Presented by Mr. M. P. Domshlak)

P/870 New radiodiagnostic techniques for investigating parenchymal and obstructive liver and kidney diseases ..... G. V. Taplin *et al.*
(Presented by Mr. Taplin)

DISCUSSION

The CHAIRMAN: We are going to deal today with the medical uses of radioisotopes and particularly with their application to the problems of diagnosis. We will hear a report on the application of I^{132} in measuring the day-to-day changes in human thyroid function, and another which deals with radioactive phosphorus

and its distribution in man. Papers dealing with the use of scintillography in medicine, with the preparation and use of oxygen-15 with particular emphasis on its value in the study of pulmonary malfunctions, with the investigation of central hemodynamics by means of quantitative radiocardiography, with radiocardiography by inhalation, and with the use of radioisotopes in encephaloscopy, will also be presented. Later we will listen to a paper about the new radiodiagnostic techniques for investigating the parenchymatous and obstructive diseases of the liver and kidney.

The interest that has been aroused in the applications of radioisotopes in medicine has logically resulted in many excellent papers which have been submitted to this session. Unfortunately, all of them cannot be presented, but we have chosen some by authors who are very well known to us for their contributions to the world's literature for presentation.

You are, naturally, more interested in listening to these authors than to me. Therefore I will ask Dr. Chamberlain to present his paper, a general survey for the United Nations, on the use of radioactive isotopes in medicine.

DISCUSSION OF P/2533, P/277, P/1222 AND P/1219

Mr. S. G. BENNER (Sweden): This is a question to Dr. Halnan. I wonder if you have considered the use of the still more short-lived isotope I^{128}?

Mr. K. E. HALNAN (UK): Yes, I have considered that after seeing the Trigar reactor in the exhibition, in which iodine-128 can be produced. Iodine-128 has a half-life of 25 minutes. It would probably need to be given intravenously, therefore, rather than orally. It might be of use in following thyroid function over hours, or in, say, checking up diurnal variation of thyroid function. However, I think for general use I^{132} is perhaps preferable.

Mr. G. JOYET (Switzerland): My question has to do with the work done by Dr. Pochin and his co-workers.

When you repeat your test on a subject who does not present any thyroid modification, if I have understood your paper well, there are variations which, according to the table you have shown us, range between a factor of 2 and a factor of 3.

I would like to ask if you can assert that these high variations are due to thyroid variations and not circulatory variations?

As far as we are concerned, when we measure thyroid function by the initial slope we do not find variations as large as these. After a period of 2–3 weeks we find modifications of the slope, which will range from 10 to 20%, but no variations with a factor as high as 2 or 3.

I would like to ask your opinion about this important difference?

Mr. HALNAN (UK): In answer to that question, first of all, I would like to point out again that the function we measure is not, of course, the percentage uptake; it is the neck–thigh ratio at two hours. Therefore, changes of the order of two or three times, which did occur, might not correspond, and in fact probably do not correspond to such large changes in purely percentage uptake determinations.

Even so, these changes are admittedly rather large, but I was interested to see that similar work has been reported by Dr. Goolden and others from Hammersmith Hospital. They find the same variation, and interestingly, they have checked on variation in thyroid activity in the same patients by determining six-hour, I think it was, urine measurements. Allowing for the difference in the function, they find these measurements correspond to the same kind of variations in thyroid uptake. Does this answer the question?

DISCUSSION OF P/278, P/1385 AND P/215

Mr. BETZ (Germany, Fed. Rep.): This is a question to Dr. Donato. We measured, using nearly the same methods as Dr. Donato, the hemodynamics of pulmonary malfunction. We also compared the form of the isotope curves with the selective endocrine picture. We found that in different parts of the lung which were only revascularized, as in tuberculosis and tumours of the lung, the curves looked like those shown to us.

This is my question: How large, do you think, is the role of the pulmonary vessel dysfunction in the curve you showed to us? We tried to inject intravenously, in the heart and in the pulmonary artery; we did not find very much difference in the form of the curves.

Mr. L. DONATO (Italy): I would like to show a slide. This slide deals with three cases of mitral stenosis with involvement of the right ventricle. I show this slide because it demonstrates clearly the peculiar change of the radiocardiographic tracing in mitral stenosis: the increased duration of the left filling time, i.e., the time interval between appearance of the activity in the left side of the heart and the left peak. This change is very marked in mitral stenosis and it is always present. It is impossible when this characteristic is present in the tracing to confuse it with the tracing of pulmonary insufficiency where an increase of filling time is never present—except when cardiac output is very decreased, but at this time all the components of the tracings are delayed. The presence of a selective alteration of this part of the tracing points directly to mitral stenosis, and this is the characteristic of the tracing which differentiates this disease from pulmonary insufficiency. I hope I have answered the question.

DISCUSSION OF P/2069 AND P/870

Mr. G. R. NEWBERY (UK): I should like to ask Dr. Domshlak whether there is any experience with scintillation-coincidence methods of the localization of brain tumours using positron-emitting isotopes in the USSR?

Mr. M. P. DOMSHLAK (USSR): No, Dr. Newbery, the authors of the paper which I have presented here have not used this method.

Session D-18

USES OF ISOTOPES IN MEDICINE, PART II

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Clinical Applications of Radioisotopes

By A. V. Kozlova

The use of radioactive isotopes for diagnosis has rightly been recognized as one of the more accurate and simpler methods of investigation in clinical medicine. Many scientists have modified their previously held opinion that radioactive substances in the small doses used clinically do not produce appreciable adverse changes in the body, and investigators in Soviet research institutes have been studying the effects of the isotopes most widely used clinically in tracer doses on the function of different systems of the body.

CENTRAL NERVOUS SYSTEM AND BLOOD FORMING ORGANS

Thus, V. P. Godin and S. I. Gorshkov,[1] experimenting on animals, studied the influence of Na^{24} on the central nervous system and used alterations in the defensive unconditioned reflex reaction time to measure the changes occurring in the nervous system. They found that the threshold dose of Na^{24} for a rat weighing 250 g was 0.5 μc. A larger dose shortened the reflex time which returned to the initial level in 8–10 days. The greatest decrease in reflex time was observed with 50 μc Na^{24}, which made the over-all dose for the three days of complete disintegration of isotope 2.8 r in β radiation. A further increase in dose lowered the functional mobility of the nervous system as revealed by an increase in the reflex time and strengthening of the inhibitory processes. V. M. Zakharov[2] reported an increase in cortical excitation and the appearance of signs of lowered lability of the cortical centres with 0.4–0.04 μc Na^{24}. Under the influence of isotopes in these amounts cortical inhibition for 6–7 days was recorded for animals with a weak type of nervous activity.

Y. V. Krivobok[3] found that 1 μc I^{131} caused changes which are reversible in the colloidal state of the cytoplasm and the karyoplasm of thyroid cells.

With tracer doses of P^{32} (1.5 μc/kg) administered to rabbits, I. V. Savitsky and A. F. Leshchinsky[4] observed intensification of plasma albumen biosynthesis during a 10–15 day experiment with a gradual return to the original state.

R. E. Kavetsky *et al.*[5] reported that a single injection of 5 μc P^{32} in a rabbit caused an increase in blood sugar of 21–63%, which is due, the authors believe, to mobilization of liver glycogen. At the same time distinct changes were observed in the blood as indicated by a decrease in the total number of leucocytes, mainly lymphocytes, in the first 4 hours after injection of the isotope and subsequent neutrophilic leucocytosis during the first 2–3 days, followed by leucopenia and finally return to normal on the 10th–12th day of the experiment. Morphological studies of blood in 52 patients after the injection of 1–2 μc I^{131} (O. S. Sergel[6]) confirmed these observations. In more than half of the patients there was a marked leucopenia and, more rarely, an increase in the number of leucocytes by 1500–2000 (in a few cases by 4000–5000 cells) per mm^3 of blood. Myelocytes and metamyelocytes (1 per 200 leucocytes) appeared in the peripheral blood of some patients during the first hours after the injection of I^{131}. Luminescent analysis of the blood (O. S. Sergel) showed pathological red luminescence of neutrophiles and the appearance of green luminescence of the plasma. Return to the original state was observed in 3–5 days.

L. B. Stolyarova and R. D. Nikitenko[7] demonstrated that the intravenous injection of 7.5 μc Fe^{59} or 3.75 μc P^{32} into rabbits not only brought about changes in the number of leucocytes (lymphopenia and neutrophilia) but also caused disintegration of lymphocytes, hypersegmentosis, karyorrhexis and chromatinolysis.

According to the data obtained by V. A. Sondak,[8] injection of 0.005–0.002 μc P^{32} per g of body weight of rats and guinea-pigs resulted in the inhibition of erythropoiesis and thrombopenia.

M. G. Durmishyan and E. N. Romina,[9] experimenting with rabbits weighing 3 kg, showed that the threshold dose (0.25 μc) of Na^{24} injected into animals caused leucocytosis of 25–30% within 4–5 days of administration and that the leucocytosis persisted for 2–3 days. If, after the injection of the isotope, the rabbits are injected with 75 μc of phosphorus organic compounds (a dose which does not produce morphological changes in the blood) leucocytosis will develop in 3 hours (reaching 10,000–20,000 leucocytes per mm^3) and disappear only after 6–8 days. Under these conditions inhibition of blood cholinesterase and reduction of the reflex time are observed. The injection of folic acid will cause a decrease in erythrocytes.

These investigations demonstrate that the administration of radioactive isotopes, even in tracer doses, will cause certain changes in the functioning of the central nervous system, in the blood-forming organs and in metabolism. These changes, depending on the

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initial state of the patient, may either intensify or depress the functions of organs and systems. Our imperfect knowledge of the limits between the normal and pathological in these changes does not permit us to draw any definite conclusions. Consequently, in Soviet medical institutions, the use of the radioactive tracer method is limited to those conditions where it is specifically indicated. It is not recommended for children and only the short-lived isotopes, I^{131}, Na^{24} and P^{32}, in the minimum doses required for diagnostic purposes are used in adults.

CIRCULATION

In the clinic for internal diseases Na^{24} was used to study the rate of blood flow and tissue blood flow. According to A. L. Syrkin,[10] for the healthy adult the resorption constant of Na^{24} from intracutaneous depots is 0.072–0.116. In diseases accompanied by disorders of water metabolism, hemodynamics and tissue permeability, the resorption rate of Na^{24} is altered. Resorption of sodium is accelerated in patients with thyrotoxicosis and conversely, in cases of polycythemia it is retarded. Resorption is considerably retarded in patients with decompensated heart disease and as decompensation progresses the decrease in the rate of resorption becomes more marked.

In a study of 100 rheumatic patients the author found in some of the subjects an acceleration of Na^{24} resorption which is explained by the increase in tissue permeability in rheumatism. Other patients who suffered from circulatory insufficiency showed a decrease in the rate of Na^{24} resorption. Slowing down of tissue blood flow in atherosclerosis and hypertensive disease (stage III) was also observed by M. N. Fateeva and K. K. Maslova.[11] K. M. Lakyin has shown that resorption of Na^{24} is considerably accelerated where pachycarpin is used for ganglionic blocks in the treatment of hypertensive crises.

THYROID FUNCTION

The use of radioactive iodine for the determination of thyroid gland function has contributed greatly to the study of thyroid physiology and of the etiology and pathogenesis of diseases connected with the thyroid. The study of the pathogenesis of thyrotoxicosis and goitre made it possible to demonstrate the existence of a close relationship between the absorption of I^{131} by the thyroid gland, cerebral function and innervation of the thyroid (N. S. Demidenko[12]). It was also found that the secretory activity of the thyroid gland and the processes of proliferation of its parenchyma are under different nervous control and need not develop concurrently. This explains the discrepancy frequently observed between the pathological picture of the gland struma and the clinical symptoms of the disease. By reproducing this discrepancy experimentally it was possible to establish that the relative integrity of the brain, the highest coordination centre, is necessary for the clinical picture to parallel the pathological process. Studies on the etiology of goitre led to elucidation of the role of some of the microelements on its genesis. It was shown that excess of cobalt results in the development of goitre while bromine has a marked thyrostatic action. The use of I^{131} demonstrated the importance of vitamin B_1 in the physiology of the thyroid gland. Vitamin B_1 deficiency results in almost complete inability of the gland to accumulate iodine, and therefore injections of vitamin B_1 would seem to be indicated in the treatment of thyroid hypofunction (B. V. Aleshin and S. V. Maksimov[13]).

The tracer technique has shown the importance of diet in the etiology of goitre. N. V. Berzhikov[14] showed that protein insufficiency causes inhibition of iodine assimilation and secretion whereas a high protein diet results in hypertrophy of the gland with increased assimilation and increased secretion of iodine.

E. A. Vasyukova, I. I. Lyubskaya and N. A. Shteiman examined 3614 patients with various disorders of the thyroid gland. They reported that the absorption rate of radioactive iodine by the thyroid at varying periods after administration of the isotope had different diagnostic significance. Figures obtained two hours after administration are most important for the early diagnosis of thyrotoxicosis and the severity of the disease is best shown by figures determined 2 and 4 hours after administration of the radioactive substance. In the diagnosis of thyroid insufficiency, uptake figures obtained 24 hr or more after administration are the most useful. The curves of iodine uptake by the thyroid gland in mild forms of thyrotoxicosis are different from the curves of the normal gland and show a marked rise in the first hours after administration. The majority of cases of severe forms of thyrotoxicosis reveal a steep rise followed by a plateau, but in a few cases a peak appeared in the curves in the first hours, followed by a depression.

A comparison of thyrotoxicosis of varying severity does not show a complete correspondence between the clinical picture and the level of I^{131} absorption.

Examination of the population in an endemic goitre region showed that in localities with iodine insufficiency the absorption of radioactive iodine is relatively greater both for the normally functioning thyroid gland and for the euthyroid goitre.

Numerous scientists in this country (M. N. Fateeva, K. K. Maslova, K. G. Nikulin, etc.) as well as abroad have shown that systemic diseases involve disturbance of thyroid function. The results of their studies show an increase in thyroid function and basal metabolism during the first stage of arterial hypertension. As the hypertension progresses, basal metabolism continues to rise while thyroid function diminishes.

Cardiovascular decompensation of varying etiology, especially when severe, is accompanied by an increase in BMR. Where decompensation is of cardiac origin, thyroid function is normal in the majority of instances or slightly reduced. There is no parallelism between thyroid function and degree of decompensation (A. G. Samadishvili[15]).

Disturbances of thyroid function were found in patients with chronic nephritis of the nephritic and hypertensive types and in amyloidosis of the kidneys (L. N. Kazakova[16]). In patients with compensated forms of the disease a rise in absorption of I^{131} by the thyroid gland was observed; and some even showed other signs of thyrotoxicosis, such as tachycardia, perspiration, loss of weight, increase of gland volume, etc. Aggravation of the process due to disturbance in kidney filtration was accompanied by an increased absorption of I^{131}. As improvement in kidney function occurred radioiodine uptake decreased. Treatment of hyperthyreosis, whenever it occurred, had a wholesome effect on the course of the nephritis.

In the majority of patients with nephropathy accompanied by massive edema and albuminuria, hypofunction of the thyroid gland was observed, and in these cases treatment with thyroxin often gave good therapeutic results.

In the acute stage of Botkin's disease, there is an increase in I^{131} uptake by the thyroid in almost all the patients and this increase is sometimes accompanied by clinical evidence of hyperthyreosis. These investigations demonstrate that a close relationship exists between thyroid gland function and the status of the internal organs.

BRAIN TUMOUR DIAGNOSIS

The use of radioactive iodine for the diagnosis of brain tumours will be described in a special report, therefore we shall not discuss this subject in this paper.

THERAPY

In the USSR radioactive isotopes are used clinically mainly for the treatment of diseases of the blood-forming organs and skin, and for the treatment of thyrotoxicosis and malignant and benign tumours. Soviet and foreign investigators have already established the usefulness of radioactive phosphorus in the treatment of the leukemias. It is also well known that this isotope will induce lengthy remissions in polycythemia. Investigations conducted during recent years were directed towards the study of the hematological changes which occur in the treatment of polycythemia by radioactive phosphorus. At the same time studies were undertaken in combining various methods of radiation therapy for treating this disease.

Polycythemia

Research showed that in some patients with polycythemia in the first days after the injection of a 2 μc-dose of radioactive phosphorus an increased number of erythrocytes, leucocytes and thrombocytes appeared in the blood. A reduction in the number of erythrocytes began in 2–3 weeks, and by the end of the course of treatment had decreased below the initial level. The greatest reduction in number of erythrocytes was observed 2–3 months after the end of the treatment. At the beginning of treatment in a limited number of patients, the hemoglobin content of the red cells increased, but more often it was reduced from the first days of treatment. By the time remission occurred, Hb content has decreased by 20–50 units (Sahli). The discrepancy between the change in the number of erythrocytes and their Hb content resulted in a change in colour index. By the end of treatment, the number of leucocytes in some of the patients decreased to the normal level but not infrequently leucopenia was observed with a shift to the left. Examination of bone marrow in the first week following P^{32} administration showed an increase in the total number of cells in the marrow and an increase in the figures of erythroblastic division. When the hematological findings become normal the erythrocyte sedimentation rate rose to 5–15 mm per hour and blood viscosity decreased to 8–12 or more Hess units.

On the basis of these observations, phlebotomy, which makes it possible to conduct treatment under more favourable conditions, is strongly recommended before P^{32} administration (M. D. Donskoi and V. K. Polenko[17]).

The research of S. A. Raevskaya[18] showed that the least favourable results with radioactive phosphorus are observed in the treatment of the splenomegalic form of polycythemia. As polycythemia is often accompanied by neuroendocrine disorders, many scientists have combined radioactive phosphorus therapy with irradiation of the hypophysial–hypothalamic region (E. N. Mozharova and V. G. Belugina,[19] E. M. Filkova[20]). Remissions in these cases were more stable. In the hypertensive form of polycythemia with a tendency to crises and disorder of cerebral circulation, the best results were obtained by irradiation of the upper cervical ganglia followed by treatment with radioactive phosphorus.

The results of the treatment of polycythemia are given in Table 1.

In the treatment of leukemia, application of neither radioactive phosphorus nor the other therapeutic agents leads to recovery. However, in many cases symptoms may be relieved and life may be prolonged where radiophosphorus is used in combination with roentgentherapy and blood transfusions. During the last three years we have treated 109 patients with chronic myelosis and lymphadenosis. Radioactive phosphorus therapy was ineffective in 31 cases. In 78 patients remissions lasting from 1 to 3 years were observed.

Thyrotoxicosis and Related Diseases

At the present time, radioactive iodine for the treatment of diffuse forms of thyrotoxicosis is very widely employed. Its use is especially indicated in the treatment of moderately severe cases of thyrotoxicosis and in the severe forms of the disease where there is also dysfunction of the cardiovascular system. It is useful when thyrotoxicosis accompanies other illnesses, such as psychic disturbances and tuberculosis, in elderly patients, and it is also useful in treating relapses of thyrotoxicosis postoperatively.

Table 1. Results of Treatment of Polycythemia

No. of patients	Duration of remission					Failures
	6–12 mo	1–2 yr	2–3 yr	3–5 yr	5–6 yr	
222	21	87	53	33	9	19

According to I. D. Kucherova, the effectiveness of radioactive iodine therapy in thyrotoxicosis depends not only on dose but also on the biological half-life period, which varies for different patients from 2 to 7 days and does not depend on the severity of the disease. Effectiveness of treatment increases with increase in the biological half-life period of the isotope. Radioiodine therapy is contraindicated in pregnancy and lactation. Leucopenia, often observed in thyrotoxicosis, is not a contraindication to the administration of I^{131} because the leucopenia disappears under treatment. Although the carcinogenic action of I^{131} has not been confirmed clinically, we believe that it should not be used in patients past 30–40 years of age.

Complications in the treatment of thyrotoxicosis are rare, and when they occur may be expressed by transient aggravation of symptoms during treatment, or by hypothyreosis (3–5% of cases) which appears a few months after cessation of treatment.

We have data on 2890 patients treated by radioactive iodine during the past few years. More than half of the patients were in the second and third stages of thyroid disease. Recovery in diffuse goitre was observed in 90% of the cases, the size of the gland returning to normal in 73%. In the nodular form of goitre, recovery occurred in 50% of the cases and in only 20% of the patients did the size of the gland become normal.[21–24]

Cutaneous and Related Diseases

The beta-emitting radioactive isotopes, P^{32}, Sr^{90} and Ce^{144}, are used in the USSR for the treatment of skin diseases, i.e., eczema, neurodermatitis, precancerous lesions of the skin and mucous membranes and capillary angiomas,[25–28] applying the same criterion for treatment that is used in selecting cases for roentgentherapy. The advantage of radioactive isotopes over X-ray therapy lies in the fact that only superficial layers of the skin and mucous membranes are penetrated by the weak β radiation. The fact that the radiation affects only surface layers is especially important because some of these conditions, such as eczema and neurodermatitis, tend to relapse and require reirradiation. We used isotopes in the treatment of eczema and neurodermatitis only when other methods proved ineffective. Treatment of precancerous lesions of the skin and mucous membranes and capillary angiomas with radioisotopes does not result in cicatrization, one of the undesirable consequences of radiation therapy.

The results of treatment of cutaneous diseases are given in Table 2.

Radioisotopes find their greatest use in the treatment of malignant and benign tumours, a therapeutic problem, however, which still remains to be solved. Radiation therapy for malignant tumours results in "cure" only when certain definite conditions are observed among which dosage and irradiation time—and these differ for tumours with different histological structure—are most important. Irradiation should cause as little damage as possible to surrounding normal tissues. These requirements were known 30 years ago; however, even today they cannot be fulfilled in every case. This explains in many cases the failure of radiation therapy, or "cure" at the cost of considerable damage to underlying structures. For example, sclerosis may occur in surrounding healthy lung tissue and in cardiac muscle after irradiation for cancer of the lung and oesophagus, and atrophy of the oral mucous membrane and salivary glands may occur with irradiation of the submaxillary area, etc.

Deep Seated Tumours

During the last years the possibility of using many radioisotopes with different penetrating power, and also the development of machines which produce radiation with high energy and greater power have made a solution to the problem seem closer. The use of "hard" rays in the rotatory gamma- and X-ray machines has made it possible to apply more successfully radiation therapy in patients suffering with tumours of the internal organs. However, even in these cases only one of the requirements is fulfilled—optimum focal dose.

The duration of irradiation depends largely on the manner in which the patient supports radiation therapy and in many cases, due to deterioration of the patient's general condition during the course of radiation, treatment must be prolonged. However, in these cases recovery does not take place despite seemingly large focal doses.

Table 2

Diagnosis	No. of patients	Recoveries (3-yr observation), %	No results %	Relapses %
Neurodermatitis	837	37	25	38
Eczema	2644	38	—	62
Capillar angioma in				
Children under 1 yr	290	87	13	—
Adults	1002	75	25	—
Precancerous cutaneous lesions	205	100	—	—
Precancerous lesions of mucous membranes	347	76	—	24

An acute local reaction of irradiated tissues will often prevent the use of radiation therapy at an adequate dose level and for the optimum period of time to produce satisfactory results.

Research in radiation therapy led to the discovery of the importance of the use of radioactive colloidal solutions of gold and phosphorus.[29] Infiltration of tumours with a colloidal solution of a β-emitting isotope produced a localized reaction in the tumour which did not cause any appreciable damage to healthy tissues and which did not give rise to serious local or general reactions. However, the actual use of radioactive colloidal solutions also revealed serious shortcomings in this method. Even when a tumour is exposed surgically, uniform infiltration of a large tumour with the colloidal solution is difficult and in cases where a direct approach to the tumour is impossible, infiltration is extremely difficult. Besides, colloidal solutions injected into tumours are rarely confined to the tumour and in highly vascular tumours the radioactive solution may enter the general circulation. Finally, it is difficult to determine and administer dosage accurately when using radioactive solutions. Our experience with radioactive colloidal gold and chromium phosphate has shown that treatment of large tumours with radioactive gold is at best an auxiliary method of radiation therapy. External irradiation still remains the best method of treatment.

The results of treatment of 66 patients with fixed and extensive metastases of malignant tumours of different organs with injections of colloidal gold were not remarkable. Subsequent telegammatherapy using a moderate total dose caused considerable decrease in tumour size, improvement in the general condition, and in 33 cases patients were able to return to work for 1–3 years.

More favourable results were obtained in the treatment of small tumours, e.g., metastases of malignant melanoma, recurrence of tumour, and sarcoma of soft tissues that are not amenable to surgical treatment. Forty-four patients with metastases from malignant melanomas (single in 23 instances and multiple in 21) were treated with a single injection of colloidal radioactive gold, and in 38 patients fibrous degeneration of the tumour was observed. Generalization of the process was noticed only in 3 cases. At present 38 patients are working and have no complaints, 9 of them have been under observation for periods up to one year and 29 have been followed for 1 to 3 years.

Radiocobalt and gold now play an important role in therapy. They are used in the form of wire segments, either with or without a nylon-thread sheath, or as a colloidal solution of radiogold for the radiosurgical method of treatment. This method makes it possible to observe the optimum dose and time-limit for irradiation and to reduce irradiation of healthy tissues to a minimum. Subsequent external irradiation after operation is not necessary. Our experience with radiosurgery convinces us that it is highly effective.

We used radiosurgery for treating 120 patients with breast cancers, metastases from tumours of the oral cavity, sarcomas of soft tissues and cancer of the bladder. In 81 cases it was not possible to excise the tumour because of its wide infiltration. In 39 patients the tumours were only partially removed. Among the patients in the first group, 62 had a 5-year cure. In the second group, 12 patients were well for 3 years, while in the remainder the tumour recurred in 1–2 years.

In treating patients with malignant tumours of low radiosensitivity (cancer of the oesophagus, the oral cavity, the female sex organs and the bladder), optimum conditions of irradiation can be created by combining irradiation methods,[30] for instance, surface and intracavitary irradiation. Thus, telegammatherapy is employed simultaneously with radioisotope irradiation applied within the affected cavity. For this purpose cylinders with solutions of radioactive sodium or cobalt are used for the treatment of cancers of the bladder and vagina, and applicators with radioactive cobalt are employed for cancers of the oral cavity, rectum, cervix and body of the uterus.[31–34]

Our experience shows that the simultaneous use of combined methods of radiation therapy appears to be more effective than the use of the same methods under the same conditions but in succession for, in the latter case, the period of irradiation is prolonged and the biological effect of the irradiation is reduced.

OVERCOMING REACTIONS

A major problem in radiation therapy of patients with malignant tumours is that of overcoming general and local reactions to irradiation. Deterioration in general condition during radiation therapy (loss of weight, progressive weakness and leucopenia) prevents intensive treatment and necessitates either interruption of treatment for varying intervals or reduction in daily dose. Cure rarely occurs when irradiation is irregular.

Drugs and transfusions of whole blood or its components, erythrocyte and leucocyte mass,[35] are used in treating radiation sickness. In view of the variability in pathogenesis of radiation sickness, the drugs used in its treatment are chosen for their influence on different systems and organs but, predominantly, for their effect on the central nervous system and hematopoietic organs. All the therapeutic agents, including blood transfusion, are more effective when used prophylactically prior to radiation, throughout the course of treatment and before the general condition of the patient deteriorates and leucopenia supervenes. Propamin and merkamin are used for prophylaxis and are administered daily before the first irradiation, and are continued throughout the course of treatment. Aminasin, bromine and quinopsin are used for their effect on the central nervous system, and leucogen, pentoxyl, tesan, iron with aloe vera, etc., are employed for their stimulating action on the blood-forming organs. In addition, blood transfusions are performed every week.

To alleviate the local reactions of skin and mucous membranes these areas are treated daily before and after irradiation with an ointment composed of aloe vera, tesan and codliver oil, and for the mucous mem-

Table 3

Site of tumour	*Method of treatment*	*No. of patients*	*Cures according to stage*								*Duration of observation, yr*
			I		*II*		*III*		*IV*		
			No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	
Uterine cervix	Telegammatherapy and intracavitary irradiation	1118	83	75.9	514	50.5	496	25	—	—	5
Lung	Telegammatherapy	110	—	—	—	—	110	—	—	—	2–5 45.4% active, asymptomatic
Esophagus	Telegammatherapy and intracavitary irradiation	201	3	—	88	—	99	—	11	—	1–3 31% active, asymptomatic
Larynx	Telegammatherapy	394	26	90	96	60	245	26	4	—	3–5
Lower lip	Surface application and interstitial	447	162	93	151	79.4	96	40	38	8	5
Skin	Surface application and interstitial	1209	612	87.8	325	71.3	134	48.0	58	10	5
Bladder	Telegammatherapy and intracavitary irradiation	331	32	93	59	67	222	—	18	—	5, for stages I, II 3, duration of life after treatment for stage III

branes alone adrenalin–novocain solution, hexerol, etc., are used.

The systematic use of all these measures for combatting general and local reactions helps to ensure the optimum conditions for treatment, and thus to increase the percentage of cures.

SUMMARY

In conclusion we present in Table 3 combined data from the Institutes of Roentgenology and Radiology in Moscow, Leningrad and Kharkov on the results of irradiation therapy with artificial radioactive isotopes in certain forms of malignant tumours.

We believe that the most urgent problem of radiation therapy of patients with malignant neoplasms is the study and determination of optimum conditions of irradiation in respect to duration, dose rate and "hardness" of ray for tumours of different histological origin, extent and localization. Equally important is the need for research to discover tumourotropic radioactive compounds, or compounds which will act as carriers of isotopes and favourably influence accumulation of the isotope in tumours. The study of these questions is very important in finding the solution to the problems of radiation therapy of patients with malignant neoplasms.

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Basic Questions in the Diagnosis and Treatment of Disease in Man Using the Radioisotope

By C. L. Dunham*

This paper concerns itself with the use of radioisotopes orally or parenterally administered for the diagnosis and treatment of disease. It does not discuss the advantages and limitations of multicurie radiation sources in teletherapy, nor the merits and problems inherent in the use of radioisotopes as fixed sources of radiation for brachytherapy or in interstitial therapy.

Radioisotopes are used in the day-to-day practice of medicine in hundreds of doctors' offices, clinics and hospitals around the world. The diagnostic and therapeutic uses of radioiodine, for example, are commonplace in many countries. It is used in thyroid uptake studies, the identification of thyroid cancer metastases, to cause thyroid ablation in selected cases of angina pectoris, cardiac failure and emphysema, and for the treatment of appropriate cases of thyroid cancer. The successful use of radioiodine for these purposes depends on selective uptake of the radioiodine by normal thyroid cells or in the case of thyroid cancer it depends on the relatively rare circumstance of the neoplastic cells retaining a sufficient degree of normal function. Radioiodine is also used in iodinated human serum albumen for blood volume and cardiac output studies and for the better localization of intracerebral neoplasms.

As a matter of fact the use of radioisotopes in medicine is becoming so popular that there is already a tendency to do things with them where simpler and more old-fashioned procedures would serve as well. This should not be taken as belittling in any sense the very great importance of isotopes insofar as they offer improvements in the practice of medicine, but rather as a reminder that medicine, like any other human endeavor, has from time to time been subject to the whims of fashion. This has been especially true where highly specific and successful methods of therapy have yet to be found for a given disease.

THERAPEUTIC USES

When to Use Isotopes

Radioisotopes are useful in therapy only as they serve as effective sources of ionizing radiation. They have a place in the treatment of disease to the extent that they provide advantage over radium and X rays in directing therapeutic amounts of radiation to those tissues or cells which the physician wishes to irradiate or in achieving significant palliation not attainable by other procedures. The advantage over more conventional methods of radiation therapy may consist in providing a simpler technique or a greater ability to irradiate preferentially the "target" tissue or cells. Procedures using radioisotopes which significantly reduce the number of days a patient is required to stay in the hospital afford an economic advantage. The therapeutic use of radioisotopes is warranted only when one or more of these advantages is assured.

Hazards

There is another consideration which is extremely important in both therapeutic and diagnostic procedures involving radiation whether the source is radium, X rays, or artificially-produced radioisotopes. This is the hazard to the patient or to his progeny arising from incidental irradiation of the gonads, of the body as a whole, or from heavy local irradiation of a part of the body. Radiation and radioisotopes are really not inherently any more dangerous to the patient than other drugs used in the practice of medicine today. In fact immediate and totally unpredictable fatalities, such as result from idiosyncrasies to drugs or diagnostic chemicals, are not to be expected as a result of the radioisotopes themselves if they are used properly either in therapy or in diagnosis. However, the physician who uses radiosiotopes in his practice should be well grounded in the fundamentals of radiation biology. He should be familiar with the nature, the significance and the probability of occurrence of the principal long-term or delayed effects (gene mutation, neoplasia and shortened life span) which could result from the particular procedure he intends to use. In other words, he should have a basic knowledge of the pharmacology and toxicology of radiation and in certain instances of individual radioisotopes equivalent to that required of him with respect to any other therapeutic agent—mercury, arsenic, digitalis, morphine and the host of newer drugs in use today in the practice of medicine.

Safety

There is another problem which on the surface seems unique to radioisotopes, the radiation safety problem.

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Depending on the nature and quantity of radioisotope to be used or handled, certain precautions are necessary in order to protect the physician himself, his technical assistants and others who may have only casual association with the isotope laboratory, or the clinic or hospital ward where isotopes are in use. With isotopes in fixed sources the problem is essentially the same as when it is encountered in the use of radium, radon seeds and X-ray devices, and the precautions are well known. With the isotopes in solution or in suspension, or in certain instances where the patient has within him appreciable amounts of high energy gamma ray–emitting isotopes, the situation may be somewhat novel and the precautions somewhat different. Actually the precautions are neither more nor less essential than those required for the use of explosive gas anesthesia nor are they more difficult to accomplish for those familiar with the problem. The important fact to keep in mind is that the consequences of carelessness in the handling of significant quantities of radioisotopes are not liable to appear so dramatically as those resulting from carelessness in handling explosive gases, but sixty years of experience with X rays and radium has shown that they can be just as real.

The exact amount of a radioisotope to be administered can be measured with great precision just as can be done for other therapeutic agents and, just as with the latter, once the material has entered the body of the patient his physiologic state, local circulatory phenomena, and in this instance the sensitivity to radiation of the cells of the target tissue determine the therapeutic result. Isotope therapy, in spite of all the fine physical measurements that can be associated with it, requires of the physician the same skills, judgment and experience in the art of clinical medicine which are needed for the successful application of any other therapeutic procedure. In no sense is it a step towards slide rule medicine. In fact, whether used in therapy or in diagnosis the more measurements that are made of the distribution and movement of the isotope in a given case the greater the skill and the judgement needed if a useful and valid interpretation is to result.

Distribution

To date, with the exception of the use of gold-198 and radioactive chromic phosphate in palliation of diffuse intracavitary malignancy, isotope treatment whether with I^{131} or P^{32} relies on the naturally greater uptake by the target cell of the radioelement available to it in soluble form in the bloodstream. For ablation of the normal thyroid gland and in the treatment of thyrotoxicosis the preferential uptake of the radioelement is very great, hence the desired result can nearly always be achieved. On the other hand the differential uptake of I^{131} by thyroid cancer cells is, in most instances, slight or absent and under such circumstances treatment with the radioisotope is useless. Removal of the primary tumor and the gland itself may improve the situation in some cases. Treatment with P^{32} for polycythema rubra vera and leukemia depends in part on there being an extra requirement for phosphorus by the cells one is trying to control so that P^{32} may be administered in inhibitory amounts many times before permanent general bone marrow aplasia results. Until the present efforts to improve elective localization of the radioisotopes on or in the tumor cell meet with success or until a method for achieving selective increased sensitivity of tumor cells to radiation is accomplished, radioisotope therapy of leukemia and other malignancies will remain in the palliative category.

DIAGNOSTIC USES

The diagnostic uses of radioisotopes are of three general types. In the case of uptake studies using radioiodine and radioiron respectively the element itself plays a key role in the physiologic function under study. With radioiodinated human serum albumen as it is used to study blood volume and cardiac output and for localizing intracerebral neoplasms, the isotope, by virtue of its being radioactive, serves merely as a convenient quantitative indicator of the movement and distribution in the body of the relatively stable tagged material. A variant of this is the use of simple salts of radioiodine or radioarsenic which pass more freely into a cerebral neoplasm than into normal cerebral tissue, or the use of P^{32} for detecting intraocular tumors. In the latter instances precise quantitative data are not needed and counting or scanning techniques though necessarily sensitive need not provide absolute values for uptake. Finally, where the radioisotope of an element is substituted in an organic molecule for the normal nonradioactive form in metabolic studies it serves to identify intermediate and end-products as coming from the molecules administered and permits quantitative measurements of them. Similar observations may be made on the incorporation of all or a part of the original molecule into a more complex one.

Of these types of diagnostic uses only the first two are in common use today outside of clinical research centers. The radioiodine uptake test is by all odds the most frequently performed in spite of the fact that it is the one most subject to error. The mere fact that there is a variety of approaches to the key problem of determining the actual amount of the radioiodine in the thyroid gland at any given time is good evidence that none of the devices or techniques now in use is completely adequate. It was thus inevitable that Dr. Marshall Brucer, at the Oak Ridge Institute of Nuclear Studies, in a cooperative study involving clinics in the United States and in England, observed that the absolute values being obtained were relatively meaningless as exact measures of thyroid uptake. On the other hand, in competent hands any reasonably good counting technique did give consistent results and experienced persons could interpret the observations in a meaningful and useful way and thus provide a sound basis for important clinical decisions. With quantitative tests involving *in vivo* counting or scanning it will always be much more difficult to get accurate results than with procedures such as the simple total iron up-

take test and studies involving labeled red blood cells where one can draw a sample of blood and count it *in vitro* under more or less ideal conditions. Nevertheless a great deal of effort is going into improving organ scanning techniques to increase the usefulness of iodine uptake studies, of studies on the iron uptake in the spleen, studies of liver function and tumor localization using radioiodinated rose bengal and function tests using iodinated diodrast.

STUDY OF DEGENERATIVE DISEASES

In spite of these and other technical problems the use of radioisotopes as a diagnostic tool has increasingly great possibilities for future development. The pathogenesis of the so-called degenerative diseases, especially those involving the cardiovascular system and the central nervous system, are beginning to yield to an experimental approach using radioisotopes in the study of the complex metabolic processes which maintain the normal state. This will eventually lead to a pinpointing of the metabolic defects associated with the various degenerative processes. In turn it is not unreasonable to expect that diagnostic tests will be devised using radioisotopes of trace elements or tritium or carbon-14 labeled compounds which will permit early recognition and perhaps correction of the defect before irreparable damage has occurred. Improved, inexpensive and reliable instruments for low-level counting are needed in order that this sort of work may go ahead rapidly in relatively normal humans because the amounts of carbon-14 and tritium which can safely be administered are extremely low.

SUMMARY

In summing up the position of radioisotopes in the practice of medicine today one can say that in a few well defined situations they offer to therapy a real advance over more conventional methods. Similarly they have made possible a limited number of extremely valuable diagnostic tests. The application to diagnosis will gradually be expanded and may be expected to lead directly or indirectly to important advances in the control of the so-called degenerative diseases. Therapeutic application of radioisotopes in the field of the neoplastic diseases will continue to be limited until our knowledge of the biochemistry and metabolism of normal and malignant cells is much more precise. This will come about in large part through the use of radioisotopes as tracers in experimental biology.

Teletherapy: Progress Since 1955; Technological and Clinical Evaluation

By M. Brucer* and N. Simon†

In March 1958 the United States Atomic Energy Commission terminated encapsulation and retail sale of cobalt-60 sources inasmuch as it was felt that government encouragement was no longer needed. In less than ten years the production and sale of cobalt-60 machines have become a commercial business.

In 1955 we reported to the first International Conference in Geneva that about 120 cobalt-60 machines were in use. At the second international congress it is significant that one producer of cobalt-60, Atomic Energy of Canada Limited, has by itself produced more than 160 cobalt-60 sources for teletherapy; the United States has made almost 200 sources.

The March 1958 date can be used as a cut-off point for precise information; production has become too widespread. This may not sound like an unusual development until you remember that exactly 10 years ago there were no teletherapy machines. The problem of supervoltage has developed from a situation involving exceedingly large outlays of money to one in which some clinicians are now referring to cobalt as orthovoltage or conventional therapy. A review of this decade of progress is in order.

At the Oak Ridge Institute of Nuclear Studies (ORINS) teletherapy has been one of the major interests. In 1948 Dr. L. G. Grimmett proposed that it would be possible to make a supervoltage teletherapy machine using cobalt-60. His original concept envisioned a simple substitution of cobalt-60 in a radium-pack type of machine. This idea was adopted but the original estimate of a 10-curie cobalt machine was soon expanded to 100 and then to 1000 curies. Dr. Max Cutler bought a small 200-curie source for test because little was known about the physical characteristics of cobalt-60 radiation. With this small 200-curie source, a field experiment was designed in 1949 in which the radiation in air from cobalt-60 was measured. From these measurements we developed a 1000-curie irradiator. In 1950 our first teletherapy machine was designed, and a contract was let to General Electric for its production. In 1951 sources and machines were available for plotting isodose curves from the first device.

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By 1952 it was obvious that the idea of using radioisotopes in teletherapy could be extended in many directions. The rapidly developing realization that shielding was one of the main expenses in the installation of teletherapy machines and the current high price of Co^{60} forced an investigation into fission-product sources. It was also realized that the 5¼-year half life of Co^{60} was not an ideally long half life. Cesium-137 was one of the obvious choices for teletherapy. With an energy half that of Co^{60}, the shielding problems were much reduced; and, with a half life six times that of Co^{60}, the problem of decay was considerably ameliorated.

Prompted by the considerable expense of 1000-curie sources in 1953, a group of universities in the United States began a program to develop a unit using smaller sources of Co^{60} (Fig. 1). Following this development other practical and clinical advantages of hectocurie devices became apparent. In 1954 commercial development of teletherapy machines was on its way (Fig. 2).

The enthusiastic acceptance of Co^{60} by radiotherapists does not mean that the physician really expects more cures. It does mean that the apparent physical advantages of cobalt have become real clinical advantages (Table 1).

The skin sparing and increased depth dose with cobalt have made radiotherapy more tolerable for the patient. With 250 kv radiation the skin is often the structure that limits effective radiation directed to a tumor at depth. With cobalt the skin is no longer a limiting factor, and the radiotherapist finds that other deeper tissues limit the patient's tolerance to radiation.

The skin-sparing effect of cobalt radiation may be a chimera unless this type of supervoltage radiation is properly used. The source and applicator must be at a distance from the skin, or a shower of electrons from the inner walls of the collimating device will contaminate the gamma-ray beam, and the secondary radiation will induce unnecessary skin reaction. A thin sheet of metal of medium atomic number should enclose the end of the applicator to provide an electron filter.

Malignant tumors, curable in the past with 250 kv X rays, are in the same way curable with cobalt-60. An example of such a lesion is carcinoma of the larynx. For more than 30 years carcinoma of the larynx has been treated with conventional X-ray therapy (180 to 250 kv). In recent years the hectocurie apparatus has been used in the treatment of scores of such lesions.

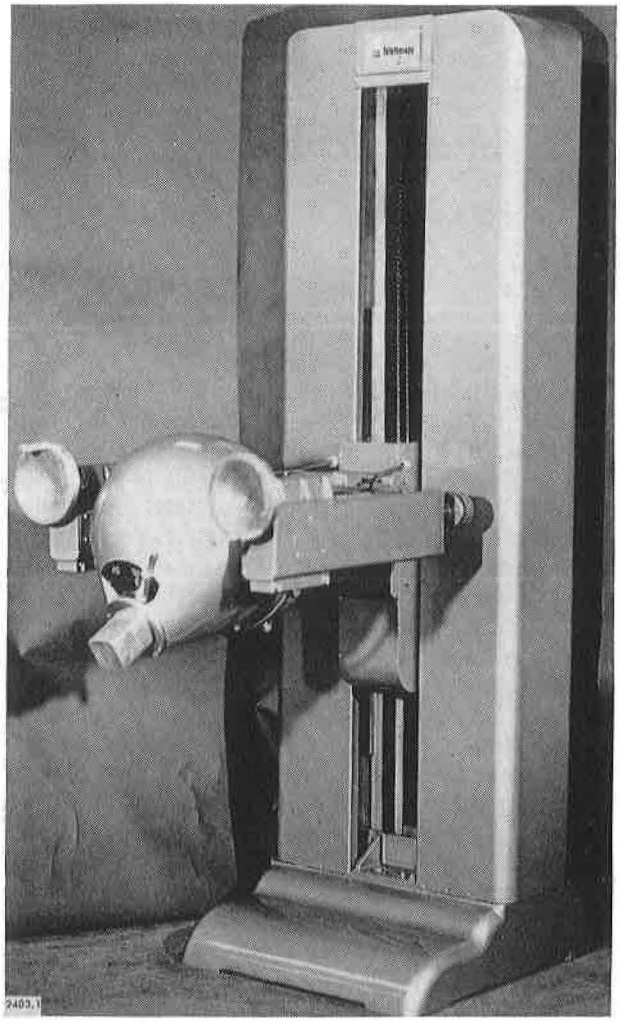

Figure 1. Hectocurie cobalt-60 teletherapy machine. Floor-stand model

The cure rate promises to be about the same; but the skin-sparing characteristic of cobalt-60 makes the treatment much more easily tolerated by the patient. Instead of a denuded, uncomfortable skin reaction from 250 kv X rays, the patient treated with cobalt-60 has only a mild erythema and tanning as his maximal skin reaction.

Unfortunately many cancers are incurable by any known method, and the palliation of these lethal tumors is an important task for radiotherapy. This is the field in which cobalt-60 teletherapy excels particularly. In the treatment of such deep lesions as tumors of the esophagus, lung, and bladder the combination of skin sparing and increased depth dose are of distinct advantage. When the skin is spared large doses of radiation may be administered through efficient portals, and treatment planning is simplified. The necessity for multiple portals and rotation is lessened.

In addition to the advantages of skin sparing, increased depth dose, and simplified technique, other advantages have contributed to the acceptance of cobalt-60. The absorption of radiation by bone is appreciably decreased, and this characteristic of cobalt radiation may represent one of its most important features. Aside from increasing the depth dose in tumors underlying bone, the decrease in bone absorption should lower the incidence of disabling radionecrosis of bone.

Table 1. Advantageous Features of Cobalt-60 Teletherapy

1. Skin sparing
2. Increased depth dose
3. Simplified techniques for treatment
4. Decreased bone absorption
5. Decreased radiation sickness
6. Dependability

Radiation sickness is less severe in patients treated with cobalt, and this seems to be associated with the lessened side scatter in the supervoltage range.

The dependability of cobalt-60 teletherapy apparatus is a feature that has contributed greatly to its acceptance. It has been the experience of users of cobalt-60 teletherapy that mechanical breakdowns are rare. When radiotherapists have had both 250 kv X-ray apparatus and cobalt-60 at their disposal, the practice has been to use cobalt-60 for most of the patients treated. This preference for cobalt-60 is based on all its advantageous features, not the least of which is its dependability.

It has been feared that cobalt-60 radiation would result in late fibrosis of the subcutaneous tissues, because the surface of the skin is spared; but the maximal dose of radiation lies only a few millimeters below the surface. The experience of radiotherapists who have treated patients for several years with cobalt-60 indicates that late subcutaneous fibrosis is not a serious problem when reasonable and effective doses are administered. Subcutaneous fibrosis tends to be induced

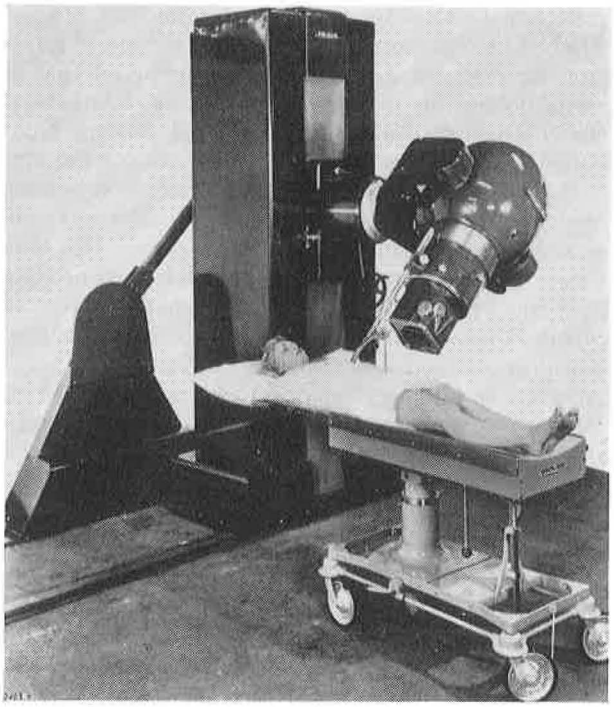

Figure 2. Kilocurie cobalt-60 teletherapy machine. Rotational model

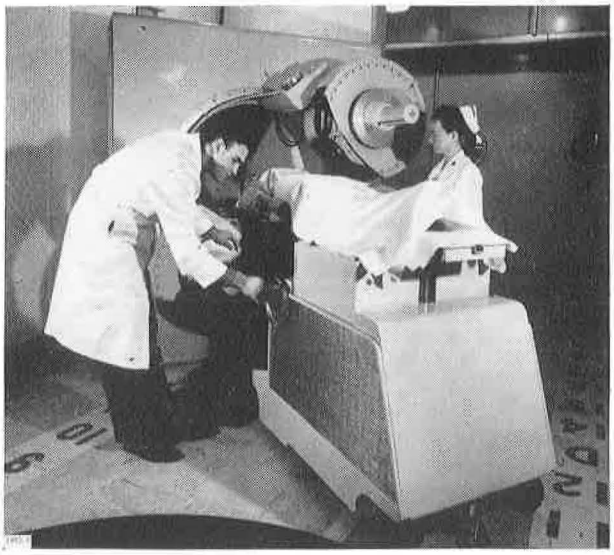

Figure 3. Double-headed cobalt-60 teletherapy machine

more readily when the overlying superficial skin has a severe reaction (250 kv) than when the surface of the skin is spared (cobalt-60).

But cobalt-60 is neither the perfect nor the only important radioisotope for teletherapy. The rapid shift to cobalt-60 from electrically generated devices marked only the first phase of the program at ORINS. During this phase we mimicked the electrical devices. The second phase was marked by extensions to unconventional supervoltage designs (Fig. 3). A third phase of the program began in 1955. It was no longer necessary to think of just cobalt-60. Rapidly expanding production of cesium-137, probable availability in pure form of many fission products, and reduced cost led to the expansion of the idea of teletherapy. By 1955 we no longer needed to consider just individual point sources of energy. We could begin to consider extended sources: sources distributed over various patterns so that they would automatically develop isodose patterns of value to the therapist. In 1955 about 30 ten-inch sources of cesium-137 in the microcurie level were made. These sources were used as a test device to investigate the idea of cylindrical and circular patterns. In 1956 the idea was extended to include very low energies. A strontium-90 source, a cadmium-109 source, and an iron-55 source were adapted to a small hand-held device. In 1957, along with the growing realization that hectocurie machines had more than just special-purpose usefulness, the idea was extended to low-intensity machines. This was especially important since the problem of replacement of cobalt-60 sources and the disposal of worn-out sources was becoming an increasing concern.

Development of the first low-intensity machine was rapidly changed to development of an interchangeable-source machine in 1958 (Fig. 4). This was not developed for therapeutic purposes. It is a machine designed to allow the interchange of sources especially made to study physical characteristics under identical conditions. With this machine we hope to evaluate the usefulness of many isotopes for special therapeutic indications. Radioactive sources of almost any energy can be made available on a theoretical basis but the practical problems of actually making them are not all solved. The desirability of these sources after they are made is still a matter of conjecture.

The teletherapy program at ORINS is not specifically directed toward the actual therapeutic use of various machines. Many hospitals with large patient loads are better fitted to investigate the truly clinical phases of the problem than we are. Eight teletherapy sources are now available at ORINS and a radiotherapist is working with them. But this is secondary to a more important problem. Investigating the practicality of sources must be done with a small clinical program but in cooperation with a large isotope-production program. Therefore, the future of the ORINS teletherapy program is to investigate the special-purpose sources and machines.

The ORINS investigation is by no means the only teletherapy program. Teletherapy has been a worldwide development. In the United States four main lines of development have occurred. The usual floor-stand model either kilocurie or hectocurie is most common. A rotational unit, usually of hectocurie size, has also been developed. A somewhat different design involves not an internal rotating wheel but a "broomstick" ON and OFF mechanism.

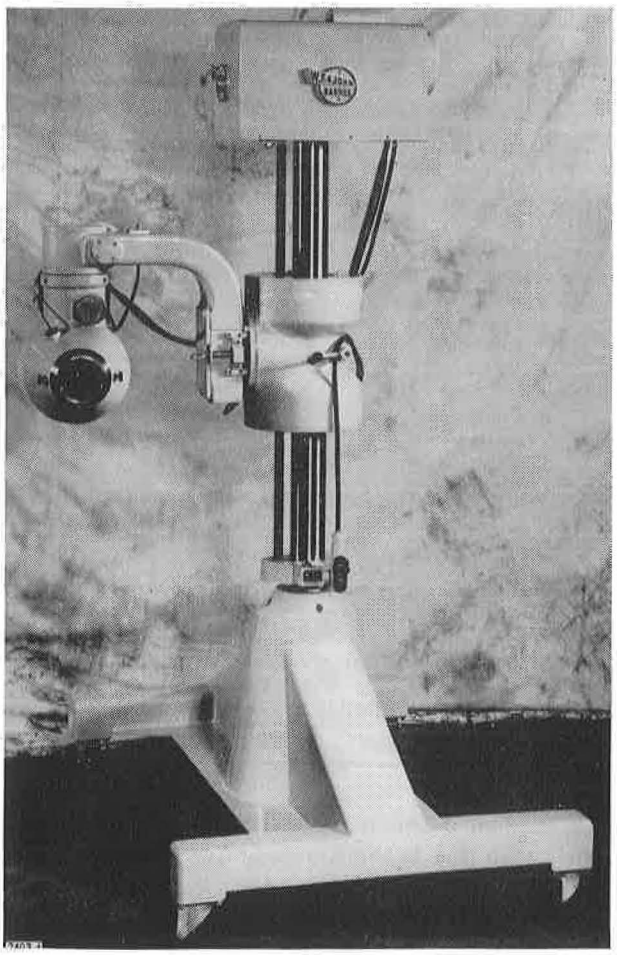

Figure 4. Interchangeable-source machine

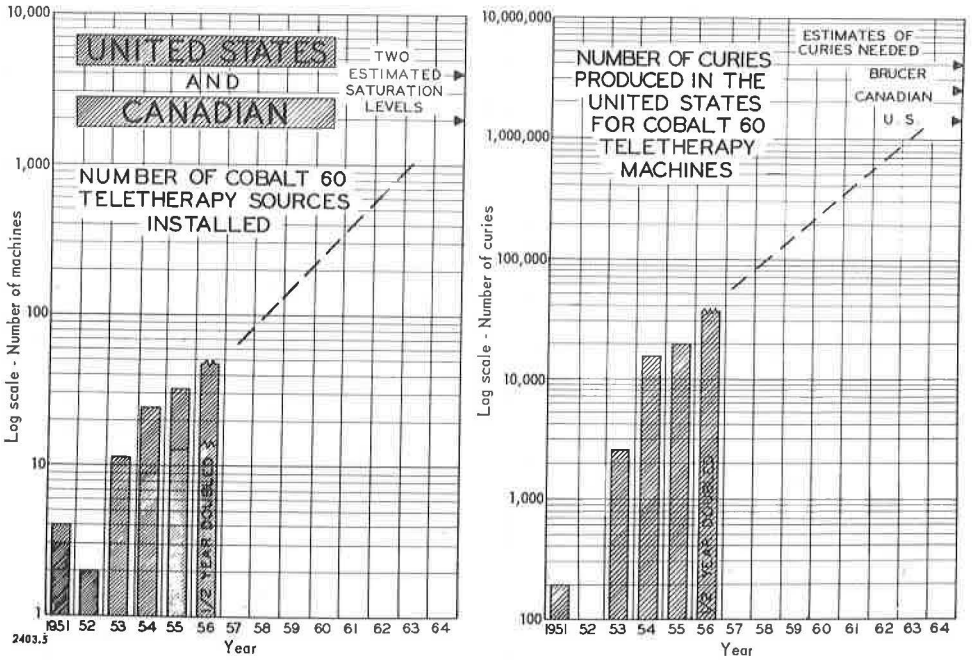

Figure 5. Charts predicting distribution and production of cobalt-60

Table 2. Distribution of Teletherapy Sources

A. Total number of sources sold from North American reactors (March 1958)

United States	171
Canada	143
Total	314

B. World-wide distribution of sources (March 1958)

1. From the United States:

Country	*No. of Curies*	*No. of Sources*
United States	110,646	105
Canada	5,944	4
Italy	15,785	12
France	13,355	13
Chile	1,707	2
England	4,955	3
Japan	5,931	6
Mexico	8,203	10
Brazil	4,112	4
Indonesia	1,948	1
Belgium	448	1
Holland	1,183	1
Philippines	1,000	1
Puerto Rico	1,621	2
Argentina	1,016	1
Germany	5,031	3
Uruguay	1,007	1
Peru	2,963	1
Total	186,855	171

2. From Canada: 143 cobalt-60 sources (March 1958)
   Curies: approximately 179,000
   Countries: Canada, United States (including Puerto Rico), United Kingdom, Spain, France, Italy, Switzerland, West Germany, East Germany, Poland, Brazil, Venezuela, India, Burma, Ceylon, Australia, New Zealand, Mexico, Lebanon, Chile.

Canadian development has progressed simultaneously with that in the United States. Four major machines have been produced. One is the single large-source teletherapy machine, and two (one large and one small) are rotating machines. Recently a hecto-curie floor-stand machine has been offered for sale.

Many other countries have developed teletherapy programs. Extensive research in England has used cesium and cobalt but also has included the development of a cerium source. One of their first teletherapy sources used an iridium isotope. Japan has made remarkable adaptations of the machinery; it is hoped that source production will begin in 1958. In the USSR a number of machines were mentioned as early as during the 1953 International Congress of Radiology.

In Sweden, Holland, and Germany and in other countries adaptations of the fundamental ideas of teletherapy have been developed.

In Fig. 5 two charts are reproduced that were first shown at the 1956 International Congress of Radiology in Mexico City. The predictions on the distribution and the production of cobalt-60 are still holding up fairly well. The production of cobalt is rising in an almost exponential manner and the distribution is world-wide (Table 2). It appears that as of March 1958 the North American reactors are producing between 10 and 15 sources each month. This is of cobalt-60 alone. Cesium-137, cerium-144, iridium-192, and strontium-90 are still in the investigative stage.

In the summer of 1956 the ORINS Medical Division was host to a seminar on supervoltage and gamma-beam teletherapy. Representatives from 12 countries were present. The clinical material has been published under the title *Roentgens, Rads, and Riddles*.[1] From these discussions it is apparent that teletherapy using radioisotopes is well on the way toward making the supervoltage therapy of the 1930's the orthovoltage therapy of the 1960's.

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Cobalt-60 Beam Therapy*

By Ivan H. Smith, J. C. F. MacDonald, P. M. Pfalzner and H. I. S. Ferguson

PART I. CLINICAL

The success of irradiation therapy in malignant disease varies inversely with the stage of the lesion. With the advent of cobalt-60 beam therapy one does not expect to alter the curability of advanced disease; yet, it was hoped that in the less advanced neoplasm the improved physical qualities of this form of supervoltage can be reflected favourably both in tumour and host response. There is ample evidence in support of this expectation from a study conducted on four sites: the oesophagus, the oral cavity, the urinary bladder and the intrinsic larynx, all of epidermoid histology with their basic inherent radiosensitivity of moderate degree. Observations were made on patients treated by the original AECL Eldorado kilocurie unit† (Fig. 1), using the multiple-field beam-directed technique, except for the oesophagus in which rotation occasionally was instituted. Skin-to-source distance was 80 cm.

Carcinoma of the Oesophagus

The physical feature of electron build-up,‡ placing the maximum dose some four to five millimetres beneath the skin, is clinically evident in the form of decreased skin reactions in a wide variety of cases. The oesophagus group is an excellent example, for seldom is a reaction beyond the mildest erythema experienced. In part this desirable advantage is attributable to the low skin-to-tumour dose ratio associated with the more penetrating radiation.

The oesophagus cases also illustrate the importance of lower integral dosage associated with irradiation in the 2–3 Mev range of X-ray energies. Irradiation sickness seldom was seen, no significant change in the leucocyte count was observed, although lassitude continuing for several weeks was quite a regular accompaniment. Applying Mayneord's formula for integral dose which ignores variations in density of tissue, the integral dose using cobalt-60 is 2.6 megagram r per 1000 r tumour dose compared with 4.5 megagram r for 250 kev under identical treatment circumstances.

Except for four cases treated by rotation, the method of management of 31 cases suitable for radical therapy (i.e., dosage per cure) was by multiple-field technique (4–5 portals, e.g., Fig. 2), using the plaster of Paris jacket for beam fixation and localization. Table 1 records tumour dose range, and over-all treatment time, each field being exposed daily, five days each week. The figures in Table 1 have not been corrected for lung transmission[4] and, in this group, the average calculated increase in tumour dose, allowing for such pulmonary transmission, was 16%.

Early experiences with 4800 to 6000 rads tumour dose in three weeks revealed local reactions that were too severe; accordingly current dosage is in the range of 5800 to 6250 rads (including correction for lung transmission) in four to four and one-half weeks. Thus far, relative biological effectiveness, clinically, is unsettled but it would seem that the patient not only tolerates a higher tumour dose of radiation at this energy but requires a small percentage increase for lethal tumour effect.

A glance at Table 2 reveals seven rather long-term survivors, without evidence of disease and with minimal physical handicap. The findings suggest, furthermore, that in this most lethal form of cancer, cobalt-60 deserves serious continued study.

Oral Carcinoma

Some pertinent observations made in the oral carcinoma study[5] have impressed us. Table 3 indicates a breakdown by site of the treated lesions and Table 4 records the type of irradiation used in the entire group registered with the Clinic during 1952 to 1955. The 50 cases treated radically, for cure, constitute the basis of this study. It is to be noted that those lesions not too

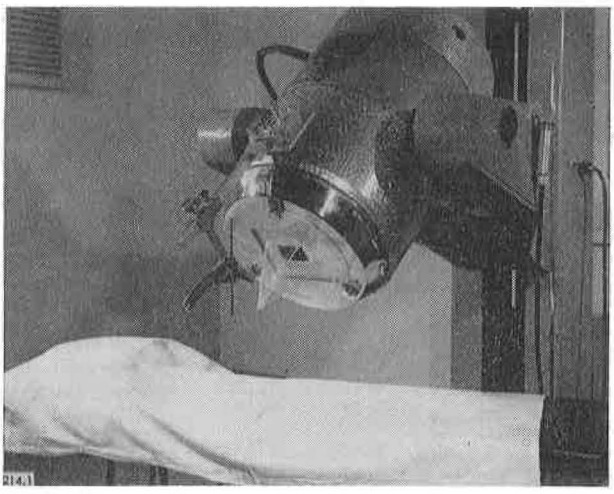

Figure 1. The AECL Eldorado kilocurie unit

*Contribution from The Ontario Cancer Foundation, London Clinic, London, Ontario.

† Made by Atomic Energy of Canada Limited, Commercial Products Division, Ottawa, Ontario.[1–3]

‡ See "Physical Measurements", Part II, eighth paragraph.

advanced for radium or radon therapy were treated accordingly. Single field, parallel opposing and multiple fields with plaster of Paris beam fixation and localization were used (Fig. 3). Tumour dosage considered optimum is at the rate of 1500 rads per week (five days) delivering 6000 rads in four weeks, carefully scrutinizing the reactions thereafter to an end mean dose ranging from 6000 rads in four weeks to 7000 rads in six weeks.

That tumour invasion of mandible can be controlled is evidenced by four pleasing responses. Of the 50 cases, four showed unquestionable radiographic invasion without obvious clinical bone exposure. One

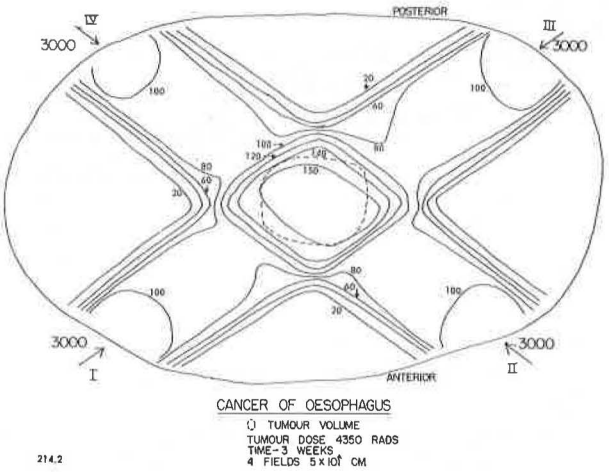

Figure 2. Isodose distribution for cancer of the oesophagus treated by kilocurie unit; plaster of Paris jacket and back pointer

Table 1. Carcinoma of Oesophagus—31 Cases Radically Treated (1952–1956)

Dosage in relation to time

No. of cases	*Tumour dose in rads Not corrected for lung transmission*	*Over-all time (in weeks)*
1	5300	2½
4	4800	3
8	4800–6000	4
8	5300–6250	4½
5	5300–6250	5
3	5300–5800	5½
2	6250–6450	7
Total 31		

Table 2. Carcinoma of Oesophagus—Survival Study of 31 Cases Radically Treated (1952–1956)

No. of cases	*Alive and well (mo)*	*Length of lesion (cm)*	*Site*
1	20	2	Upper third
1	44	5	Mid-third
1	48	6	Post cricoid and cervical
1	48	12.5	Lower third
1	48	5	Mid-third
1	56	4	Post cricoid
1	60	4	Mid-third
Total 7			

Table 3. Oral Carcinoma by Site

Radical treatment with cobalt-60 (1952–1955)

Buccal surface of cheek	7
Tongue	7
Palate and upper alveolus	5
Floor of mouth and lower alveolus	17
Tonsil and fauces	14
Total	50

Table 4. Cases of Oral Carcinoma Treated by Radiotherapy (1952–1955)

Deep X-ray therapy		10
Radium or radon seed implant		33
Cobalt-60 teletherapy		79
radical treatment	50	
palliative treatment	29	
Total		122

case died 25 months following treatment at 80 years of age, with complete mucosal repair. The other three are totally healed without pain or fistula for 34, 61 and 66 months following therapy.

It has been noted that complete regression of disease, recurrent after previous X-ray therapy, is possible. Five of the 50 were admitted as such recurrences: one died of disease, three are well and free of complications, while one is free of disease but with necrosis of mandible (Table 5).

Control of metastatic lymph node invasion has been recognized in six cases. Nine of the 50 cases had such nodes within the treatment field for the primary disease. One case died of intercurrent disease without

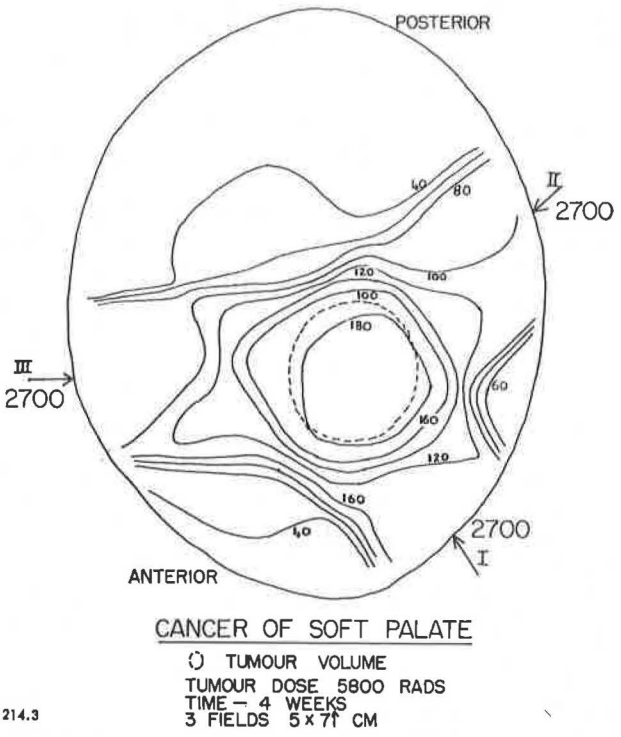

Figure 3. Isodose distribution for cancer of soft palate treated by kilocurie unit; plaster of Paris collar and back pointer

Table 5. Oral Carcinoma: Recurrent Disease (following X-ray therapy) Treated by Cobalt-60 Beam Therapy (1952–1955)

Site	*No. of cases*	*Survival (mo)*	*Tumour dose (rads)*	*Time (wks)*	*Field size (cm)*
Alive without disease					
Tongue	1	49	5300	3	7 × 10
Floor of mouth	1	62	5800	4½	10 × 12
Tonsil	2	60	5300	3	7 × 7
		63	4150	2½	5 × 5
Died of disease					
Buccal mucosa	1	4		3	10 × 8

signs of cancer at autopsy; two died of cancer, whereas six, as recorded in Table 6, are alive and well.

Where there was no clinical evidence of bone exposure nor radiographic evidence of invasion, a total of 43 patients, there has been no evidence of spontaneous bone necrosis. This observation supports the view that an advantage is gained in decreased differential absorption per gram of bone tissue when cobalt-60 therapy is used. That irradiation osteitis occurred, however, is suggested by the fact that two of the patients developed bone necrosis following tooth extraction 41 and 58 months following treatment. In one instance a segment of mandible, free of malignancy, required resection; in the second, a dry socket persisted for 12 months. Both have been free of disease for 74 and 66 months respectively.

In general the less extreme and short-lived skin and mucosal reactions from cobalt-60 mean relative comfort and often permit the frail or elderly patient to tolerate a "curative" rather than a lower palliative dosage.

Carcinoma of Bladder

Location of bladder tumours was done by shift radiography and beam direction by pin and arc through three or four fields (Fig. 4). It has been learned that protraction of exposure over a basic six weeks' period is preferable to shorter, more intensive therapy. A dose of 5800 to 6250 rads over six weeks is a requisite minimum for "curative" tumour treatment, although protraction beyond this point is occasionally well tolerated and advisable (Table 7).

Our particular bladder series (29 treated radically) consisted mostly of recurrent multiple lesions, those beyond the size suitable for radon seed implant or those not resectable except by total cystectomy. Twenty-one additional cases which were well beyond the anatomical limits of the bladder were treated palliatively by large fields and low dosage. Table 8 is a record of treatment effectiveness and survival. The proliferative transitional cell variety was most favour-

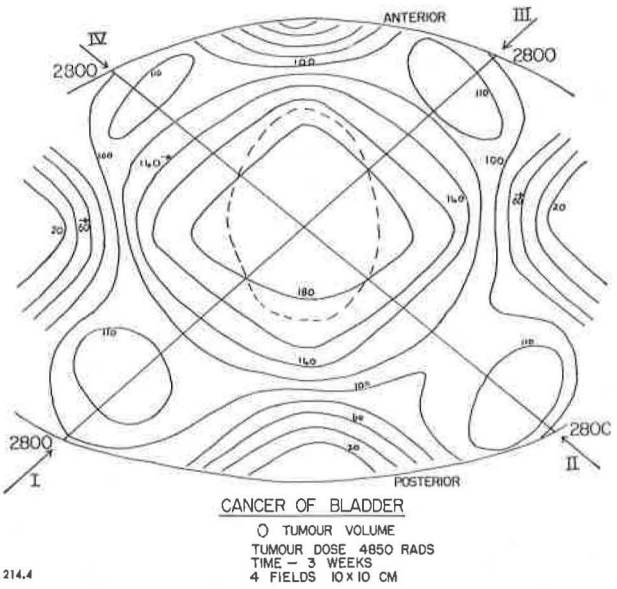

Figure 4. Isodose distribution for cancer of bladder treated by kilocurie unit; pin and arc

Table 6. Radical Cobalt-60 Therapy of Oral Carcinoma including solitary clinically significant lymph node within treated volume (1952–1955)

Site	*No. cases with lymph node*	*Duration (mo)*
Alive and free of disease		
Floor of mouth	1	61
Tongue	2	49
		48
Upper alveolus	1	56
Tonsil	1	39
Buccal mucosa	1	36
Died of disease		
Tongue	1	15
Floor of mouth	1	17
Died of intercurrent disease		
Lower alveolus	1	4
Total	9	

Table 7. Carcinoma of Bladder—Tumour Dose Range

No. of cases	*Tumour dose (rads)*	*Time (wks)*
5	4800	3
7	4800–5800	4
7	4800–6225	4½
4	4800–5700	5
3	4550–6100	5½
2	6100–6250	6½
1	6250	7
Total 29		

Table 8. Carcinoma of Bladder—Survival Study (1952–1955)

	Radical therapy		*Palliative therapy*	
	Cases	*Duration (mo)*	*Cases*	*Duration (mo)*
Alive without disease	7	26–58	2	38–42
Alive with disease	4	20–66		
Dead	18		19	
Total No. cases	29		21	

ably influenced. The low-grade ulcero-infiltrative type was the most refractory. In the long-term survivors without disease, bladder capacity and comfort were extremely satisfactory. Should irradiation fail to control the disease, it is our opinion that the attempt should not jeopardize the patients' chances by subsequent cystectomy. With increasing information

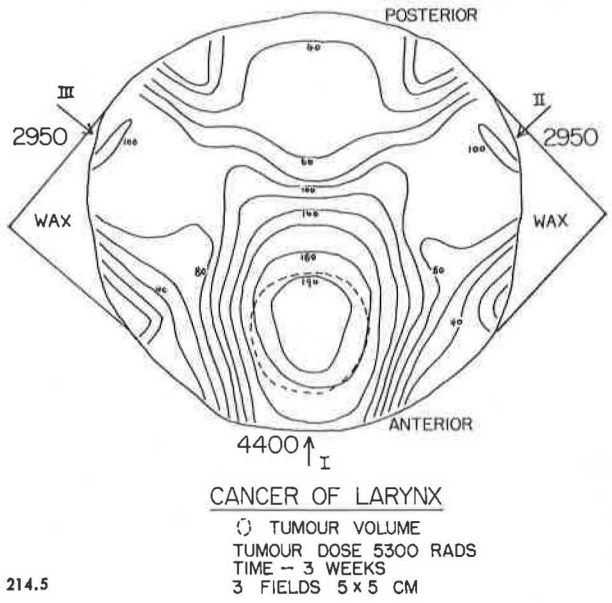

Figure 5. Isodose distribution for cancer of larynx treated by kilocurie unit; plaster of Paris collar and back pointer

about critical lethal tumour dose level and adjacent tissue tolerance, and with greater knowledge of the technical factors involved, a significant increase in the already heartening results is a real possibility.

Intrinsic Carcinoma of Larynx

Observations have been made on 13 cases treated between 1952 and 1954. All were confirmed histologically as squamous or epidermoid carcinoma. Twelve were staged as two in which involvement had gone beyond the limits of a solitary cord, in particular across the anterior commissure. One case staged as three had extended to both true cords, the right false cord and the arytenoids being fixed.

All cases, except one treated through a single field, were managed by a three-field technique with beam direction and localization through a plaster of Paris collar. A typical isodose distribution is exhibited in Fig. 5. The field sizes averaged 5 × 5 cm to 6 × 8 cm. Tumour doses ranged from 4350 to 6750 rads in three to five weeks. Skin reactions were dry except for an occasional patch of moist dermatitis anteriorly. With the short over-all time and rather stout dosage used in the early years of our cobalt-60 experience, heavy fibrinous mucosal reactions occurred somewhat earlier but as a rule subsided more rapidly than would be the case if treated by a lower cobalt-60 weekly dose rate or by conventional X ray. At present we aim to deliver 5800 to 6750 rads in four to five weeks depending on patient tolerance.

Complications have been minimal. One true case of cartilage necrosis occurred in a patient treated as a child by X-ray therapy for what probably was papillomatosis of the larynx. He remains free of disease after four and one-half years, yet with laryngeal fistula. Huskiness is the rule, and is associated with an asymptomatic dryness of laryngeal mucosa.

Although in most instances the skin remains soft and pliable, we are now seeing some delayed anterior telangiectasis. This conceivably may be corrected by the use of wedge filters. There has been no spinal cord damage.

Of all anatomical sites it is our belief that carcinoma confined to the intrinsic larynx is the most favourable type for cobalt-60 irradiation. Table 9 is a record of the results of treatment. Eleven of the 13 are without disease from 31 months to six years; one case died of pulmonary metastases after 50 months, the primary remaining well; one case died after 16 months, there being a combination of recurrence and necrosis.

Table 9. Intrinsic Carcinoma of the Larynx (a study of survival)

Year	*No. of cases*	*Alive and well*	*Duration*	*Died with local recurrence*	*Died without local recurrence*
1952	6	5	4 yr, 10 mo to 6 yr	1	0
1953	5	4	4 yr to 4 yr, 3 mo	0	1
1954	2	2	2 yr, 7 mo to 3 yr, 5 mo	0	0
Total	13	11		1	1

PART II. PHYSICAL DATA RELATING TO A HECTOCURIE ROTATIONAL COBALT-60 UNIT

General

Kilocurie cobalt-60 beam-therapy units are now accepted as the major part of the deep therapy armamentarium in large cancer treatment centres in many parts of the world. Since the physical advantages of high energy gamma-ray beams have been found to have clinical parallels, it is natural that this type of therapy is finding increasing favour with radiotherapists, and that new designs of units are being developed. Such designs aim at greater flexibility and lower cost as to both equipment and housing facilities, and, where possible, make maximum use of the proven advantages of cobalt-60 therapy. Many different types of units in the hectocurie range of activities are now being installed in smaller cancer clinics, private offices, and as second units in some of the larger clinics. Some of these installations are in places where the services of a radiological physicist are not available and where, as a result, optimal use of the equipment cannot be made because of a lack of essential physical data. A typical cobalt unit of this type is the "Theratron Junior".§ This part of the paper describes methods used to obtain the basic physical data necessary for the clinical use of this kind of unit, together with the results of the physical measurements. Apart from variations in dose rate due to differences in source activity, these data should be directly applicable to all Theratron Junior units and will have limited applicability to other hectocurie units operated at similar treatment distances.

The Theratron Junior unit (Fig. 6) has, as a basic framework, a heavy steel yoke, at one end of which is the lead and tungsten alloy source shield, while at the other end is a heavy lead-filled disc which serves the dual purpose of a counterweight and an attenuator of the primary and narrow-angle scattered radiation beams. The source remains fixed at the centre of the shield and a tungsten alloy sliding block serves as a shutter. Continuously adjustable square and rectangular field sizes ranging from 2 × 2 cm up to 15 × 15 cm are available by changing the separation of tungsten blocks in a diaphragm assembly mounted on the front of the head at a distance of 25.9 cm from the source. By means of a motor drive mounted within the support stand, the yoke can be rotated about a horizontal axis through its centre in such a way that the source is constrained to move in the vertical plane in a circle of 55 cm radius. The useful beam of radiation, whatever the orientation of the yoke, always points at the centre of this circle. Thus, the unit is capable of 360° circumaxial rotation therapy, and it incorporates adjustable limit switches which permit its use in arc therapy. The treatment stretcher is part of the unit proper and, with one rotational and three translational degrees of freedom, makes possible the easy positioning of any part of the prone or supine patient at the centre of rotation. The cobalt-60 source of the unit described in this paper has the form of a right circular cylinder, 2.4 cm in height and 1.5 cm in diameter. All measurements quoted are normalized to an exposure dose rate of 47.6 roentgens per minute at 55 cm from the source obtained with a beam of 100 cm^2 cross section at that distance.

§ Made by Atomic Energy of Canada, Limited.

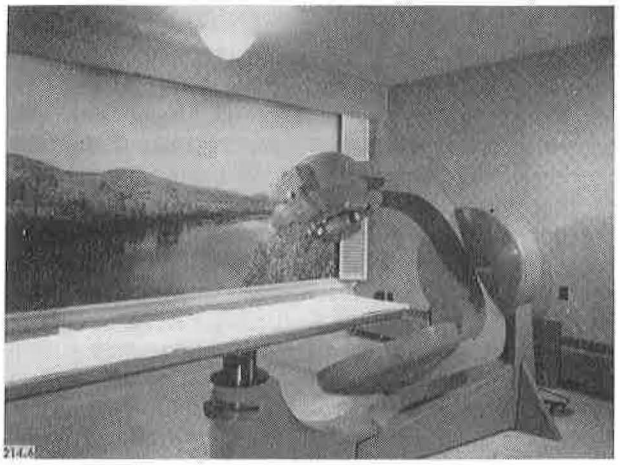

Figure 6. The Theratron Junior installation in the London Clinic of the Ontario Cancer Foundation

This unit could be used in the manner conventional to fixed field therapy, i.e., with a fixed source-skin distance, and with the dose at the tumour represented as a percentage of the maximum dose 0.5 cm beneath the skin. It is more logical, however, to place the tumour at the centre of rotation and to use the method of tumour-air ratios developed for rotation therapy, to arrive at an estimate of tumour dose. This method is as applicable in fixed field therapy as it is in arc and rotation therapy. The tumour-air ratio method has been extensively described in the literature.[6,7] To use this method it is necessary to know (*a*) the exposure dose rate in air at the centre of rotation as a function of field size, and (*b*) the ratio of absorbed dose rate at this point to exposure dose rate, in rads per roentgen, as a function of field size and depth of overlying tissue. In order to arrive at a knowledge of dose distribution within the irradiated body, either in fixed field or in rotation therapy, it is necessary to have a variety of isodose charts which give information as to the dose at other points within the radiation field as a percentage of the dose at the centre of rotation. Since the source-tumour distance is fixed, the source-skin distance varies depending on the thickness of overlying tissue. For a given field size at the centre of rotation, the absorption characteristics of the radiation beam are dependent upon the source-skin distance and, upon first consideration, it would appear that separate isodose distributions would be necessary for each small increment in skin-tumour distance. It has been found, however, that for each field size a set of isodose curves representing the distribution for each of three thicknesses of overlying tissue is adequate for clinical purposes.

Physical Measurements

The exposure dose rate as a function of field area and shape at the centre of rotation was measured using an ionization chamber with a Townsend-balance circuit, loaned to us by the X-Rays and Nuclear Radiations Section of the National Research Council of Canada. Calibration of the instrument was based upon a value for the specific gamma ray emission of radium of 8.25 roentgens per hour at 1 cm.[8,9] Under the normalized conditions mentioned above the variation of exposure dose rate with field area was as shown in Fig. 7. Reproducibility of the readings was within 0.5%. Exposure dose rate dependence upon field elongation was measured; the maximum deviation from that for a square field of equal area was found to be 1.5%.

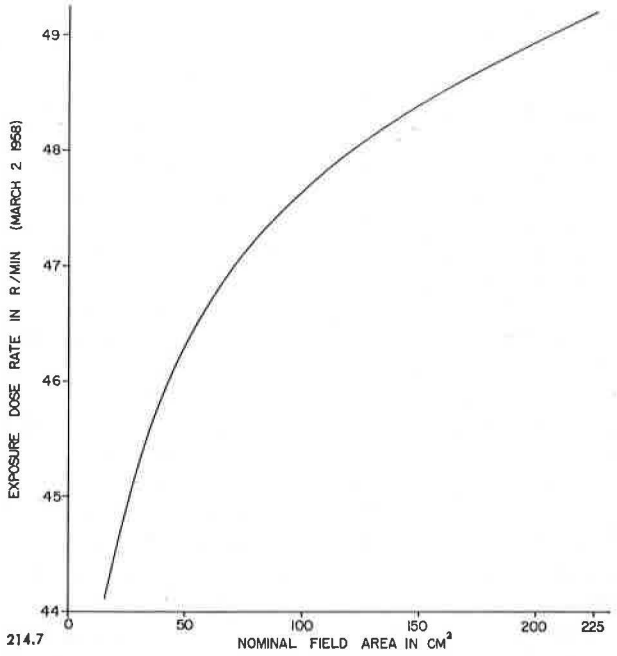

Figure 7. Variation of exposure dose rate at the centre of rotation (55 cm from the source) with field area

It was necessary to consider the question of what is meant by size of field in a unit where the beam penumbra is not negligible. Dose plots taken across the measured isodose curves at the level of the centre of rotation confirmed the fact that the diaphragm-setting dials give the field width at the level of the 50% isodose curve. One of these cross plots is shown in Fig. 17. The field dimensions quoted in this paper are those to the 50% isodose curves at the centre of rotation. In clinical applications, the significant dimension is that of the separation of the 90% isodose curves at that level. This is shown in curve B (90%) of Fig. 16.

Figure 8 shows schematically the instrumentation used in the measurement of tumour-air ratios and of isodose distributions. The ionization chamber, of internal dimensions 20 mm in length and 6 mm in diameter, could be moved by means of remote selsyn drives anywhere in a plane which included the central axis of the gamma-ray beam. The water phantom, of

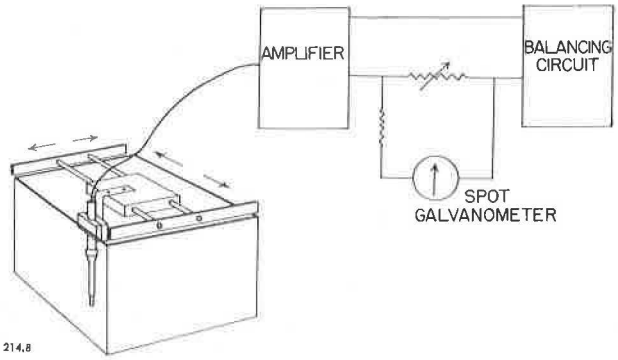

Figure 8. Instrumentation used in the production of isodose curves. The selsyn drives, which position the ionization chamber, are not shown

dimensions 50 × 50 × 30 cm, was supported on the treatment table, and the front face was positioned at the desired distance from the centre of rotation. With the ionization chamber at the centre of rotation, the variable resistance was so adjusted that the reading on the spot galvanometer was 100. As the probe was moved in a systematic way throughout the water phantom, the spot galvanometer read directly in percentages of the absorbed dose rate at the centre of rotation. By this method a complete isodose distribution could be plotted on squared paper in approximately 45 minutes. The position of the ionization chamber was known to within 0.5 mm, and the instrument readings were reproducible to better than 1%. Isodose curves for 13 field sizes and surface-tumour distances of 5, 10 and 15 cm have been produced in this way. A comparison of isodose curves for an 8 × 8 cm field at surface-tumour distances of 5 and 10 cm is shown in Fig. 9.

For measuring tumour-air ratios the beam was directed downward and the ionization chamber, supported from the treatment head, was fixed in the centre of the beam at a distance of 55 cm from the source. With the water phantom in place on the treatment table, the level of water overlying the chamber could be adjusted to any desired depth by means of the elevating mechanism. Measurements were taken with various overlying depths of water, and the ratios of these readings to those of the instrument when the water phantom and treatment table were swung out of the way were calculated. Each ratio was then expressed in rads per roentgen by multiplying by 0.965,[10] and, therefore, represents the numerical ratio of the absorbed dose rate in soft tissue to the exposure dose rate in air, both taken at the centre of rotation. The ratios are given in Table 10 as functions of depth of overlying soft tissue and of nominal field area.

These tumour-air ratios are greater than those previously published,[7] the differences ranging from a minimum of under 2%, for small depths of overlying tissue, up to 4–5% at depths in the range 12–15 cm. The per cent differences are somewhat dependent upon field size, with a flat maximum for a diaphragm setting of 10 × 10 cm. In attempting to account for these discrepancies, we investigated (*a*) central axis per cent depth dose data, (*b*) backscatter factors and (*c*) inverse

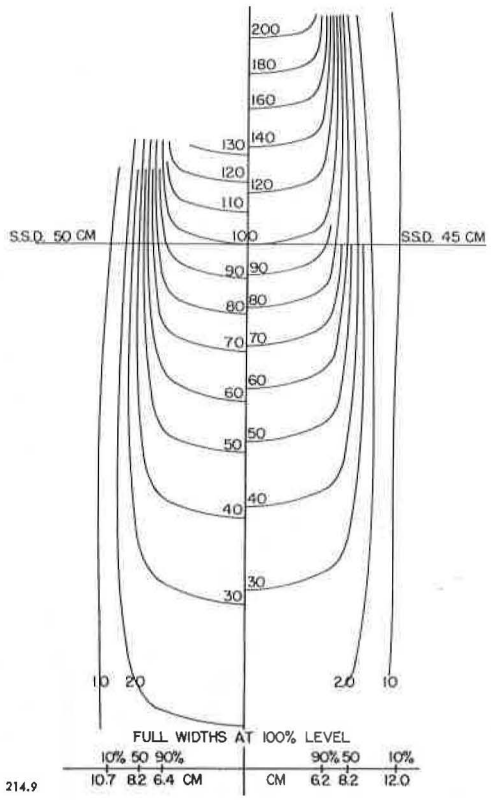

Figure 9. Comparison of isodose distributions for a nominal 8 × 8 cm field. Left: 5 cm surface-tumor distance. Right: 10 cm surface-tumor distance. Penumbra widths are shown below

square law dependence. Our central axis depth dose data agree within 1% with those previously published.[11] Our measured backscatter factors are 1–2% lower than those of other authors. The method of calculating tumour-air ratios from central axis depth dose data,[6,7] assumes that the exposure dose rate varies strictly as the inverse square of the distance from the source. Exposure dose rate measurements along the central axis of the radiation beam showed an increasing departure from inverse square law dependence with decreasing distance from the source. At the minimum distance of 35 cm, the measured exposure dose rates were 3–5% higher than values calculated by inverse square law from the exposure dose rate at 55 cm. These per cent deviations reach a flat maximum for a diaphragm setting of 10 × 10 cm and can be ascribed to scatter contributions from the diaphragm assembly and to finite source size. These investigations establish the validity of the tumour-air ratios of Table 10 for this unit, and indicate that calculated tumour-air ratios should be used with caution where significant departures from inverse square law dependence exist.

The treatment table is of $\frac{3}{16}$ inch (4.8 mm) thick duraluminum sheet supported at the sides by duraluminum angle beams. Where the table intercepts the beam during treatment, corrections must be applied to the tumour dose. Using an integrating dosemeter, it was found that the table reduced exposure dose at the centre of rotation by 5% during one 360° rotation. The magnitude of this correction was found to be relatively insensitive to table position. When the stationary radiation beam was directed vertically upward through the centre of the table, the table absorption was found to be equivalent to that of 1.2 cm of soft tissue.

Using the ratemeter circuit of Fig. 8, the variation with beam angulation of exposure dose rate at the

Table 10. Tumour–Air Ratios (rads/roentgens)
(Ratio of absorbed dose in soft tissue to exposure dose at the centre of rotation)

Soft tissue thickness (cm)	*Field area (cm²)*					
	16	*25*	*50*	*100*	*150*	*225*
0.5	0.977	0.982	0.993	1.007	1.015	1.018
1.0	0.967	0.973	0.986	0.999	1.007	1.012
2.0	0.943	0.951	0.965	0.980	0.989	0.995
3.0	0.907	0.919	0.936	0.954	0.964	0.972
4.0	0.863	0.880	0.901	0.923	0.933	0.943
5.0	0.819	0.839	0.863	0.889	0.900	0.911
6.0	0.777	0.797	0.825	0.854	0.866	0.879
7.0	0.735	0.755	0.784	0.817	0.830	0.846
8.0	0.694	0.712	0.743	0.779	0.795	0.814
9.0	0.654	0.672	0.705	0.741	0.760	0.780
10.0	0.614	0.633	0.665	0.704	0.725	0.744
11.0	0.577	0.596	0.629	0.669	0.690	0.710
12.0	0.541	0.562	0.595	0.634	0.657	0.678
13.0	0.510	0.529	0.561	0.601	0.625	0.647
14.0	0.480	0.497	0.530	0.569	0.593	0.616
15.0	0.451	0.468	0.500	0.538	0.562	0.586
16.0	0.423	0.440	0.473	0.509	0.533	0.557
17.0	0.398	0.413	0.445	0.480	0.504	0.529
18.0	0.374	0.389	0.419	0.454	0.476	0.500
19.0	0.351	0.365	0.393	0.427	0.449	0.474
20.0	0.330	0.342	0.369	0.402	0.425	0.449

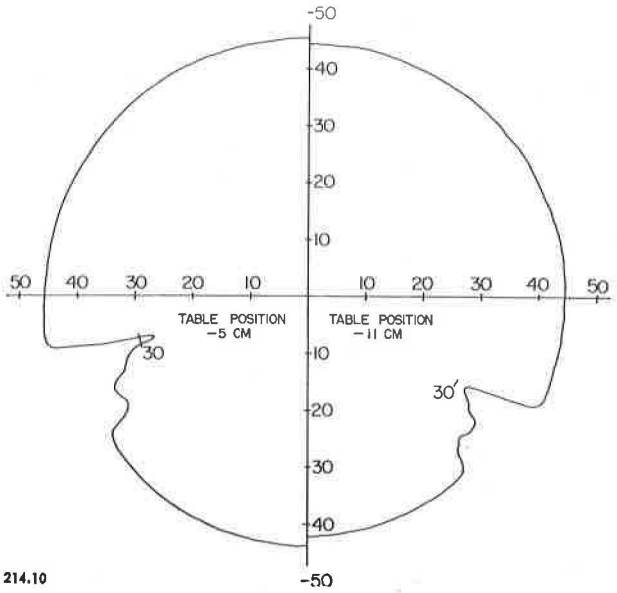

Figure 10. Polar diagram showing variation with beam angulation of the exposure dose rate at the centre of rotation. Field size 10 × 10 cm. Table centrally located and at a distance below the centre of rotation of 5 cm (left) and 11 cm (right)

centre of rotation was determined for various field sizes and table positions. Two radial plots obtained in this way are shown in Fig. 10. The reduction due to absorption by the angle beams and by the table top is clearly shown. It is apparent that fixed field therapy through any part of an angle beam should not be attempted, since this would result in a radical variation of dose rate across the field. A light wooden extension support, which can be fastened to one end of the table, permits treatment of head and neck lesions without the complication introduced by table construction. The dimensions of the treatment table, and its geometrical relationship to the head, limit the use of 360° rotation therapy to mid-line lesions whose centres are not more than 11 cm above the table top. Where the lesion is not on the mid-line, this distance is further reduced.

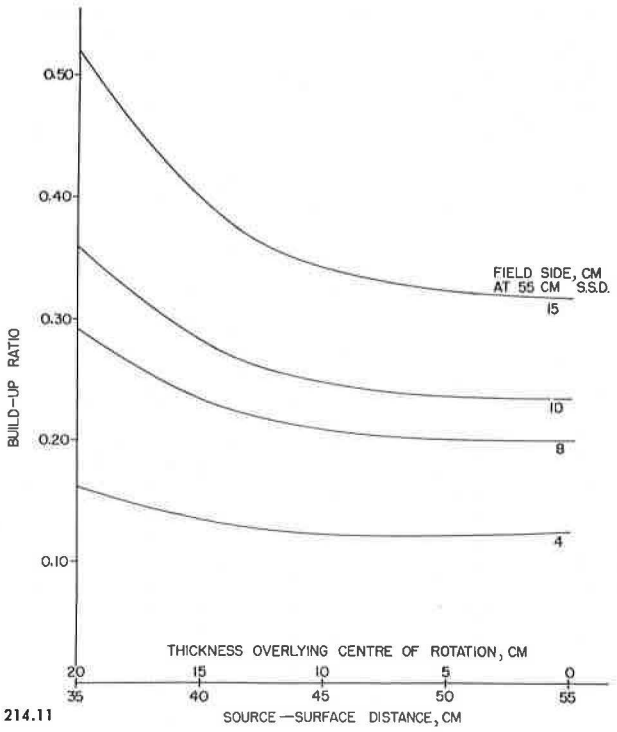

Figure 11. Ratio of ionization current measured with no overlying material to that measured with 500 mg/cm², plotted against field area with source-surface distance as parameter

The dependence of "build-up" ratio[12] near the irradiated surface under various therapeutic conditions was determined. The flat ionization chamber employed was 4 cm in diameter with an interelectrode spacing of 2 mm. The upper electrode was of graphited lens paper of thickness 2.4 mg/cm², and the collecting electrode was 1.6 cm in diameter. The chamber was set into the surface of a block of unit density wax and connected to a modified Baldwin-Farmer dosemeter.

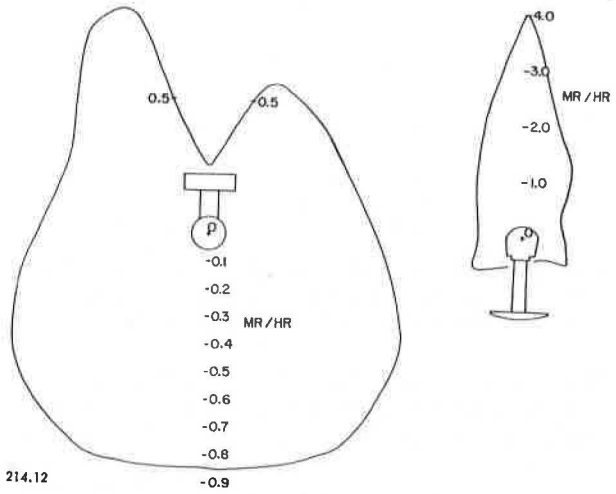

Figure 12. Polar diagrams showing the angular variation of leakage radiation exposure dose rate measured at one metre from the source. Left: in a plane through the source at right angles to the axis of the useful beam. Right: in a plane through the source and containing the useful beam axis. (Note difference in scales)

The mean of the readings obtained with opposing voltages applied to the upper electrode was taken.[13] Increasing thicknesses of unit density material were placed over the chamber and the distance between the source and the presenting surface was kept constant. The results of these measurements, using square fields, are shown in Fig. 11. It is apparent that the build-up ratio is strongly dependent upon size of treatment field, but is relatively insensitive to source-surface distance in the range of overlying tissue thicknesses likely to be used in therapy. Cross plots of these data show an essentially linear dependence of build-up ratio on the perimeter of the field, indicating that the principal source of electron contamination is in the diaphragm assembly.

It is essential, before putting a new unit into operation, to check details of design and construction that are important from the aspect of therapeutic accuracy. We have investigated (*a*) shutter opening and closing times, (*b*) accuracy of the light beam which simulates

the useful radiation beam, (*c*) accuracy of the diaphragm settings, (*d*) accuracy of the height scale on the treatment table and (*e*) calibration of the rotation speed control. All of these adjustments were found to be satisfactory for clinical application.

A survey of the leakage radiation from the source was made using a large pressurized ionization chamber instrument employing a Neher-White circuit. Leakage radiation exposure dose rates measured at one metre from the source are shown in two principal planes in Fig. 12. Photographic dosimetry was used to measure leakage radiation levels on the surface of the source shield. It will be apparent from Fig. 12 that the leakage radiation levels are well within accepted limits.[14] It should be pointed out, however, that in a source shield of this size the acceptable maximum level allows a maximum dose rate at the surface of 160 mr/hr. In our case, the dose rate at the back surface of the head was found to be 55 mr/hr. In the direction of the useful beam, a thin plane of leakage radiation reached a value of 35 mr/hr at the centre of rotation. Since this level could be reduced by closing the diaphragm, it was apparent that it was the result of imperfect shutter closure. This fault is now being corrected.

Applications

The setting up of a patient for treatment with the unit is simple and accurately reproducible, and is essentially the same for both fixed and moving beam therapy. It is, of course, essential that the location and extent of the volume to be treated be known with reference to markings on the skin. It can be seen that three such marks suffice, all lying in the transverse plane through the tumour centre T (Fig. 13). Two lateral marks, A and B, define a horizontal line ATB through T, while C defines a line CT at right angles to ATB. To define the directions of TA, TB and TC, all in the plane perpendicular to the rotational axis, collimated light beams meeting at the centre of rotation can be used. Although these could be projected from walls and ceiling, it has been found that a projector mounted on the back-shield, the cross lines on the diaphragm illuminator and a removable jig, as shown, are satisfactory. The jig mount serves also as a mount for a front pointer, wedge filters, and penumbra trimmers where these are required.

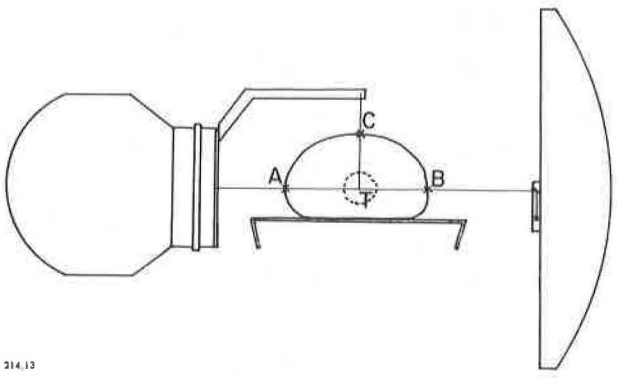

Figure 13. Arrangement for placing the tumour centre T at the centre of rotation

Table 11. Essential Information for Prescription and Records

Fixed Field Therapy: Information Necessary for each Field

1. Field description
2. Diaphragm settings
3. Angle setting (degrees)
4. Table height (cm)
5. Number of treatments, this field
6. Tumour dose contribution, this field (rads)
7. Skin-tumour distance (cm)
8. Tumour-air ratio (rads/roentgen)
9. Exposure dose rate at tumour (r/min)
10. Tumour dose rate (rads/min)
11. Tumour dose per treatment (rads)
12. Exposure time per treatment (min)
13. Maximum skin dose (rads)

Rotational and Arc Therapy

1. Technique description
2. Diaphragm settings
3. Arc limits: Start (degrees), End (degrees)
4. Table height (cm)
5. Number of treatments, this technique
6. Tumour dose contribution, this technique
7. Effective tumour-air ratio (rads/r)
8. Exposure dose rate at tumour (r/min)
9. Average tumour dose rate (rads/min)
10. Tumour dose per treatment (rads)
11. Exposure time per treatment (min)
12. Number of cycles
13. Rotation speed control setting
14. Maximum skin dose (rads)

When, by means of the table adjustments, the three light spots have been made to coincide with points A, B and C, the tumour centre T lies on the centre of rotation and, whatever the orientation of the radiation beam, its central axis passes through T. In fixed field or arc therapy, a removable front pointer is used to measure the skin-tumour distances in order that the tumour-air ratio for that field or arc may be determined. In rotational applications, an integrating dosemeter, mounted at the centre of the back shield, measures the transit dose ratio and hence permits calculation of the effective tumour-air ratio.[15,16] The pertinent data may be conveniently laid out in the treatment record sheet in the order shown in Table 11. A special calculator, based on slide rule principles, for the rapid determination of absorbed tumour dose rates is shown in Fig. 14. Its design allows for periodic adjustment to compensate for radioactive decay of the source.

Complete isodose distributions may be readily determined in fixed field therapy by standard methods using the isodose curves previously described. Distributions in arc and rotational therapy can be calculated, albeit somewhat laboriously, using the isodose curves and making due corrections for the absorption of the table where it lies in the treatment beam. It has been found, however, that the shape and separation of the isodose surfaces in 360° rotation is relatively insensitive to the size and shape of the irradiated body section and to the length of the field.[17] Thus, for most clinical purposes, a number of measured distributions for various field widths will suffice. Figure 15 shows one such distribution measured in the plane of rotation

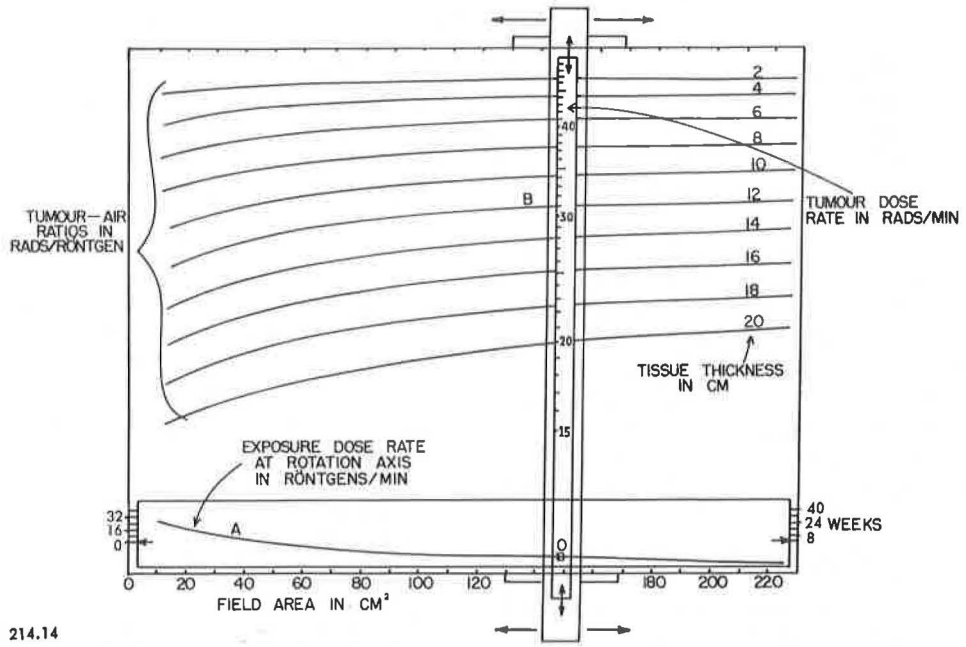

Figure 14. A simple calculator for the determination of absorbed dose rate in soft tissue. The exposure dose rate curve A is a groove in a Lucite sheet in which the pin O slides as the cursor is adjusted to the desired field area. The tumour dose rate may then be read on the sliding vertical scale at its intersection with the appropriate tumour-air ratio curve. The curve A can be adjusted periodically to allow for decay of the source

for a beam of cross section 7 × 15 cm at the centre of rotation. It is seen that the shape is somewhat affected by the presence of the treatment table. For comparison, a rotational distribution, measured using the kilocurie unit of Fig. 1, is also shown. Since interest lies in the volume raised to an absorbed dose in the range 90–100% of the maximum, curves have been prepared (Fig. 16) relating the widths and heights of the 90% isodose surfaces to the diaphragm settings. The size of the 50% volume may also be determined from the figure.

The maximum field size obtainable with this unit is 15 × 15 cm at the centre of rotation, i.e., at 55 cm from the source. Provided the increased penumbra is acceptable, larger field sizes for fixed field therapy are obtained by the expedient of positioning the tumour centre at a distance greater than 55 cm from the source. By this method field sizes up to 20 × 20 cm may be obtained, but separate set-up procedures must be used for each field. If the variation of exposure dose

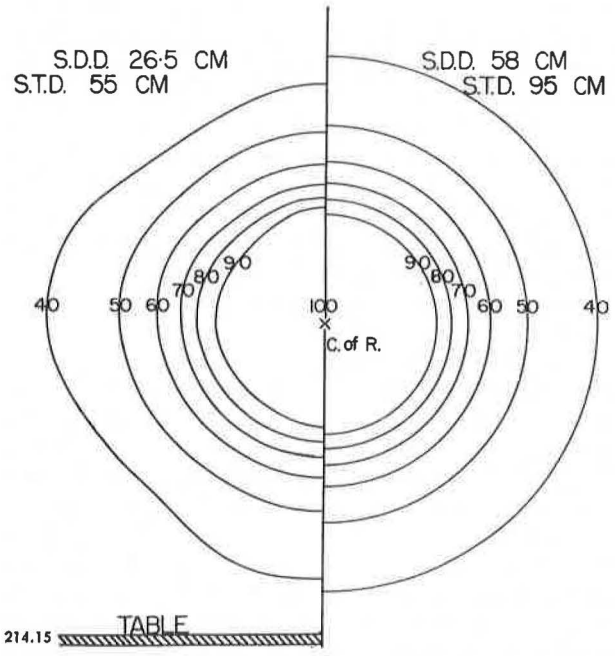

Figure 15. A comparison of 360° rotational dose distributions measured in a water phantom for a field area at the centre of rotation of 7 × 15 cm. Left: Theratron Junior, showing displacement upward of the 90% line due to absorption by the treatment table. Right: Eldorado unit, patient rotating about vertical axis through the tumor

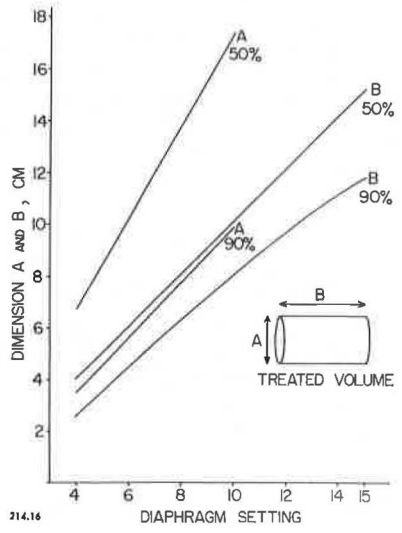

Figure 16. Graphs showing the dependence upon diaphragm setting of the widths and heights of the volumes receiving 90% and 50% of the absorbed dose at the centre of rotation

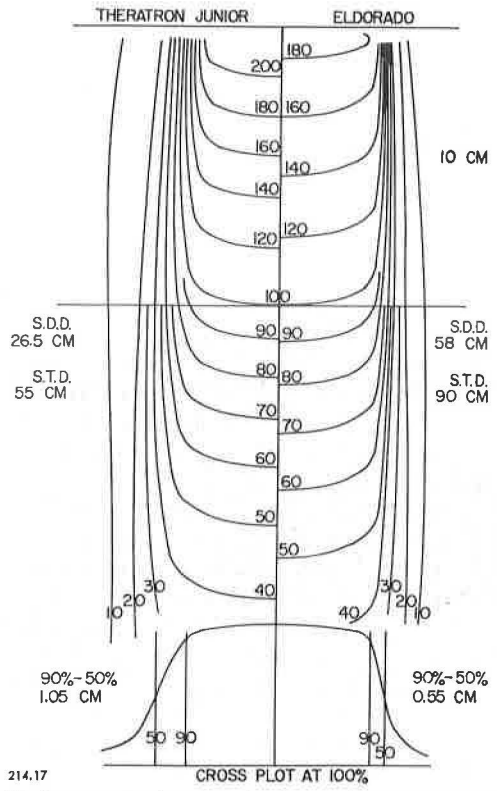

Figure 17. Comparison of isodose distributions (normalized to 100% at 10 cm beneath the skin) for source-diaphragm and source-tumour distances as shown. The difference in penumbra widths is illustrated

rate with source-tumour distance and field size is known, the absorbed dose rate at the tumour may be estimated using the tumour-air ratios of Johns *et al.*[7] At the greater source-tumour distances, these values are more likely to be accurate than those of Table 10. It should be pointed out that if one wishes to express tumour doses in rads, these tumour-air ratios must be multiplied by the conversion factor given in the discussion in connection with Table 10.

In comparing a hectocurie unit with its kilocurie counterpart, it must be remembered that the smaller unit is a compromise between cost and optimal design. As shown in Fig. 17, the shorter treatment distance of the hectocurie unit gives rise to a smaller half-value thickness in tissue, so that a higher skin dose is necessary to obtain the same tumour dose. As in other units designed for rotational therapy, the distance between the diaphragm and the centre of rotation is dictated by table clearance requirements. This results in an increased geometrical penumbra (Fig. 17) which is undesirable from the viewpoint of integral dose. In this unit, this disadvantage is offset to a limited extent by a reduction in source diameter. In fixed field and arc therapy applications, auxiliary diaphragms positioned closer to the patient would reduce the penumbra still further. Studies are under way to determine the best design of such "penumbra trimmers". The limitations to therapy imposed by the treatment table design are more annoying than serious, since corrections can be made to the dose distributions. When a patient is treated through the table top, a more intense skin reaction can result because of secondary electron emission from the aluminum. This problem is also under investigation.

The design of the Theratron Junior hectocurie unit permits advantage to be taken of the proven merits of cobalt-60 therapy, with limitations as mentioned above. Its principal advantages over beam therapy units not designed for rotational therapy lie in its flexibility of operation. This flexibility results in precision and rapidity of beam alignment for both fixed field and rotational therapy. Reduction of room shielding requirements due to the provision of a backshield is a secondary advantage.

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Principles Underlying the Therapeutic Use of Megavoltage Radiation

By Ralston Paterson*

The pattern of radiation therapy as applied to the treatment of malignant disease has changed greatly in the last decade. This change is the consequence of an increasing availability of radiation equipment, operating in the megavoltage ranges. It now seems certain that such radiations will provide better therapy with improved cure rates and lessened reactions. Megavoltage plants in this context cover for practical purposes two distinct types of equipment.

1. Radiation plants of various types, including: the resonance transformer, the Van de Graaff, the linear accelerator, the betatron, and the synchrotron.

2. Mass radio-isotope units using cobalt-60 sources in kilocurie quantities. These produce two monochromatic gamma radiations at 1.1 and 1.3 Mev and correspond effectively to 3 Mev X-ray plants. Radioactive caesium has also been used in mass units but these should not be regarded as megavolt equipment and are markedly inferior to cobalt units.

It is probable that megavoltage in one or other of these forms will largely supersede for serious therapy, conventional radiation at the 200–500 kv levels, which has held the field as "deep therapy" for over a quarter century. The advantages of megavoltage would not appear to be related to any biological superiority of the shorter wavelength of the radiation, and it is found in practice that the nature of the response at the locus of action to equivalent quantities of radiation delivered remains unchanged. Nevertheless the new radiation does introduce many new technical features and differences in methods of application. The experience on which this report is based was with a 4 Mev linear accelerator and a 20 Mev betatron. The principles developed, however, should apply equally well for the mass cobalt units which are more directly of interest to this Conference.

The properties of megavoltage radiation on which it has been possible to build are now so well recognized that they are listed here only by way of introduction:

1. The point of highest energy absorption is below a free surface. Clinically, therefore, the highest dose zone in a single beam can be placed deep beneath the skin. This depth increases from 6 mm for cobalt radiations to about 150 mm for the 70 Mev synchrotron (at San Francisco).

2. The radiation is highly penetrating in the approximately water equivalent body tissues. As a result the rate of fall of dose in any treatment beam from the highest dose point onwards is low.

3. There is a negligible additional energy absorption in relation to atoms of medium atomic number such as calcium or sulphur. Clinically this lessens energy absorption in bone and certain other tissues.

4. Because of the low scatter component in tissue the radiation beam itself can be flattened or wedged by appropriate filters. It then maintains the flattened quality or oblique isodose shape at all depths in a manner which has been impossible to achieve with conventional therapy.

These facts were fully appreciated before megavoltage radiation became available in clinically applicable form. In actual use many problems arose which in essence represented the detailed technical application of these key properties. The significance of many of these was not at first fully appreciated. They therefore seemed to me to be worth examination.

HIGHEST DOSE BELOW A FREE SURFACE

To make use of greater depth dose as a means of reducing skin damage, requires that treatment fields have to be "open." Two simple consequences are that the older designs of solid ended X-ray applicators are no longer needed and that the use of bolus bags, wax, or other scattering material lapses. The differences can be illustrated by contrasting two different types of X-ray beam direction shell such as used for conventional therapy and for megavoltage. Such devices are illustrated in Fig. 1. With open fields, however, many treatment beams are of necessity incident at an oblique angle to the surface. This raises relatively complex problems of isodose dosimetry, and, incidentally, reduces the skin saving property. The dose distribution from such an obliquely incident field is illustrated in Fig. 2. It is impracticable to carry isodose curves for all field sizes at all possible angles, so some kind of approximation becomes necessary to cope with the varying situations which arise. Such approximations have been devised but they are not as simple as desired. A requirement of an approach which places the highest dose beneath a free surface is that one must keep constantly in mind the possibility that the tumour itself may have infiltrated the surface layer be-

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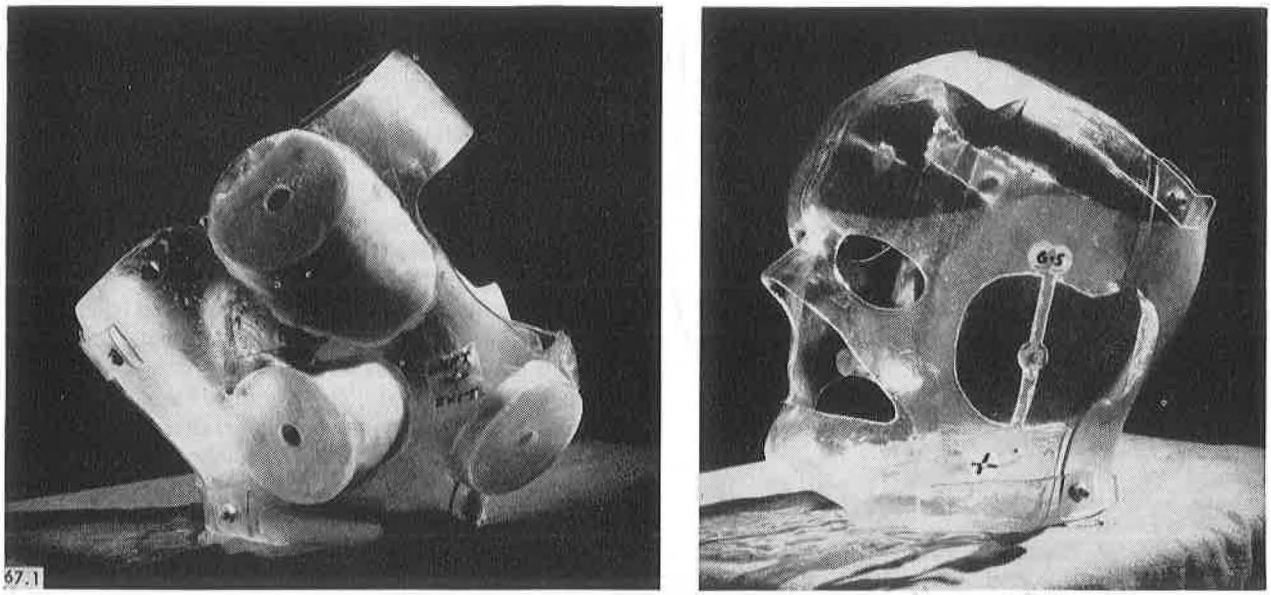

Figure 1. Two beam direction "shells" contrasting the wax applicator seatings used in conventional (kilovoltage) therapy with the "open" fields rendered necessary in megavoltage therapy

tween high dose level and the skin. The remedy for this is possible; this is appropriate added packing over that area to bring the absorbed dose nearer to the surface (Fig. 3). This may seem entirely obvious but it is widely neglected. In the early days, we lost a number of cases by lack of appreciation of this simple practice. The most educative case was a patient with a tumour of the ethmoid, so large that its successful initial treatment was a minor triumph. The tumour recurred first in the surface of the eyelid which had not been covered with wax.

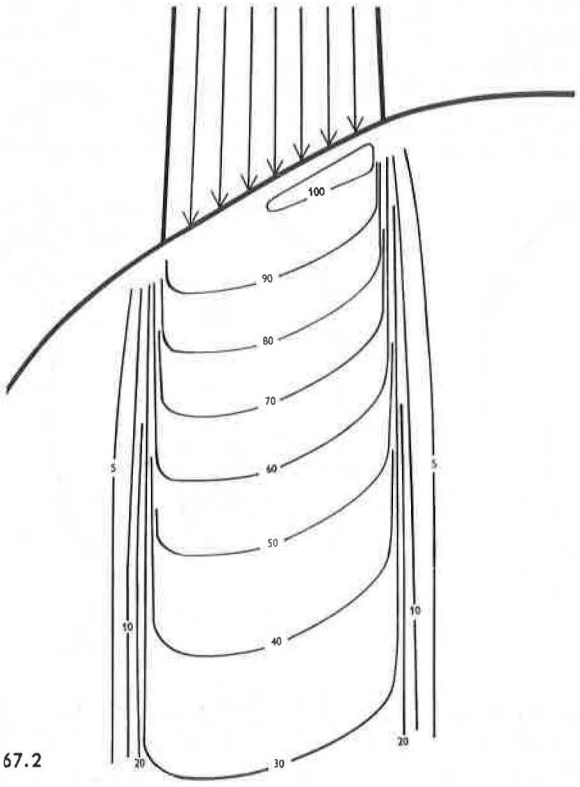

Figure 2. Isodose distribution from an "open" field at 4 Mev incident at an oblique angle to the surface

PENETRATION

In one sense, the key quality of short wavelength radiation at megavoltage levels is, of course, its great penetrative capacity in tissue. Delivery of substantial quantities of radiation to any desired depth in the human body is for the first time entirely simple. This very ease of delivery, however, has led to the employment of unwise and over-simplified techniques. For

Figure 3. Added wax packing used in the treatment of an antral tumour which might have invaded through to the skin surface

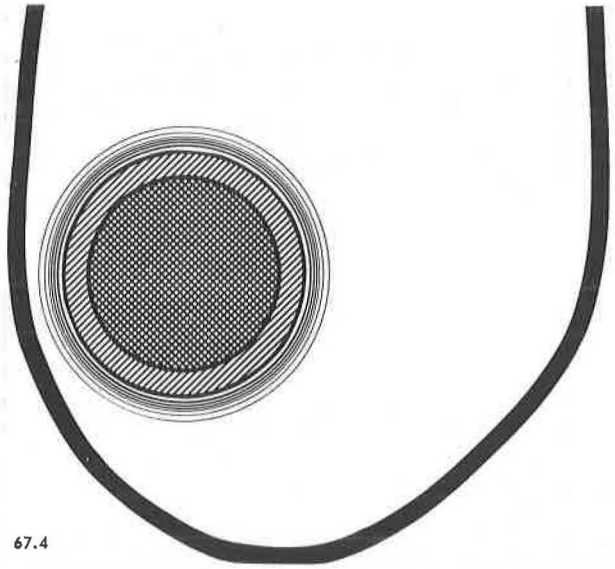

Figure 4. Idealized dose distribution. The estimated tumour (central hatched area) has to be included in a rather wider zone of tissue to form the "treated volume" (lined area). This achieved, however, the dose should thereafter fall off to zero in the immediately surrounding tissue in minimal distance

growths relatively near the surface adequate tumour dosage can seem to be obtained by one field alone. At 20 Mev, particularly, the 100% high dose zone of a single field can often be superposed on tumour, but as we will see later this should not be done. Alternatively using 4 Mev to directly opposed fields can easily deliver doses well above skin dose levels to any growth in head and neck or limbs, and, using 20 Mev, to any point in the average sized body. At first glance this seems satisfactory, but more critical analysis shows this to be quite wrong for many types of treatment. To show why this is so, I shall consider an important general principle of all high dose therapy to volumes of limited size. The theoretical ideal is homogeneous irradiation of any desired volume containing tumour with effective zero radiation outside that volume. This unachievable ideal is illustrated diagrammatically in its simplest form in Fig. 4. In practice, even using interstitial radium, there is inevitably some rind of normal tissue irradiated with a falling dose. With external radiation there may also be tissue irradiated by the beam in transit to the treated volume. Let us call this rind of superfluously irradiated tissue the "marginal zone."

Biologically the best results are achieved when exposure of this "marginal zone" is minimal. Technique should be regarded as less than perfect whenever this additional irradiated volume is substantial in amount, even if excellently homogeneous irradiation of the desired treatment zone has been achieved. Conversely, it should be regarded as optimal when that marginal zone is least. This process, particularly as it affects small volume therapy, is quite different from and much more important than integral dose. The principle involved can best be illustrated by an example. In Fig. 5, three approaches to delivery of the same tumour doses to a growth in the region of the tonsil are charted.

In Example A, a single megavoltage field at 20 Mev is used. The high dose zone of the single beam with its centre at about 5 cm depth covers almost exactly the desired volume. Because of the low rate of fall of dose beyond the growth, however, there is a substantial block of tissue beyond the tumour which is also heavily irradiated. Indeed, this goes through to the exit skin. The shaded area shows a considerable amount of additional tissue raised to a level in excess of 75% of the tumour dose. In Example B, two opposed 4 Mev fields are used. Again there is a homogeneous cover but the total fully irradiated volume is in fact a cylinder through the neck that receives full dosage except for a half centimetre layer at each end. At least half of the volume is unnecessarily irradiated. In Example C,

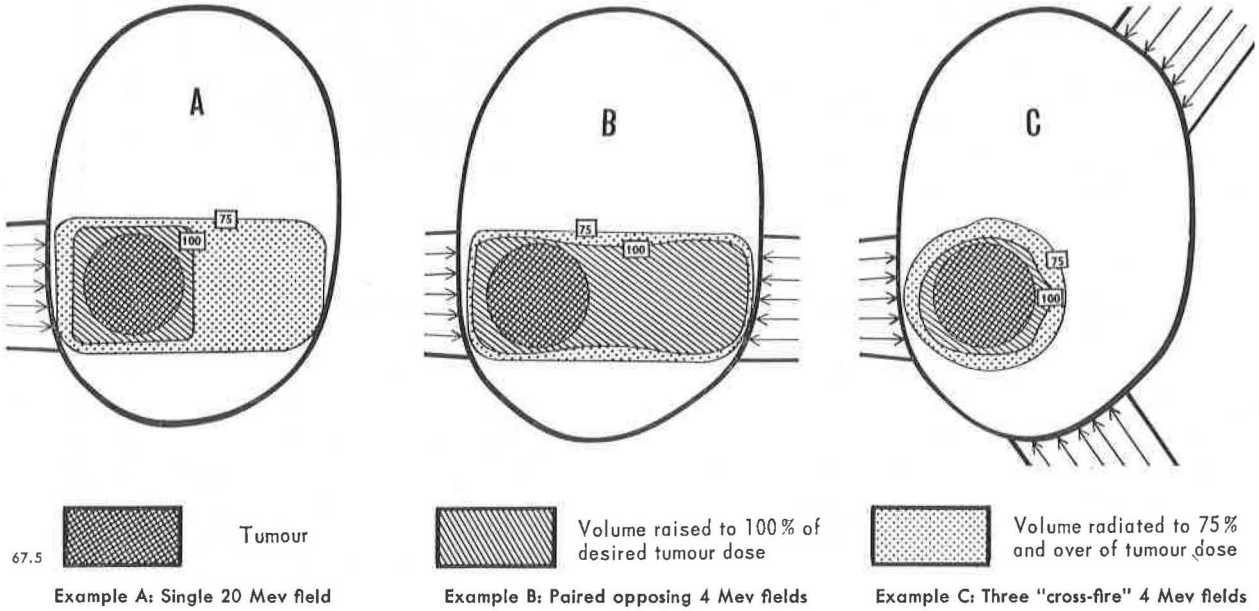

Figure 5. Contrast of three dose distributions for the same tumour

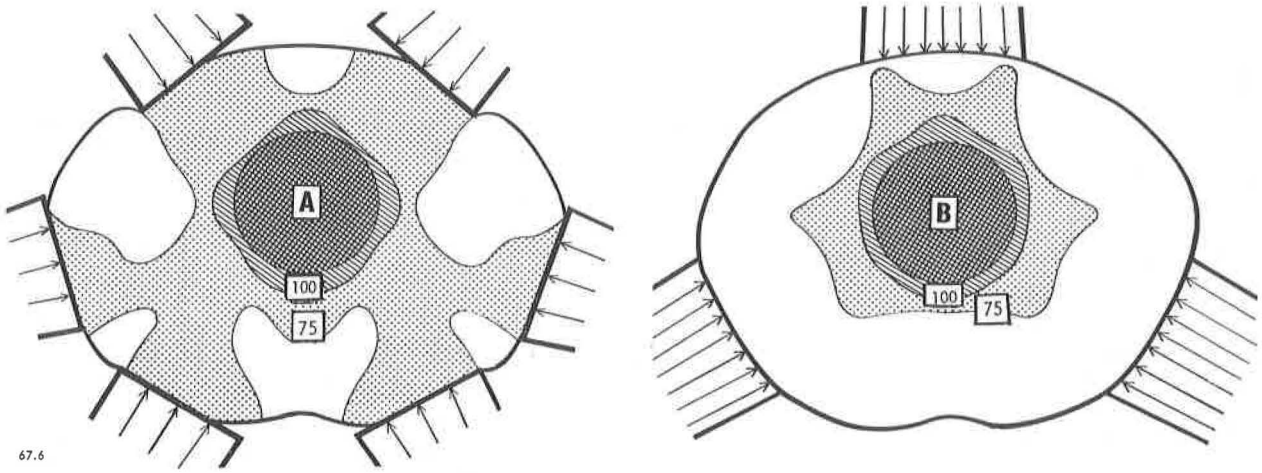

Figure 6. Contrast of dose distributions from 4 Mev and 300 kv in treatment of a bladder tumour (code as in Fig. 5). A: 300 kv six fields (the minimum possible to get desired dose); B: 4 Mev, three fields

three fields are used crossing at the centre of the growth, with the result shown. As seen the marginal zone in excess of 75% of desired dose has been cut to a small fraction. The third technique is thus demonstrably superior. While this is but one example, it has been found in practice to demonstrate a general principle; furthermore, it has shown that in all small and medium volume therapy the optimal field pattern for megavoltage therapy requires a minimum of three fields, and that simpler arrangements are not as good.

The paired wedge field approach to be analysed later is an exception of rather different nature. Figure 6 provides the basis for an instructive commentary on this principle. In Example B is charted the marginal zone at 75% and over of the desired tumour dose which results from a three field approach using 4 Mev in the treatment of a bladder tumour. Diagram A in contrast shows the same tumour charted to achieve the same 100% treated volume but using 300 kv with appropriate multiple fields. There is a vastly larger marginal zone at over 75%. Indeed, this contrast almost epitomises in one diagram many of the technical advantages of megavoltage therapy. A further minor consequence of the low rate of fall of dose beyond the treated tumour is need to consider structures in the beam beyond the tumour, for example the spinal cord, to ensure that no specially vulnerable tissue is overdosed.

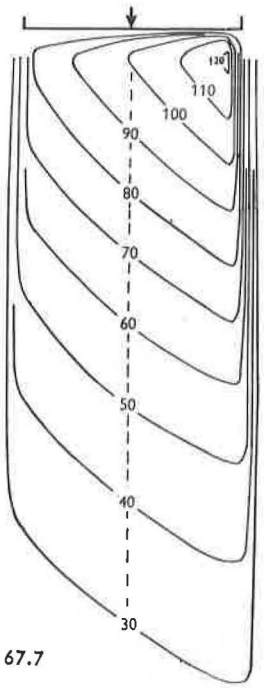

Figure 7. "Wedge field" at 4 Mev; isodose distribution in tissue of a beam into which has been inserted a wedge-shaped filter

ENERGY ABSORPTION IN BONE

The consequences of different relative absorptions in bone and water equivalent tissues for conventional therapy and for megavoltage require examination next. In the practical calculation of depth dose for conventional therapy, the existence of a lessened transmission of radiation through skull and through pelvis or other bony barriers has always been appreciated, but seldom allowed for scientifically. Dosage inside the skull or inside the pelvis was ordinarily overstated. With megavoltage there is practically no density effect and dose assessed simply on depth dose charts is generally accurate. Two consequences arise; the first is that dosimetry is in fact more exact, and the second is that experience from conventional techniques must be carried over with caution or overdose will result.

Another factor is the reduced characteristic radiation from calcium; this lessens the actual energy released in bone for any given treatment as compared with that obtained from conventional therapy. In theory this procedure of treatment should lessen the incidence of bone necrosis wherever related solely to radiation effects and not to previous invasion of bone by tumour. Bone necroses, however, ought not to be common even with conventional therapy if properly used. Actually, there is really no way of assessing this value in quantitative terms or even of demonstrating its existence. At one time I gained the impression that

the lessened characteristic radiation in bone might have lowered the bone marrow effects noted in large volume therapy (radiation baths). Careful contrast of two groups did not support this point of view and the haemopoietic effects of large volume radiation seemed insignificantly different for equal dosage, provided the RBE factor is allowed for (see later).

MODIFICATION IN NATURE OF THE RADIATION BEAM

This is the last of the technical features that require review. With megavoltage the distribution of radiation within the beam itself can be modified in various ways and yet maintain the more favourable pattern to considerable depth in tissue. Similar adaptation is not possible with conventional therapy except at one selected

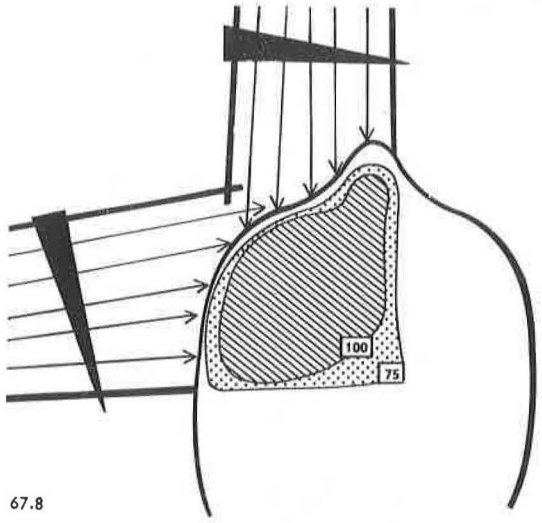

Figure 8. A.4 Mev wedged field treatment for a cancer of the maxillary antrum (code as in Fig. 5). Note the very limited volume of the marginal zone at 75% and over of the desired tumour dose

depth. One such adjustment is becoming almost universal practice in modern megavoltage equipment, namely "beam flattening" by an appropriate conical filter. This need not concern us, however, except to note it as of value. The other adjustment results from insertion into the beam itself of an appropriately graded wedge of lead or other suitable material to produce an oblique isodose field such as that illustrated in Fig. 7.

The use that can be made of such fields is best indicated by an example. Figure 8 shows the resulting dose distribution from two such fields applied to a cancer of the maxillary antrum. The 100% dose area gives homogeneous irradiation of the desired volume and yet there is a remarkably low marginal zone of additional irradiated tissue. This kind of approach, using two wedged fields in appropriate sites therefore yields a dose distribution with minimal marginal zone very similar to the idealised three field pattern previously described (Fig. 5). Indeed, the use of wedges often offers such elegant techniques that, with us at least, it has become almost a craze. It can be applied to

Table 1. 4 Mev Compared with 300 kv as 100

Material	*RBE*
Drosophila—dominant mutations	.78
Chick embryo	.83
Mice—whole body radiation	.74
Mice—loss of organ weight	
Testis	.79
Spleen	.86
Thymus	.92
Skin tolerance	.84
Clinical: Estimated tolerance	.87–.82

growths of the antrum, the alveolus, the larynx, the middle ear, the anterior mediastinum and many of the more superficial brain tumours. Even then its scope has not been exhaustively explored for 4 Mev and not at all for 20 Mev. It is indeed possible that the wedged field approach may become the most characteristic feature associated with usage of radiation in the megavoltage ranges.

RELATIVE BIOLOGICAL EFFICIENCY

This last topic is one of a rather different order altogether. So far we have been considering how to deliver radiation in the best way for any given circumstances. Of equal moment is the question of how much radiation to deliver. Of necessity much of the experience acquired in older deep therapy work has been carried over into megavoltage practice. The question therefore arose quite early as to whether for irradiation of like volumes over identical times equal biological effects would result from equal dosage. One possibility was that equal energy delivered would produce equal biological effects. Experience shows that this does not happen and that there are differences. The differences appear to be related to different linear energy transfer factors (LET) for the various radiations. The ratio of effectiveness dose for dose of different radiations is known as the RBE (relative biological efficiency). In fact greater dosage of megavoltage radiations are required to produce effects equal to those from conventional radiations. To measure RBE on a purely clinical basis is difficult. Ordinary crude comparison based merely on impressions of available tissue tolerance of conventional and megavoltage practice is quite inadequate. It has proved essential to secure composite data from both clinical experience and from laboratory experiments. Our own contribution to this problem was in the form of a joint clinical and laboratory study contrasting 300 kv with 4 Mev.[1] A summary of the main findings is given in Table 1. As a reasonable working

Table 2. 20 Mev Betatron Compared with 4 Mev as 100

Material	*RBE*
Drosophila—dominant mutations	.96 ± .04
Mice—whole body radiation	.89 ± .03
Mice—loss of testis weight	.96 ± .04
Clinical: Some difference in tolerance can be appreciated	

interpretation of the figures we have accepted the effectiveness of 4 Mev radiation as $^{85}/_{100}$ of 300 kv radiation. The dose required for like circumstances has therefore to be augmented in the ratio 100:85. Similar studies have been going on this last year to assess the relationship between 4 Mev and 20 Mev. The results will be published in detail when mature but the tentative figures in Table 2 may be of interest. Note that in this contrast the 4 Mev unit has been taken as a base line at 100. The 20 Mev shorter wavelength radiations would seem just slightly less effective still, dose for dose, than 4 Mev. More work, however, is required before an exact figure can be put on this value.

DISCUSSION

I am conscious that this paper has been concerned primarily with what are essentially technical or physical factors involved in making the best use of high energy radiations. I have deliberately avoided the purely clinical aspects of the subject, except by way of illustration, as I was anxious to elicit broad general principles, regardless of diseases to be treated. It therefore seems desirable to add in conclusion that provided the special qualities of megavoltage radiation be kept in mind and properly used there already seems little doubt that atomic research, in providing such radiations, has given medicine a new medium of great value. I am tempted to link this conclusion with a somewhat propagandist comment. While the experience on which this paper was based depended on megavoltage equipment of essentially elaborate design, there is, nevertheless, no doubt that radiocobalt is the key to provision of megavoltage on a more universal scale. Has supply been made adequate to world need? Medicine and its basic sciences have been armed with almost unlimited supplies of isotopes, in microcurie quantities. Let me remind you that as another customer, yet unsatisfied and asking for megacurie quantities, is the therapist concerned with the treatment of cancer.

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A New Approach to Electron Therapy

By Lester S. Skaggs,* Lawrence H. Lanzi* and Robert T. Avery†

Ever increasing numbers of high-energy electron accelerators are being used, not for physics research, but for biologic research and for X-ray and electron therapy. The accelerators are used chiefly as X-ray rather than electron sources because of the greater ease of X-ray beam production. However, all of the high-energy electron accelerators now available have means of electron beam extraction.

The Van de Graaff type produces electrons in the low-energy range of therapeutic usefulness.[1] Betatrons constitute higher energy electron sources and are now available for electron therapy with energies of 6, 15, 20, 31, and 50 Mev.[2] Another cyclic accelerator from which an external electron beam is obtainable is the synchrotron. With this machine, electron beam energies ranging from 19 to 70 Mev have been used.[3]

The problems of beam extraction with linear accelerators are far less formidable than with the cyclic accelerators. The reason for this is, of course, that in cyclic accelerators, the electrons must be freed from the circular orbit to which they are confined by a magnetic field; in a linear accelerator, the electrons need only emerge from the accelerator tube without change in direction to be free. The range of energies of present-day linear accelerators for electron therapeutic use is from 10 to 70 Mev.[4,5]

The direct use of high-energy electrons in deep-seated cancer therapy has followed the methods employed with X and gamma radiations. That is, a single beam whose cross section equals that of the lesion to be irradiated is directed toward the patient, using either single or multi-port techniques.

The development of a new method of electron therapy will be discussed here. This involves the use of a beam scanning device. The device, which is being used in conjunction with a linear accelerator, directs a high-energy electron beam of small cross section to scan over any arbitrary field size and shape. The device is capable of accepting electrons from 5 to 50 million electron volts with a beam diameter of one centimeter or less. The scanning device has the following advantages: (1) the depth of penetration within a single field can be varied by varying the energy of the electrons in the course of scanning to give any desired changes; (2) rapid field size selectability including circles, rectangles, as well as irregular shapes is possible; (3) single field, multi-port and revolution therapy can be used; and (4) the patient is immobilized in a recumbent position.

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ELECTRON SOURCE: LINEAR ACCELERATOR

Of the several successful electron linear accelerator designs which have been developed since World War II, one outstanding example is that of Hansen, Ginzton *et al.*,[6] of Stanford University. This is the design used with appropriate modifications in this development. The fundamental principle of operation of the linear accelerator involves two important facts. First, an electromagnetic wave, produced when a radio-frequency pulse is directed into a hollow metal tube, can be made to travel through the inside of the tube parallel to its axis in such a way that its velocity is equal to that of electrons injected into the tube. Secondly, a sufficiently high fraction of electrons which are injected will remain in the hollow tube and will be accelerated to the desired energy.

Figure 1 is a schematic drawing of the Argonne Cancer Research Hospital linear accelerator. This drawing indicates only some of the major radiofrequency components. The vacuum, high voltage, metering, and other systems are not shown here. The accelerator tube proper consists of two evacuated sections of waveguide, each 2.43 meters in length. Each section is supplied with radiofrequency power from a separate 20 Mw klystron. These two klystrons function as power amplifiers and are both driven by a single magnetron oscillator at a frequency of 2857 megacycles.

The klystrons are pulsed at full power for a period of 1.6 μsec with a repetition rate of 60 times per second. Their output power is fed into the accelerating tube, and this radiofrequency energy travels down the tube at one-hundredth the velocity of light. In 0.8 μsec, the tube is completely filled; and at this time electrons are injected for a period of 0.6 μsec into the first section of the accelerator where their energy increases from the injection energy of 100 kv to 25 Mev. Upon leaving the first section, they enter the second and are further accelerated to 50 Mev. The force on the electrons is in the direction of the axis of the accelerating tube over its entire length. The inset of the figure shows the general shape of the traveling wave electric field E for one particular instant. Function of the series of disks is to "load" the tube in such a way that the phase velocity of the radiofrequency wave is reduced to the velocity of light in free space

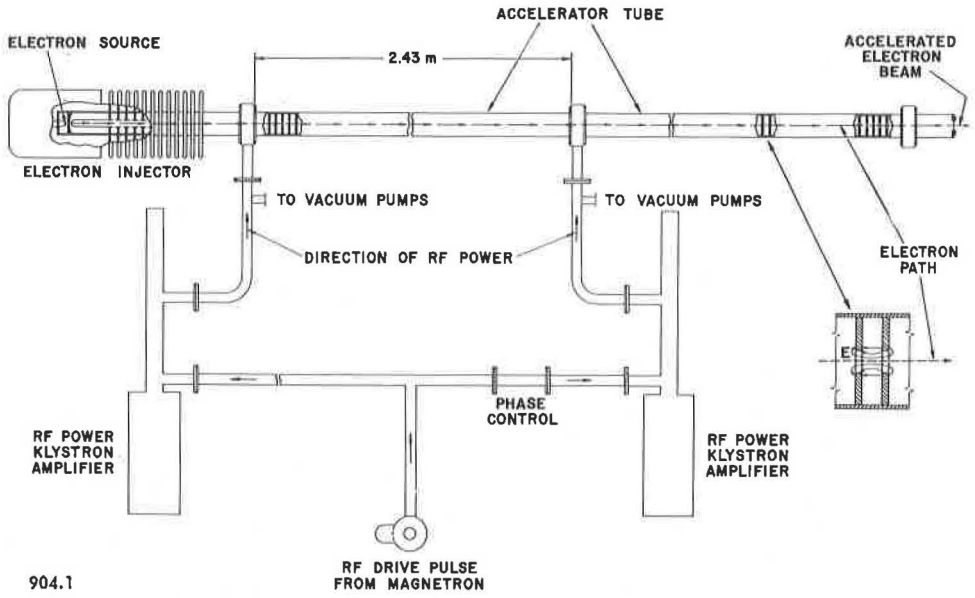

Figure 1. Schematic drawing showing some of the major microwave components of the 5 to 50 Mev traveling wave linear accelerator of the Argonne Cancer Research Hospital

since this is the velocity with which the electrons, after attaining a few Mev, will travel.

For therapy, it is desirable to have a variable electron energy. This is achieved by controlling the relative phase of the two sections of the accelerator tube. If, within the radiofrequency pulse, the phase relationship of the electric fields of the two accelerator sections is such that their wave maxima are synchronized, the electrons when traveling through the second section will receive the maximum possible energy. If the electric fields are not synchronized, less than full energy will be acquired by the electrons. Phase changes are easily introduced and may be controlled with accuracy. In this way, one can continuously control the energy of the emergent beam between 5 and 50 Mev.

Another method of obtaining a variable energy is to vary the radiofrequency power delivered to the accelerator by controlling the voltage pulse height to the klystrons. The feature of energy variability over a wide range was the dominant reason for the choice of a linear accelerator for our purposes.

Detailed measurements of the output electron energy and current have been made under various operating conditions while varying parameters such as frequency of magnetron, temperatures along the accelerator tube, output power of klystrons, relative phase between klystrons, pulse timing sequence and others. Such measurements not only were of interest in assessing the unit, but also led to an understanding of the degree of stability required of numerous components. Figure 2 shows the measured electron spectrum of the unit when it is operated with a single klystron and tuned for a sharp single peak. The full width at half maximum intensity is 1.7%. The time average of the integrated current was 5×10^{-8} amp. Comparable spectra are obtained with the operation of both sections of the accelerator if the two wave maxima are in phase.

A second example of a type of spectrum obtainable is shown in Fig. 3. Here, both klystrons were operated. This type of spectrum is typical of a double peaked variety which is predicted theoretically. This figure also shows the over-all stability of the unit since the six overlapping spectral curves were taken over a period of forty minutes.

Figure 4 is a photograph showing part of the linear accelerator. The structure on the right-hand side is one of the klystron stations. The klystrons are housed within lead shields. The upper section of the picture shows a portion of the protective housing of the accelerator tube, which is rectangular in shape. The main vacuum system is just visible to the extreme left of the picture. The injector and klystron power supplies are contained in the high voltage protective cage to the rear in the photograph.

The control console for the linear accelerator, beam-deflecting apparatus, and auxiliary measuring and recording equipment are shown in Fig. 5. Excessive

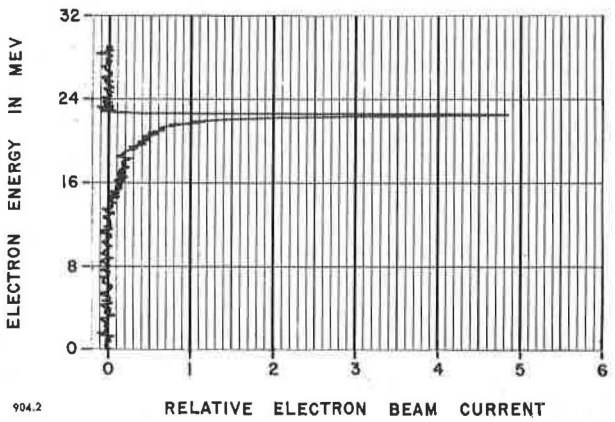

Figure 2. Example of electron spectrum obtained from the linear accelerator using the first section (2.43 m) only. The unit was tuned for a sharp single peak

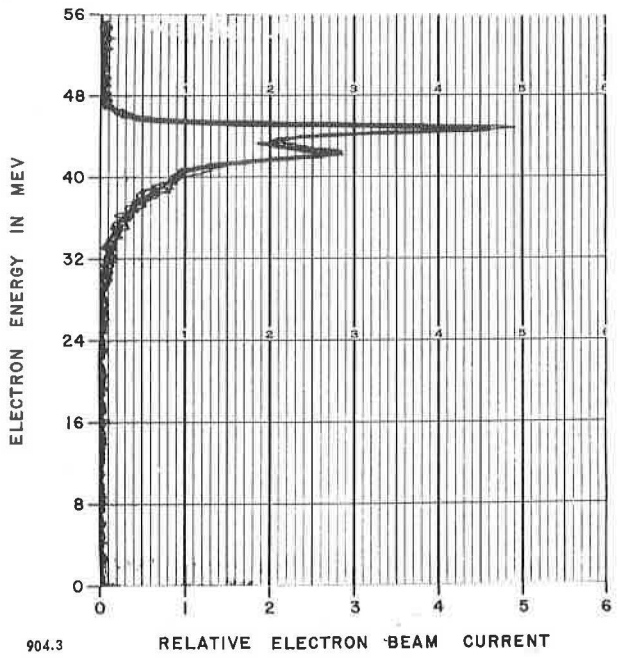

Figure 3. Example of electron spectrum obtained, using both sections of the linear accelerator and demonstrating the stability of its output. The unit was tuned for a double-peaked spectrum. The reproducibility of the output is indicated by the overlapping of six spectral curves taken over a period of forty minutes

heat from operation of the many electronic circuits in the control console is removed by the exhaust system visible above the console.

DIRECTING DEVICE: MAGNETIC DEFLECTING AND SCANNING UNIT

The magnetic deflecting and scanning unit provides the variability in beam direction and treatment area required in practical radiation therapy. The great length of the accelerator precludes easy directing of the beam by moving the accelerator tube proper. It has been the authors' experience that it is best to arrange such apparatus so that the patient may be placed in a recumbent rather than a sitting position, and that the patient be held immobile rather than in motion during treatment. To this end, the beam deflecting and scanning device was designed and built.

The device includes two electromagnets, which cause a 71 cm linear displacement of the horizontally directed beam by the method of Panofsky and McIntyre.[7] A third magnet deflects the beam through 90 degrees so that its final direction is normal to that of the initial beam. Figure 6 is a sketch showing this system. Scanning for a conventional single field is accomplished by combined linear and rotational motions of the third magnet alone. Moving-beam or

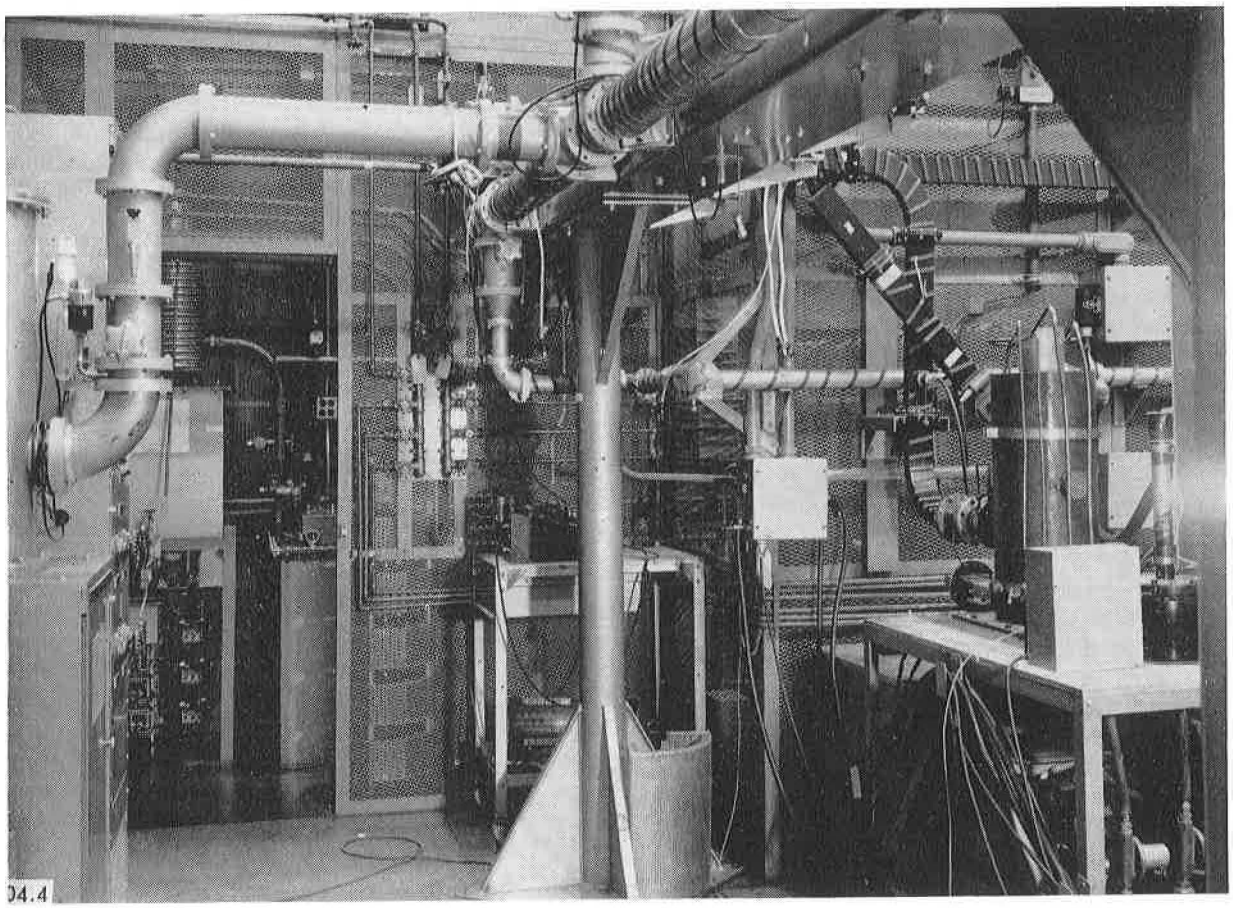

Figure 4. Photograph of a portion of the linear accelerator installation. The accelerator proper is contained in the rectangular housing shown in the upper right-hand corner of the picture. One of the klystrons is shown on the right side. The main vacuum system is shown on the extreme left. The klystron and injector power supplies are housed within the protective cage shown in the rear

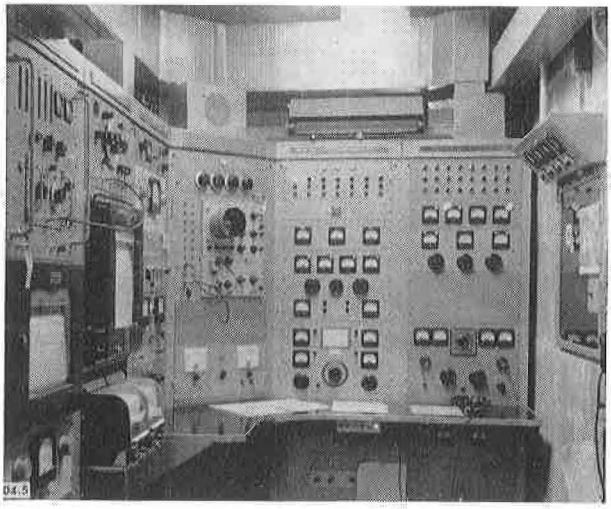

Figure 5. The control console for the linear accelerator, the deflecting and scanning unit, and auxiliary measurement and recording equipment is contained within the six bays shown here

revolution therapy is produced by the linear motion of the third magnet, combined with a rotation of all three magnets about the initial beam direction.

The power supply for the magnets is so designed that a selected energy band of electrons is passed through the system, allowing the energy of the band to be arbitrarily varied during treatment by varying the current through the magnets. As shown in the figure, the tumor area is placed on the axis of rotation of the deflecting device (axis AA'). The patient is supported on a treatment cot.

The vacuum system of the linear accelerator is connected directly to that of the deflecting device. Thus, the electrons travel in an unobstructed path, avoiding scattering and energy loss which occur during passage through vacuum windows. The first magnet deflects the electrons through a 45 degree angle. The second magnet deflects them in the opposite direction and also through 45 degrees, thus producing the linear displacement of the beam. The first magnet is designed to provide a horizontal focus halfway between it and the second magnet. (In common usage, "horizontal focus" is the focus in the plane of the magnet poles, and "vertical focus" that normal to the plane of the poles.) Thus, all beam electrons of a given energy are focused from a finite cross section into a line perpendicular to the plane of the poles. Electrons of the proper energy are deflected through an angle of exactly 45 degrees and pass through the energy-selecting collimator; those with too high or too low an energy are intercepted by the collimator at the point C. The collimator has been designed to pass an energy band of between 1 and 2%.

Much of the stray radiation, consisting of both bremsstrahlung and neutrons, is produced at the collimator. Since the bremsstrahlung is produced mainly in the forward direction, it is not directed toward the patient.

Since the second magnet is identical to the first, its focal distance is the same. Thus, electrons entering it from its focus emerge in a parallel beam. In both the first and second magnets, the beam enters and leaves normal to the pole faces. This means that there is no fringe focusing vertical to the pole faces.

The 90 degree deflecting magnet is of the sector focusing type with a uniform magnetic field. It provides both vertical and horizontal focusing on the exit side from an initially parallel beam. The position of the horizontal focus is shown at point D; the vertical focus is on the axis of the accelerator. An energy focus also exists near the accelerator axis.

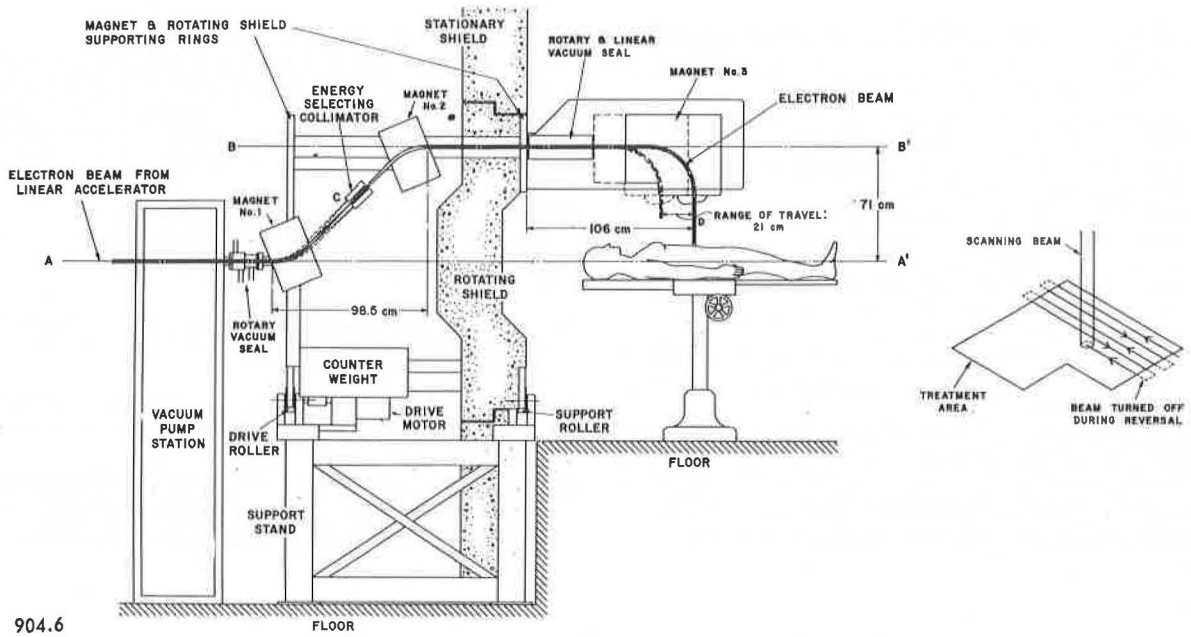

Figure 6. This schematic drawing of the deflecting and scanning unit shows the arrangement of the triple magnet system, counterweight, rotating shield, treatment cot and patient. The electron beam is contained within a vacuum chamber which is not shown in this drawing. The inset on the right side illustrates scanning over a single portal field

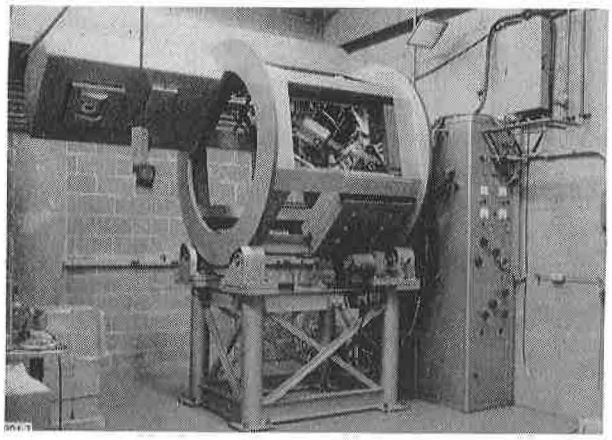

Figure 7. Photograph of the beam deflecting and scanning apparatus taken during its installation. The cabinet on the right-hand side contains the vacuum system of this unit. The rotating cage shown in the center of the picture supports magnets number one and number two within its framework and magnet number three in cantilever on its side. The counterweight, drive motor, and support stand are shown in the lower central portion of the picture

Figure 7 is a photograph of the deflecting device taken during installation. The vacuum system is shown in the right-hand side of the picture. Magnets number one and two are supported rigidly within a framework consisting of two steel rings joined by six cross members to which they are welded. The third magnet is mounted in cantilever and is visible on the left-hand side of Fig. 7. The rings together with the cross members form a rotating cage and provide the mechanism for revolution therapy. Not included in the photograph but schematically shown in Fig. 6 is a rotating radiation shield within the cage, and the stationary shielding wall surrounding it, which protect the patient area from stray radiation.

The revolution of the cage about axis AA′ combined with the linear motion of the third magnet along axis BB′ produces the necessary motions of the magnets for revolution therapy. An arbitrary sector of revolution up to a maximum of 360° and an arbitrary linear motion of up to 21 cm can be employed.

On the other hand, scanning for a conventional type single field is accomplished by the same linear motion of the third magnet along axis BB′, combined with a rotation of the third magnet only, also about axis BB′. Arbitrary field sizes and shapes up to 21 × 21 cm are automatically traced out with the aid of a template. The inset of Fig. 6 shows a scanning pattern, indicating that the electron beam is on during coverage of the main field, but is turned off while the scan is being reversed and indexed.

The scanning time rate and electron beam current are held constant for all field sizes. The time to scan an entire 10 × 10 cm field is 2.5 minutes. The beam is monitored[8] by means of a thin-foil transmission calorimeter which is placed at the beam exit port of the system.

CONCLUSION

This combination of a linear accelerator and beam deflection and scanning unit promises to take full advantage of the unique depth dose properties of high-energy electrons. It further provides full flexibility of beam direction in treating a recumbent patient; easy control in selection of field size and shape; conventional single portal as well as revolution therapy; and protection of the patient from stray radiation.

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Biological and Medical Studies with High Energy Particle Accelerators*

By J. L. Born, A. O. Anderson, H. O. Anger, A. C. Birge, P. Blanquet,† Tor Brustad,‡ R. A. Carlson, D. C. Van Dyke, D. J. Fluke,§ J. Garcia, J. P. Henry, R. M. Knisely, J. H. Lawrence, C. W. Riggs, Bo Thorell,‖ C. A. Tobias, P. Toch and G. P. Welch

In contrast with the widespread use of X rays, gamma rays and electrons, accelerated positive ions have been applied to biological studies in relatively few laboratories. Working at the Radiation Laboratory of the University of California, the authors found several areas of radiobiological interest relating to heavy ions, some of which are described below.

Protons, deuterons and alpha particles of some hundred million volts of energy have been used for producing highly localized radio lesions in accurately predetermined positions in the body. Because of the reduced scattering and deep penetration of these particles, they can be made to travel in narrow, almost parallel bundles or even brought to focus.

The linear energy transfer of accelerated heavy ions increases as they slow down in matter, until the ionization comes to a broad maximum at the "Bragg ionization peak" just before the end of the range of the particles. This reaction may be utilized as the basis for delivering high doses at almost any predetermined depth in tissue, with intervening and deeper layers of tissue hardly affected at all.

Linear energy transfer of heavy ions increases as the square of their charge, so that it is now possible to investigate the quality and quantity of radiation effects in domains of ionization which previously were not easily accessible to the experimental approach. Since primary cosmic radiation in interplanetary space has many highly ionizing primaries, and since nuclear transmutations produced in the living body also produce heavy recoils, there is potential practical interest in this field as well.

Finally, there are now several machines in existence which produce brief pulses of unusually intense heavy ions, followed by radiationless intervals. These machines may in the future give opportunity for studies of radiation-produced intermediates in a millisecond, and perhaps later in a microsecond, and for explorations of dose rate effects lead to a better understanding of the kinetics involved.

Below is a brief description of some selected areas of current interest.

STUDIES WITH VERY HEAVILY IONIZING PARTICLES

Fluke, Brustad, Birge and Tobias have for the past few years been engaged in studying small biological systems and macromolecules with the beams of heavy ions from the 60-inch cyclotron and the Berkeley Heavy Ion Linear Accelerator.[1] Available radiations include protons, deuterons, alpha particles, and carbon, nitrogen, oxygen, and neon ions, all with energies corresponding to ten million electron volts per nucleon. Heavy ions of this energy pass through material as nuclei stripped of electrons. As a consequence of the high nuclear charge, these particles are characterized by very high values of linear energy transfer (LET), up to 10^{10} ev g^{-1} cm^2 or five times the highest ionization of alpha particles. Their range in biological material, however, is only a few hundred microns.

Intense monoenergetic beams of these particles permit studies which bear on the consequences of fission fragments and other recoil nuclei produced within an organism, and on the hazards of heavy primary cosmic-ray particles which will be encountered in space travel. The radiations are also of theoretical interest in testing the validity of various theories of the biological action of ionizing radiation. The target theory of Dessauer,[2] Lea[3] and Pollard[4] emphasizes the direct action of individual ions or ion clusters. The intermediate action theory of Zirkle and Tobias[5] considers the migration of excitation energy and the formation of chemical intermediates. The role of multiple ion pairs placed close together in tracks may be clarified by the work with heavy ions. The results of heavy ion irradiation indicate the importance of delta rays and offer hope of further elucidation of mechanisms of delta ray effect.

A schematic diagram of the apparatus used for the heavy ion irradiations is shown in Fig. 1. Here the material is irradiated in the dry state in vacuum, and the dose is measured by means of a Faraday chamber. For irradiations in air, the beam is allowed to pass through the thin end window, and the dose is measured by means of an ionization chamber.

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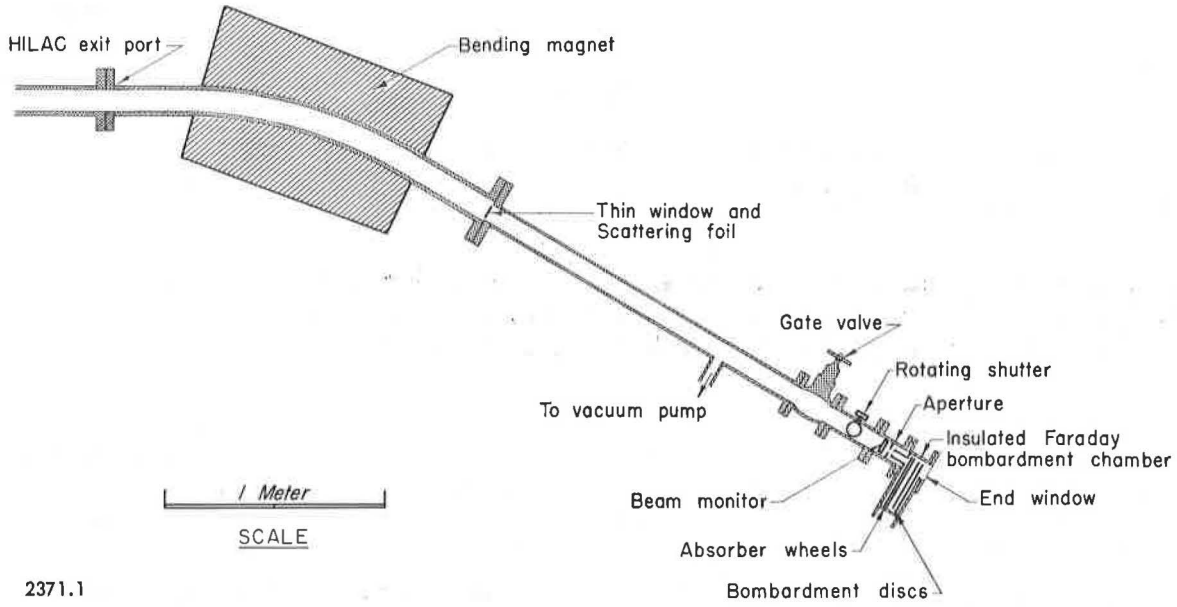

Figure 1. Schematic diagram of the apparatus used for the heavy ion irradiations. The beam is first magnetically analysed, then passed through a long evacuated tube before it impinges on the biological specimens. Dry molecules and phage are exposed within the vacuum chamber; wet specimens are exposed in air. The vacuum chamber is also used as a Faraday cage. Absorbers mounted in a disc are used to control the range of the particles

The materials studied thus far include vegetative yeast cells of *Saccharomyces cerevisiae* by Birge and Sayeg,[6,7] dry spores of *B. subtilis*, dry T-1 bacteriophage, and the enzymes lysozyme trypsin and desoxyribonuclease by Fluke and Brustad.[8,9] All these materials show an exponential dose-effect relationship. Consequently, it is possible to express the results of irradiation as cross section values, or the apparent area that the various molecules or organisms present to the bombarding particles. This description is convenient for heavy ions, where the exposure is often measured as the density of bombarding particles over an area rather than as the energy absorbed per unit mass. In this representation a constant relative biological effectiveness (RBE) corresponds to a cross section that is proportional to linear energy transfer (LET). On the other hand, a cross section that approaches a constant value for increasing LET corresponds to a rapidly falling RBE.

The data are summarized in Fig. 2, where the measured inactivation cross section is plotted as a function of LET for several different systems. In earlier work the haploid[5] yeast cells and *B. subtilis* spores[10] had both shown an increasing RBE at the highest LET values attainable with alpha particles. Both these materials are now shown to have a decreasing RBE at still higher LET. Dry T-1 bacteriophage shows a relatively flat RBE for radiations of intermediate LET, and a decreasing RBE at very high LET. Preliminary calculations of the effect of delta rays indicate that for high LET the corrected cross section is not larger than the virus particle silhouette and may be smaller.

While the heavy particle experiments on phage T-1 and bacterial spores give cross sections in fairly good agreement with the models previously obtained for the mechanism of inactivation, the lysozyme cross sections with oxygen nuclei are considerably (about 10 times) higher than one would expect from simple hit theory on the basis of the known molecular weight. It is well known that when the measured cross sections are corrected for delta rays the inactivation cross sections will be reduced. If a large part of the effect on lysozyme is due to delta rays, experiments of this type might give us more definite knowledge about the delta ray energy distribution than we have now. The possibility remains that further refinements beyond accounting for delta rays will have to be made in the theory of action of radiations before the cross section data of Fig. 2 can be fully explained.

The techniques also make it possible to irradiate the surface of animal tissues and to irradiate thin layers of wet biochemical systems.

BIOLOGICAL STUDIES WITH 340 MEV PROTONS, 190 MEV DEUTERONS AND 300 MEV ALPHA PARTICLES

Since our report on the initial development of techniques for biological uses of high energy deuterons,[11] we have carried out a number of studies. Most of these take advantage of the fact that the proton, deuteron or helium particles may be collimated to form a small penetrating pencil of rays which may be used to produce localized radiation damage in various deep-lying body structures.

Interest in these investigations centers about the physiological processes which are partially or fully controlled by activity of the pituitary gland and by hypothalamic control centers. For many years physiological investigations tended to show that homeostasis, the balance and control of the level of a great

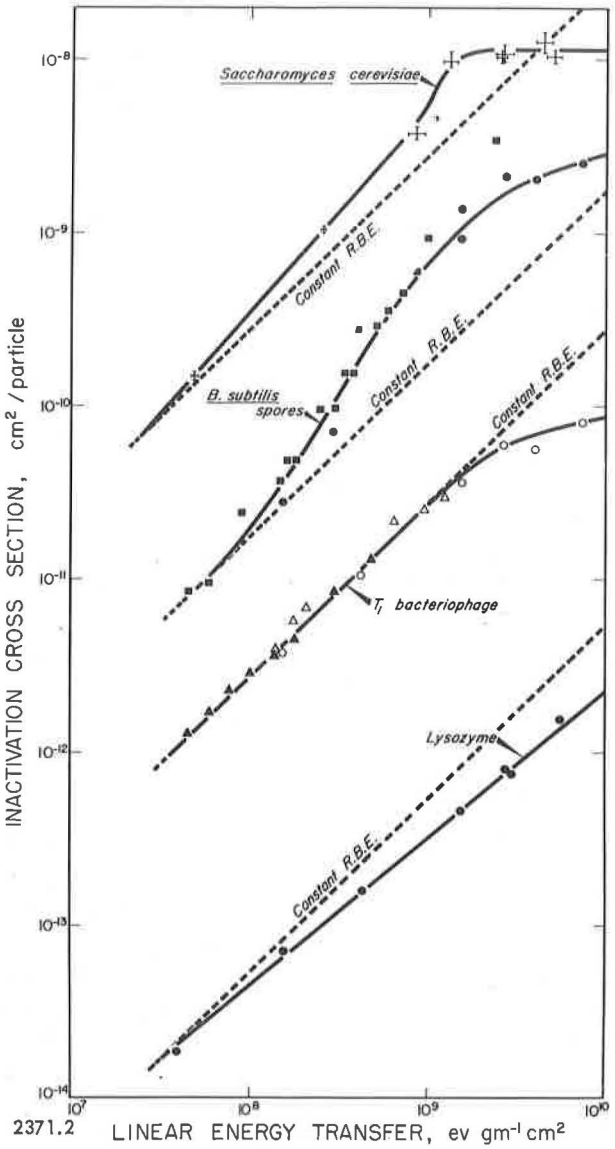

Figure 2. The measured cross section for inactivation of several biological materials as a function of the mean linear energy transfer of the irradiating particles. ✠ Data of Sayeg and Birge.[6,7] ■ Data of Donnellan and Morowitz.[20] ▲ Data of Forro and Fluke[10] at Brookhaven National Laboratory. △ Data of Fluke at Yale University cyclotron. ○, ● Data obtained in the present study at the University of California by Fluke and Brustad[8,9]

many physiological processes, lies in the hypothalamus, but it has not been fully resolved whether or not each homeostatic variable, e.g., temperature, water turnover, etc., is controlled independently, and the extent to which the various centers are involved in the so-called "stress reaction." The advantages of ion beams in this study lie in the ability to produce lesions without operative procedures and in investigating the possibility that neurons and nerve fibers might be affected differentially. The well-known latency of radiation lesions and the time required for developing them appear to be a disadvantage.

Several authors have pointed out the connections between the hypothalamus and pituitary (see for example ref. 12) and the possibility of a feedback relationship in homeostatic control. In our experiments we have postulated the existence of a feedback arrangement (one general form of which is shown in Fig. 3), which may mediate the response of the body to various stimulating or deleterious effects. According to this model, the pituitary gland acts under control of neural and humoral agents from the hypothalamus. This latter is in turn under the influence of information received from the body tissues and endocrine target organs and is, in addition, in connection with the higher brain centers as well. Thus any imbalance in any part of the system may react on the other parts and bring about corrective or divergent changes in performance.

PITUITARY IRRADIATION

A reasonable body of data has been accumulated on the effects of deuterons on rat pituitary by Tobias, Van Dyke, Simpson, and Koneff over the past five years.[13,14] In this work a small beam of particles, triangular in cross section, 1 mm height 2 mm apex, was utilized, and groups of 22-day-old male Long Evans rats were exposed to single doses, ranging from 945 rad to 40,000 rad. Many of the animals were studied, for the rest of their life span, to obtain information on the nature and duration of the effects on efficiency of production of various pituitary hormones. The measurement of skeletal development and body mass indicated early that, in order to achieve a physiological state comparable to surgical hypophysectomy, massive doses (above 10,000 rad) were required and that in general, hypopituitarism appeared earlier and earlier as the dose increased. It is of interest to note, however, that when sufficient time was allowed, even the lowest

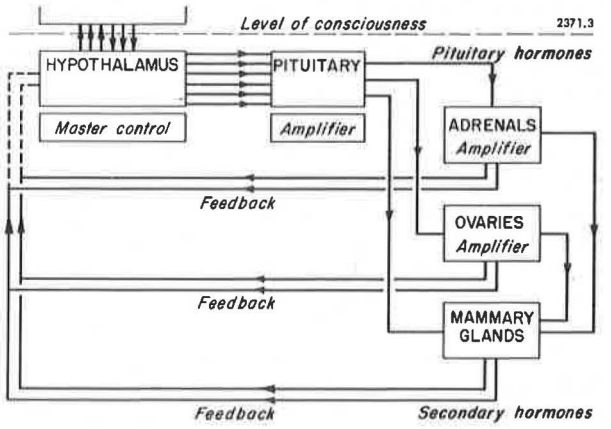

Figure 3. Pituitary hormones are assumed to be controlled by neural and humoral mechanisms from the hypothalamus. The endocrine "target" organs give rise to hormonal secretions under the influence of the pituitary hormones. The levels of metabolic activity in someway, as yet unknown, feed back to the hypothalamus. This latter has also neural connections with upper centers in the brain. When any part of this system changes its level of function, the rest of the system tends to modify its activity to return the system to normal ("Homeostasis"). Carcinogenic activity is expected from this system when a part of it has subnormal activity due to sublethal injury to its cells. Pituitary tumorigenesis following 945 rad dose is assumed to occur on the basis of feedback stimulation of the subnormally active, sublethally damaged hypophyseal tissue

dose of highly localized rays had profound effects on the animals. Even at low dose levels, clear-cut differences were apparent in the ability of the pituitary to produce various hormones as evidenced by the size of the target organs, none of which had received appreciable doses of radiation.

The effect on body weight and tail length of some of the animals, as a function of dose, is shown in Fig. 4.

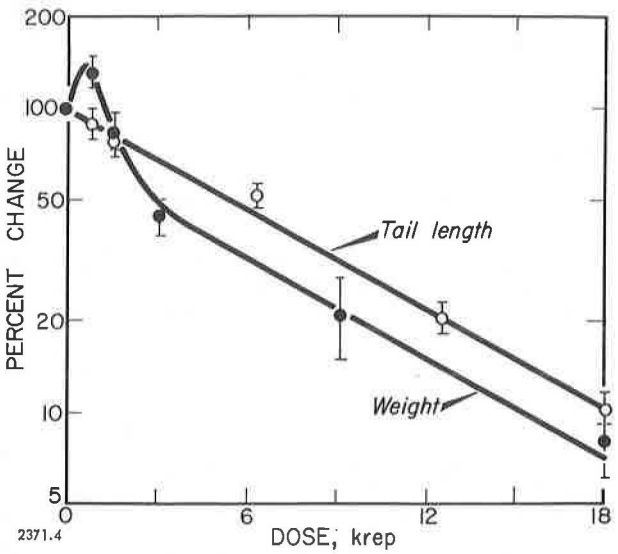

Figure 4. Relative increase in tail length and of body mass as function of deuteron dose to the pituitary gland, measured 18 months following exposure

Regression of thyroids, adrenals, and gonads is indicated in Fig. 5. It is apparent that dose-effect relationship for secondary suppression is different for each organ. Reduction of weight gain or tail growth to one-half normal takes about 6000 rad, while a similar degree of effect on adrenals and thyroids is reached at 2000–3000 rad. The gonads take somewhat more, 3300 rad, for the same effect. One curious effect at 945 rad was the gain in weight of the animals in the post-irradiation period during which this lowest dose group exhibited characteristic changes of obesity. We do not know at present whether this finding is entirely due to malfunction of the pituitary gland. Or, could it originate in surrounding injured structures? The well-known "obesity center" of the hypothalamus is far enough away to have received only a few roentgens.

Hypophyseal function is known to be related in some way to tumor formation. It was of interest, when high doses of pituitary irradiation were given, to find that at 24 months' post-irradiation the over-all incidence of tumors of the body as found at autopsy was about one-half the incidence in nonirradiated controls. On the other hand, at the lowest exposures (945 rad) the incidence of pituitary tumors showed a striking increase. Fifteen months post irradiation 100% of these animals had pituitary adenomas, with an average of 3.5 tumors per gland. The pituitary tumor incidence is shown on Fig. 6. Among 70 animals that received over 3000 rad, not one had a pituitary tumor! The authors believe that this finding adds to the evidence pointing

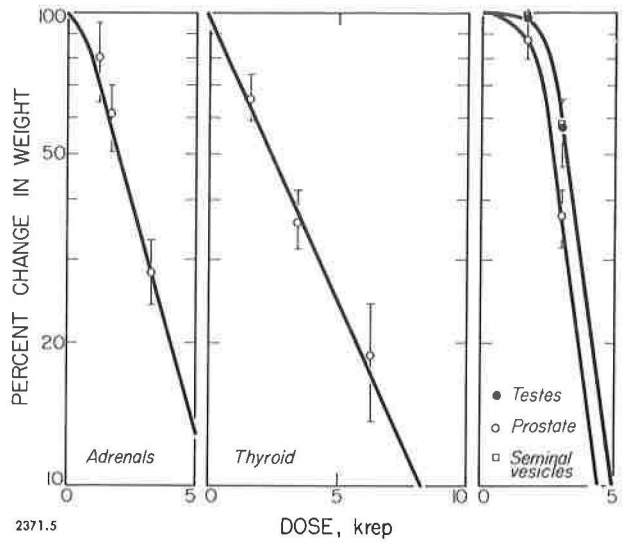

Figure 5. Relative decrease in endocrine organ weights 18 months after various doses of pituitary deuteron irradiation

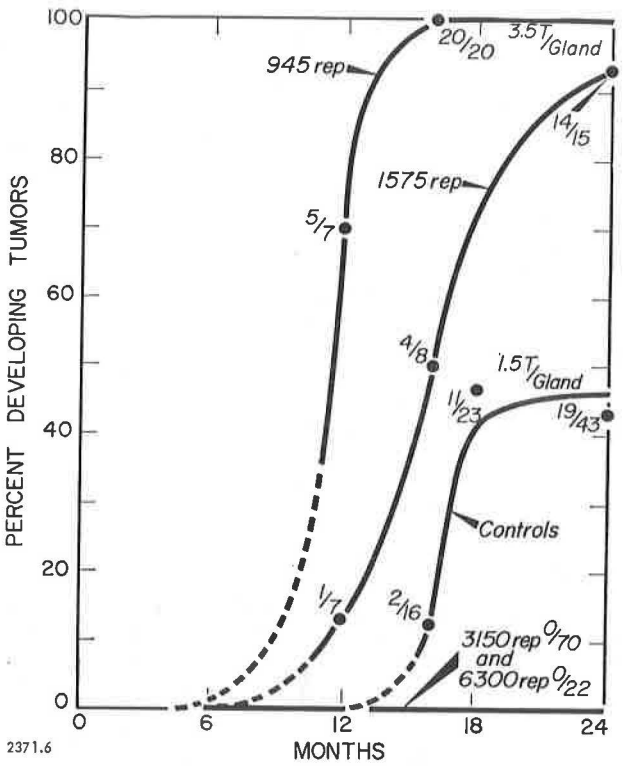

Figure 6. Development of pituitary tumors in normal rats and in rats that received various doses of pituitary deuteron irradiation at 28 days of age. The lowest dose, 945 rad, caused pituitary tumors in practically all animals, which appeared earlier than tumors in the controls. At high doses pituitary tumors were essentially absent

to endocrine factors in carcinogenesis. Apparently, radiation carcinogenesis occurs following sublethal injury to the cells of a given tissue and is accelerated by feedback stimulation (Fig. 3). If so, tumor growth may be initiated in response to need for more pituitary hormones. Furth[16] found that head irradiation induced pituitary tumor formation in mice. Pituitary tumors following radiation or chemical thyroidectomy are well known.

The above explanation for tumor induction fits in well with the findings of Bond, *et al.*[16] who found that mammary tumors in rats were induced by whole body irradiation and that the onset of such tumors is dependent on the function of the intact ovaries.

HYPOTHALAMIC RADIATION STUDIES

Since it seemed that chronic physiologic changes might be induced by pituitary irradiation, it became of interest to study proton and deuteron effects on brain and hypothalamus in order to determine the radiosensitivity of these tissues and to find out if high energy particles can be useful tools in a study of feedback mechanisms of homeostatic control. During the past several years, many groups of rats have been exposed to deuteron beams ranging in diameter from 1.6 mm² to areas of 20 mm². Many of these suffered lethal effects. High doses resulted in shorter survival time than low doses. However, at constant dose, survival time decreased with increased irradiated volume. There is a correlation between integral dose and survival time, shown in Fig. 7.

In an attempt to ascertain the effects of deuterons on the entire hypothalamus, an aperture was fabricated which would cover a major portion of the region. Parts of the mesencephalon, posterior to the hypothalamus, were also included; the shape of the aperture was designed to exclude the pituitary. Survival as a function of dose is shown in Fig. 8. After receiving 9500 and 11,000 rad, the animals failed to gain weight and 10–15 days following irradiation exhibited marked rage. The animals were extremely difficult to handle, biting everything within reach. The rage continued until 2–3 days prior to death, at which time the animals assumed a "hunchbacked" motionless position and ceased to eat or drink. At autopsy, all animals in these groups were consistently found to have gross petechial hemorrhages at the site of irradiation in the hypothalamus and anterior mesencephalon.

Next, two groups of 20 rats each were irradiated with a deuteron beam of 3.2 mm diameter. In one group the beam was directed to the anterior hypothalamus, in the other to the posterior hypothalamus.

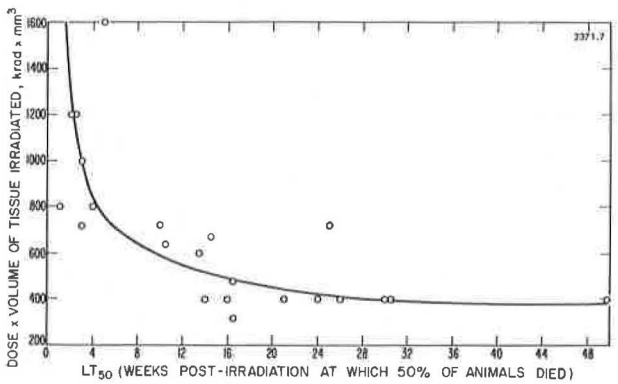

Figure 7. Survival of rats receiving various doses of deuteron irradiation to various areas of the brain. There is an apparent correlation between survival and volume of tissue irradiated as well as dose delivered

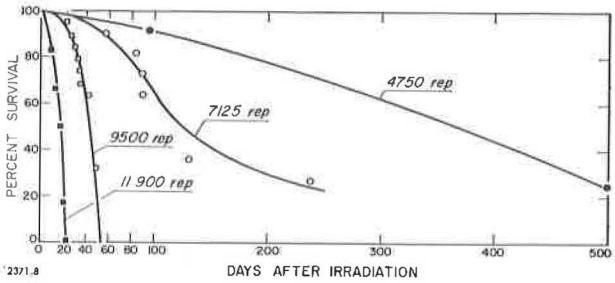

Figure 8. Survival of groups of rats receiving various doses of deuteron irradiation to the entire hypothalamus

Each received the same dose—13,500 rad. These animals also exhibited rage and the characteristic hypothalamic radiation syndrome described above. In addition, convulsions, enophthalamus, ptosis, blindness, and bloody exudate from eyes and nose were exhibited. On autopsy, many were found to have gastric ulcers and hemorrhages in the stomach or intestinal tract. Some of these findings are shown in Table 1.

Table 1. Acute Findings in Hypothalamic Deuteron Irradiation

	Location of lesion	
	Anterior dorsal hypothalamus	*Posterior dorsal hypothalamus*
Size of beam aperture, mm	3.2	3.2
Dose (rad)	13,500	13,500
Number of animals	20	20
Survival time days	18 ± 5	18 ± 5
No. with gastric ulcers	5	7
No. with hemorrhages in stomach or intestine	7	3
No. with hemorrhagic lesions at irradiated site	8	10
No. with bloody exudate from eyes or nose	3	1
Convulsions	5	4
Rage	6	7
Ptosis	0	7
Enophthalamus	2	7
Blindness	1	2

Following these initial experiments, the sagittal area of the hypothalamus of the rat was divided into 6 regions. By passing deuteron beams of varying cross sections through these, we hoped to reproduce various physiological effects attributed to surgically produced lesions as illustrated in Fig. 9. We now wish to report briefly only on area IV, the median eminence, and area III in the posterior dorsal hypothalamus.

The animals which were irradiated in area IV, the region of the median eminence, frequently developed lesions which matched in appearance the contour of the irradiated area. In the center of the region, complete necrosis and liquefaction had occurred, and at the edge one could often observe microscopically a sharp region of demarcation between reasonably normal-appearing tissue and complete necrosis. An example is shown in Fig. 10. A detailed time-dose study of

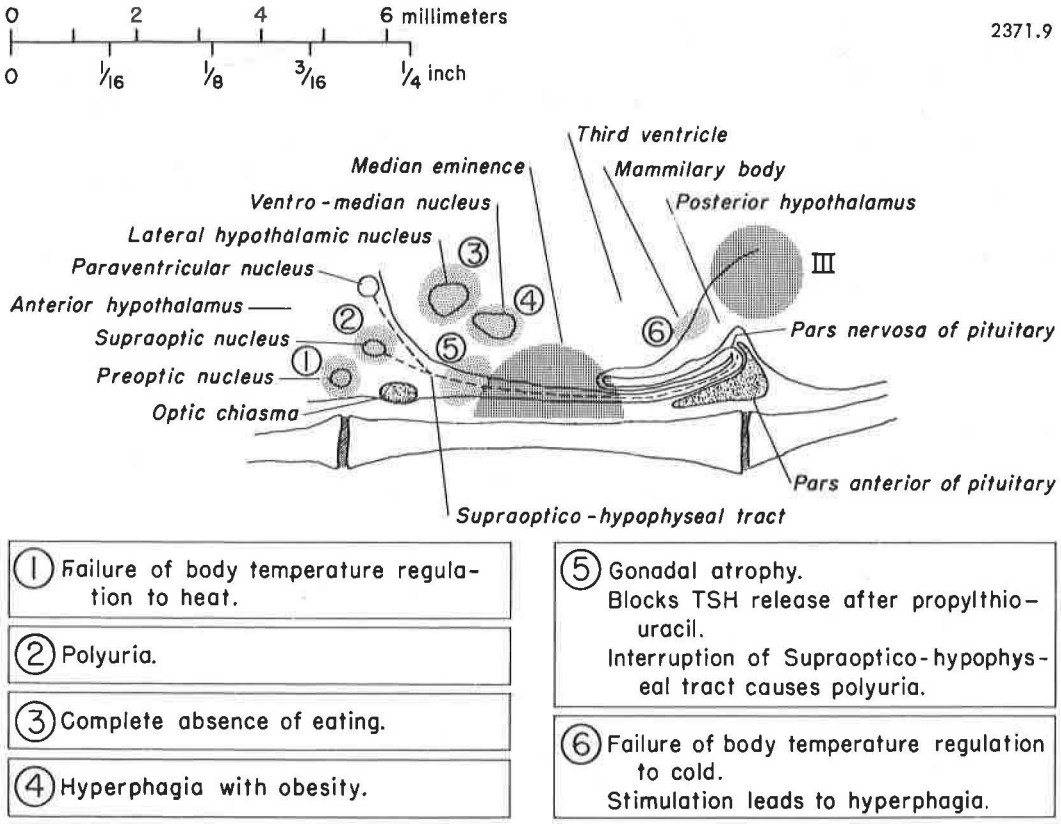

Figure 9. Lateral view of the rat hypothalamic region illustrating the effects of bilateral destruction of various structures. The location of two radiation-induced lesions is also shown

the histological changes is in progress. Physiological changes in the animals are frequently observed even before evidence of complete necrosis. With time, the lesions may spread to other regions in the brain along channels of vascular supply or nerve trunk degeneration. The most immediate physiological changes observed in these animals were polyuria and polydipsia, increased food intake with transient hyperphagia, glycosuria, regression of the testes and thyroid metabolism abnormality. The urine output increased in some animals to twelve times normal in a period of fifty days. Regression of the testes occurred progressively with time, and in producing this result the hypothalamus seemed more sensitive than the directly irradiated pituitary.

Blanquet and Tobias[17] found that this group of animals, injured at the median eminence, exhibited a curious defect in thyroid metabolism: the iodine^{131} uptake of the thyroid remained normal, but the gland seemed to fail almost completely in its production of thyroxine although labeled mono- and diiodotyrosine appeared in normal amounts. In this respect, the median eminence irradiated animals seemed to differ from hypophysectomized ones, which showed low amounts of each amino acid. The results of analysis are shown in Fig. 11, where ion exchange analysis of the different iodinated compounds was used to obtain a quantitative measure of each present in the thyroid hydrolysate. This effect, which has been produced repeatedly, may eventually lead to the identification of more than one pituitary thyrotropic hormone and to the better understanding of the mechanism of hyperphagia.

Irradiation of area III, in the posterior hypothalamus, led to a retarded development of bone growth as well as to decreased rate of body weight gain, as shown in Fig. 12. At the same time, adrenals, thyroid, and

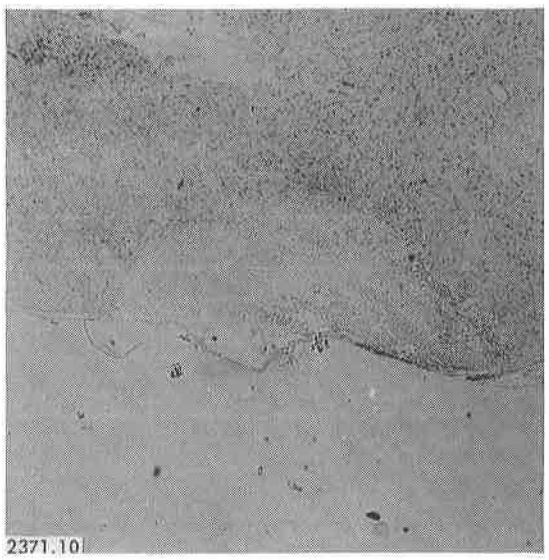

Figure 10. Transverse section of rat brain at level of and lateral to the median eminence showing demarcated destruction of nervous tissue 24 days after a dose of 20,000 rad deuterons

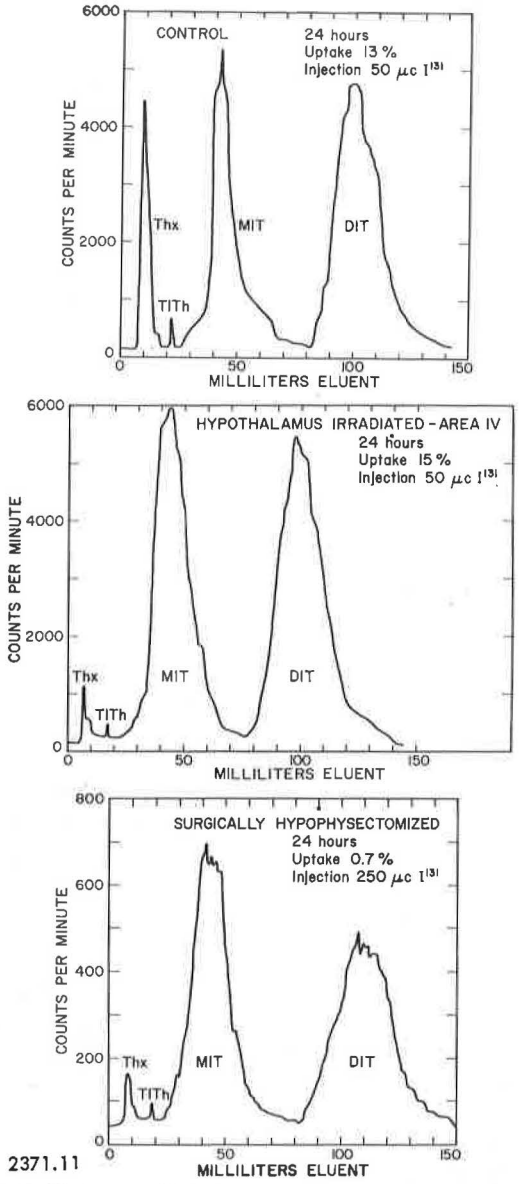

Figure 11. Diagrams obtained by ion exchange chromatography of rat thyroid hydrolysate from (upper figure) Normal control, (middle figure) Hypothalamic irradiated, and (lower figure) Surgically hypophysectomized. Note the relatively low activity contained in the surgically hypophysectomized and the relatively small amount of thyroxin found in the hypothalamic irradiated animals

gonads were developing at nearly normal rate. The first explanation might be that the hypothalamic "appetite center" is disturbed. However, the "appetite center" was not in the radiation field. Thus there is a possibility that the lesion had to do with control of growth and production of growth hormone by the pituitary gland. Thorell, working with us, studied the pathology of the pituitary gland and found that the pituitary acidophilic cells of the irradiated group were almost entirely depleted of their granules and these cells would not show the staining reaction so characteristic of acidophiles. Thus it appears as though irradiation of the posterior hypothalamus would lead to impaired bone growth and less weight gain. More work is being done on this problem at the present. It

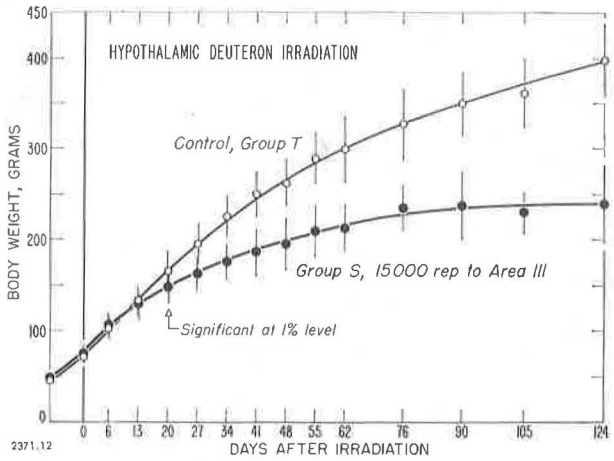

Figure 12. Retardation of growth in rats receiving deuteron irradiation to Area III of the hypothalamus. See Fig. 9 for lesion location

is apparent that irradiation of several hypothalamic areas can influence growth rate, and some of these areas are so close to the pituitary itself that part of the effect might be caused by direct pituitary radiation.

INVESTIGATIVE THERAPY OF MAMMARY CANCER BY PITUITARY IRRADIATION

In 1954 we treated some dogs with metastatic mammary adenocarcinoma, giving them single doses of pituitary radiation. Of 15 animals so treated, objective remission was obtained in 5, as measured by the diameter of tumor. One of these animals, in which the disease seemed to be arrested, lived for three years, and at death none of her metastases appeared active.

PROTON AND HELIUM ION HYPOPHYSECTOMY IN MAMMARY CANCER

Human application of high energy protons was initiated in 1954 by irradiating the hypophyses of 26 patients who had advanced metastatic mammary carcinoma. The method was described at the Geneva conference in 1955,[18] and a more detailed report has recently been published.[19]

The internal beam of the 184-inch cyclotron is at present deflected by the magnetic regeneration method, magnetically sorted and focused into an approximately parallel stream of particles, arriving at the medical exposure room about 50 feet from the cyclotron. The beam, which was precollimated to about ¾ inch diameter, is then shaped by passing through a brass aperture which has been individually designed for each patient. The electrical center of the beam is accurately kept on a hypothetical axis running parallel to an optical bench. Alignment of the object to be irradiated with the beam is accomplished by the use of two diagnostic X-ray machines, mounted at right angles to each other. As a result, any part of an animal or human body may be exposed to any shaped area of the parallel beam. While the beam is on, the body may be rotated around the center of the irradiated area. A photograph of the apparatus is shown in Fig. 13. The

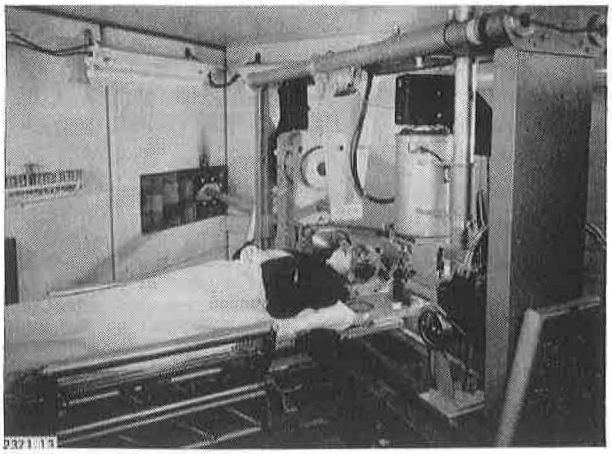

Figure 13. Patient being exposed to 900 Mev helium ions at the Berkeley 184-inch cyclotron. Note the plastic face mask for holding the head, which is continually in pendulum-rotatory motion. The beam enters on the right through the brass aperture

procedure has been greatly speeded up by use of X-ray television image amplifiers for alignment and for checking alignment during rotation of the patients. In 1957, the Berkeley 184-inch cyclotron was rebuilt, and it now operates with 900 Mev He^4 ions as well as with 450 Mev deuterons and 700 Mev protons. The range of the helium ions in tissue is about 22 g/cm², while the deuterons penetrate about twice as far and the protons stop at 190 g/cm². The mean linear energy transfer of helium ions is about 15 Mev g/cm², or quite similar to linear energy transfer of secondary electrons from a 250 kev X-ray machine.

In the first series, 26 patients with metastatic breast carcinoma received pituitary proton irradiation. These patients were carefully selected with respect to the presence of progressive metastatic lesions. In all these cases, generally accepted forms of surgical and radiological treatment had been administered previously and the responses of the patients to palliative procedures such as oophorectomy, adrenalectomy, and endocrine therapy were evaluated. Twenty-three of the patients had previous mastectomy, 19 oophorectomy, and 16 bilateral adrenalectomy. Two-thirds of all patients were in a rapidly failing stage of their disease at the onset of pituitary irradiation and could be classed as terminal.

Proton irradiation was given in fractionated doses three times a week. Since protons have never previously been used to irradiate a human being and we had no direct knowledge of the pituitary radiosensitivity, the initial patients were treated with conservatively low doses over a protracted time period. In order to obtain evidence of the degree of pituitary damage obtained, the patients were divided into three groups, receiving 13,000 to 20,000 rad, 20,000 to 26,000 rad, and 30,000 rad, respectively, "nominal" dose. These "nominal" doses were the amounts delivered to the geometrical center of head rotation, that is, the center of the pituitary gland. The beam, shaped to fit the sella turcica in each individual, entered the head laterally; body positioning and head rotation achieved

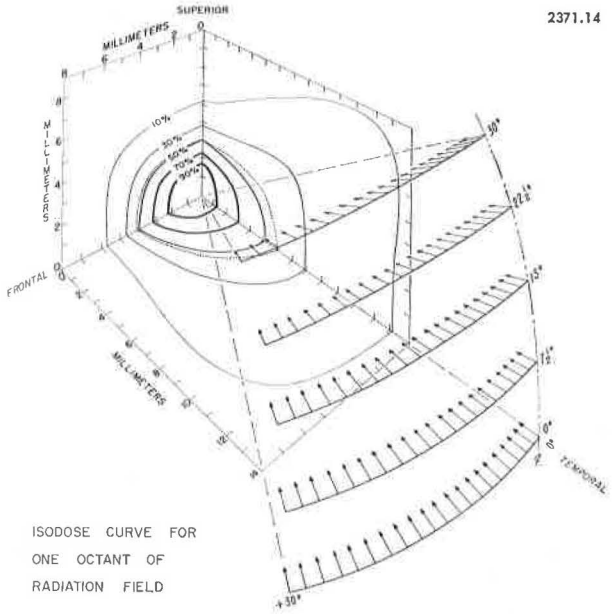

Figure 14. Isodose curves for pituitary proton irradiation in humans. The center of the coordinate system is at the anatomical center of the pituitary. Distances are indicated in mm

a very rapid fall-off of the dose outside of the gland. A typical three dimensional isodose distribution plot as measured by Welch is given in Fig. 14. The greater part of the optic chiasm, the median hypothalamus, and mesencephalon were intentionally avoided in irradiation. As the subsequent clinical, physiological, and pathological evidence indicate, the hypophysis is destroyed as time progresses after radiation exposure, with higher doses accelerating the process. Objective evidence of decreased pituitary function was given by various measures. Decrease in pituitary gonadotropins (Fig. 15) and thyroid I^{131} uptake (Fig. 16) seemed most significant. The radiation caused progressive cytological destruction in the hypophysis. Several weeks after receiving the 30,000 rad dose, one pituitary had regressed so profoundly that on autopsy less than an estimated 5% of the cells remained. The progressive development of the atrophy of the gland is illustrated

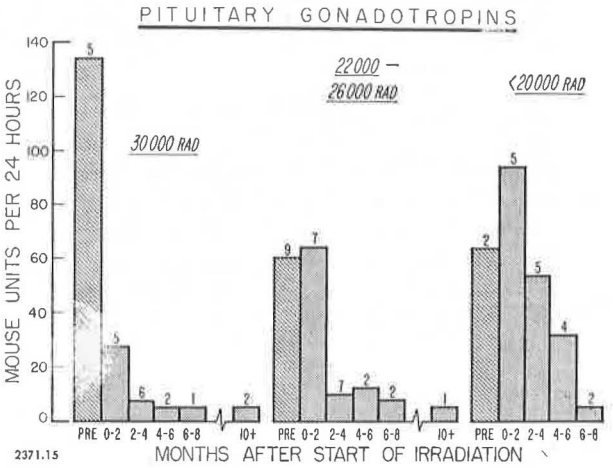

Figure 15. Urinary FSH measurements in patients exposed to various doses of hypophyseal proton irradiation

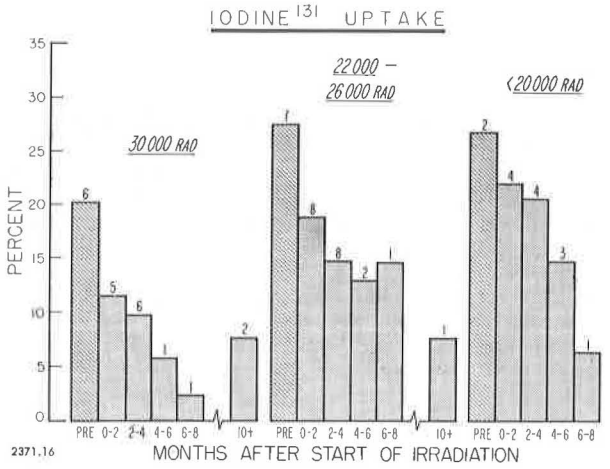

Figure 16. Twenty four hour I^{131} uptake in patients exposed to various doses of hypophyseal proton irradiation

by Fig. 17. The sequence appears to consist of a latent period during which morphologic changes are mild. This is followed probably in several weeks by extensive but subtotal necrosis. The cells lose their staining ability, develop cytoplasmic and nuclear vacuoles, and develop fragmented and clumped pyknotic nuclei. Later, when the debris has been removed the gland atrophies and fibrous tissue predominates. Parenchymal cells, however, still can be identified. They are pyknotic and presumably nonfunctioning. They tend to be grouped at one or another margin of the gland.

In view of the generalized nature, advanced state and rate of progress of the metastatic mammary carcinoma at the time of treatment, one could not expect very dramatic prolongation of life of the patient. It is believed that 10 of the 26 patients had objective remissions for various durations of time. Of these, 7 occurred among 13 patients treated at the higher dose levels and 3 among 13 patients with doses of 20,000 rad or below. One patient is still in good remission 2½ years after radiation. Objective remissions involved regression of intra-abdominal carcinomatosis, bone lesions, primary breast tumors, and lung and skin lesions. No benefit was seen in patients with liver or brain metastases. The postirradiation period was remarkably free of adverse secondary effects. Symptoms of endocrine deficiencies could be corrected by administration of hormone replacements. Three patients developed diabetes insipidus, which was managed satisfactorily. Third, fourth, and sixth cranial nerve palsies have been observed at the highest doses given. However, these remained stationary or improved with time. One patient, treated at 30,000 rad, developed occasional uncinate fits which have been satisfactorily controlled by anticonvulsant therapy.

In October 1957, investigative therapy of mammary carcinoma was again instituted, using 900 Mev alpha particles. We hope to irradiate a sufficient number of patients to gain some statistical idea of the value of this procedure. A few patients with pituitary adenomas and one with advanced diabetes mellitus were also exposed to pituitary alpha irradiation. It is expected that full evaluation of the patient program may consume several years. At the date of this writing (April 1, 1958) 30 patients in the new series have been irradiated.

In summary, objective evidence was obtained to show that the course of advanced metastatic mammary carcinoma can be temporarily altered in some patients by massive doses of high energy protons to the pituitary gland. These same doses cause progressive destruction of the pituitary and its function with a minimum of adverse side effects.

ACKNOWLEDGEMENTS

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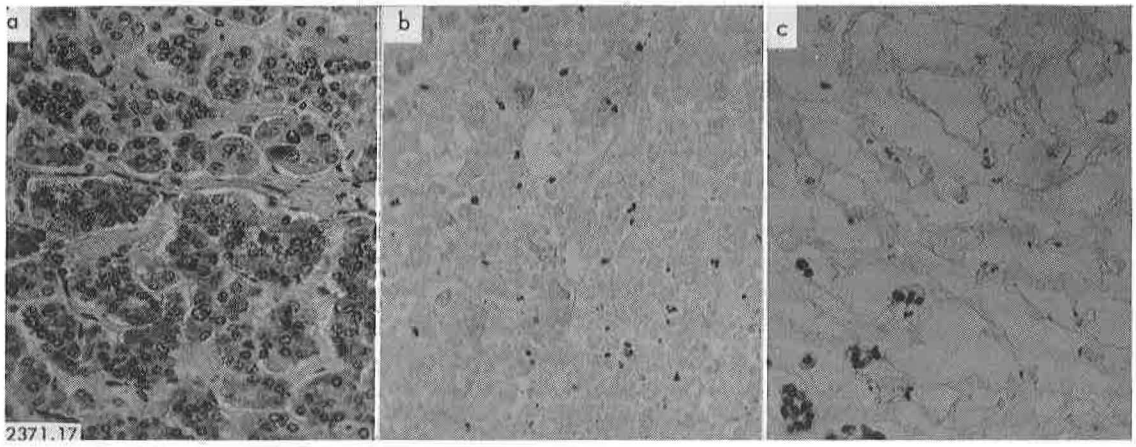

Figure 17. Human anterior hypophysis.

a. Nonirradiated human anterior hypophysis, hematoxylin eosin stain.

b. Human anterior hypophysis 2 weeks following 20,000 rad dose to the pituitary stained as 17a. Acute radiation necrosis is setting in. Notice nuclear and cytoplasmic vacuoles and fragments, and loss of selective staining ability.

c. Human anterior hypophysis 14 weeks following 30,000 rad dose to the pituitary stained as 17a. Dead cells fragment and completely disintegrate. Cellular debris is gradually eliminated. Note the appearance of a few viable cells with pyknotic nuclei

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The Biologic Effect of Single Large Dose Irradiations in Anesthetized Man

By O. Costăchel and St. Grigoresco*

The numerous experimental radiobiologic investigations which have been carried out in recent years have focussed attention on the need for many more chemical agents offering protection against radioactivity as well as on their effectiveness. The protective agents in use at the present time do not provide sufficient protection, especially against the noxious effects of large single doses of radiation.

The present paper presents data collected in the course of the clinical use of large, single therapeutic radiation doses, under the protective cover of anesthesia, for cancer.

The single dose of 2500 r (over a surface of 200 cm^2) used clinically gave more precise information of the effectiveness of the protective agents than could be obtained from the administration of the same quantity of radiation in divided doses, where the response evoked is to a large extent compensated by the reaction of the whole organism.

Since 1950 the role of the central nervous system in the appearance and development of radiobiologic effects in the body has been studied at the Bucharest Oncologic Institute. The results of these studies[1–9] have shown that inhibition of the central nervous system by means of anesthesia during irradiation confers definite protection against the noxious effects of X rays administered in a single large dose.

This finding suggested the possibility of employing large single doses, protected by anesthesia, for improving the results of fractionated radiotherapy of tumours, especially in the treatment of advanced cases. We have called this method *protected radiotherapy*.

Seitz and Wintz[10] used a single radiation dose for the treatment of cancer of the cervix uteri forty years ago, but the local and generalized reactions were often so serious that they prevented cure or even caused death. The main complications described by Seitz and Wintz were leukopenia, protracted cystitis and hemorrhagic proctitis, serious cutaneous burns followed by atrophy, telangiectasis, etc., and at times intestinal accidents such as obstructions, perforations, etc.

Despite these frequent serious complications, the clinical results were sometimes excellent. Nonetheless, the severity of the complications obliged these workers to abandon their method of therapy.

The use of anesthesia as a radioprotective agent for eliminating the harmful effects of large single doses, while preserving their curative effectiveness, raises the problem as to whether or not the tumour as well as the rest of the organism does not also become resistant to radioactivity.

In previous experimental studies[2,3,8] we have shown that besides the direct effect of radiation there is also an indirect distant effect on nonirradiated tissues as well as an indirect local effect, the two being elicited by the reaction of the organism as a whole to the physicochemical changes produced by radiations in the irradiated tissues. These considerations also proved to be useful in the clinical application of radiotherapy to tumours using single or few large doses of radiation.

We have obtained excellent protection against the indirect distant effects (nausea, vomiting, radiation sickness), less protection against the indirect local effect which nevertheless is apparent (in that shrinkage of the tumour was generally less than if irradiation had taken place in the unanesthetized state) and almost no protection against the direct local effect which produced in many cases an exudative epidermitis similar to that which occurs with irradiation in the absence of anesthesia.

It seems, therefore, that these three effects are produced by different mechanisms and require different means of protection.

Anesthesia has proved especially useful against the indirect distant effect, that is, radiation sickness which involves the great integrative elements of the organism as a whole: the nervous system, the endocrine system, etc. Other means of protection are still needed against the direct and indirect local effects; at the same time, the effect on the organism must, of course, be differentiated from the effect on the tumour. This we have called *differential protection*.

METHODS AND TECHNIQUES

This communication presents the biologic reactions of the body to large single doses of radiation. The data are derived from the treatment by means of protected radiotherapy of 70 patients with histopathologic diagnoses of cancer in the following sites:

	Cases
Cervix uteri	36
Lung	6
Various neoplastic adenopathies	4
Skin, ovary, bone, larynx, etc.	24

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With the exception of one case, stage II cancer of the cervix uteri, all the cases were advanced (stages III and IV) and inoperable, radiotherapy being applied as a palliative measure.

When protected radiotherapy was first used, anesthesia was induced with sodium evipan given by intravenous drip; later it was replaced by a "lytic cocktail" (Laborit) which possessed great advantages from the standpoint of anesthetic risk and the reaction of patients. This "cocktail" produces sufficiently deep anesthesia within 15–60 minutes, depending on the rate of administration, with or without the previous administration of morphine–atropine.

The irradiation constants, the dimensions of the fields and the size of doses used have varied since the newness of the method necessitated various trials aimed at improving the conditions of irradiation. The majority of patients (63 of the 70) were treated with an irradiation dose of 180 kv, 10 ma using a 1 mm Cu filter, a 40 cm skin–focus distance and a rate of 35 r/minute.

The dose was calculated for skin, and under the conditions to be described the following single doses have been derived: 3000 r per field 6 × 8 cm, 3000 r per field 8 × 10 cm, and 2500 r per field 10 × 15 cm.

The largest dose per single field (8 × 10 cm) was 4050 r in two sittings at an interval of 14 days. The largest dose in one sitting was 4100 r applied to 2 fields (8 × 10 cm and 10 × 15 cm) and 5000 r applied to 3 fields (6 × 8 cm).

Despite having data on the local and generalized reactions of the organism to irradiation under anesthesia, up to the present we have not been able to establish exactly the maximal dose tolerated by the different regions of the body without damage. But as far as the dose at the tumour focus is concerned, we estimate that a single dose of 2–3000 r is required when irradiating under anesthesia (taking into account protection against the indirect local effect).

In the majority of the cases irradiated we did not expect significant therapeutic results because, with the exception of 3 cases of cutaneous epitheliomas, the dose of 3000 r at the tumour focus was not attained. The local and general reactions which occurred showed very marked variability and so far we have not been able to find any significant correlation with the various conditions of irradiation (depth of anesthesia, age of patients, region irradiated, etc.).

CLINICAL OBSERVATIONS

Cutaneous Reactions

One of our first observations was that the size of the field (6 × 8 cm to 10 × 15 cm) does not play an important part in the appearance and development of cutaneous reactions. In some instances paradoxical reactions have been observed: slight erythema with a dose of 2500 r and an exudative reaction with a dose of 2000 r when the same size field (8 × 10 cm) and the same irradiation constants were used.

In general, the cutaneous reaction to single doses of over 1500 r develops in the following manner: 4 to 6 hours after the irradiation, 30% of the cases show slight cutaneous edema which precedes shortly or develops at the same time as a slight and transient erythema which disappears the next day. In these cases a second wave of erythematous reaction appears during the subsequent days (3rd and 4th day), persists for 5 to 10 days to be replaced soon after by a progressive pigmentation or a dry or exudative epidermitis. When there is no cutaneous edema, transient or persistent erythema appears and follows the course described above.

The pigmentation which occurs is lasting and of varying intensity. A correlation between its incidence and the dose administered has not been established.

Dry epidermitis was encountered in only 3 cases in which doses of 1100 r, 1250 r and 1500 r per field of 10 × 15 cm had been used. Exudative epidermitis appears at variable intervals after irradiation (14–30 days) and with great regularity when doses exceed 2000 r, irrespective of the extent of the field irradiated. The exudative epidermitis appears first at isolated points around the hair follicles and spreads to occupy the whole irradiated surface. This reaction disappears in 10–14 days.

Epithelitis was observed in 2 cases. In one case epithelitis appeared on the left side of the tongue 2 weeks after a single dose of 3000 r for an epithelioma of the cheek; in the second case, an epithelitis of the endolarynx appeared 12 days after a dose of 3500 r was given in two sittings (2 fields) for an epithelioma of the larynx.

Regional visceral reactions are negligible. Irradiation of the lower abdomen is accompanied on rare occasions by irritation of the bladder and the rectosigmoid which disappears in 1–3 days without special treatment. Irradiation of the thorax by our method is incomparably better tolerated than irradiation of this region in divided doses.

General Reactions

Among the blood changes leukocytosis of 18,000–20,000 occurs regularly; it appears 4–6 hours after irradiation and disappears the following day with a return to normal value or even a slight leukopenia, but always above 4000/mm^3. The erythrocytes appear to be less affected; in certain cases a moderate and transient erythropenia (3½ million erythrocytes/mm^3) appears after approximately 20 days; it may or may not be accompanied by anisocytosis. No conclusive alteration in the leukocyte formula has been noted.

During irradiation the majority of patients show a lowering of axillary temperature to 36°C or even to 35.5°C. In most cases a slight febrile reaction (37.5–38°C) supervenes after the irradiation and disappears in 1–3 days with or without the administration of antibiotics. However, in those cases in which inflammatory reactions were present prior to irradiation the fever persisted for a longer period, yielding only to antibiotics.

From the point of view of febrile reactions the behaviour of patients with bronchopulmonary tumours was remarkable. Treatment of these cases by fractionated irradiation produced frequent febrile incidents and intrapleural effusions, particularly in advanced cases, at times making continuation of treatment impossible; irradiation under anesthesia caused neither febrile complications nor pleural effusions despite the large single doses used—this was especially the case when antibiotics were administered prior to irradiation.

The patients' general condition was not appreciably affected by irradiation under anesthesia. Some patients showed enhanced appetite (compared to appetite before irradiation) on the evening of the day irradiation was given. A slight asthenia was usually observed during the first few days after irradiation, but this disappeared spontaneously in 4–5 days.

Nausea and vomiting are more frequent after irradiation of the abdomen, and appears on recovery from anesthesia. These manifestations completely disappear after a period varying from several hours to 24 hours. Only in one case, given a dose of 2500 r over a field of 13 × 15 cm for an inoperable ovarian adenocarcinoma, did relatively slight vomiting persist for 8 days.

Radiosensitivity in Tumours

It is not possible to state from the data in the available literature on the behaviour of tumours after irradiation under anesthesia to what degree the reaction of the tumour is analogous to the reaction of the organism with respect to the development of resistance to radioactivity produced by the anesthesia.

Bacq *et al.*[11] state that prolonged treatment with large doses of mercaptoethylamine produces no obvious decrease in radiosensitivity in tumours in man. On the other hand, Hervé and Neukomm[12] found that the same protective agent diminished slightly the radiosensitivity of the Gaspari adenocarcinoma of the breast in mice after local irradiation with 3000 r.

We undertook a further investigation of this question. Tumour carriers (rats) were anesthetized with alpha-chloralose (0.1 g/kg intraperitoneally). The experiments were performed on transplanted rat fibrosarcoma I.O.B.X., and local irradiation of the tumour was carried out with a Monopan-Siemens apparatus (60 kv, 4 ma, 0.2 mm Cu filter, focus–tumour distance 1.5 cm, 1100 r/minute). The first two attempts, using doses of 4400 r and 2200 r, failed to demonstrate any differential action of anesthesia on the irradiated tumours. The curves for the involution of the tumours were the same for rats irradiated under anesthesia and the controls irradiated in the unanesthetized state.

Differences became apparent when a dose of 1100 r was used. It was found that the tumours in animals irradiated under anesthesia acquired a more rapid rate of involution than the tumours in the controls; they appeared to have become more radiosensitive. By contrast, administration of anesthesia immediately after irradiation of the tumours, repeated daily for 9 days, caused these tumours to become resistant to radiation, and to progress (see Fig. 1).

Our experimental data show that *anesthesia given during irradiation does not transmit to tumours the resistance to radioactivity* which it confers on the organism; on the contrary, it appears to make the tumours more sensitive to radiation.

Clinical observations made in the course of irradiating 70 patients did not confirm these experimental results. In fact, the diminution of general reactions in patients irradiated under anesthesia was accompanied by similar behaviour on the part of the tumour. For example, Seitz and Wintz state that 110% of the erythema dose is sufficient for "sterilization" of the tumour when administered in a single dose. In our patients "sterilization" of the tumour could not be obtained even though the above-mentioned dose was greatly exceeded. This finding is related to the important biologic problem dealing with the relationship between the organism and the tumour for which it acts as host.

Other means of protection against radioactivity, with preferential action on the organism and not the tumour, are therefore needed; that is, some means of augmenting the differential of radiosensitivity between the tumour and the host organism affected by cancer.

Large single doses of radiation given under anesthesia were accompanied by progressive aggravation in three of our patients whose case histories are cited briefly below:

Case 27, patient F.M. This 60-year-old male had a diagnosis of right plantar ulcerated melanoid tumour, 4–6 cm in diameter, and right inguinal adenopathy adherent to the underlying deep tissues; X ray of the chest was normal. He was treated with a "lytic cocktail" anesthesia followed by irradiation of the lymph nodes with a single dose of 2000 r (180 kv, 10 ma, focus–skin distance 40 cm, field 8 × 10 cm) on November 11, 1957. No serious local or general reactions occurred. Three weeks after the irradiation, adenop-

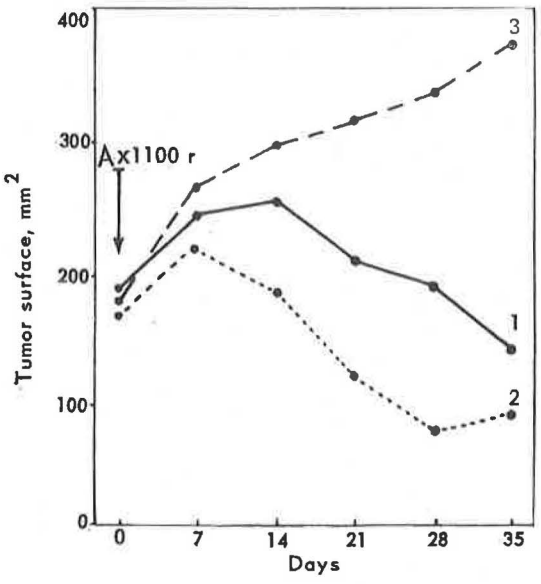

Figure 1. Effect of irradiating tumours under α-chloralose anesthesia. 1, control; 2, administration of α-chloralose during irradiation; 3, administration of α-chloralose after irradiation

athy was unchanged and diffuse metastases occupying the entire lung fields and general deterioration were evident.

Case 30, patient C.F. A 44-year-old male had a diagnosis of histioreticulosarcoma of the left lateral cervical ganglion with marked adenopathy in a chain from the mastoid to the sternoclavicular articulation on the left side. The tumour was hard, painless and deeply adherent. It was also adherent to the skin which appeared inflamed.

Treatment with "lytic cocktail" anesthesia and irradiation of the tumour with a single dose of 2030 r (180 kv, 10 ma, focus–skin distance 40 cm, field 12 × 15 cm) on December 21, 1957 produced no serious local or general reaction.

Examination on February 11, 1958 revealed: (*a*) almost complete disappearance of the irradiated tumour; only a small, hard, painless nodule measuring 2 × 2 cm and situated under the sternocleidomastoid on the left side remaining, (*b*) mobile, painless left subclavicular adenopathy measuring about 1.5 cm of recent origin, (*c*) Bernard–Horner syndrome on the left side, and (*d*) left hemiparesis of the tongue.

Case 37, patient N.F. A 41-year-old male in whom a diagnosis of left inguinal ganglion reticulosarcoma had been made showed marked left inguinal adenopathy with hard, deeply adherent nodes measuring 13 × 18 cm. There was edema of the left thigh and of the scrotum. The patient was treated with "lytic cocktail" anesthesia and irradiation of the tumour with a single dose of 2088 r (180 kv, 10 ma, focus–skin distance 40 cm, field 15 × 18 cm) on October 22, 1957. Local reaction showing pigmentation, and general reaction with pyrexia on the evening of the day of irradiation and during the next two days occurred.

The result of treatment was a spectacular disappearance of the tumour in 7 days and diminished edema. However, 10 days later left facial paresis, aphasia and vomiting, indicating appearance of cerebral metastases, appeared.

The progressive deterioration of these cases, despite their small number (3 out of 70), would appear to indicate some connexion between the downhill course and the method of treatment, especially with large doses administered at one time. The systemic character of the disease in these cases must also have played a certain part and this seems quite likely because such rapidly progressing deterioration has not been generally observed. This is demonstrated by a brief description of three clinical case histories in which the results were favourable:

Case 12, patient B.A. A male, 50 years old with a diagnosis of nondifferentiated epithelioma of the nasopharynx, marked right laterocervical adenopathy 7 × 9 cm and multiple left laterocervical adenopathy was treated with "lytic cocktail" anesthesia and irradiation of the right laterocervical tumour in two sittings with a total dose of 3000 r at an interval of 2 weeks. The left laterocervical multiple adenopathy was also treated with "lytic cocktail" anesthesia and irradiation with a dose of 1950 r over a field 8 × 10 cm on October 24, 1957. The adenopathies disappeared and there were no signs of recurrence when examined February 1958.

Case 32, patient L.R. Another male patient, age 65, had a diagnosis of osteosarcoma of the upper half of the right humerus, swelling of the upper half of the right arm, edema of the arm and weakness of the limb. The radiologic picture was characteristic. The patient was given a "lytic cocktail" anesthesia and the tumour was irradiated at two sittings with a total dose of 4060 r. There was a local reaction with exudative epidermitis of the axilla but no general reactions. The treatment resulted in a reduction of the swelling, disappearance of the edema and recovery of function of the arm. No change in the radiologic picture occurred. This result was still apparent when the patient was seen in February 1958.

Case 21, patient C.I. A 67-year-old female with a basal cell epithelioma of the left cheek was treated with a "lytic cocktail" anesthesia and irradiation of the tumour with a dose of 3000 r. The tumour was ulcerated with raised borders, irregularly round in shape and 6 cm in diameter. Local reactions appeared after 12 days and there was a marked exudative lesion, epithelitis of the left half of the tongue and of the corresponding buccal mucosa; a general reaction producing pyrexia which responded to antibiotics occurred. Resolution of the tumour occurred 35 days after the irradiation and epithelization began after 2 months.

Comparison of these last cases with the first three presented demonstrates the importance of therapeutic indication in choosing cases for radiotherapy under anesthesia. Large single doses of radiation have proved to be both beneficial and nonbeneficial.

The failures (cases 30 and 37) are the result of dissemination of the tumour; the local results were excellent. At present we are trying to prevent metastases by using either chemotherapy (sarcolysine) or microdoses of total irradiation (X rays or P^{32}).

DISCUSSION

We wish to draw attention from the outset to the particular difficulties presented by a discussion and interpretation of the results of administering large single doses of radiation under the protection of anesthesia.

Local reactions as those of the skin, and reactions of the viscera and of tumours are different from those reactions associated with fractional radiotherapy. We are, therefore, justified in thinking that the reactions under anesthesia must be different. These reactions are characterized by a diversity which is in marked contrast to the constant nature of the reactions obtained in the nonanesthetized state.

Thus, with doses below 2000 r for the cervix uteri, we have produced, all with the same doses, cutaneous reactions ranging from slight erythema followed by slight pigmentation to exudative epidermitis. The same doses applied to the skin of the thorax have always resulted in slight erythema and even pigmenta-

tion, at times without exudative epidermitis. The same variability in reaction has been noted over the skin of the neck and of the hypogastrium.

These facts suggest that conditions may exist under which it would be possible to avoid the cutaneous reaction at a dose of 2000 r, but we do not as yet know these conditions. There is then the possibility of discovering these conditions by studying particularly the circumstances under which indirect radiobiologic reactions[13] affect the nervous system and the other integrative systems of the organism.

Another fact which supports the existence of this indirect effect is the absence of general reactions: with large single doses of radiation the reaction of hemapoietic tissues is negligible and disappears without treatment as contrasted with the violent reactions caused by similar doses in the unanesthetized state, and even with reactions sometimes caused by fractionated methods of irradiation. These observations are also applicable to visceral reactions, to radiation sickness and to pyrexia.

The attempts to augment general and local protection by cortisone have given results which require further verification. A case of inoperable cancer of the larynx was given at a single sitting a dose of 3500 r applied to 2 lateral fields after preliminary tracheotomy. Marked edema of the neck and of the glottis occurred and disappeared rapidly (24 hours) upon administration of cortisone. This hormone, according to our observations, accelerates the healing of epidermitis caused by large single doses under anesthesia. It has not yet been tried as a preventive measure against cutaneous reactions.

It might be possible, therefore, to further increase single radiation doses by developing other means for cutaneous and general protection. The possibility of establishing and obtaining, under protection of anesthesia, single cancer-destroying doses which would not involve serious damage to the patient remains to be determined. Up to the present the doses we have used have been trial ones designed to ascertain tolerance to radiation.

SUMMARY

1. Anesthesia suppresses to a large extent the general noxious effect of large local doses of radiation both in animals and in man.

2. The influence of anesthesia on the local effects of radiation, particularly radiation of the skin, is much less marked. However, anesthesia protects deep-lying structures against local radiation since the effect produced on a tumour by 2500–3000 r given under anesthesia is less than that produced by 2000 r given by Seitz and Wintz in the nonanesthetized state.

3. The marked differences in protection conferred by anesthesia on different parts of the organism suggest that the mechanism of the radiobiologic effect is different in these parts, and that therefore a variety of protective measures is required. For this reason we use complex differential protective procedures in clinical practise.

4. The means of protection against radioactivity used clinically today are to a large extent effective against the indirect effects of radiation, particularly the distant effect; their effectiveness against direct local reactions is much less pronounced.

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Teletherapy with Cobalt-60*

By Osolando J. Machado

Although radiotherapy has been used for more than twenty years, only during the last decade has supervoltage radiotherapy been accessible in some centres for routine use. Convinced of the importance of more penetrating radiations, radiotherapists have asked for X-ray apparatus with more and more voltage. Besides the 200 kv equipment used earlier, they began to use apparatus of 400 kv, 600 kv, and one million volts. Only during the past five years has multimillion-volt or supervoltage therapy commenced to progress rapidly and to provide encouraging clinical results.

In the beginning, progress in supervoltage radiotherapy was due to development and perfection of equipment that generated radiations at the expense of electric energy, such as resonance transformers, Van de Graaff generators, the betatron, the synchrotron and, recently, the linear accelerator. Development of such devices was slow on account of cost, size and difficult maintenance. With improved designs, better insulating materials and new technical knowledge, there appeared compact machines that are more adaptable for clinical use, thus allowing for greater application of supervoltage radiotherapy, though cost and maintenance of such equipment has restricted installation and use in advanced centres.

The development of nuclear reactors has provided a means for making radioactive isotopes with a great capacity for emitting gamma radiation. Such isotopes, with protective shielding, were used immediately in teletherapy inasmuch as gamma rays with proper characteristics could be substituted for X rays in the 200 kv to 3 million-volt range.

Before discussing teletherapy units, we wish to consider both the advantages and the disadvantages of supervoltage radiotherapy as a means of defining the character of the problem.

ADVANTAGES

Supervoltage radiotherapy presents various advantages over the conventional deep radiotherapy of 200 and 250 kv. The first and most ponderable advantage is increase in deep dose percentage which to some extent follows parallel to the rise in radiation energy. This increase takes place rapidly from 250 kv up to the level of 20 million volts, beyond which it continues to rise slowly. Increased depth dose allows treatment of deep tumors with greater doses despite use of a smaller number of fields and simpler techniques. This advantage diminishes the integrated body dose, thus improving tolerance.

With increase in radiation energy level, there is a progressive decrease of retrograde radiation, as well as of the lateral dispersion, which makes the radiation beam more defined within the geometrical projection of the cone. Besides diminishing the integral dose, supervoltage radiation does not damage so severely the tissues or organs which are near the radiation beam, thus causing recuperation of the patient to be less of a problem.

With respect to low energy radiations, maximum absorption takes place in the skin, which of course is not the case when higher energy radiations are used. This is why the skin dose is smaller with supervoltage radiotherapy than with conventional deep roentgentherapy. Greater depth dose is one of the greatest advantages of the supervoltage techniques as it permits higher doses per treatment field without risk of damaging the skin, thereby facilitating the treatment of deep tumors.

Another advantage comes from the fact that bone tissue, according to Spiers, absorbs more low energy than high energy radiations. However, after a level of 4 or 5 million volts has been reached, owing to increase in production of ion-pairs, the situation changes and the dose received by the soft tissues in and near bone increases with the energy of the radiation. So far as bone tissue is concerned, therefore, there is advantage only in the use of supervoltage radiotherapy within certain limits—those between 1 and 5 million volts.

LIMITATIONS

As we have said, there are also certain limitations to the use of supervoltage techniques. To begin with, it would seem that the more penetrating the radiation, the better it would be for treatment of deep-seated tumors. This is not necessarily true, because of increase in exit dose. If we compare incident dose with tumor dose, we see that, beyond a certain energy level, the advantages of low skin dose and elevated tumor dose disappear as a result of increase in exit dose.

Another disadvantage of the use of high energy radiation is a decrease in diameter of maximum intensity of the radiation beam which tends to concentrate in the approximate direction of the current of electrons.

* Read at the 6th Radiological Meeting in Belo Horizonte, 2nd to 9th September 1957.

As a consequence of this, after a certain energy level has been reached, it becomes necessary, for clinical purposes, to use compensating filters to make the radiation beam homogeneous, a procedure which greatly reduces dosage rate. This does not happen, however, when the radiation comes from radioactive cobalt which provides a monochromatic beam.

The last of the limitations is the fact that the greater the energy capacity of the apparatus, the larger it will be in size—also that the protection problems of the room where the apparatus functions will be more complicated and expensive.

Analyzing, comparatively, the favorable factors of supervoltage, such as the higher depth-dose percentage, the negative skin dose and the smaller absorption by bone tissue, in relation to the unfavorable factors, such as increase of the skin dose in the exit beam region, increase of the absorption by bone tissue with rise in the energy capacity and the increase of size of the apparatus, together with the necessity for greater protection, it is concluded that the ideal limit of supervoltage for therapeutic use is about 3 to 4 Mev. According to Meredith, there are within these limits, at the present time, two types of apparatus of better adaptability—linear accelerators and the teletherapy units with sources of radioactive isotopes of high radiation activity. On account of the difficulties of maintenance, the teletherapy units are believed to be more ideal for clinical use in the large centres of Brazil. For this reason, we shall consider only the studies with teletherapy units having sources of more than 50 cm skin-source distance, inasmuch as the others present a depth dose percentage equivalent to that of the conventional deep radiotherapy apparatus.

In the study of the teletherapy units of high activity, we need to consider the radioactive source, the source-skin-distance, the container and the collimator system, as each of these factors has, aside from its finality, advantages and inconveniences.

SOURCE

In search for the ideal source of radiation, there have been studies of natural radioactive elements like radium and radioactive isotope producers of gamma rays. However, the sources suitable for teletherapy must fulfill various conditions; for example, they must (1) emit gamma radiation of high energy, (2) have a substantial half-life, (3) have high specific activity, and (4) be produced in abundance at accessible cost.

In conformity with the foregoing, we did not consider radium due to its very low specific activity (in spite of presenting a good percentage of high radiation energy) and because more than 30% of the gamma radiation emitted by it corresponds to an energy of 1.5 Mev. Its specific activity, being low, causes many difficulties in teletherapy notwithstanding efforts made to overcome them. Consequently, it remains for us to consider the radioactive isotope sources which for practical purposes Aebersold has classified as sources of high, medium and low energy (Table 1).

With reference to isotopes, we shall discuss only those which have a reasonably long half-life period. This limitation is imposed inasmuch as rapid decrease of radiation intensity in proportion to time would necessitate constant adjustments of exposure and frequent replenishment of radioactive source materials. The latter could cause an interruption of treatments and cause complications relative to the well-being of technical personnel. We shall therefore give attention only to cobalt-60, cesium-137 and europium-152 and 154. The three will be discussed together in order that we may consider the advantages and disadvantages of each one.

With reference to durability, cesium-137 is especially suitable, having a half-life of 37 years. Europium-152 and 154 have half-lives from 13 to 16 years while cobalt-60 has only 5.3 years. Accordingly, cesium-137 is distinctly the most advantageous element. However, cobalt-60 may be regarded as more suitable because it emits higher energy radiation (1.17 to 1.33 Mev). Europium emits radiation with energy from 0.3 to 1.2 Mev, which when filtered, produces a gamma component identical with that of cobalt-60. Cesium-137 produces gamma radiation with energy scarcely equivalent to 0.662 Mev. In certain respects, the lower energy radiation from cesium-137 is advantageous since less protection is required, inasmuch as the radiotherapy apparatus can be more compact.

A source of energy for radiotherapy must be evaluated, not only for its specific activity, but also for the intensity of radiation it produces at one meter distance. The specific activity of 51.5 c/g for europium-152 and 154 is higher than the 20 c/g for the other two isotopes. However, with the new nuclear reactors, greater improvements can be expected for cobalt-60. From a practical point of view, as we have stated, one of the most important factors, other than energy content, is intensity of the radiation at one meter distance from the source. Further, without taking into consideration auto-absorption, the hourly roentgen production per curie of each isotope at one meter distance is: europium, 0.55, cesium, 0.36, and cobalt, 1.30, there being the possibility of increase as soon as nuclear reactors of higher potentiality commence to function (Table 2). We may compare the irradiation capacity of a Co^{60} teletherapy unit with the linear accelerator in the likelihood of obtaining sources capable of producing 100 r/min at one meter distance.

THE UNIT

Cobalt-60 as a source is distributed in pellets which are kept in a standard container with a diameter from 1 to 3.5 cm. Sources of smaller diameter are best inasmuch as an increase in diameter of the source enlarges the penumbra around the beam.

The capsule, containing the cobalt-60 source, is placed inside a spheroidal head of the unit which is built of lead, steel and tungsten, thus giving adequate protection to operating personnel. There is also a system of obturation, the mechanism of which varies in accord-

Table 1. Isotopes Emitting Gamma Rays
According to Aebersold

Isotope	*Half-Life*	*Gamma rays—Mev*
High energy (above 1 Mev)		
Co 60	5.3 years	1.17, 1.33
Ag 110	270 days	10 γ's: 0.676 to 1.516 0.885 (81%), 1.389 (33%)
Eu 152, 154	13. 16 years	~0.3, ~1.2
Ta 182	117 days	33 γ's: 0.0462 to 1.237 0.66, 0.885, 0.9 more intense
Medium energy (0.5 to 1 Mev)		
Cs 137	37 years	0.662 (2.6m Ba-137)
Cs 144	275 days	0.13 (abundant)
Pr 144 (daughter)	17.5 months	2.2 1.5 } 10% 0.7
Ir 192	70 days	12 γ's: 0.137 to 0.651
Low energy (<0.5 Mev)		
Se 75	127 days	10 γ's: 0.067 to 0.405
Tm 170	127 days	0.084
W 185	73.2 days	0.134
Hg 203	43.5 days	0.286

ance with the type and manufacture of the equipment. Likewise, collimation is provided for, in order to limit and give shape to the radiation beam emitted by the source. The whole head is maintained by a system of support which allows for ample movement for clinical work.

The final subject for consideration with respect to teletherapy apparatus is the system of collimation, which, in addition to necessitating a special design for its obvious finality, must be made in such a manner that it does not contaminate the radiation beam with secondary rays. Further, we desire to call attention to the co-relation existing between the skin source distance, the collimator source distance, and the diameter of the source, inasmuch as the diameter of the radiation penumbra around the primary beam depends upon it.

INDICATIONS

As yet, the numerous uses of telecobalt-60 units are not well defined, varying, in part, with required techniques and with the inclination of specialists who use them. To begin with, cobalt teletherapy is indicated when there is need for greater depth dose and for sparing the patient from intense skin and other general reactions. We are using it in particular for cancer patients who previously were treated with 400 kv X rays and for cases of larynx, lung, esophagus, bladder, advanced carcinomas of the mouth, carcinomatous metastatic lymph-nodes and intracranial tumors—also for irradiation of the internal mammary chain, and of the axillary and supraclavicular lymph nodes according to the McWither technique for post-operation treatment of breast cancer. As an exclusive therapeutic element, or complement to intercavitary radium application, or even for patients with more than 18 cm pelvic diameter, we use it for treatment of cancer of the cervix. Further, we have found it advantageous for the treatment of pelvic glands secondary to carcinomas.

Table 2. Radiation at 1 meter distance
According to J. Maisin

Element	*r/h/c*
Radium	0.84
Co^{60}	1.30 or 1.36
$Eu^{152,154}$	0.55
Ta^{182}	0.61
Cs^{137}	0.36
Ir^{192}	0.27

Telecobalt as a substitute for high voltage has indications as listed by Evans but modified slightly by us as follows:

1. Tumors close to bone or cartilage, unsuitable for local radium treatment and where radiation sequelae probably will be less than with medium voltage X rays (examples: mouth, larynx, pharynx and anus).
2. Deep-seated tumors, where conventional radiotherapy necessitates complicated arrangements for its application and where local radium treatment is impracticable (examples: esophagus, uterine cervix, vagina and bladder).
3. Radioresistant tumors which do not respond well to conventional roentgentherapy and which are unsuitable for such treatment (examples: sarcoma of soft parts, cerebral tumors, malignant melanoma and inoperable metastatic lymph nodes). We desire to make clear that for cases of melanoma we can only contemplate the use of telecobalt for palliative treatment of inoperable glands and which may cause immediate disturbances to the patient.
4. Palliative treatment in cases for which previous irradiation was unsuccessful and where the treatment is easier to administer to a debilitated patient.

RESULTS

With progress in treatment of our patients, we have observed that the indications set forth in the foregoing

list are practical and rational. With reference to ailments in our first group of patients, we have treated advanced cases of carcinoma of the tongue (Fig. 1), and principally of its base, lesions of the gums affecting the fauces, and lesions of the floor of the mouth and tonsils. In the same group, we have observed good results in the treatment of carcinoma of the hypopharynx (Fig. 2). Reactions of the mucosa of the upper respiratory and digestive tract have been noteworthy, but the patients withstand them better than those produced by X rays. Likewise, recovery of the mucosa is better because its condition after healing is practically normal even with regard to its elasticity and moisture content. The skin and the subcutaneous tissue react less and do not lose elasticity; moreover, they present a more normal appearance after treatment.

With respect to reactions of the second group, the progress and results ran parallel to those of the first group. Since the lesions were located deeper in the body, the use of telecobalt was advisable. In this group we have had remarkable success, principally with cancer of the lung (Fig. 3) and bladder (Fig. 4). In cases of lung cancer, patients during the first week or part way through the treatment, were relieved from development of certain symptoms of illness such as pain, cough and hemoptoic sputum. Further, we have noted that the patients undergo treatment without nausea which is so frequent when deep radiotherapy is used; actually they gained weight during the course of the applications. As indicated already, we used telecobalt for advanced cases of cancer of the uterine cervix as an exclusive therapeutic element and as an adjunct to radium; we have done this in order to irradiate the parametrium and pelvic walls of the patients having more than 18 cm pelvic diameter. Good results have been obtained in advanced cases with primary lesions in the vagina where treatment with radium was not possible.

We have also had some similar experience with advanced carcinomas of the anus and even anu-rectal lesions.

Referring to ailments of the third group, we have preferred to irradiate practically all cerebral (intracranial) tumors with telecobalt because beyond obtaining a better dose with a more homogeneous distribution, bones of the skull absorb less radiation than is the case with conventional radiotherapy. The inoperable glands secondary to carcinomas or adenocarcinomas (deep as well as superficial) have responded very well to telecobalt therapy, and, in general, the symptomatologies provoked are smaller or disappear quickly.

In connection with those in the fourth group, we have had experience with advanced cases of cancer of the pelvis previously treated with radiation, and with debilitated patients having abdominal tumors. For the first type, although the course of treatment is more difficult, the results have been more lasting. For the latter, the results depend upon the histological cell type, extension of the lesion, and general condition of the patient. However, after taking into account the results obtained with telecobalt, we are changing toward selection of more advanced cases, thus becoming more interventionists—that is to say, we are

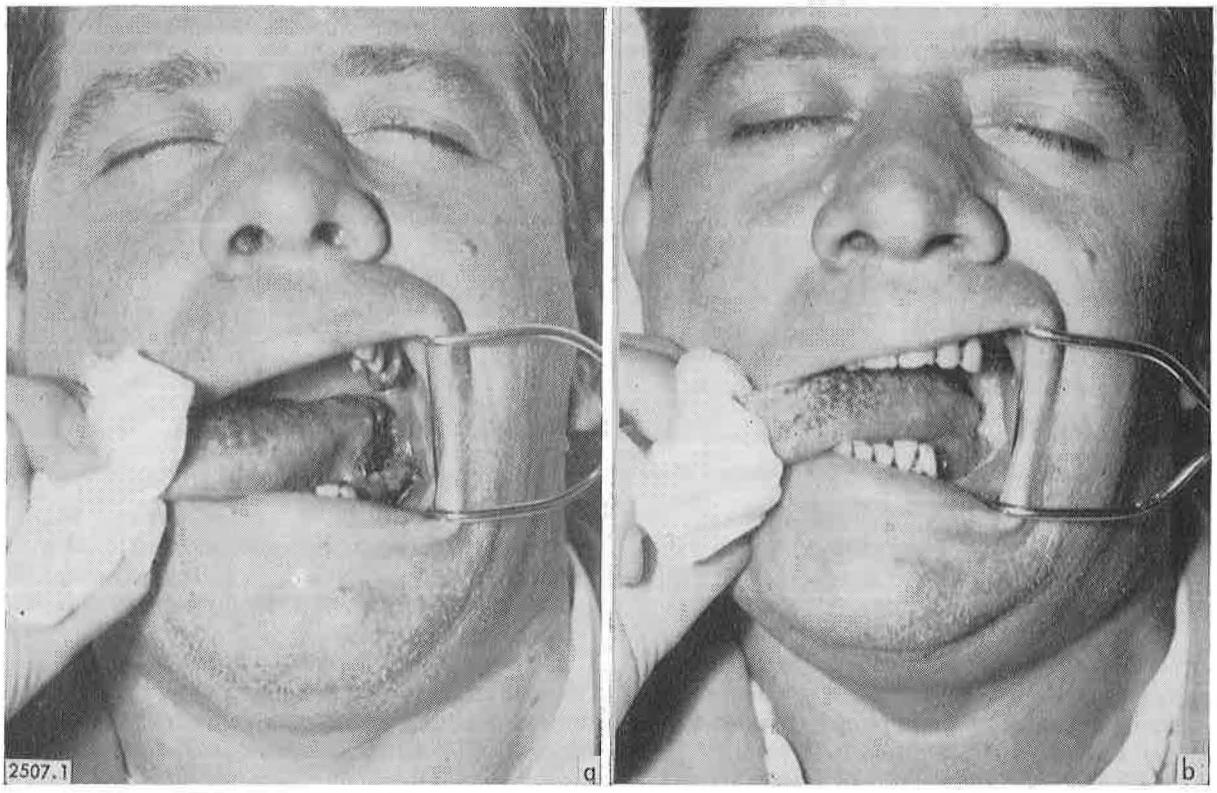

Figure 1. Carcinoma of the base of the tongue; (a) before the treatment, and (b) after treatment, showing the scar

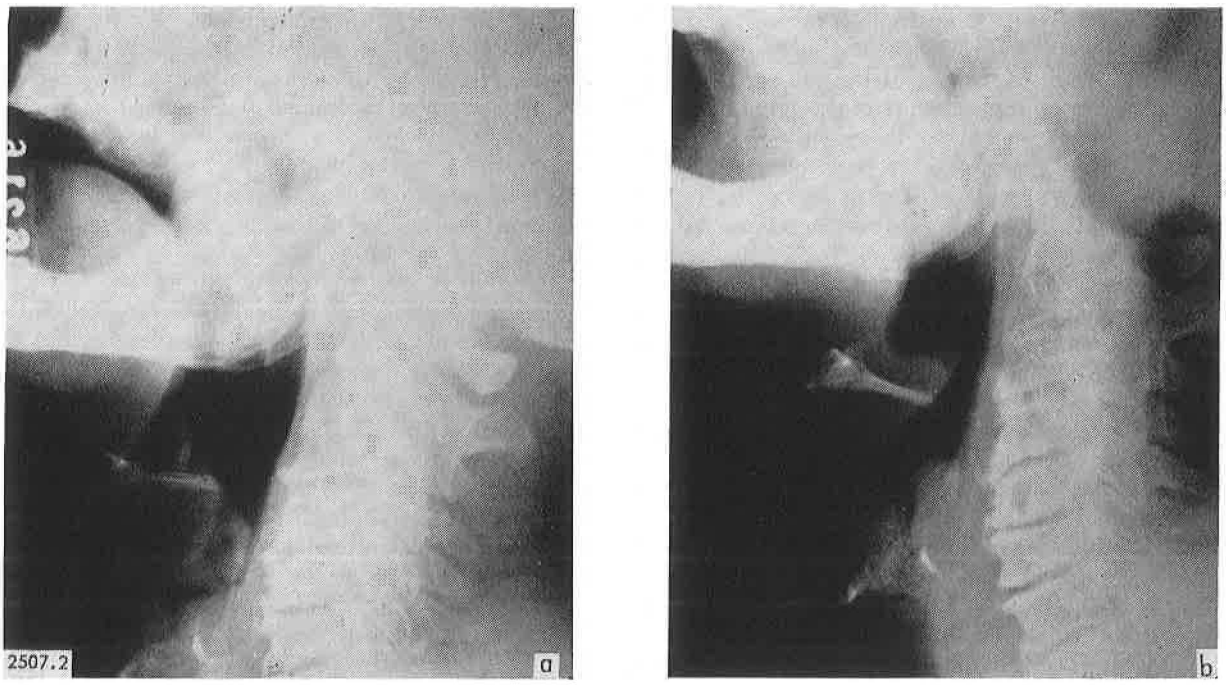

Figure 2. Carcinoma of the vestibular face of the epiglottis; (a) before treatment, and (b) after treatment

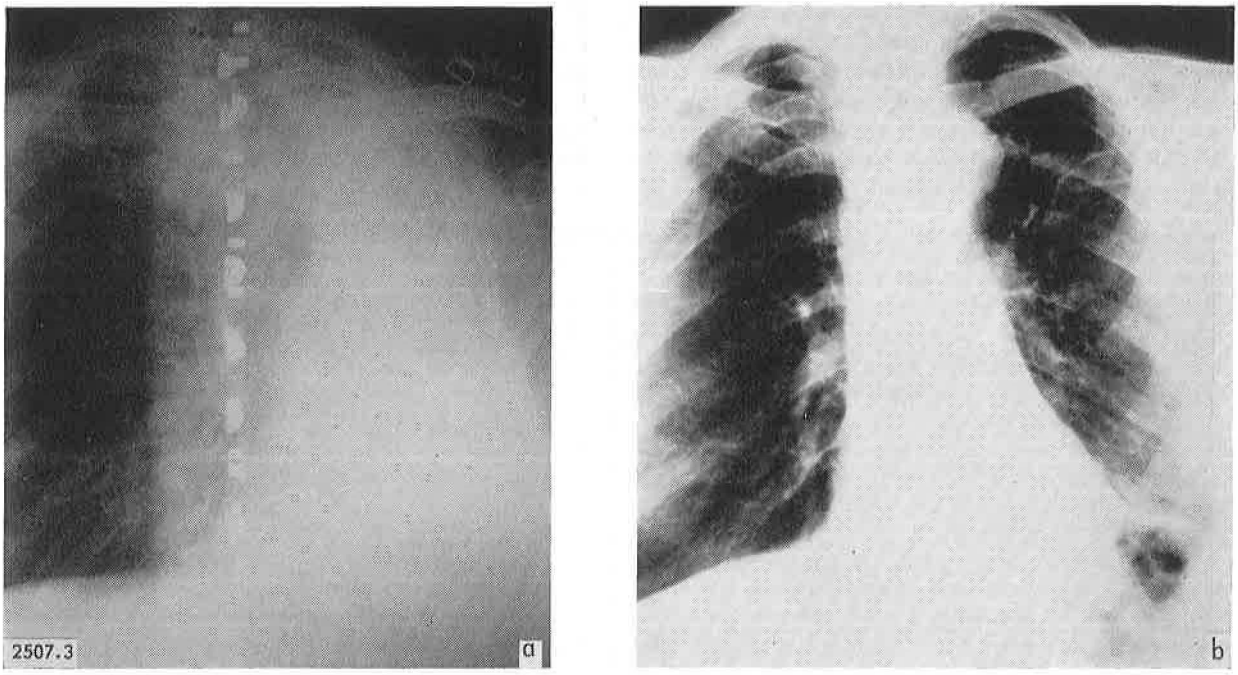

Figure 3. (a) Bronchogenic carcinoma showing total atelectasis of the left lung, and (b) after the treatment, showing normal transparency due to reduction of the tumor

administering palliative treatment to cases which previously we would not have treated.

COMMENTS AND CONCLUSIONS

In conclusion, we desire to confirm that telecobalt therapy has enabled great progress in the treatment of cancer, and that the results obtained are more favorable than those obtained heretofore.

With advance in the knowledge of physics, came the necessity of employing machines capable of generating radiation of ever increasing energy. However, the routine use of radiation of high energy became possible only with the advent and employment of radioactive isotopes in teletherapy.

Supervoltage radiotherapy presents certain advantages over conventional radiotherapy, such as: (1) increase of depth-dose percentage, (2) relatively smaller skin dose, (3) better geometric definition of radiation beam, and (4) less bone absorption. On the other hand, such radiations have the disadvantage of increasing

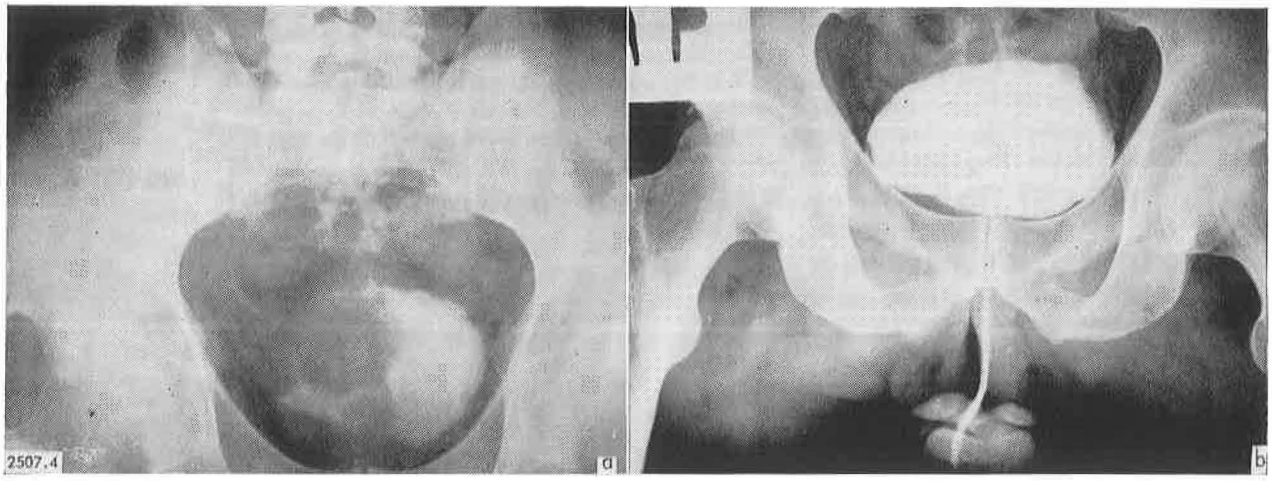

Figure 4. Carcinoma of the bladder; (a) before treatment, and (b) at the conclusion of treatment

the skin dose on the exit region of the radiation beam.

The radioisotope source in order to be valuable in clinical teletherapy should fulfill various conditions: (1) emit gamma radiation of high energy, (2) have a substantial half-life period, (3) have high specific activity, and (4) be available in abundance at accessible cost.

Teletherapy units are composed of one head having the radioactive source, and obturation system, and a collimation system. The head is provided with various movements, including vertical, to facilitate positioning of the patient towards the treatment.

Theoretically, the indications for employment of teletherapy are the same as those for deep-seated tumors but every day we are amplifying them due to the excellent results being obtained.

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Biochemical Applications of Large Radiation Sources with Special Reference to Pharmaceutical Products

By T. Horne*

This work was carried out jointly by the organizations listed below and the Isotope Division of AERE. Its object was to make a brief survey of the effects of radiation, at a sterilizing dose, on a range of pharmaceutical products in current use. The samples were generally taken from the normal production line, with no special requirements for purity. Details of the assay techniques are given in only a few instances. They are all to be found in the latest issues of the British Pharmacopoeia[1] and the British Pharmaceutical Codes.[2]

IRRADIATION CONDITIONS

The irradiations were all carried out at room temperature (15–25°C) using gamma radiation from a cobalt 60 source. This consisted of four rods, arranged at the corners of a square.[3] The samples were packed in a cylinder which was rotated in the centre of this arrangement. The mean dose rate under these conditions as measured, using a ferrous sulphate dosimeter, was 140,000 rad/hr. By placing dosimeters at different points within the cylinder, it was found that the maximum range of dose was less than $\pm 5\%$ of the mean. Two dose levels were used; a low level of 2.5×10^6 rad and a high level of ten times this (25×10^6 rad). These levels were fixed after it had been shown by preliminary work with freeze dried suspensions of several different types of micro-organism, that heavily contaminated samples were not inactivated with a dose of 2.0×10^6 rad. *Bacillus subtilis* was the most resistant organism used, with *Staphylococcus aureus*, a *Penicillium* species and *Pseudomonas pyocanea* progressively more sensitive. Other work with *Bacillus anthracis* and *Clostridium tetani* showed that their resistance to radiation was similar to that of *Bacillus subtilis*.

The levels of contamination used in this study were much higher even than those likely to occur accidentally during normal processing. Since the radiation killing is an exponential process, less heavily contaminated samples would be inactivated more readily. However, the view was taken that if radiation were to take its place as a recommended method of sterilisation, it will have to be used at such a level that the most heavily infected samples will be rendered sterile, with a certain margin of safety. Although in other reports[4–7] a dose of 2.0×10^6 rad has been used, it may be noted that in work on food irradiation,[8] a dose of 4.8×10^6 is suggested as necessary if normal standards of safety are to be achieved.

ANTIBIOTICS

Previous workers had reported that several antibiotics were little affected by 2.0×10^6 rep. In the present study, the effects of higher levels of radiation on different forms of penicillin, streptomycin, polymyxin and bacitracin were studied.

The compounds were irradiated as a powder, except where indicated otherwise, and were assayed microbiologically by the standard methods. It will be seen from the Tables 1a–1c that in general, 2.5×10^6 rad caused little loss in potency, though in several cases the irradiated solid was a pale yellow and this colour persisted in aqueous solution.

This colouration became more marked at 25×10^6 rad and many powders and solutions were brown in colour. Even so, the loss in potency is still small, frequently within the limits of experimental error.

ORGANO-METALLIC COMPOUNDS

Mersalyl acid was irradiated as the free acid and as the sodium salt. Both were dry white powders before irradiation. The free acid (organically bound mercury 41.2%) gave a colourless 5% solution in 0.5% NaOH and no trace of mercuric salts could be detected before irradiation.

After 2.5×10^6 rad, the powder was a grey brown colour, with an odour of charring. The assay for 'organic' mercury was only 22.5%, that is, a 48% loss. It gave a yellow solution in caustic soda and left an insoluble deposit of free mercury. Mercuric salts could be detected in solution.

After 25×10^6 rad, the powder was nearly black in colour and the odour of charring was more pronounced. The solution in caustic soda was yellow brown and there was an even greater insoluble fraction.

The sodium salt behaved similarly when exposed to radiation. When irradiated as a 10% aqueous solution mersalyl was rather more resistant to radiation. There was a small amount of precipitated matter (<10% of the original solid content) at the lower level of irradiation, and the assay for organically bound mercury

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Irradiated Antibiotics. Table 1a

Product	*Assay*	*Appearance before irradiation*
Penicillin V (phenoxymethyl penicillin free acid)	100%	Off-white powder, solution in aqueous sodium bicarbonate, clear and colourless
Penicillin G (sodium benzyl penicillin)	1,660 units/mg	White powder, aqueous solution clear and colourless
Benzathine penicillin (solid)	650 units/mg	White crystalline powder, aqueous solution clear and colourless
Aqueous suspension	282,000 units/ml	White suspension
Neomycin sulphate	666 γ/mg	White powder aqueous solution clear and colourless
Polymyxin sulphate	6,940 units/mg	White crystalline powder
Streptomycin sulphate	742 units/mg	White powder, aqueous solution clear and colourless
Dihydrostreptomycin	750 units/mg	White powder, aqueous solution clear and colourless
Zinc bacitracin	65.6 units/mg	Pale cream powder

Table 1b

Product	*2.5 × 10⁶ rad*	
	Assay	*Appearance*
Penicillin V (phenoxymethyl penicillin free acid)	99%	Off-white powder, solution in aqueous sodium bicarbonate, clear and pale yellow
Penicillin G (sodium benzyl penicillin)	1,650 units/mg	Off-white powder, aqueous solution clear and colourless
Benzathine enicillinp (solid)	640 units/mg	Off-white crystalline powder, aqueous solution clear and colourless
Aqueous suspension	284,000 units/ml	Off-white suspension
Neomycin sulphate	639 γ/mg	Aqueous solution very pale yellow
Polymyxin sulphate[a]	7,960 units/mg	Faintly off-white crystalline powder
Streptomycin sulphate	720 units/mg	Cream powder, aqueous solution, clear and pale yellow
Dihydrostreptomycin	759 units/mg	White powder, aqueous solution clear and colourless
Zinc bacitracin	60.94 units/mg	Pale cream powder

[a] Chromatography of hydrolyzed and unhydrolyzed materials before and after irradiation showed no abnormal spots, in butanol, acetic acid, water 4:1:5.

Table 1c

Product	*25 × 10⁶ rad*	
	Assay	*Appearance*
Penicillin V (phenoxymethyl penicillin free acid)	97%	Brown powder, solution in aqueous sodium bicarbonate clear and brown
Penicillin G (sodium benzyl penicillin)	1,611 units/mg	Buff coloured powder, aqueous solution clear and pale brown
Benzathine penicillin (solid)	630 units/mg	Pale cream crystalline powder, aqueous solution clear and off-white
Aqueous suspension	279,000 units/ml	Cream suspension
Neomycin sulphate	644 γ/mg	Aqueous solution orange
Polymyxin sulphate[a]	9,136 units/mg	Cream crystalline powder (definite caramel odour)
Streptomycin sulphate	706 units/mg	Brown powder, aqueous solution clear and brown
Dihydrostreptomycin sulphate	711 units/mg	Pale brown powder, aqueous solution clear pale brown
Zinc bacitracin	48.1 units/mg	Cream powder

[a] Chromatography of hydrolyzed and unhydrolyzed materials before and after irradiation showed no abnormal spots, in butanol, acetic acid, water 4:1:5.

was >90% of the original value. However, pH of the solution had fallen by about one unit. At the higher level of irradiation, the breakdown was more marked, approximately 50% of the organically bound mercury being liberated.

Sodium antimonyl gluconate was irradiated as a white granular, odourless powder. A 5% aqueous solution of the untreated compound was clear and colourless, pH 6.1, and was stable for at least two hours at room temperature.

After high level irradiation, the powder was buff coloured, and was off-white after 2.5×10^6 rad. It had a caramel-like odour, even at the lower level. At both levels, the aqueous solution was discoloured, and became colourless and opalescent within a few minutes of being prepared. At the higher level, marked precipitation occurred.

Vitamin B12 was irradiated as a dilute aqueous solution of cyanocobalamin. The potency was reduced almost to zero, even at the low level of irradiation as is shown in Fig. 1.

It will be seen that all the organo-metallic compounds examined were very adversely affected by radiation. None of them was in an acceptable condition after 2.5×10^6 rad and none could have been used therapeutically.

ALKALOIDS

Morphine sulphate was irradiated both as a dry powder and as an injection solution (1.5% in water).

Both powder and solution changed colour on irradiation, passing from a pale lemon at 2.5×10^6 rad to a bright yellow at 25×10^6 rad. However, a solution prepared from the irradiated powder was clear, as was the irradiated solution. In neither case was a significant change in the pH noted. No loss of potency could be detected in the irradiated solution, but there was a slight fall in its optical rotation.

After irradiation the solid salt showed a fall in anhydrous morphine content (84% initially, falling to 82% at the low level, and 81.5% at the high level of irradiation) with an increase in the amount of other alkaloids. The pH of solutions prepared from untreated samples fell from 4.6 to 4.4 to 4.3.

Atropine sulphate also was irradiated both as a dry powder and as an injection solution. The dry salt was slightly but progressively discoloured, and solutions

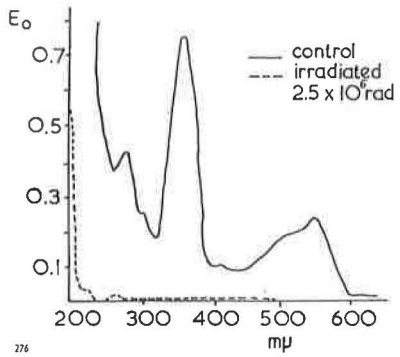

Figure 1. Injection of cyanocobalamine B.P.

prepared from the irradiated solid although clear were off-white. The melting point of the dried solid fell from 193°C for the untreated samples to 191°C at 2.5×10^6 rad and 189°C at 25×10^6 rad.

Even after 2.5×10^6 rad, some indication was obtained for the presence of apo-atropine in the sample. The irradiated injection solutions of atropine sulphate discoloured and showed a complete loss in potency even at 2.5×10^6 rad.

Ergometrine maleate before irradiation was a faintly greyish white powder. A 2% aqueous solution was colourless and showed a blue fluorescence under ultraviolet light. Its melting point was 195–196°C with slight decomposition. Even after 25×10^6 rad, the assay, determined by UV absorption or colorimetrically with dimethylamine benzaldehyde was virtually unchanged. No trace of ergometrinine could be shown by chromatography. At both levels of irradiation the melting point was slightly reduced. A 2% solution in water of the salt irradiated at 2.5×10^6 rad was yellow in colour and faintly opalescent, at 25×10^6 rad it was a greenish brown colour with a flocculent, insoluble deposit. Both solutions still gave a blue fluorescence under UV, but had a slightly elevated pH.

When irradiated in solution (0.125 mg/ml sealed under nitrogen) the changes were more marked. Even at 2.5×10^6 rad, the colorimetric assay showed only 10–20% of the original activity, and at neither level did the solution exhibit any blue fluorescence with UV. It is interesting, that even with such marked degradation as shown colorimetrically the UV adsorption figures for both the irradiated solutions were still about 75% of the control values. Chromatography showed no trace of either ergometrine or ergometrinine. The pH of the solution had risen from 3.1 control to 4.8 at 2.5 and 5.6 at 25×10^6 rad. The irradiated samples passed the B.P. test for toxicity.

STEROIDS AND OTHER COMPOUNDS

Progesterone was markedly resistant to irradiation. The adsorption at 241 m was virtually unchanged even after 25×10^6 rad. The same is true of the rotation and melting point. The colour of the highly irradiated material however, was a bright yellow and it had a markedly resinous odour.

Heparin was irradiated as a freeze dried powder, and its activity determined by a standard clotting test,[9] and by a modification of the toluidine blue test.[10] There was a progressive loss in biological potency as the irradiation dose increased (Table 2). This, as expected, was greater than the loss shown by the toluidine blue test. The latter always tended to give a higher value than the clotting test with samples of heparin which were depolymerised or otherwise damaged.

The loss in activity when the heparin was irradiated in solution was more marked. Injection solutions of *insulin* and *protamine zinc insulin* were both irradiated. The combined form was slightly more resistant, but in both cases, there was marked degradation.

Table 2. Irradiated Heparin

Irradiation dose	*Clotting test*	*Loss %*	*Toluidine blue test*	*Loss %*
		Solid		
0	112.3 units/mg	0	116 units/mg	0
2.5×10^6 rad	110.5 units/mg	1.6%	114 units/mg	1.7%
25×10^6 rad	84.0 units/mg	25.2%	97.5 units/mg	16.0%
		Solution		
0	5020 units/ml	0	5355 units/ml	0
2.5×10^6 rad	4370 units/ml	13%	4972 units/ml	7.2%
25×10^6 rad	857 units/ml	82.9%	3240 units/ml	39.5%

After 2.5×10^6 rad, with protamine zinc insulin the assay was reduced to 10% of the initial value, and after 25×10^6 rad to less than 2%. With the free protein, less than 2.5% survived even the low irradiation.

The effects of irradiation upon *talc* (a purified native magnesium silicate) were also studied. The colour and alkalinity of the solid were unaffected but a significant increase in acid soluble matter was recorded. This substance was included in the work, because it is one of the few substances of which any great weight is used in the pharmaceutical industry.

COST

Since large scale sources of fission products are not yet available, only an approximate and generalized estimate of the cost of a gamma irradiation unit can be given.

We are at present assuming that Cs^{137} will be used as the source of radiation and that its cost, when first available in megacurie quantities, will be about 10 shillings per curie. Then, for a source capable of irradiating 200 lbs/hour with a dose of 2.5×10^6 rad, that is, 1.6×10^6 lbs in a year if in operation 24 hours a day for 350 days, we shall require approximately one megacurie of Cs^{137}.

This further assumes that it will only be possible to utilize some 20% of the radiation emitted by the caesium. With improved source design and standardized packages, this figure could be improved, possibly even doubled, with a consequent reduction in the amount of caesium required and hence in the cost. Owing to its long half life, a caesium source will only require replacement at an average rate of 2.5% per annum. If to this, we add 6%, being the rate of interest on the capital investment, we reach an annual source cost of 8.5% of the initial outlay. At 10 shillings per curie, this is about £42,000 per annum for a one mega curie source or 6 pence per pound of material irradiated. If in the long term it proves possible to reduce the cost of Cs^{137} substantially, this cost would fall in proportion. Thus, if as has been suggested in other countries that the equivalent of 1 shilling per curie might be reached, the cost of radiation would then be reduced to 0.6 pence per pound per 2.5 Mrad.

So far we have considered only the cost of the radiation itself. To this must be added a handling charge, to cover the depreciation of the shield and the conveyor system used to carry the products into the irradiation space, labour costs and overheads.

An accurate assessment of these figures is only possible in specific instances. As a rough generalization, however, we may take a figure of 2.5 pence per pound. This gives a total cost for the irradiation unit of 8.5 pence for every pound of material treated, a figure which should certainly not be exceeded, since the assumptions made have tended to be conservative.

CONCLUSIONS

It will be seen that in this study, the degradation brought about by 2.5×10^6 rad is in several instances sufficient to render radiation sterilization unattractive at first sight. It is worth while, however, to give further consideration to the use of radiation in those cases where existing methods of sterilization are unsatisfactory and as new products are developed.

The cost of the process is likely to exclude its use as an added stage in processes where aseptic handling techniques are now in operation. However, if the price of caesium falls sufficiently low, this position may change.

It is felt that the early uses for radiation in the pharmaceutical industry may well be for the sterilization of synthetic high cost, low volume lines, where present methods are inapplicable, and of bulky items like talc and dressings.

This programme was carried out in collaboration with a working party set up by the Association of British Pharmaceutical Industry, the following companies taking part in the investigation: Abbott Laboratories Ltd., Allen & Hanburys Ltd., Boots Pure Drug Co. Ltd., The British Drug Houses Ltd., Burroughs Wellcome & Co., The Distillers Company (Biochemicals) Ltd., Evans Medical Supplies Ltd., Glaxo Laboratories Ltd., Imperial Chemical Industries Ltd., May & Baker Ltd., Paines & Byrne Ltd., and John Wyeth and Brother Ltd. The Department of Pharmaceutics, University of London also co-operated in the work.

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Principles of Using Ionizing Radiation in the Production of Bacterial Preparations

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Some suggestions have been made regarding the cold sterilization of antibiotics.[1,2] But, apart from general statements, the present authors do not know of any data dealing with the possible use of ionizing radiation in the production of protective vaccines and medical sera.

Ionizing radiation may be used in the manufacture of bacterial preparations in a number of ways. First of all, the use of radiation for cold sterilization should be borne in mind. Sterilization is the essential feature of any technological process for the production of bacterial preparations. It is done either in autoclaves by superheated steam under pressure, or at high temperature in dry-heat chambers, or, lastly, by the addition of antiseptics.

The possibility of sterilizing preparations already sealed in air-tight packages or ampoules opens up prospects of an improved and more reliable method of sterilization, as compared with the methods at present in use.

Moreover, the use of radiation sterilization in the production of bacterial preparations may affect the quality of the preparation and, perhaps, eliminate the harmful effects of, for example, formalin or heat when these are used for sterilizing vaccines.

The following materials have to be sterilized in the bacteriological industry and in bacteriological research: nutrient media for growing bacteria, killed microbic vaccines, the so-called "chemical" vaccines—i.e., combinations of antigens, extracted from the bodies of microbes—toxoids, medical sera, the glassware widely used in bacteriological operations and, finally, waste products from the bacteriological industry, which must be rendered harmless, for which purpose several large autoclaves are in constant use at large institutions.

The starting point for development of a method of radiation sterilization which would answer all the above needs is determination of the bactericidal dose of gamma rays which will kill not only vegetative forms of bacteria, but spore-bearing microbes as well. In the methods for cold sterilization of dressings and penicillin suggested by American workers, $1.5–2 \times 10^6 r$ have been suggested as a sterilizing dose.

Original language: Russian.

An experimental gamma-radiator was used in our tests as the source of radiation. It consisted of a combination of preparations of radioactive cobalt (Co^{60}) with a total activity of 5000 c (8000 gram-equivalents of radium). The dose rate was $600r$/min. Irradiation was carried out in a field of uniform volume, with a drop not exceeding 5%. Temperature in the irradiation chamber varied from 13°C to 15°C.

It was found that under such conditions, even when sterilizing samples of soils, including manured ones containing particularly resistant spore-bearing forms of microbes, irradiation with $1.5 \times 10^6 r$ was sufficient to ensure sterility. A smaller dose of $10^6 r$ kills the overwhelming majority of such microbes, but about 0.01% of them, apparently the most radioresistant, preserve their vital activity. At the same time, experiments have proved that a dose of $0.6 \times 10^6 r$ is enough to kill bacteria of the intestinal group even when the concentration of bacteria in a suspension is as high as 30 to 40×10^9 microbe bodies per ml.

Photographs taken with the electron microscope show that the bactericidal effect of large doses of gamma rays is related to the destruction of the cells of the microbes—their lysis—a process which does not, however, deprive them of their immunogenic properties (Fig. 1).

Some experimental data are presented below to prove the principles of using ionizing radiation in the production of bacterial preparations. Our study was carried out along those biological and immunological lines which are of primary importance in appraising the properties of the preparations in question.

THE USE OF RADIATION FOR STERILIZING NUTRIENT MEDIA

Hottinger's agar, based on the products of the tryptic digestion of meat, is one of the best-known nutrient media used in medical bacteriology. The prepared medium was divided into three portions: the first was subjected to ordinary sterilization in an autoclave at 120°C, the second was irradiated with a dose of $1.5 \times 10^6 r$ after treatment in an autoclave, and the third was sterilized directly by irradiation with the same dose.

The irradiated media emitted an unpleasant putrid odour which gradually disappeared in the course of a few days. The sterilized media were tested after 1, 7

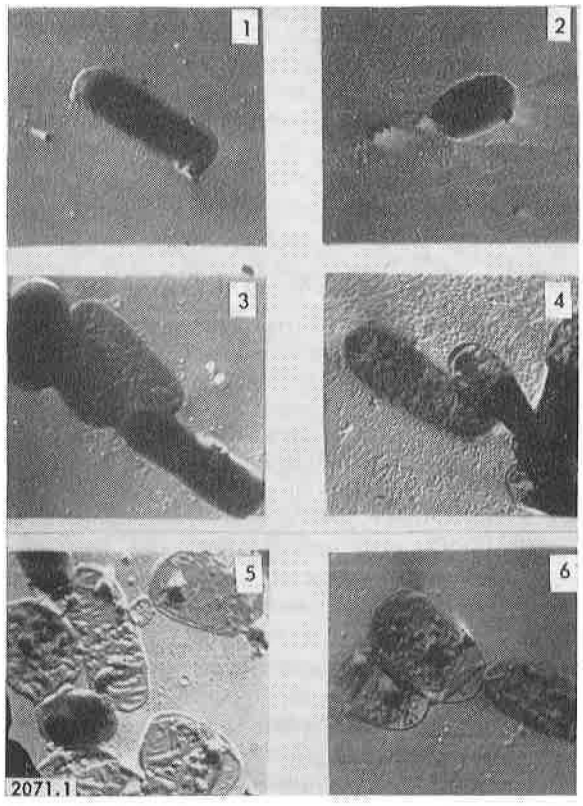

Figure 1. Electronphotomicrographs showing the effect of γ-rays on *B. coli* (×6400). 1 and 2: non-irradiated; 3 to 6: irradiated; (3: with a dose of 0.5 × $10^6 r$; 4: with a dose of 3 × $10^6 r$; and 5 and 6: with a dose of 1 × $10^6 r$)

and 14 days, the following cultures being inoculated into the media in open Petri dishes: two strains of typhoid bacteria and two strains of Flexner's dysentery bacteria, equal amounts of the same bacterial suspension being used for the purpose. The number of colonies which grew in the dishes after 24-hour incubation in a thermostat at 37°C was then determined.

As will be seen from Fig. 2, in which the number of colonies that grew in the medium sterilized by autoclaving alone has been taken as 100%, the number of colonies which grew in the irradiated media invariably exceeded that of the colonies growing in the autoclaved medium. In some cases the difference was very considerable, amounting to 180–200%.

Thus, far from weakening the nutrient properties of meat media for the intestinal group of bacteria, irradiation actually enhanced them to some extent.

It was also important to establish whether irradiation of a broth prevents the formation in it of the diphtheria toxin which forms the starting point for the preparation of diphtheria toxoid. Experiments have shown that the amount of toxin formed in the medium irradiated even with a dose of 1.5 × $10^6 r$ is not less, but usually even more, than that formed in media sterilized in the autoclave (Fig. 3). Moreover, no change was observed either in the nitrogen (total, protein or amino) or amino acid or polypeptide contents of the medium, or in its pH value (Table 1).

THE EFFECT OF RADIATION ON THE ANTIGENIC AND IMMUNOGENIC PROPERTIES OF BACTERIA

Only scanty data exist on the effect of ionizing radiation on the antigenic and immunogenic properties of bacteria.[3,4]

To study the properties of vaccines and antigens from irradiated microbes, we prepared dysentery and typhoid vaccines and the corresponding antigens from bacteria killed by irradiation.

We irradiated with a dose of 1.5–2 × $10^6 r$ a washing of one-day agar culture (28–70 × 10^9 microbe bodies per ml of a physiological solution of common salt) of typhoid or dysentery bacteria in 100–200 ml glass phials or in litre flasks. The dose was undoubtedly bactericidal, and no growth was recorded on inoculation from the bottles in which the microbe culture washing had been irradiated. From the microbe culture thus killed we prepared a vaccine ("radiovaccine") with a fixed concentration of bacterial bodies per ml, or extracted the complex of immunogenic polysaccharide protein ("radioantigen").

To assess the quality of the preparations thus obtained, their antigenic and immunogenic properties were tested, as well as their capacity to preserve the Vi-antigen and toxicity.

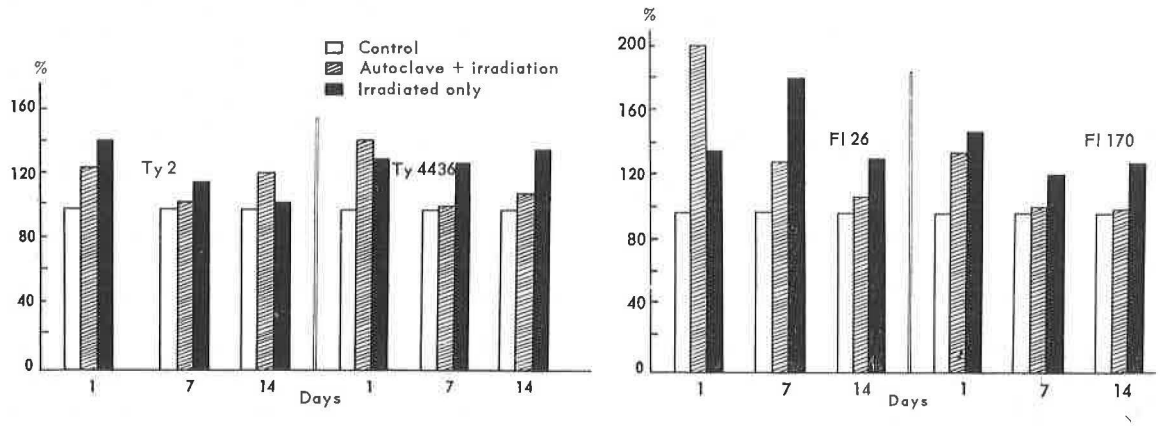

Figure 2. Left: colony growth of two strains of typhoid bacteria in Hottinger's agar irradiated with a dose of 1.5 × $10^6 r$; right: colony growth of two strains of Flexner's dysentery bacteria in Hottinger's agar irradiated with a dose of 1.5 × $10^6 r$; 2: key

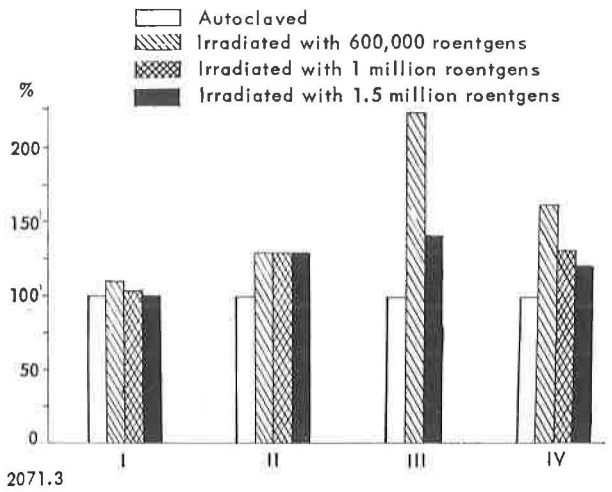

Figure 3. 1: Diphtheria toxin obtained in a series of tests (I–IV)

The toxicity of the preparations was determined by the death rate of animals (mice and rats) after endoabdominal and hypodermic injections of various doses (0.5 ml for the mice and 1 ml for the rats) of the preparations under investigation, as well as by the skin reaction of rabbits to intracutaneous administration. The toxicity of ordinary formalinized and heated vaccines was compared with that of vaccines prepared from microbes killed by irradiation ("radiovaccines") and with that of ordinary formalinized vaccines irradiated for purposes of sterilization. In determining the toxicity of the polysaccharide protein antigens, other antigens prepared from the following materials were also studied: formalinized microbes, living cultures of microbes, microbes killed by irradiation, and antigens prepared from formalinized microbes and then sterilized by irradiation. As can be seen from Table 2, the radiovaccines or irradiated formolvaccines did not differ in toxicity from ordinary formalinized vaccines.

The toxicity of typhoid vaccines was also investigated by the skin reaction of rabbits. The vaccines were injected intracutaneously.

As compared with the reaction provoked by the injection of ordinary vaccines, the reaction following the injection of radiovaccines was characterized by the delayed appearance of infiltration, its smaller extent, and the absence of necrosis.

The toxicity of the fluid part of the vaccine was also investigated in the experiments on the intracutaneous injection on rabbits. These experiments showed that the fluid part of radiovaccines caused no infiltration, whereas the fluid part of vaccines prepared by the traditional method was responsible for the formation of a dense area of infiltration of considerable extent, which did not disappear during a period of one week. This justifies the conclusion that radiovaccines are less capable of producing a reaction than heated or formalinized vaccines.

Table 1. Effect of Radiation on Marten's Nutrient Broth

Experiment No.	*Treatment*	*pH*	*Nitrogen, mg %*			*Amino acids and polypeptides, mg %*	
			Total	*Protein*	*Amino*	*Amino acids*	*Polypeptides*
I	Non-irradiated	7.6	473.0	12.4	91	30.56	66.08
	Irradiated with $0.6 \times 10^6 r$	7.5	476.0	10.9	97	—	—
	Irradiated with $1.5 \times 10^6 r$	7.5	465.0	12.4	98	34.86	68.18
II	Non-irradiated	7.9	453.6	6.58	94.5	27.04	75.52
	Irradiated with $0.6 \times 10^6 r$	7.9	456.4	6.86	94.5	27.04	75.52
	Irradiated with $1.5 \times 10^6 r$	7.9	455.0	6.58	94.5	27.04	75.52
III	Non-irradiated	8.0	359.8	—	95.2	34.86	78.68
	Irradiated with $0.6 \times 10^6 r$	8.0	357.6	—	93.8	34.86	78.68
	Irradiated with $1.5 \times 10^6 r$	7.9	357.0	—	93.1	34.86	78.68
IV	Non-irradiated	7.6	—	—	88.2	33.04	79.24
	Irradiated with $0.6 \times 10^6 r$	7.6	—	—	88.2	29.36	78.54
	Irradiated with $1.5 \times 10^6 r$	7.6	—	—	88.2	29.36	75.04
V	Non-irradiated	7.7	—	—	94.5	43.96	80.08
	Irradiated with $0.6 \times 10^6 r$	7.7	—	—	94.5	41.72	81.20
	Irradiated with $1.5 \times 10^6 r$	7.7	—	—	95.9	41.72	81.20

Table 2. Toxicity of Radiovaccines

Animal	*Experiment No.*	*Preparation*	*Irradiation dose* $r \times 10^6$	*Dose of vaccine, microbe bodies* $\times 10^9$	*Number of animals*		
					Total	*Survived*	*Died*
Mice	1	Flexner's formolvaccine No. 4437	—	2	15	14	1
		Flexner's radiovaccine No. 4437	1	2	15	13	2
	2	Flexner's formolvaccine No. 26	—	2	15	14	1
		Flexner's radiovaccine No. 26	0.5	2	15	14	1
	3	Formolvaccine Ty_2	—	2	15	13	2
		Irradiated formolvaccine Ty_2	1.7	2	15	14	1
	4	Heated vaccine Ty_2	—	2	40	23	17
		Formolvaccine Ty_2	—	2	40	9	31
		Radiovaccine Ty_2	1	2	40	25	15
		Radiovaccine Ty_2	1.5	2	40	32	8
	5	Heated vaccine Ty_2	—	2	40	28	12
		Formolvaccine Ty_2	—	2	40	35	5
		Radiovaccine Ty_2	1	2	40	38	2
		Radiovaccine Ty_2	1.5	2	40	36	4
Rats	6	Heated vaccine Ty_2	—	4	15	15	0
		Formolvaccine Ty_2	—	4	15	14	1
		Radiovaccine Ty_2	1	4	15	12	3
		Radiovaccine Ty_2	1.5	4	15	14	1
	7	Heated vaccine Ty_2	—	4	15	11	4
		Formolvaccine Ty_2	—	4	15	12	3
		Radiovaccine Ty_2	1	4	15	15	0
		Radiovaccine Ty_2	1.5	4	15	14	1

A number of experiments were devoted to checking the anaphylactogenic properties of the prepared vaccines. Formolvaccines and vaccines from microbes killed with a dose of $1.5 \times 10^6 r$ provoked a reaction accompanied by necrosis (the Sanarelli-Schwarzman phenomenon), provided the test was carried out during the first month following the preparation of the vaccines. If, however, the vaccines were tested two months or more after their preparation, neither the radiovaccines nor those prepared by the usual methods provoked the Sanarelli-Schwartzman reaction.

When the toxic properties of antigens prepared from microbes killed by irradiation were tested, it was found that radioantigens are less toxic than antigens prepared from formalinized microbes or from microbes which had not been killed before the antigen was prepared (Table 3). If, however, an antigen prepared from formalinized microbes was irradiated, it differed slightly in toxic properties from the nonirradiated antigen.

The following results were obtained when testing on rabbits the toxicity of polysaccharide protein antigens prepared from typhoid germs. The rabbits received a single intravenous injection of various doses of antigen diluted in 1 ml of saline solution. Three doses—1, 2 and 4 mg—of each preparation were tested, and three rabbits were used for every dose. Not a single rabbit died from 1 mg of radioantigen, but all of them died from 2 or 4 mg. When antigen produced from living microbes was administered, two rabbits died from 1 mg, all the rabbits died from 2 mg, and one of the three rabbits survived from 4 mg. This experiment suggests that the radioantigens made from typhoid microbes did not differ in toxicity from ordinary antigens.

The antigenic properties of radiovaccines were investigated on rabbits. Each group of rabbits (five animals) was immunized three times at 7-day intervals by subcutaneous injection of the vaccine. For the dysentery vaccines, the number of microbe bodies was increased from 5×10^8 at the first injection to 1×10^9 at the second and third injections. For the typhoid injections, the figures were 2.5×10^8 and 5×10^8 for some experiments and 5×10^8 and 1×10^9 for others. The agglutinins were determined in serum prepared from the immunized rabbits after the following intervals: 7 days after the first injection, 7 days after the second injection and 7, 14, 21, 36 and 50 days after the third injection.

No normal antibodies were detected in the sera from the rabbits' blood before immunization. As will be seen from Table 4, both the dysentery and the typhoid radiovaccine led to the formation of antibodies (agglutinins). The average titres of the sera from rabbits immunized with the typhoid radiovaccine hardly differed from the average values found in rabbits immunized with ordinary formol typhoid vaccine. So far as the dysentery radiovaccine was concerned, some increase in the average titres of the sera was recorded as compared to the average titres of sera from rabbits immunized with ordinary formol dysentery vaccine. Thus, the microbes killed by irradiation did not lose their antigenic properties, and the radiovaccines led to the formation of antibodies in the same way as ordinary vaccines obtained from formalinized microbes.

Immunization with the dysentery vaccines was carried out twice, subcutaneously, at an interval of five days. In the first injection the dose was 5×10^8, and in the second 1×10^9, microbe bodies. The animals were infected with different doses of dysentery bacteria endoabdominally seven days after completion

Table 3. Toxicity of Radioantigens

Animal	Experiment No.	Preparation: polysaccharide protein antigen	Irradiation dose, $r \times 10^6$	Antigen dose, mg	Number of animals		
					Total	Survived	Died
Mice	1	From Flexner's formalinized bacteria No. 170	1	1	5	5	0
				2	5	2	3
				4	5	0	5
		From Flexner's irradiated bacteria No. 170	1.5	1	5	5	0
				2	5	4	1
				4	5	1	4
		From Flexner's formalinized and irradiated bacteria No. 170	1.5	1	5	1	4
				2	5	0	5
				4	5	0	5
Rats	2	From Flexner's formalinized bacteria No. 26	—	0.5	5	0	5
				1	5	0	5
				2	5	0	5
		From Flexner's irradiated bacteria No. 26	1.5	0.5	2	2	3
				1	5	1	4
				2	5	2	3
		From Flexner's formalinized and irradiated bacteria No. 26	1.5	0.5	5	2	3
				1	5	0	5
				2	5	0	5
	3	From formalinized typhoid bacteria Ty_2	—	0.5	5	5	0
				1	5	5	0
				2	5	4	1
				4	5	0	5
				6	5	0	5
		From irradiated typhoid bacteria Ty_2	1.5	0.5	5	5	0
				1	5	5	0
				2	5	5	0
				4	5	1	4
				6	5	1	4
		From formalinized and irradiated typhoid bacteria Ty_2	1.5	0.5	5	5	0
				1	5	5	0
				2	5	4	1
				4	5	0	5
				6	5	0	5
Mice	4	From living bacteria Ty_2	—	1	20	17	3
				2	20	16	4
				4	20	8	12
		From Ty_2 microbes killed by irradiation	2	1	20	20	0
				2	20	19	1
				4	20	17	3

Table 4. Formation of Agglutinins with Typhoid and Dysentery Bacteria in the Blood of Rabbits Immunized with Radiovaccines and Ordinary Formolvaccines

Experiment No.	Antigen used for immunization	Average titres of agglutination reactions after various intervals						
		7 days after			Days after third injection			
		1st inj.	2nd inj.	3rd inj.	14	21	36	50
1	Typhoid radiovaccine	1:450	1:4000	1:5600	1:5100	1:1200		
	Typhoid formolvaccine	1:1200	1:5300	1:5300	1:6000	1:1200		
	Flexner's radiovaccine No. 4437	1:900	1:1100	1:3500	1:1400	1:1100		
	Flexner's formolvaccine No. 4437	1:450	1:750	1:1000	1:1150	1:900		
	Heated vaccine Ty_2	1:5120	1:5120	1:10000	1:6000	1:2560	1:2560	1:1120
2	Formolvaccine Ty_2	1:5120	1:5120	1:10000	1:44000	1:5120	1:5120	1:640
	Radiovaccine Ty_2 ($1.5 \times 10^6 r$)	1:2560	1:5120	1:5600	1:5120	1:2560	1:2560	1:640
	Radiovaccine Ty_2 ($1 \times 10^6 r$)	1:2560	1:5120	1:6400	1:8320	1:5120	1:5120	1:1280

Table 5. Immunogenic Properties of Radiovaccines

Vaccine	*Number of mice*	LD_{50}, *in microbe bodies* $\times 10^6$	*Resistance index*
Flexner's dysentery radiovaccine No. 4437 (irradiation with $1 \times 10^6 r$)	50	1000	2.9
Flexner's dysentery formolvaccine No. 4437	50	1060	3
Irradiated typhoid formolvaccine Ty_2 (irradiation with $1.7 \times 10^6 r$)	50	212	4.2
Typhoid formolvaccine Ty_2	50	274	5.4

of immunization. Immunization with the typhoid vaccines was carried out once, subcutaneously, with a dose of 5×10^8 microbe bodies. The immunized mice were infected endoabdominally ten days after injection of the vaccine. The results were evaluated by Reed and Mench's method. The resistance index is the ratio between the dose of microbes required to cause the death of 50% of the immunized mice and that required to cause the death of 50% of the non-immunized controls.

It follows from the data presented in Table 5 that the dysentery radiovaccine does not differ in its immunogenic properties from ordinary formalinized vaccine. For example, the resistance index of the dysentery radiovaccine was 2.9, and that of the formolvaccine 3. When already prepared formolvaccine was irradiated, its immunogenic properties were only slightly impaired by comparison with ordinary non-irradiated formolvaccine (resistance indexes 4.2 and 5.4, respectively).

The second group of experiments comprised tests on typhoid vaccines prepared from microbes of the Ty_2 strain, prepared by various methods: heating, formalinization and killing the microbes with doses of 1×10^6 and $1.5 \times 10^6 r$ respectively. The mice and rats were immunized once, subcutaneously, by the following doses: 5×10^8 microbe bodies in 0.5 ml of saline solution for the mice, and 1×10^9 microbe bodies in the same volume for the rats.

The animals were infected 10 days after immunization with various doses of a live culture of typhoid bacteria in semi-liquid agar. In testing the immunogenic properties, 50 animals were used for each vaccine. The results obtained are given in Table 6.

It should be noted that in this series of experiments vaccination was carried out using the same vaccines, the immunogenic properties being tested at various intervals after the preparation of the vaccines. Thus in experiment No. 1, the test was made three, and in experiment No. 2 four, months after the preparation of the vaccines. It is noteworthy that after storage for four months the immunogenic properties of the radiovaccines were better than those of the heated or formolvaccines. The data presented show that microbes killed by irradiation preserve their capacity to create immunity against infection by living microbes for a longer period than ordinary vaccines.

The same conclusion can be drawn both about antigens prepared from microbes killed by irradiation and about irradiated antigens prepared from formalinized microbes (Table 7).

The rats were immunized with typhoid antigens twice, subcutaneously, at an interval of 7 days. Each injection consisted of 0.25 mg of antigen in 0.5 ml of a physiological solution of common salt. The animals were infected endoabdominally ten days after completion of immunization with various doses of a live culture of typhoid microbes.

The mice were immunized twice, subcutaneously, with dysentery antigens at an interval of 7 days. The same amount of antigen was injected on each occasion, namely, 0.1 mg in 0.5 ml of a physiological solution of common salt. The mice were infected endoabdominally two weeks after completion of immunization with an absolute lethal dose (5×10^8 microbe bodies) of live Flexner's dysentery microbes (strain No. 170). As can be seen from Table 7, the typhoid radioantigens strengthened resistance to living microbes (resistance indexes: 12.8 and 12). The immunity thus created was, however, weaker than that of animals immunized with an antigen made from formalinized typhoid microbes (resistance index: 16). When the mice were infected with an absolute lethal dose of living dysentery microbes, repeated immunization with antigen prepared from microbes killed by formalin was capable of saving the life of 33.4% of the animals. As to the percentage of survivals, immunization with an antigen made from microbes killed by ir-

Table 6. Immunogenic Properties of Radiovaccines

Experiment No.	*Animals*	*Dose of vaccine for immunization, microbe bodies* $\times 10^3$	*Heated vaccine*		*Formolvaccine*		*Radiovaccine* $10^6 r$		*Radiovaccine* $1.5 \times 10^6 r$		*Controls (immunized animals)* LD_{50}, *in microbe bodies* $\times 10^6$
			LD_{50}, *in microbe bodies* $\times 10^6$	*Resistance index*	LD_{50}, *in microbe bodies* $\times 10^6$	*Resistance index*	LD_{50}, *in microbe bodies* $\times 10^6$	*Resistance index*	LD_{50}, *in microbe bodies* $\times 10^6$	*Resistance index*	
1	Rats	1	474	16	400	14	375	13	325	11	28
2	Mice	0.5	2	4	2.44	48	48.7	96	37.7	74	0.5

Table 7. Immunogenic Properties of Radioantigens

Experiment No.	*Antigen*	*Immunization dose, mg*	*Number of animals*	*LD_{50}, microbe bodies $\times 10^6$*	*Resistance index*	*Percentage survival*
1	Polysaccharide protein antigen from formalinized microbes Ty_2	0.5	49 rats	3200	16	—
	Polysaccharide protein antigen from Ty_2 microbes killed by irradiation with $1.5 \times 10^6 r$...	0.5	50 rats	2560	12.8	—
	Polysaccharide protein antigen from formalinized Ty_2 microbes, irradiated with $1.5 \times 10^6 r$.....	0.5	50 rats	2400	12	—
2	Polysaccharide protein antigen from Flexner's formalinized microbes No. 170.....	0.1	48 mice	—	—	33.4
	Polysaccharide protein antigen from Flexner's microbes No. 170 killed by irradiation with $1.5 \times 10^6 r$.....	0.1	46 mice	—	—	43
	Polysaccharide protein antigen from Flexner's formalinized microbes No. 170.....	0.1	47 mice	—	—	38
3	Polysaccharide protein antigen from typhoid bacteria Ty_2....	1.0	80 mice	250	1000	—
	Polysaccharide protein antigen from typhoid bacteria Ty_2 killed by irradiation with $2 \times 10^6 r$.....	1.0	80 mice	275	1131	—

radiation, or with one irradiated after preparation from formalinized microbes, saved the life of an even greater number of animals (43% and 38% respectively).

To determine the ability of a radiovaccine to generate preventive antibodies in the vaccinated organism, rabbits (five in each group) were immunized three times with the vaccine in doses of 5×10^8 and 10^9 microbe bodies at intervals of 7 days. The preventive properties of the rabbit sera were tested one week after completion of immunization: a mixture of sera was injected subcutaneously into the mice, the dose being 0.25 ml, and four hours later the animals were infected endoabdominally with various doses of a living typhoid culture in agar. The doses of microbes required to cause the death of 50% of the animals injected with the serum prior to infection and of 50% of the controls, into which no serum was injected, were then determined.

To determine the ability of the radioantigens to form preventive antibodies in the organism, the rabbits were immunized in the following way: a first injection of 0.1 mg of antigen was given subcutaneously and another six injections intravenously at 5-day intervals, in steadily increasing doses of 0.2, 0.4, 0.6, 0.8, and 1 mg. The preventive properties of the sera were tested two weeks after completion of immunization.

As can be seen from Table 8, the sera obtained by immunization with radiovaccine prepared from microbes killed with a dose of $1 \times 10^6 r$, did not differ in their preventive properties from those obtained by the immunization of the rabbits with a heated vaccine. An increase in the dose of irradiation up to $1.5 \times 10^6 r$ caused a diminution in the capacity of the radiovaccines to generate preventive antibodies in the organism. On the other hand, antigens obtained from microbes irradiated with $2 \times 10^6 r$ did not differ from

Table 8. Preventive Properties of Sera

Experiment No.	*Sera from rabbits immunized with the following preparations*	*LD_{50}, microbe bodies $\times 10^6$*	*Resistance index*
1	Heated typhoid vaccine	20.6	15
	Typhoid radiovaccine ($1 \times 10^6 r$)	17.5	12
	Typhoid radiovaccine ($1.5 \times 10^6 r$)	3.9	2.7
	Controls (untreated animals)	3.12	—
2	Heated typhoid vaccine	60	42
	Typhoid radiovaccine ($1 \times 10^6 r$)	70	50
	Typhoid radiovaccine ($1.5 \times 10^6 r$)	5.6	4
	Controls (untreated animals)	3.12	—
3	Antigen from living typhoid microbes	32	42.6
	Antigen from microbes killed by $2 \times 10^6 r$	32	42.6
	Controls (untreated animals)	0.75	—

Table 9. Determination of Vi-antigen in an Irradiated Culture of Microbes

Antigen	*Solution of Vi-serum*						
	1:2–1:16	*1:32*	*1:64*	*1:128*	*1:256*	*1:512*	*1:1024*
Culture of typhoid microbes Ty_2, irradiated with $1.5 \times 10^6 r$ microbe bodies	+	+	+	+	–	–	–
Ditto—liquid part of the vaccine	++++	++	++	++	++	++	–
Formolvaccine Ty_2—microbe bodies	–	–	–	–	–	–	–
Ditto—liquid part of the vaccine	++++	++++	++	++	+	+	–
Washing of Ty_2 typhoid microbe culture	+	+	+	–	–	–	–
Ditto—liquid part of the washing	++++	++++	++++	++++	++	++	–

ordinary antigens: in both cases the resistance index was 42.6.

The question of preserving the Vi-antigen in radiovaccines is of considerable interest in defining their properties. The effect of irradiation on the Vi-antigen in microbe bodies was determined by means of the hemagglutination reaction.

A washing from the agar of a 24-hour culture of typhoid microbes (Ty_2) was divided into three parts, one of which was irradiated with a dose of $1.5 \times 10^6 r$, the second treated with formalin and the third kept as a suspension of living microbes.

From the data presented in Table 9 it will be seen that the hemagglutination reaction obtained with the irradiated culture was quantitatively and qualitatively the same as that obtained with a culture which had not been subjected to irradiation.

The results of the experiments carried out indicate the possibility of using gamma-radiation for the preparation of intestinal vaccines and antigens, as well as for sterilizing the corresponding bacterial preparations, since even massive doses of gamma rays do not change, or hardly change at all, the antigenic, immunogenic and toxic properties of bacteria of the intestinal group.

THE EFFECT OF RADIATION ON TOXOIDS

Diphtheria and tetanus toxoids were irradiated with doses of 1.5×10^6 and $2 \times 10^6 r$. Both native preparations and those adsorbed on aluminium hydroxide, which, as is well known, improves the immunogenic properties of the preparations, were irradiated.

To test the immunogenic properties of irradiated diphtheria toxoid 112 guinea-pigs were immunized twice with native preparation or once with adsorbed preparation. Immunity was checked one month after completion of immunization by administering various doses of the toxin to the guinea-pigs. The results of the experiment are given in Table 10.

As can be seen from this table, irradiation did not affect the immunogenic properties of the native toxoid; but it greatly impaired those of the adsorbed toxoid.

The immunogenic properties of irradiated tetanus toxoid were determined in experiments with white mice. The results (Table 11) differed but little from those obtained in the experiments with diphtheria toxoid.

It follows that native toxoids can be subjected to sterilization by irradiation without impairing their immunogenic properties, but that the problem of sterilizing adsorbed preparations requires further study.

THE EFFECT OF RADIATION ON ANTITOXIC SERA

Both native anti-diphtheria sera and those concentrated and purified by the "Diaferm-3" method were irradiated with a dose of $1.5 \times 10^6 r$, as well as with one of $0.6 \times 10^6 r$, which, as already pointed out, is sufficient to kill the vegetative forms of many bacteria. The antitoxin titre was determined (*in vitro*) by the flocculation method and also on guinea-pigs by Roemer's method. The relative viscosity of the sera was also determined.

As will be seen from Table 12, irradiation with a dose of $0.6 \times 10^6 r$ either did not reduce the antitoxic titre of the sera at all, or did so only to a very slight degree, whereas irradiation with a dose of $1.5 \times 10^6 r$ had a marked effect on it, the average reduction being as much as 27% in case of native sera and 16% in that of the purified ones. A still greater reduction in the

Table 10. Effect of γ-rays on Diphtheria Toxoids ($1.5 \times 10^6 r$)

Immunization of guinea-pigs with toxoids	*Dose of toxin to test immunity DLM*	*% survival of guinea-pigs immunized with toxoids*	
		Non-irradiated	*Irradiated*
Native	30	50	54.4
	20	85.7	92.3
Adsorbed	1000	0	0
	500	22.3	0
	250	80	9.1
	125	93.4	50

Table 11. Immunogenic Properties of Irradiated Tetanus Antitoxins

Preparation	*Number of immunizations*	*Dose of injected toxin DLM*	*Dose of irradiation to preparation*	*Kind of animals*	*Number of animals*	*Survived*	
						Total	*Per cent*
Native	Two	100	Non-irradiated	Mice	60	14	23.3
		100	$2 \times 10^6 r$	Mice	60	18	30
Adsorbed	Once	100	Non-irradiated	Mice	57	57	100
		100	$2 \times 10^6 r$	Mice	50	43	86
Adsorbed	Once	500	Non-irradiated	Mice	25	22	88
		1000	Non-irradiated	Mice	25	13	52
		500	$1.5 \times 10^6 r$	Mice	25	17	68
		1000		Mice	25	9	36

antitoxin titre was recorded after irradiation of anti-perfringens sera with a dose of $1.5 \times 10^6 r$ (Table 13). It should be noted that most of the native sera irradiated with a dose of $0.6 \times 10^6 r$, and all those irradiated with one of $1.5 \times 10^6 r$, ceased giving the flocculation reaction, whereas the purified sera did not lose their flocculation power, although the time required for flocculation was considerably increased. The relative viscosity determinations revealed an increase in the viscosity of the sera after irradiation, which indicates denaturation of the protein.[5,6]

Refractometer measurements showed that the protein content of the native sera did not fall after irradiation with a dose of $1.5 \times 10^6 r$ (Table 14). However, some homogenization of the globulins occurred in the irradiated sera, and the percentage ratio of the protein fractions showed an abrupt change. As can be seen from Table 14, electrophoretic examination revealed a reduction in the percentage of albumens and γ-globulins and an increase in that of the β-globulin fraction in all the native sera subjected to irradiation with a dose of $1.5 \times 10^6 r$. Figure 4 shows photographs of some typical electrophoresographs and photomicrographs of irradiated and non-irradiated antitoxic sera produced therefrom.

As the total amount of protein in the irradiated serum did not change, the increase in the β-peak, established by electrophoresis, may be regarded as a result of denaturation of the protein and the consequent formation of a new protein complex with an electrophoretic mobility close to that of the true β-globulins. It is possible that irradiation with a large dose causes fragmentation of part of the protein molecules, with their subsequent recombination and the formation of a new denatured complex.[5] It is interesting that a similar phenomenon has been observed by other workers during the ultra-violet irradiation of sera.[7]

The spectrographs likewise indicate that large doses of radiation produce in sera physico-chemical changes proportional to the intensity of irradiation. As Fig. 5

Table 12. Effect of γ-rays on Antitoxic Anti-diphtheria Sera

Type of serum	*Serum No.*	*Titre of antitoxin*						*Relative viscosity*		
		By flocculation			*By Roemer*					
		Non-irradiated	*0.6 × $10^6 r$*	*1.5 × $10^6 r$*	*Non-irradiated*	*0.6 × $10^6 r$*	*1.5 × $10^6 r$*	*Non-irradiated*	*0.6 × $10^6 r$*	*1.5 × $10^6 r$*
Native	333	400	—[a]	—[a]	375	375	325	2.0	2.1	2.3
	358	615	—[a]	—[a]	600	500	400	2.0	2.2	2.7
	358	163	—[a]	—[a]	150	125	100	1.8	2.0	2.1
	591	890	—[a]	—[a]	900	750	600	1.85	2.2	2.65
	596	730	730	—[a]	650	600	450	2.0	2.3	2.7
	615	1210	1000	—[a]	1200	1100	900	1.8	2.3	2.4
	638	450	—[a]	—[a]	450	400	350	2.1	2.2	2.7
	639	1150	1150	—[a]	1100	1000	900	2.1	2.4	2.6
	640	730	730	—[a]	650	600	450	1.65	2.0	2.2
Purified and concentrated	1270	2500	2500	2000	2500	2400	2000	3.2	3.4	3.7
	1273	2100	2100	2000	2100	2100	1800	4.3	4.5	4.8
	1277	2100	2100	1900	2100	1800	1800	3.6	3.8	4.0
	1278	2350	2350	2100	2300	2100	1900	4.0	4.3	4.6
	1203	2000	2000	1810	1900	1800	1600	3.8	4.1	4.5
	1233	2500	2350	2100	2500	2400	2000	2.7	2.7	3.1
	1323	2390	2390	2250	2300	2200	2100	3.7	4.0	4.3
	1339	2570	2570	2250	2500	2400	2000	4.0	4.3	4.6
	1333	2770	2770	2570	2500	2500	2500	4.3	4.3	4.5
	1351	2580	2390	2250	2500	2300	2100	4.3	4.5	4.8

[a] Denotes absence of flocculation reaction.

Table 13. Effect of γ-rays on the Antitoxic Properties of Anti-perfringens Sera

Sera	Serum No.	Antitoxin titre, in AE			
		Non-irradiated	Irradiated with		
			0.6 × 10⁶r	1 × 10⁶r	1.5 × 10⁶r
Native	520	200	175	150	125
	742	200	175	125	125
	709	100	100	—	75
	740	100	75	75	50
	731	125	100	—	75
Diaferm-3	174	900	800	800	600
	1131	1200	—	1100	800
	175	900	600	600	500
	172	1000	800	750	600

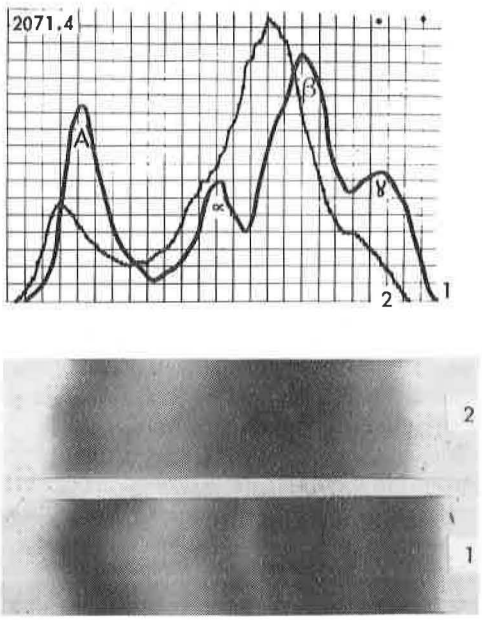

Figure 4. Electrophoresographs of antitoxic equine sera. 1: non-irradiated serum; and 2: the same serum irradiated with a dose of 1.5 × 10⁶r

shows, the spectrophotometric curves of the absorption coefficients in the ultraviolet part of the spectrum show maximum and minimum values for irradiated and non-irradiated sera in the very same parts of the spectrum. The curves run parallel to one another, differing only in intensity. Alexander and others[8] obtained similar curves, although, naturally, differing more considerably in intensity, when working with very large doses of irradiation (8 × 10⁶r).

PRELIMINARY CONCLUSIONS

The above data enable some preliminary conclusions to be drawn about ways of using ionizing radiation in the manufacture of bacterial preparations.

The starting point for developing this subject is the proved sterilizing effect of γ-rays. We were able to confirm this fact, already known to us from the literature, by our own investigations. It was important to prove experimentally that sterilizing doses of γ-rays have a bactericidal effect even on the dense suspensions of microbe bodies obtained with modern methods of preparing microbic vaccines, which reach a concentration of 30 to 40 × 10⁹ microbe bodies or more per millilitre.

Table 14. Percentage Ratio of Protein Fractions of Native Sera Irradiated with 1.5 × 10⁶r

Serum No.	Albumen		α-globulin		β-globulin		γ-globulin		Albumen/globulin factor		Protein %	
	1	2	1	2	1	2	1	2	1	2	1	2
639	18.1	6.3	11.3	11.0	65.3	80.9	5.3	2.7	0.22	0.05	10.44	10.96
538	14.1	9.7	8.0	11.1	69.9	76.7	8.0	2.4	0.15	0.10	9.88	
615	16.6	9.4	13.2	11.5	57.4	73.6	12.5	5.4	0.20	0.20	9.91	10.07
591	25.6	15.8	11.9	18.6	43.1	59.6	19.3	5.9	0.34	0.18	9.57	9.61
596	11.6	7.8	8.2	6.6	71.4	81.4	8.7	4.0	0.13	0.08	9.63	
333	25.4	18.4	14.0	10.3	50.0	63.9	10.7	7.4	0.32	0.22	9.95	9.76
638	26.6	17.2	9.3	17.2	45.3	55.2	18.7	10.3	0.36	0.21	9.72	10.24
358	30.4	28.2	19.5	23.1	35.0	41.0	15.0	7.7	0.44	0.39	8.56	8.53
M	21.0	14.0	12.0	13.7	54.7	66.5	12.3	5.7	0.26	0.17	9.96	9.86
±m	2.4	2.6	1.4	1.9	4.7	5.1	1.9	1.0	0.03	0.03	0.2	0.3
t	1.6		0.6		1.7		3.1		0.9		0.3	
V	0.1		0.5		0.1		0.01		0.5		0.5	

M—arithmetical mean.
m—mean square error.
t—reliability of the difference between two M's.
V—probability of the resulting error being fortuitous.
1—non-irradiated.
2—irradiated.

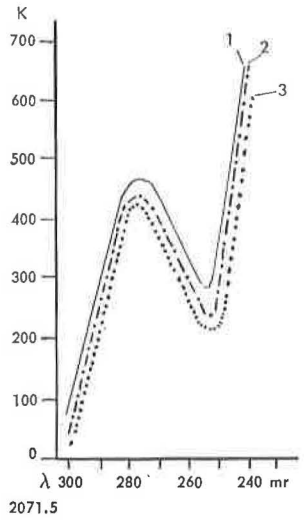

Figure 5. Effect of irradiation on absorption in the ultra-violet part of the spectrum; 1: standard; 2: 0.5 × 10^6r; and 3: 2 × 10^6r

There is no doubt about the feasibility of the cold sterilization of waste matter from the bacteriological industry, i.e., infectious material in the liquid or semi-solid state or dirty glassware, or of that of clean glassware before it is used in the production process. The only problem consists in developing the most economical plant with sufficient capacity to meet the production requirements of a given industrial establishment.

The present object of research is to explore the possibility and economic feasibility of using the various types of gamma-radiation source which the development of the atomic energy industry has placed at our disposal. Mainly such sources are: some types of reactor cooling circuit; spent fuel elements during the "cooling off" period; and fission products enriched with the gamma-radiating isotopes caesium-137 and cobalt-60. As stated above, "cold" sterilization may be used for sterilizing glassware and for treating waste materials from the bacteriological industry, such as infectious matter and dirty glassware. Calculations have shown that, with current prices of radioactive isotopes and enriched fission products, the cost of sterilizing such materials by gamma-radiation would be considerably greater than that of using steam, as at present. However, a considerable reduction in the cost of radiation sources can be expected over the next few years. Hence the possibility of using gamma-radiation to sterilize glassware and wastes from the bacteriological industry should not be ruled out, especially when the many advantages of "cold" sterilization are taken into account.

A more important trend in the use of ionizing radiation in the production of bacterial preparations is, as mentioned above, its application to the preparation of nutrient media and to the production of corpuscular and chemical intestinal vaccines and diphtheria and tetanus toxoids. Antitoxic sera deteriorate when subjected to the action of sterilizing doses of radiation, but smaller doses, sufficient to kill the vegetative forms of microbes, can be used in the production of purified antitoxic sera without harmful effects. It should be emphasized that in many cases it is not so much a matter of using an improved or more reliable method of sterilization as one of developing a new type of preparation.

The development of a gamma source for such purposes is an eminently solvable problem. According to our calculations, a source with an activity of 3 to 5 × 10^5 gram equivalents of radium should suffice for a daily processing of up to 6 or 7 tons of material (working a 20-hour day with a sterilizing dose of 1.5 × 10^6r). The possibility of designing a combined plant for the simultaneous treatment of nutrient media and the sterilization of finished products must also be borne in mind.

In view of the relatively small size of the radiation sources, it may be assumed that fission products enriched with gamma-radiating isotopes and radioactive cobalt, the latter of which is more readily available at the present time, will be the most suitable.

Safety measures and protection against the radiation used are extremely important considerations in the operation of gamma-sources. Research carried out in recent years[9] has shown that the best solution to the problem is to submerge the source under water. It must be assumed that this method will prove equally suitable for the design of the gamma-sources to be used for the production of bacterial preparations.

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The Properties of a New Cesium-137 Plesiotherapy Unit Shielded with Tungsten Alloy and Uranium

By Johan Baarli*

The use of teleradium units during the last 35 years has revealed the need for special equipment operating at relatively short source–skin–distance (SSD) in radiation cancer therapy. This kind of equipment can be designated plesiotherapy units compared to teletherapy units where a long SSD is used.

The usual range of SSD in plesiotherapy is from 5 to 10 cm, and this is employed principally for treatment of cancer located no deeper than 4 to 5 cm below the skin surface. At these depths bone is frequently encountered and the γ rays from radium have the advantage over conventional X rays of combining a more homogeneous irradiation of the tumor region with less severe skin reactions.

The short SSD employed in plesiotherapy makes it possible to influence the depth-dose and isodose distribution so that an optimal relation between the total tumor-dose and the volume-dose can be achieved when treating relatively superficially located tumors.

There are a number of cases in which plesiotherapy is to be preferred to teletherapy or to conventional X rays. Typical examples are metastases to the lymph nodes in the supraclavicular region, along the *mammaria interna* and in the axillae. Primary tumors also are frequently found in locations suitable for plesiotherapy. In such cases it is essential to employ a type of radiation which decreases steeply with depth in order to avoid overexposure of radiosensitive organs located deeper than the tumor region. This is achieved by using short SSD and γ rays which combine reduced absorption in bone together with reduced skin reaction.

Because of the scarcity, high cost and low specific activity of radium, teleradium units have been suitable for plesiotherapy only. The clinical experience gained from the use of such units and the discovery of the artificial radioactive isotopes have led to the conversion of teleradium units into similar cobalt-60 units where the radium packs have been replaced by cobalt-60 sources.[1] Specially designed plesiotherapy units using cobalt-60[2] or iridium-192[3] have also been reported.[1]

Recently the radioactive isotope cesium-137 has been made available in fairly large quantities, and considerable interest has been aroused in the use of this isotope in cancer therapy.[4,5] This isotope, which is a fission product, has a half-life of 30 years and emits one γ-ray line with an energy of 0.662 Mev. The decay properties of cesium-137 are shown in Fig. 1. Cesium-137 emits two groups of β particles. Eight per cent of the decays result directly in the stable isotope barium-137 and 92 per cent decays over the excited state of barium-137 which by emission of a γ ray of 0.662 Mev results in the stable nuclei.

The number of roentgens per hour at one meter from one curie of this isotope is determined by using the fractional number of the γ rays per disintegration, the photon energy, the internal conversion coefficient including Auger-processes and the energy of the characteristic γ rays from barium-137. Disregarding self absorption, 0.314 roentgen per hour at one meter per curie is obtained. In practice this value must be corrected for self-absorption and will depend upon the geometry of the source, the specific activity and the chemical composition of the active material.

Cesium-137 is now available in two chemical compounds, CsCl produced at Harwell and Cs_2SO_4 at Oak Ridge. The densities of these materials are 3.97 g/cc and 4.24 g/cc respectively. The available specific activity is now of the order of 100 curies per cc.

Table 1 shows the relevant properties of the isotopes used in plesiotherapy.

It is seen from this table that the half-lives of the artificially produced isotopes range from 30 years for cesium-137 to 70 days for iridium-192. This requires the replacement of a cesium-137 source every 15 years and of an iridium-192 source every 35 days to fulfil the requirement that the replacement be carried out when the radiation intensity is reduced by 30 per cent. The use of iridium-192 will therefore require ready access to a reactor for reactivation.

Table 1 shows that both radium and iridium-192 emit γ rays of fairly low energy together with the high energy component which is of primary interest. Cesium and cobalt, however, emit practically monoenergetic γ rays in the high energy region.

In practical therapy the use of radium or iridium-192 will give, due to the low energy γ-ray components, a relatively higher skin-dose than either cobalt-60 or cesium-137. In this respect a comparison of cobalt-60 and cesium-137 would be expected to show a slight difference in favor of cobalt-60. The γ ray energies of the isotopes listed in Table 1 also show differences in absorption in bone. Approximately 15 per cent more

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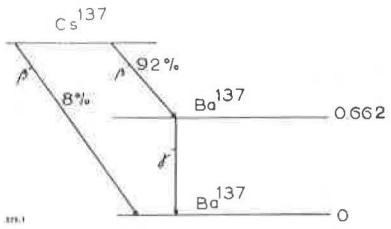

Figure 1. The decay properties of cesium-137

of the radiation from cesium-137 will be absorbed when compared with cobalt-60 γ radiation.

The specific activities of the isotopes are of minor importance since the primary object of this kind of treatment is to achieve a steep decrease of the dose with depth. This is considered more essential than a very small penumbra.[6]

The γ-ray energies also considerably influence the design of a therapy unit in respect to its safety of operation. In order to obtain the same reduction in intensity, using lead as shielding material, cobalt-60 requires approximately twice the thickness required by cesium-137. This means that a therapy unit using cesium-137 might be made much lighter and thus more easily manoeuvrable than a corresponding cobalt-60 unit.[7]

A 50 CURIE CESIUM-137 PLESIOTHERAPY UNIT

For radiotherapy of tumors located down to a depth of 3–4 cm below the skin surface, a special plesiotherapy unit was designed for The Norwegian Radium Hospital.† This unit was intended primarily to replace a 3.5 gram teleradium unit for treatment of tumors in the supraclavicular region and in the axillae. In these cases it is essential to avoid high dose to the lungs. Considerations based upon physical properties of isotopes suitable for this purpose resulted in the design of a unit using cesium-137.[7] It was necessary for the unit to possess the highest possible degree of flexibility and be easy to use. Shielding materials are partly tungsten alloy and uranium which made it possible to reduce the weight and at the same time afford a high degree of protection.

A cross section of the unit is shown in Fig. 2. This is equipped with two treatment ports and a 50 curie cesium-137 source movable from shielded to "on" position. The unit has three main parts: the shielding, the nozzle arrangement with the treatment ports, and the drive mechanism for moving the source from the

† The unit has been built by Nuclear Engineering, Ltd., London, according to specifications.

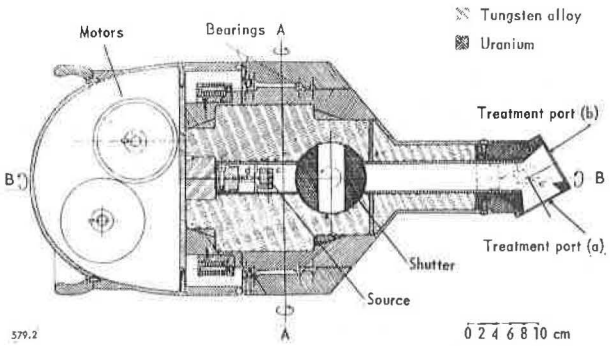

Figure 2. A cross section of the plesiotherapy unit. The source is shown in the shielded position

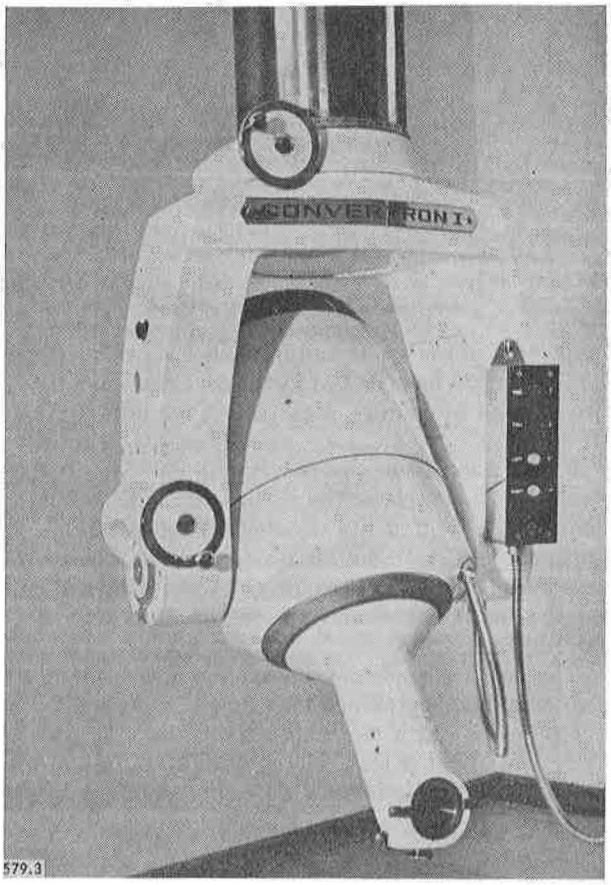

Figure 3. The plesiotherapy unit

shielded to the treatment position. The whole unit is supported in a large bearing mounted in a yoke which is carried at the lower end of a telescopic tube and which provides motion in the vertical direction. The telescopic tube holding the whole assembly is not attached to the ceiling but rests on wheels which provide

Table 1

Isotope	*Half-life*	*Energy in Mev*	*Specific activity*	*rhm/curie*	*Mode of production*
Radium	1590 years	0.2–2.2	5	0.86	Nat. occ.
Cesium-137	30 years	0.662	95	0.314	Fission
Cobalt-60	5.3 years	1.25	800	1.33	Neu. ind.
Iridium-192	70 days	0.1–0.613	975	0.5	Neu. ind.

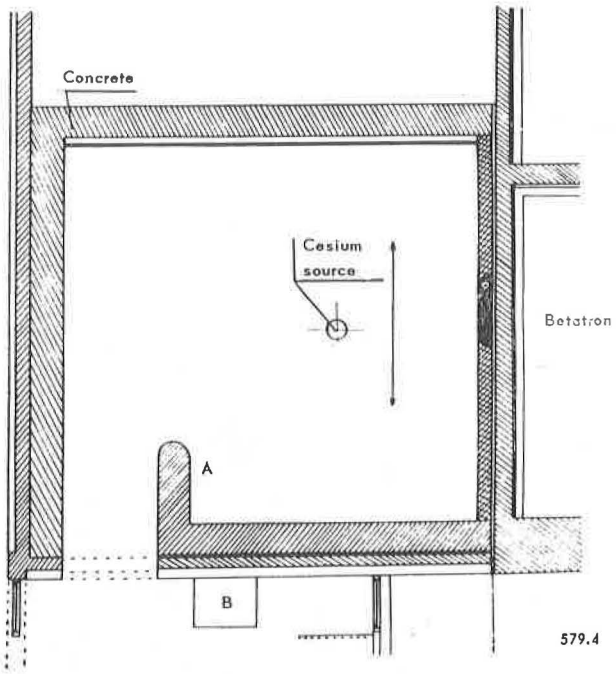

Figure 4. The room arrangement. The arrow indicates the horizontal movement of the whole therapy unit

movement of the whole unit in the horizontal direction limited to 30 cm back and forth. All these movements are effected by motors. A picture of the unit is shown in Fig. 3.

Figure 2 shows the source in the shielded position. A uranium shutter closes the channel through which the source is moved to the treatment position. When in this position, the radiation dose on the surface of the unit does not exceed 0.5 mr/hour except for two points on the back of the unit where the dose-rate is 2.5 mr/hour.

The nozzle is made of uranium and is furnished with two treatment ports, one making an angle of 30° and the other 60° with the main axis of the unit. One of these treatment ports is closed with an uranium plug when the other is in use. By using uranium in the

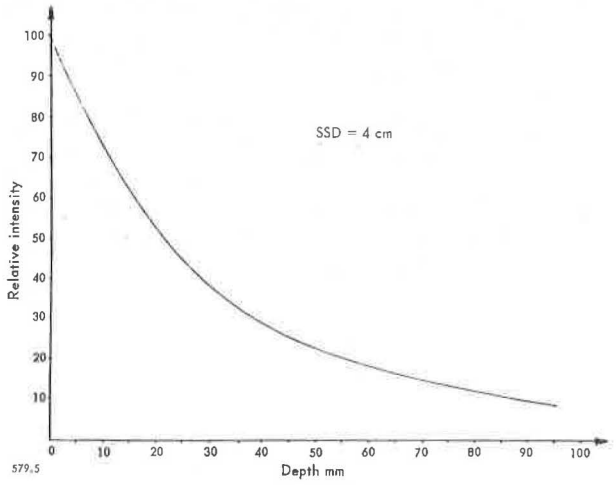

Figure 5. Depth-dose distribution measured in water at SSD 4 cm with circular radiation field 6 cm in diameter

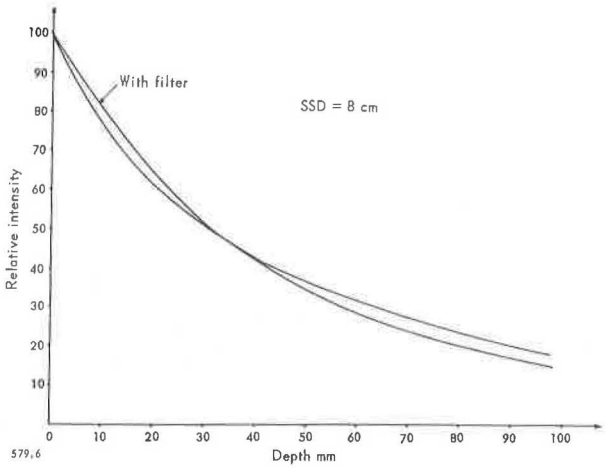

Figure 6. Depth-dose distribution measured in water at SSD 8 cm and circular field 6 cm in diameter, with and without a ring shaped filter

nozzle, it is possible to radiate a circular field 6 cm in diameter at a SSD of 4 cm. The transmission through the uranium collimator is 0.6 per cent of the radiation in the center of the field. Radiation fields are varied by inserting applicators attachable to the nozzle.

The source contains 50 curie cesium-137 and was made for the unit by Oak Ridge National Laboratory, USA. The active material is enclosed in a housing and has a ring shape with an outer diameter of 2.6 cm and an inner diameter of 1.7 cm. In front of the active material is one millimeter of stainless steel to absorb the β particles from the decay of cesium-137. The geometrical form of the active material has been chosen to obtain a reduction of the dose in the center of the field. This is important when operating at the smallest source–skin distances.

The source is attached to a forked holder in such a way that it can be swung in one plane to bring the source surface parallel to the front of the treatment port.

The source holder is attached to a cylindrical bar of shielding material and is moved from the "off" to the "on" position by means of a stout flexible drive operated by electric motors at the end of the unit. The source is moved by remote control. Lights on the control panel indicate whether the source is in either of the positions or is in motion. Door switches are connected to the remote control for safety so that when the door is opened the source is automatically brought back to its shielded position.

The high degree of mechanical flexibility has been possible due to the small dimensions and the low weight of the unit. Figure 2 indicates the mechanical movement of the treatment head when adjusting the radiation to the patient. The axis of the rotation B–B is made possible by bearings shown on the figure. The movement is 360° around B–B. An additional changing of position is accomplished by revolving the unit around the axis A–A. For all rotational motions, angularly graded scales indicate the positions. These movements are manually operated.

Figure 4 shows the room arrangement indicating the

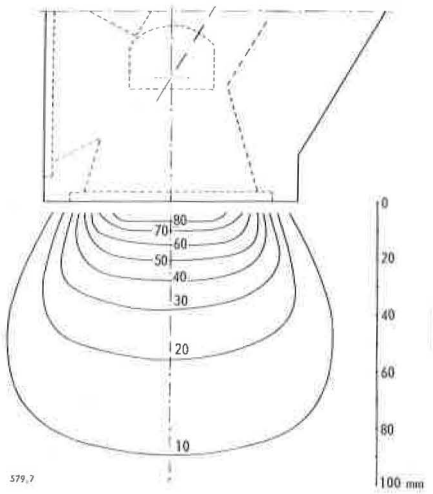

Figure 7. The isodose distribution measured in water at SSD 4 cm using a circular field 6 cm in diameter

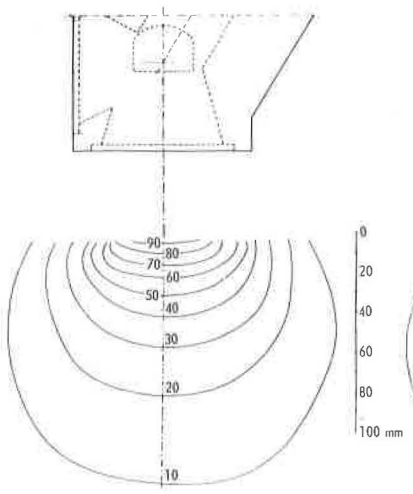

Figure 8. The isodose distribution measured for SSD 8 cm and circular field 6 cm in diameter using filter

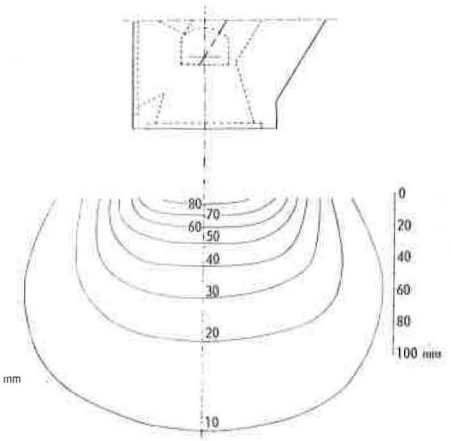

Figure 9. The isodose distribution measured for SSD 8 cm using a circular field 10 cm in diameter

position of the unit. In order to avoid a heavy door, an additional wall A acts as shielding for the primary radiation. Arrows on the figure indicate the horizontal movement of the whole unit. The control panel is shown at B. The operator has the patient under observation during treatment by means of a mirror arrangement.

THE PROPERTIES OF THE RADIATION FIELDS

The medical application of this unit for cancer treatment requires accurate knowledge of the isodose distributions, the depth-dose distributions and the surface dose. In each individual case the radiation is administered under optimal physical conditions, aiming at a maximum ratio of the tumor dose to the total volume dose. This is achieved from the isodose distribution which is greatly influenced by the field size and SSD. A number of isodose distributions under various conditions have been measured using a water phantom and a small ionization chamber.[8] The ionization chamber had a volume of 0.1 cc, and it was possible to make measurements from a depth of 5 mm. During the measurements the collimator wall was lined with one millimeter brass. This insert reduces the skin dose caused by scattered radiation in the collimator walls.

Figures 5 and 6 show the depth-dose distribution for a circular field with a diameter of 6 cm and a SSD of 4 and 8 cm. It is seen from these figures that at SSD 4 cm the dose decreases rapidly with depth reaching 50 per cent at 2.2 cm below the entering surface. Twenty per cent of the entering dose is found at a depth of 5 cm. The depth-dose distribution shown in Fig. 6 for an SSD 8 cm was measured with and without a filter. The filter had a ring shape and was made of brass. From this curve it is seen that 50 per cent of the dose at the entering surface is found at a depth of 3.2 cm below the skin surface and 20 per cent at a depth of 8 cm. Comparing the measurement with and without the filter, it is seen that there is a slight difference in favor of the use of filter.

Figures 7, 8 and 9 show the isodose distributions at 4 cm and 8 cm SSD. In Fig. 7 the SSD is 4 cm and the field size 6 cm circular. Figure 8 shows the same for SSD 8 cm and field size 6 cm in diameter. Figure 9 shows the isodose distribution for SSD 8 cm and a field size 10 cm in diameter.

It is seen from these curves that the relatively large size of the source gives rise to a rather large penumbra. In some cases where multiple fields have to be used this might be an advantage. This is due to the overlapping of the fields in such treatment.

Figure 10 shows the arrangement used for measuring the surface dose. This was carried out by a thin wall ionization chamber[8] and water as phantom material. The front wall of the ionization chamber has a thickness of 0.2 mm and the thickness of the water layer in front of this chamber was determined by adding a known amount of water to the container. The results of these measurements which were carried out at SSD 4 and 8 cm are shown in Fig. 11. From these curves it is seen that secondary electrons scattered by the γ rays in the collimator wall or in the air-space are absorbed in the first half millimeter of water. The build-up of secondary electrons in the water phantom increases

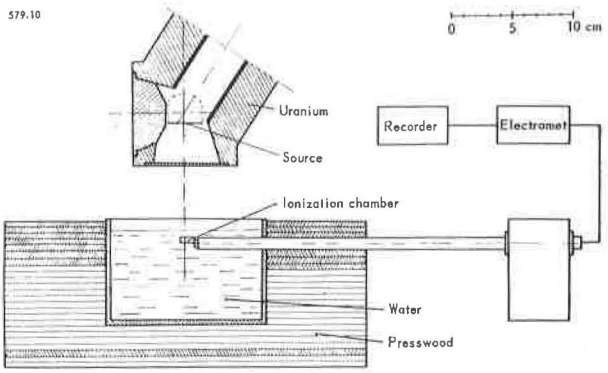

Figure 10. Arrangement used for measuring the dose in the first millimeter in water

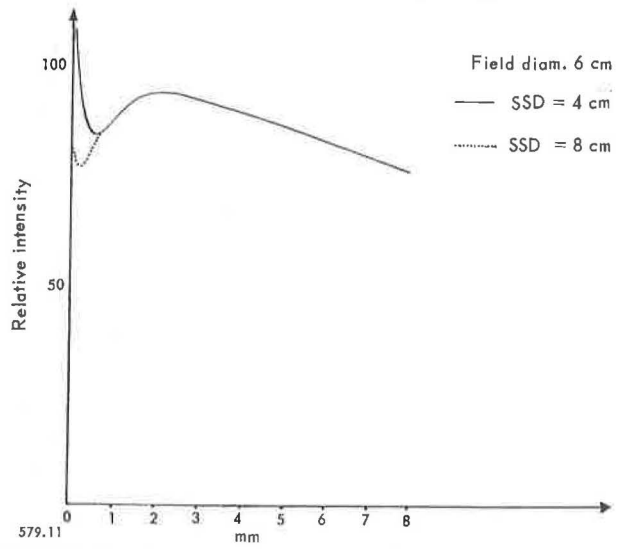

Figure 11. Dose distributions in the first millimeters of water at SSD 4 and 8 cm and circular fields 6 cm

to a depth of 2 mm below the entering surface where a maximum is reached.

The radiation output from this unit was measured using a calibrated ionization chamber of the Victoreen type. These measurements were carried out in air. At SSD 4 cm and a radiation field of 6 cm in diameter without any filter, a dose-rate of 104 r/min was obtained. At SSD 8 cm, a value of 33 r/min was obtained with a field size of 6 cm in diameter. At this distance, measurement was also carried out using the brass filter and a value of 32 r/min was obtained.

It can be concluded from the experience with the use of this unit so far that it possesses a very high degree of flexibility which is due to the low weight of the unit. It has also the great advantage of being very safe from a radiation point of view for the operators.

SUMMARY

A brief description is given of a plesiotherapy unit using cesium-137 manufactured by Nuclear Engineering, Ltd., London, for the Norwegian Radium Hospital, Oslo. This unit contains a doughnut shaped 50 curie cesium-137 source, movable from a shielded to a treatment position. The nozzle arrangement is furnished with two separate treatment ports and is made of uranium which makes it possible to operate the unit at a source-skin-distance of 4 cm, with well defined radiation fields. Detailed studies of the depth-dose and isodose distributions using various fields are reported. Special attention is paid to the filter and lining materials in order to reduce the skin dose caused by secondary electrons. As a result of these studies, it has been found that the unit is very suitable for treatment of cancer metastases to the glands of the supraclavicular region while reducing the dose to the lungs beneath. The unit can be operated at a source–skin distance between 4 and 10 cm, with dose rate varying from 104 to 27 r/min at these distances respectively.

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New Medical and Chemical Research Irradiation Units

By D. S. Beard and G. Munday*

CAESIUM-137 TELETHERAPY UNIT

The problem of treating tumours lying close to the skin and in such regions as the head and neck has given rise to much thought on the difficulties of delivering an adequate dose of radiation to the tumour site without excessive irradiation of healthy tissue. Early ideas led to development of the well known radium guns utilising up to about 10 grams of radium. These have been used very extensively for many years. One of the principal difficulties with such units is the large volume of shielding material necessary to provide adequate screening of the source around the beam-defining applicator. Size of the treatment nozzle depends upon two factors, firstly the high penetrating power of gamma radiation from the radium salt, and secondly the physical size of the source.

The importance of the second factor has been reduced in recent years by replacement of the radium by cobalt-60 of high specific activity. Standard radium units have been converted for use with up to 100 curies of cobalt-60. Since the penetrating power of gamma rays from cobalt-60 is of the same order as that of radium gamma rays, the large thickness of material necessary to provide adequate shielding is not reduced by this substitution.

Recently Baarli[1,2] has considered the relative merits of several of the new radioactive materials now available and has concluded that the use of Caesium-137 offers many advantages in the treatment of tumours lying close to the skin. Furthermore the small bulk of an adequately shielded treatment nozzle on a caesium-137 therapy unit offers easy access to the most difficult treatment positions around the head and neck and body apertures.

A unit has been designed and constructed which utilises a source of 50 curies of caesium-137. Since it was intended that this source should be used at a minimum source-to-skin distance of about 4 to 5 cm, it has been fabricated in the form of a flat annulus having internal and external diameters of 1.5 cm and 2.5 cm, respectively, and a thickness of approximately 0.24 cm. Construction of the source in this geometrical form provides a partial flattening of the isodose curves at short source-to-skin distances relative to those which would be obtained using a compact source. Further flattening of the beam is achieved by the use of suitably shaped filters. Calibration of output and depth dose curves obtained with this source have been reported elsewhere by Baarli.[3] Because of the thinness of the source material there is no significant loss of radiation due to absorption.

In order to reduce bulk of the treatment nozzle to a minimum, it has been constructed of depleted uranium. A minimum thickness of 2.5 cm of uranium was provided in all directions around the nozzle apertures. This allows the transmission of about 0.6% of the gamma rays emitted by the source.

Size of the treatment nozzle is such that it provides a maximum treatment field of 6 cm diameter at a minimum source-to-skin distance of 4 cm.

The treatment nozzle is mounted at the end of a hollow lead shielded arm projecting from the main storage head (Fig. 1) and it is provided with two treatment apertures with their axes at 30° and 60°, respectively, to the axis of the supporting arm. The storage head is mounted within a large bearing which allows the entire unit to be rotated by hand about the nozzle arm axis.

During treatment it is necessary that the ring shaped source should lie perpendicular to the central axis of the treatment applicator. In order to achieve this, the stainless steel cylindrical capsule containing the source is provided with two spigots and mounted in a pair of trunnions supported on a cylindrical bar of tungsten alloy. The tungsten bar, or so called source pencil, moves along a tube leading from the centre of the storage head, through the hollow lead shielded arm to the treatment nozzle. A light spring (Fig. 1) holds the source capsule with its axis in line with that of the source pencil. For treatment a uranium plug is clipped into one of the apertures in the nozzle and an applicator is inserted into the other. The form of the inner portion of the applicator is such that when the source capsule is moved to its final treatment position in the nozzle it is automatically rotated into the correct orientation by contact with the applicator.

When positioning patients, and otherwise when not in use, the radioactive source must be adequately shielded by enclosing it within a large mass of heavy metal. In the present unit the intensity of radiation at the surface of the storage head, when the source of 50 curies of caesium-137 is in the shielded position, is about 2 mr per hour.

* Nuclear Engineering Limited, London.

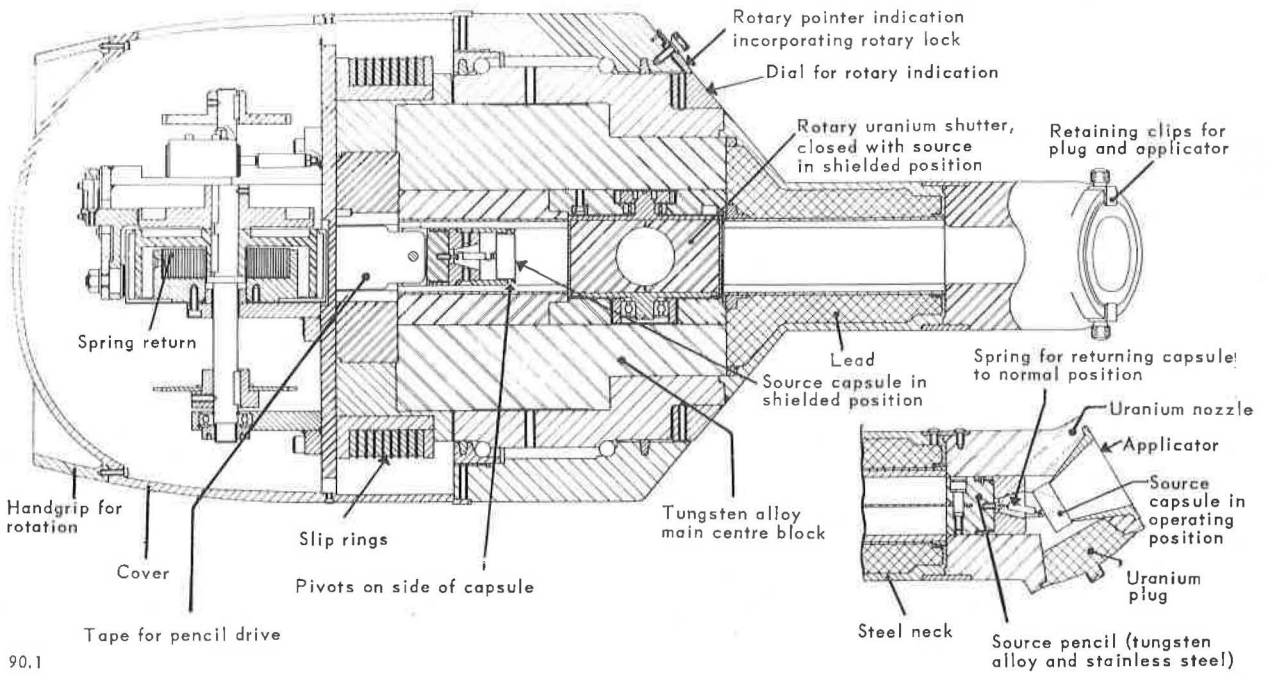

Figure 1. Principal section through 50 curie caesium-137 plesiotherapy unit

Because the provision of adequate shielding requires a large volume of metal, the source for treatment purposes is moved out into the much smaller applicator nozzle. Only by such an arrangement is it possible with ease to position the source close to any part of the patient's body.

Immediately in front of the source, when in the shielded position, is a rotating uranium shutter. This is in the form of a thick disc having a diametral hole through which the source pencil may pass. When the source is not in use, this shutter is rotated so that the hole is at right angles to the axis of the source pencil, whereupon the aperture leading from the source to the outside of the unit is sealed (Fig. 1).

When exposure of the source is required, the shutter is rotated through 90° and the source pencil is then pushed down to the treatment nozzle by means of a steel tape passing through the storage head. A special cam mechanism ensures that these two motions cannot occur independently, or in the wrong sequence, thereby jamming the source pencil.

Throughout a treatment, the source is held in the exposed position by the action of an electric motor in the stalled condition. The thrust exerted on the steel tape, and hence on the source pencil, is opposed by a powerful spring.

At the end of the pre-selected treatment time the motor is switched off and the spring returns the source to the shielded position. Thus in the event of a power failure during treatment the source is automatically returned to the shielded position. An exposure can be ended at any time merely by switching off the power to the drive motor.

If for any reason the spring return mechanism should fail to operate, the source may be returned to its safe position by reversing the electric motor drive. An emergency stop button is provided on the remote control panel for this purpose. As an ultimate emergency safeguard, a manual drive is incorporated into the mechanism so that the source can be retracted into the storage head by simply turning a handle which is easily accessible at the rear of the unit. This is so arranged that it is not possible to expose the source by means of the hand drive.

The unit is operated from a remote control panel incorporating all the usual items; exposure timer, start and stop buttons, emergency stop button, indicator lights and a warning buzzer which operates if the source does not return at the end of the pre-selected exposure time.

The main shielding of the storage head is provided by tungsten alloy contained within a thick steel shell. The entire head is roughly cylindrical in shape and the large ball race in which it is mounted is supported in a steel ring on which are mounted two spigots. These allow rotation within a hanging yoke about a horizontal axis. This yoke, which is carried on a telescopic tubular ceiling mounting, may also be rotated about the vertical axis (Fig. 2).

A similar unit for use with kilo-curie sources of caesium-137 and incorporating either an applicator nozzle or a variable diaphragm has also been developed.

COBALT-60 TWIN SOURCE TELETHERAPY UNIT

Principles of mechanical design similar to those described above have been used in the construction of a twin-source cobalt-60 teletherapy unit.[4] In this arrangement two source pencils, each carrying a compact cylindrical source, lie side by side in the main storage head. In front of each is a rotating cylindrical shutter (Fig. 3).

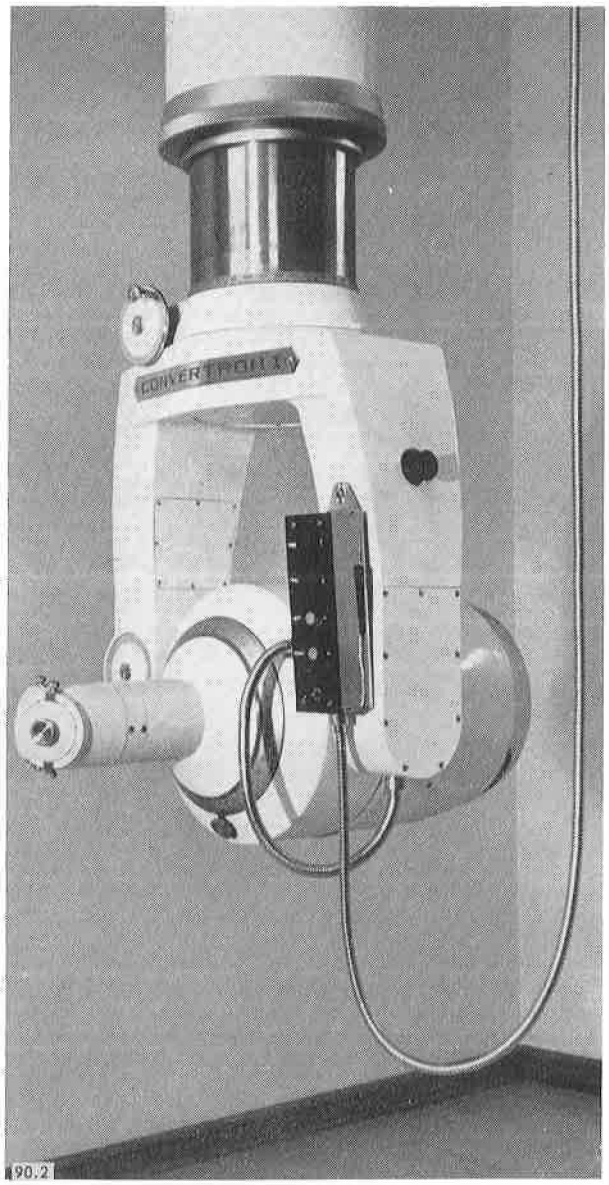

Figure 2. Fifty curie caesium-137 plesiotherapy unit

The source exposure mechanism consists of one electric motor which may be connected by means of electric clutches to either of two steel tape drives with associated return springs and manual return handles. At the front of the unit is a single rotating treatment nozzle of tungsten alloy. This is provided with two treatment apertures, one in line with the main axis of the unit and the other at right angles to it. This nozzle, which has a transmission factor of 0.6% for cobalt-60 gamma rays, provides a maximum treatment field of diameter 8 cm at a source-to-skin distance of 10 cm when using cylindrical cobalt-60 sources up to approximately 12 mm in length and diameter. During treatment a tungsten alloy plug is inserted into the aperture of the nozzle which is not in use and an applicator into the other. An electrical interlock ensures that a source may not be exposed unless the plug is in position.

In order to assist in arranging a patient, a lamp with a small compact filament may be inserted into the aperture which is not to be used. Position of the filament then coincides with the centre of the radioactive source when in the treatment position, and the light beam emerging through the treatment applicator in the other nozzle aperture may be used to define the treatment beam.

The source to be used is selected simply by sliding the treatment nozzle, which is pivotally mounted, into line with the appropriate source pencil (Fig. 4). The electric drive selection is automatically linked with this. The main shielding of the storage head is of lead within a steel shell and, with a total source strength of the order of a thousand curies of cobalt-60, the intensity of radiation at the surface of the unit is about 6 mr per hour.

This unit is intended to provide a range of treatment techniques for short and medium distance teletherapy[4] and in its present form is carried in a yoke suspended from a telescopic ceiling mounting which provides motion in the vertical direction. The head rotates about a horizontal axis within the yoke which itself rotates about the vertical axis of the telescopic tube. All motions are motorised and are precisely controlled from a pendant hand switch box. The remote control panel incorporates the standard items indicated above for the caesium-137 unit and the same provisions are made for return of an exposed source to the shielded position under normal and emergency conditions.

Further details of the output and isodose curves obtained with this unit and descriptions of associated clinical techniques are being published elsewhere.

IRRADIATION RESEARCH UNIT

A number of irradiation facilities have been described[5,6] which employ sources ranging from a few tens up to several thousands of curies of cobalt-60. In most of these the radioactive source is static and the necessary shielding is obtained either by submersion in water or storage in a subterranean cave or suitably designed concrete enclosure. In such installations material or equipment to be irradiated must be transported into and out of the radiation field. For the purpose of investigating the influence of ionizing radiations on the progress of chemical reactions and processes under controlled conditions, it is an obvious advantage to be able to bring the radioactive source to the apparatus concerned. This facility is provided by the type of installation built at Wantage[7] by the United Kingdom Atomic Energy Authority. In this unit chemical experiments involving heavy or cumbersome equipment may be set up in a shielded enclosure into which the source can be mechanically propelled from its shielded storage chamber which forms part of the structure of the facility.

The unit described below has been designed specifically for chemical research. It is free-standing and has been constructed in the form of a block with a work table top, situated within a suitably shielded enclosure such as a modified air raid bunker (Fig. 5).

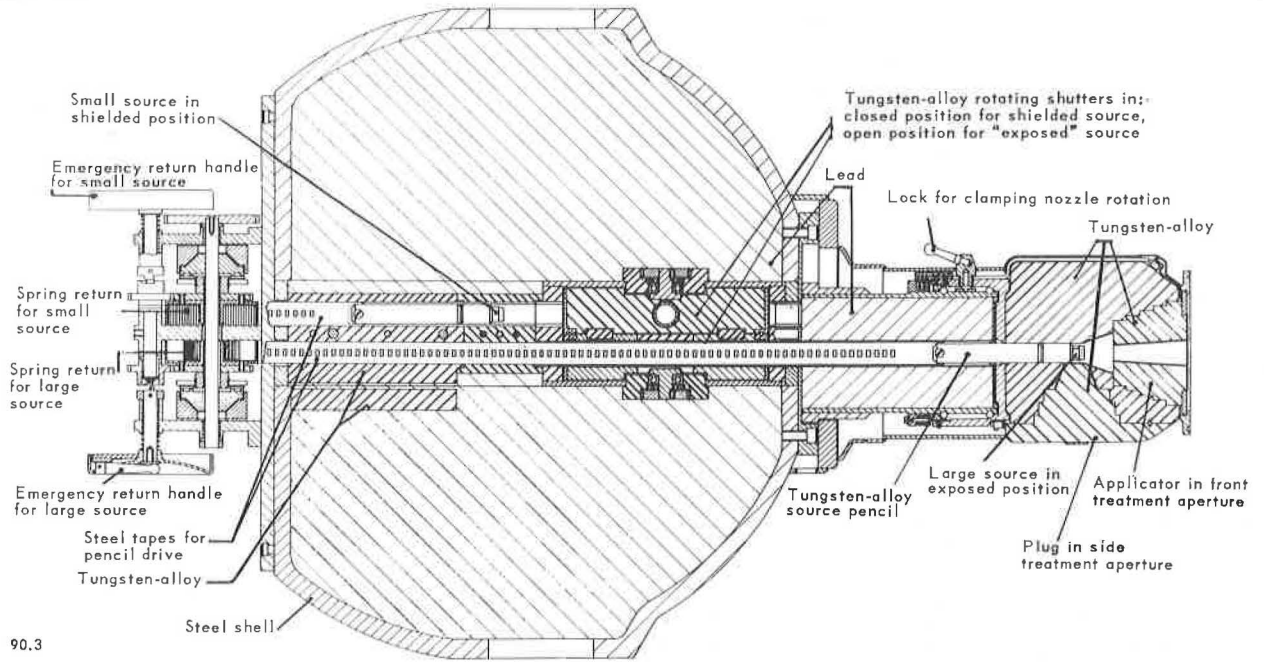

Figure 3. Principal section through twin-source cobalt-60 teletherapy unit

The unit has the following general characteristics: (*a*) the shielding of the container housing the radioactive source ensures that the radiation near the surface of the unit does not exceed 2 milliroentgens per hour at any point with a source of 10,000 curies of cobalt-60 in the "safe" position; (*b*) the source is in the form of a hollow cylinder of active material which provides an inner region of high and relatively uniform flux in addition to the external radial flux; (*c*) the source can be raised above the flat working table in order that it may be exposed; (*d*) provision is made for carrying out chemical research with small scale pilot plant and conventional apparatus under controlled conditions; (*e*) safety devices are provided to control exposure of the source and access to the shielded enclosure under all foreseeable conditions; and (*f*) provision is made for safe maintenance of the exposure mechanism and for easy replacement of sources from time to time.

As mentioned above the irradiation unit forms a free-standing table and it comprises three main parts: an inner "transport" container, an outer static shield, and a shutter assembly (Fig. 6).

The source (Fig. 7), which is housed in the inner container, consists of 108 cylindrical slugs of cobalt-60 each encapsulated in aluminium; the slugs are contained in 12 tubes arranged in the form of a cylinder having internal and external diameters of 8 and 11.5 cm, respectively; the complete cylindrical source holder has an active length of 25 cm and a total length of 73 cm; the active cobalt-60 slugs are contained in the upper portion of the stainless steel tube assembly and a gap 2 cm wide extends from the top for a length of 39 cm; and the inner container is a lead-filled steel drum, designed to meet current transport regulations for shipping of radioactive materials. When used for

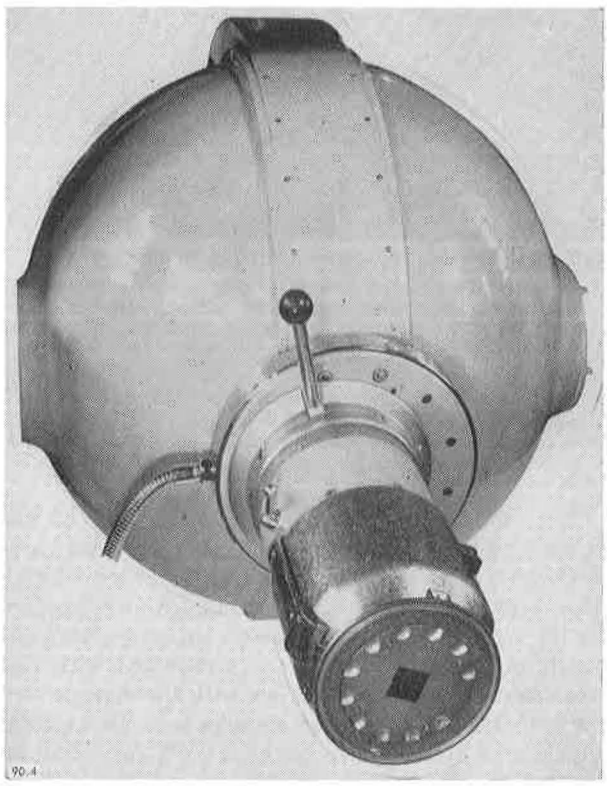

Figure 4. Front view of twin-source cobalt-60 teletherapy unit

transporting the source assembly, protective skids are mounted on the base. These are removed prior to installation. By adopting this arrangement the source can be loaded into this single container, shipped directly to the laboratory, and inserted into the irradiation unit of which the container is an integral part.

To reduce the radiation level to 2 mr/hr near the

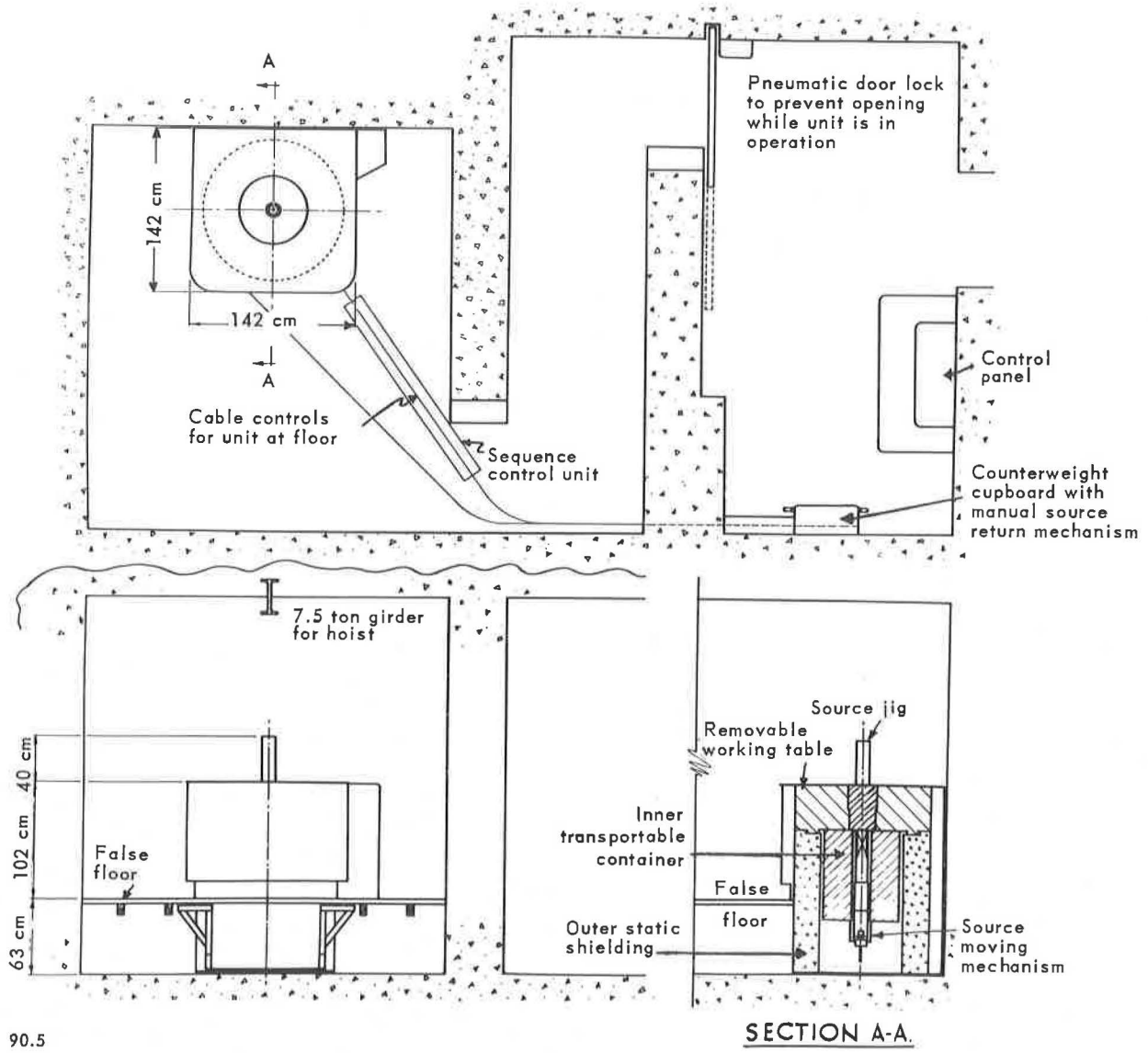

Figure 5. Typical layout of cobalt-60 irradiation unit

surface of the unit the inner container is surrounded by another container. This consists of a cylindrical steel shell filled with a suitable high-density material such as barytes powder or cement. The shell is made in three segments two of which are bolted together *in situ* to support the inner container. The third segment which completes the outer cylindrical shell is detachable, and when removed provides access to the source raising mechanism for erection and maintenance purposes. In this manner it is possible to install the unit in a room which has a relatively low ceiling.

Because of the height of the source (25 cm), and the requirement that it should be raised 15 cm or more above the working table top in the exposed position, the distance through which the source must be moved is considerable. In order to keep the top of the table at a reasonable working height above the floor the source is moved by compressed air. For a given movement, a pneumatic mechanism provides the most compact arrangement. A cylindrical bore is accurately machined in the centre of the inner container. Into this is inserted a removable precision machined tube which houses the cylindrical source assembly and the piston which is attached at its lower end.

When the source is lowered into the "safe" position it is obviously necessary to close the top of the cylinder with a shutter, and to provide additional shielding if the dose rate at the surface of the working table (Fig. 5) is not to exceed 2 mr/hr. This extra shielding is provided by iron blocks which extend to the limit of the outer shield. The shutter is constructed mainly of iron with a tungsten alloy insert which is located directly above the source cylinder when the unit is closed. The whole upper iron assembly with sliding shutter is attached to the inner container to ensure that the exit aperture in the shutter is accurately aligned with the axis of the inner container. The shutter is moved by a double-acting pneumatic piston, con-

trol of which depends on the movement of the source.

The working table consists of a stainless steel plate mounted on the top surface of the assembly. To facilitate setting up of experiments a stainless steel "jig," into which the source rises during exposure, is located at the centre of the working table and is attached to the shutter framework to ensure accurate alignment. This jig serves to protect the source against mechanical damage and also provides some thermal insulation.

The jig is constructed in the form of a hollow cylinder extending to a height of 40 cm above the table. Its internal and external diameters are 7.5 and 12 cm, respectively. When fully exposed the radioactive source occupies the upper 25 cm of the jig. A slot 1.5 cm wide extends the whole length of the jig and this allows cable or tubular connections to be made at any height to equipment inside the jig (Fig. 8).

A disc of polished aluminium, 60 cm in diameter, which forms the central portion of the working table around the jig, may be removed complete with any assembly of apparatus attached to it. In this way a series of standard set-ups may be swiftly exchanged in turn for irradiation. Since the over-all height of the table is 165 cm above the base level of the unit, a false floor is constructed to give an effective working height of about 100 cm. This obviates the need for specially built ducts to house the controls and power leads, and also the services to the unit. These are carried under the false floor and are easily accessible for maintenance purposes. Entrance to the irradiation chamber is through a labyrinth which is closed by a gate. The control panel for the unit is located in the adjacent control room (Fig. 5).

To expose the source after setting up an experiment the following sequence of operations must be carried out. The operator in the irradiation chamber, having checked that all persons other than himself have left, turns a key-switch close to the irradiation unit; this switch remains closed for a limited period of about 20 seconds. The operator then takes the key to the control panel in the adjacent room where he turns a second switch with the same key; this second switch causes the labyrinth gate to be locked by a pneumatic device and makes the control panel "live." The 20 seconds delay allows just enough time to leave the irradiation chamber, shut the entrance gate and close the second switch; it also ensures that no other person can have time to enter the irradiation chamber. If for some reason the operator does not close the second key-switch within the time interval provided, or fails to shut the gate properly, he must re-enter the chamber and close the first switch again before proceeding.

After setting the pre-selected duration of exposure on the timers in the control panel the source can be exposed. Pushing the "expose" button first causes the shutter to move; when the shutter is fully open it closes a limit switch to operate the air supply to the source cylinder. Return of the source to the shielded position involves the reverse procedure; a limit switch operating at the end of the source movement allows the shutter piston to operate and seal the unit. A mechanical interlock ensures that the shutter and source can move only in the correct sequence.

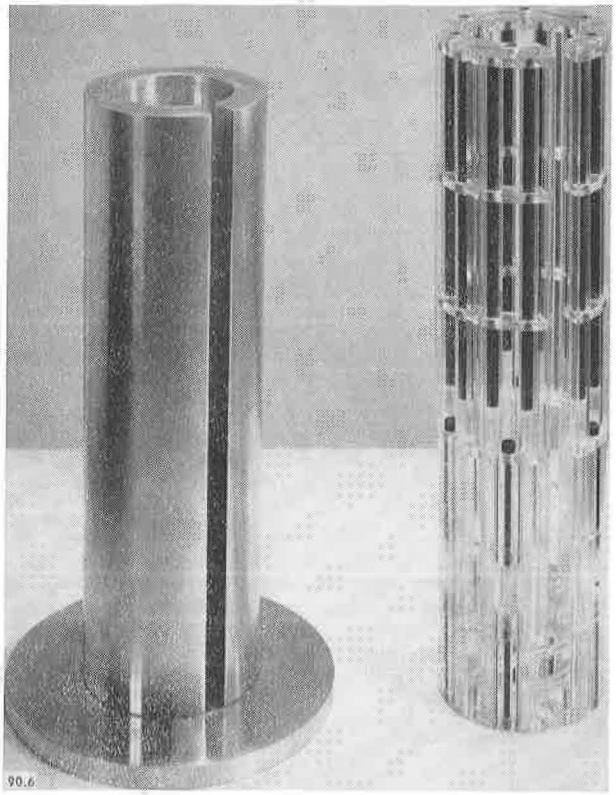

Figure 6. Sectional view of cobalt-60 irradiation unit

The source and piston are stored in the "safe" position at the lower end of the cylinder in the inner container and are raised in a few seconds by compressed air entering the cylinder through a control valve. They return to the safe position by exhausting the cylinder, allowing the source to fall under gravity. The rate of fall is controlled by an adjustable air flow regulator and near the end of its travel the source is cushioned by a further restriction of the air flow.

The controls have been designed to ensure that the unit "fails safe" in all foreseeable circumstances, e.g. interruptions in the electrical and/or air supplies, inadvertent opening of the entrance gate due to a failure in the locking device, etc. An ample reservoir of compressed air is available in normal circumstances to complete the sequence of operations for "failing safe"; nevertheless provision has been made for direct mechanical effort to be applied to the source and the shutter to enable them to be returned to the safe and closed positions in the event of a breakdown in the pneumatic system.

The source piston and the sliding shutter are directly connected by cables to two control weights suspended in a cubicle in the adjacent control room. Such a connection has a number of advantages: (1) it provides a positive indication of the positions of the source and shutter; (2) it provides a means of limiting the upward movement of the source if required; (3) a strong direct pull can be exerted on the source and shutter in an emergency if the normal methods of return fail; and

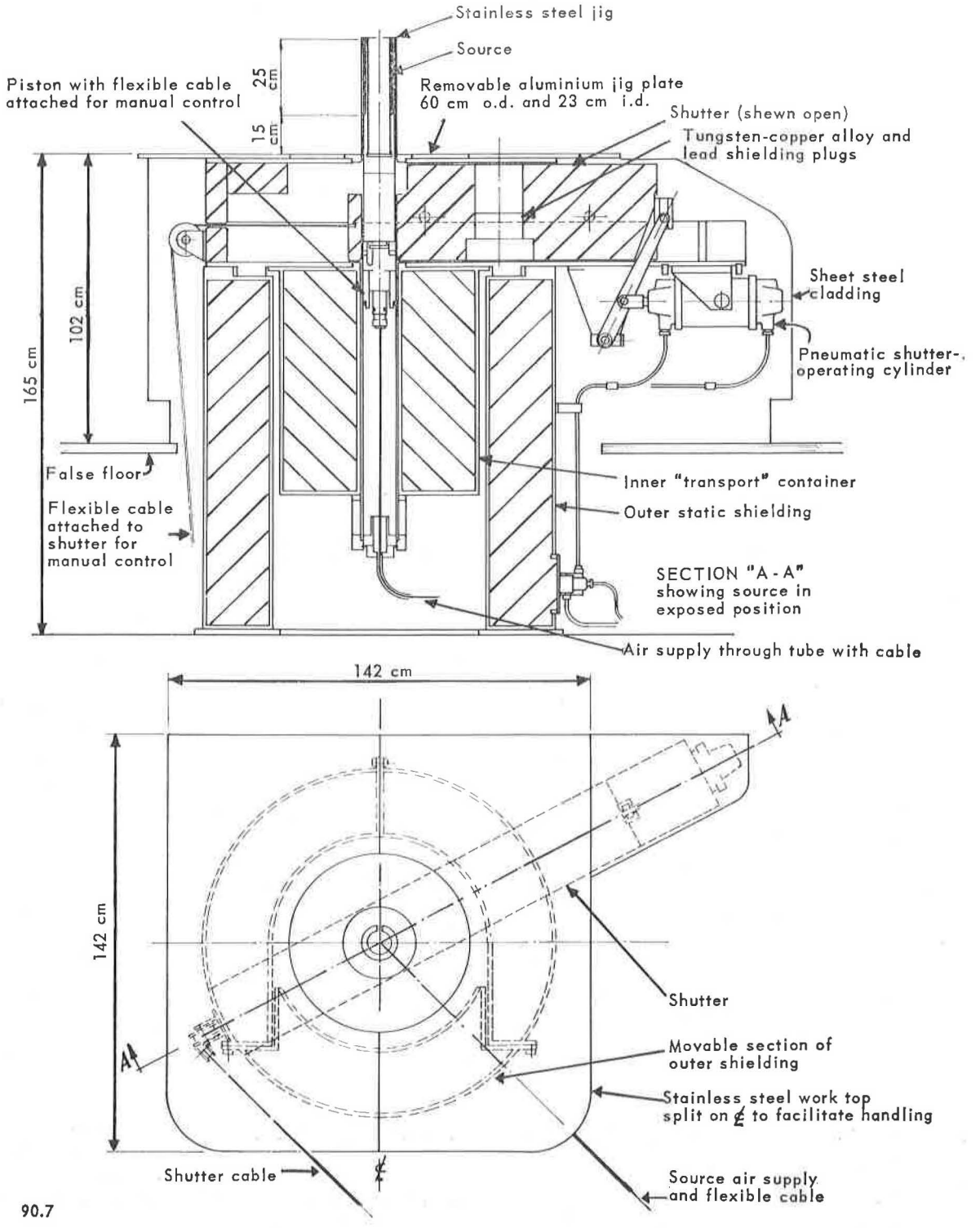

Figure 7. Sectional view of cylindrical source assembly and irradiation jig

(4) a simple and certain interlock of the source and shutter movements is possible. The total weight of the source assembly and its piston is about 38 kg and the two control weights weigh approximately 70 kg each.

In an emergency the shutter and source are moved to the "safe" position by geared handwheel drives acting on the control weight cables. Both are fitted with limit stops to prevent over-travel.

A range of automatic control switches and relays actuated by changes in temperature, pressure, voltage, etc., may be incorporated into the circuits of the remote control panel according to requirements.

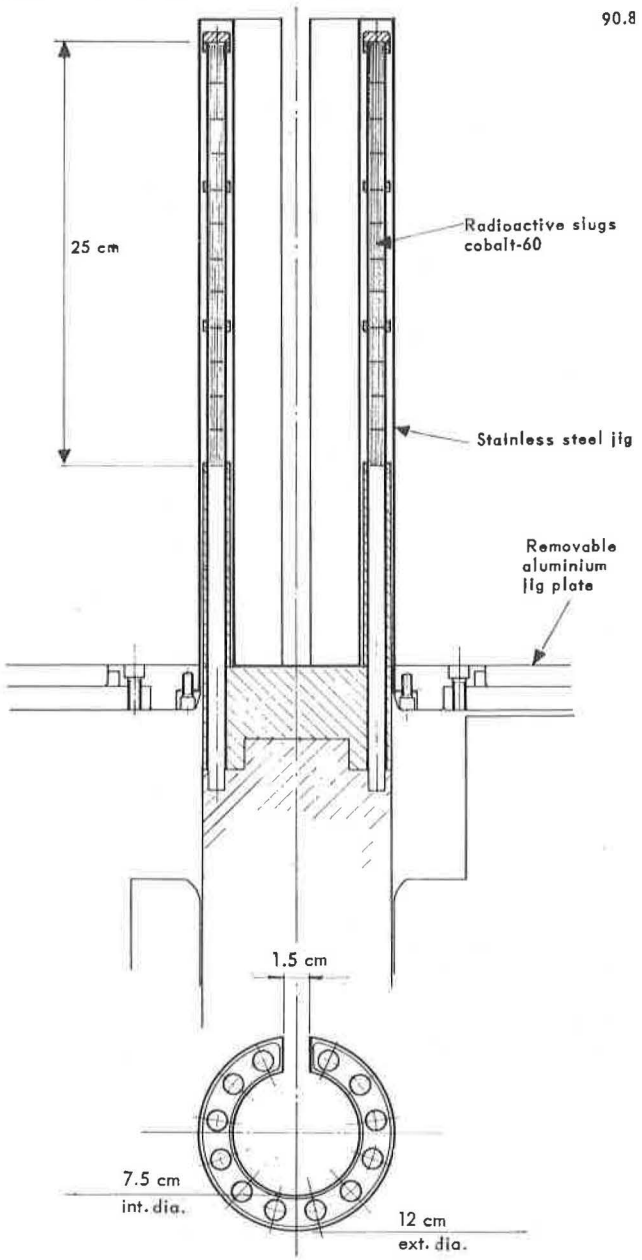

Figure 8. Stainless steel irradiation jig and model of source assembly

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Clinical Experience with a Strontium-90 Applicator in the Treatment of Ophthalmic Conditions

By Ibrahïm Abou Sinna*

Announcement of the discovery of a mysterious type of rays in 1895 by Roentgen was the starting time for utilization of ionizing radiation in the treatment of disease. Since then various reports have appeared concerning successful treatment of various inflammatory conditions. The early development was followed in 1900 by reports about the treatment of malignant diseases with X rays.

Management of superficial eye lesions by means of ionizing radiations should be carried out carefully to avoid deleterious effects on vital structures of the eye —especially the lens. Unfortunately, the early attempts to utilize ionizing radiations in the treatment of eye diseases has formed a dark chapter in the history of radiotherapy. The unhappy consequences of such therapy, caused by a great deal of primitive and unsound experimental work, served to retard its development and application in ophthalmology. Soft X rays were used in the treatment of eye conditions because of their limited power of penetration. Beta particles emitted from the natural radioactive element, radium, discovered in 1896, or from artificial radioactive elements that came into being after the discovery of neutrons in 1932, are also used to treat of eye disease.

With the progress of experimental work and better understanding of the physical properties and biological effects of radiations on tissues, the radiotherapist is now able to approach quite safely the problem of irradiation of eye lesions.

PHYSICAL PROPERTIES OF BETA PARTICLES

Beta rays are in reality high speed negatively charged particles or electrons. Their mass is negligible compared with alpha particles. The mass of the electron is 1/1850 that of the neutron or proton and carries a single negative charge.

Beta rays cause ionization with resultant chemical and biological changes in tissues essentially the same as X rays and gamma rays which are electromagnetic radiations. Beta rays penetrate tissues to a small degree and the amount of penetration is proportional to their original energies. Energy of the particles is designated by a suitable unit called the electron volt. This unit is defined in terms of the mass and speed of the particles. Beta particles have varying energies depending on the nuclear disintegrations of specific radioactive elements so that a spectral distribution of energy results. Peak energy is generally three to four times the average energy. Strontium–90 emits beta particles with a peak energy of 0.65 Mev and decays to its daughter product yttrium–90 which emits beta particles with a maximum energy of 2.16 Mev. Beta particles possess a unique and special advantage in the treatment of superficial lesions as their penetration into tissues is limited.

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CHOICE OF A BETA RAY EMITTER

It is now possible to produce in considerable amounts many radioactive elements suitable for use in beta ray applicators. The criteria for selection of a beta ray emitter are:

1. The emitter half-life should be sufficiently long so that replacement or replenishment is at a minimum.
2. The isotope should be a pure beta ray emitter unaccompanied by gamma rays so that the problems of deep penetration and protection of the operator are more easily resolved.
3. The energy of emitted beta particles should be sufficient so that their range in tissues is suitable for biological purposes.
4. The radioisotope should have suitable chemical characteristics so that it may be manipulated and handled easily when being placed in an applicator.

Radioactive strontium is one of the ideal elements fulfilling these criteria. It has a half–life of about 25 years which means that there is comparatively little change in its radiation intensity over any considerable length of time. It emits pure beta rays and has energetic particles of adequate penetration for biological purposes. The energy falls off very rapidly with depth in tissues so that at 1 mm it is 50%, at 2 mm 25% and at 3 mm 15%. Strontium–90 can be handled comparatively easily as it is quite soluble in acid solutions; further, it decays to yttrium–90 which has a half–life of 62 hours and emits energetic beta particles to form the stable isotope of zirconium–90.

CONSTRUCTION OF THE APPLICATOR

The applicator contains 40 mc of strontium–90 in equilibrium with its daughter product yttrium–90 in a plaque made of stainless steel and aluminum sealed by

a double hermetic seal. The protective metal covering, which is approximately 100 mg per cm^2, separates the radioactive source from the irradiated tissues. Diameter of the applicator without covering is 5 mm while the over-all diameter is 12.7 mm. The surface of the covering material is fixed to a shaft about 15 cm long so that it can be held firmly against the eye lesion at a distance from the operator's hand. A circular plastic shield, which slides along the shaft, gives extra protection to the hand. Treatment output of this applicator as used is in the range of 45 rep/sec. The beta ray emission is accompanied by soft X rays known as "Bremsstrahlung."

BETA RAY DOSAGE UNIT

Ionization, one of the consequences of beta particle irradiation, is the means by which energy is transferred to tissues. It has proved profitable, during the years in which X rays have been used for therapeutic purposes, to utilize a dosage measurement which is dependent on ionization in air. The unit of measurement, the roentgen, is concerned with the ionization produced in a fixed mass of air as a result of incident X rays or gamma rays. Recent attempts have been made to utilize the roentgen unit or one very closely related to it for the measurement of radiation dosage for all types of ionizing electromagnetic radiations or particles. This has resulted in the conception of an equivalent roentgen as a measure of the dose, or the energy absorbed in tissues from the incident radiation, called variously: the gram roentgen, roentgen equivalent physical (rep) or tissue roentgen. All of these have the same basic concept, that is, energy absorbed in tissues.

One rep is considered to represent 84 ergs of energy absorbed in one gram of tissue, and is based on the energy absorbed from one roentgen in one gram of air. In the case of beta ray sources, it is therefore possible to calculate dose in rep by measuring the number of particles of known energy absorbed in a known volume of air at the surface of tissues exposed and taking into account the absorption in the tissues which is directly related to the energy.

BIOLOGICAL ACTION OF BETA PARTICLES

Friedell, Thomas and Krohmer[4] did biological calibration of a strontium–90 applicator relative to various tissues and studied the effect on the skin as the general characteristics of skin erythema are fairly well known. Studies on the tolerance of normal and vascularized cornea were made. The response to radiation of the latter appears earlier than in normal corneas. The newly formed vessels are more sensitive to radiation than the cornea proper. Their studies in both human beings and animals showed that infiltration of young fibroblasts and vascular buds are sensitive indicators of radiation effect. It is a general finding in radiotherapy that normal tissues are less sensitive than pathological tissues. The thyroid gland, for example, is not sensitive to doses which will produce profound effects when the gland is in a state of hyperfunction. Radiotherapy is based in part on this variation of radiosensitivity—that is, the difference in tolerance of normal and pathological tissues.

It is also important to compare tolerance of various ocular structures. Early experiments of von Hippel, Boussuet and Pagenstecher indicate that irradiation of the pregnant uterus of guinea pigs, rabbits and dogs may cause developmental anomalies of the lids and degenerative changes of the crystalline lens of the foetus. Exposure of the rapidly growing eye of young animals may cause retardation of development of the eyeball as a whole and pathological alterations in the lids, conjunctiva, cornea, lens and iris. Retardation of development is greater the younger the animal and diminishes rapidly with age at the time of exposure. It varies in degree with the dose of roentgen rays and with the time elapsed between irradiation and observation. Wilson[14] has shown that the minimal inflammatory reaction is seen only after exposure to 35,000 rep. A similar observation has been made by Friedell *et al.*[4] These authors performed a study to determine the effect of high doses on the human cornea in a case in which the eye had to be removed because of a tumor. A single dose of 30,000 rep was administered. Within one week there was epithelial injury, and three weeks later when the eye was removed there was extensive damage to the epithelium and stroma of the cornea.

Clinical observations of the three cases of tumors of the limbus, which will be reported in this paper, indicate that the cornea can stand very high dosage levels.

Depth dose curves of the applicator show that there is rapid fall of the energy so that only a very small fraction of the dose reaches the lens which then remains undamaged and radiation cataract is thus avoided. Such damage is extensive if X rays or gamma rays are employed.

DOSAGE SYSTEM

Fractionated dosage is the usual method employed in the treatment of eye lesions. The single fraction dose and the interval between successive fractions varies according to type of lesion, its duration and its extent. The usual single dose varies between 600 and 1800 rep. The usual interval is one week. The total dose depends on type of lesion and its response to the treatment. The importance of fractionation lies in the opportunity to assess effectiveness of the treatment and to decide on total dosage according to the response. This approach permits some individualization of each case and serves to enable selection of the lowest effective total dose.

For benign lesions, it is important to obtain a satisfactory response with minimum dose in order to avoid permanent radiation injury. Fractionated treatments also permit the radiosensitivity differences between normal and pathological tissues to become operative.

CLINICAL APPLICATIONS

My experience with this applicator covers a period of four years during which 65 cases were treated in

private practice. These are distributed as follows: tumors 3 cases, vernal catarrh 17 cases, pterygia 21 cases and corneal vascularization 23 cases. Detailed reports are presented of the cases treated, including the dosage given, the response to treatment, some clinical observations and the results of treatment.

Corneal Vascularization

Lederman[10] in 1952 considered X rays for the treatment of corneal vascularization. Development of beta ray sources has overcome most of the original objections to this form of treatment. The beta ray applicator found its primary usefulness in efforts to obliterate corneal vessels. Friedell and associates reported good results in cases designated as candidates for keratoplasty.

Anaesthesia of the eye is achieved by application of 1% pontocaine followed by immobilization of the lids with a sterilized speculum. The applicator is applied directly to the vascularized area along the limbus to affect the vessels near their origin.

Twenty three cases of superficial corneal vascularization were treated. Out of this series, 15 cases were referred for post-keratoplasty irradiation. The first case was a 65-year-old male patient who was referred two months after operation. On examination, the graft was seen to be opaque and accompanied by superficial vessels. The vessels were obliterated by 9000 rep given at weekly intervals over a period of one month. This was considered as a pre-operative course. Another operation was performed with rapid development of new vessels. Unfortunately, this patient was referred for post-operative irradiation at a late date when the graft was already opaque. The remaining 14 cases received post-operative irradiation at periods which varied between 10 and 20 days after operation and their dosage levels between 6000 and 12,000 rep. Two cases showed moderate response while the rest showed good results. The remaining 8 cases received a pre-keratoplasty course over a period of one month with a total dosage level of 6000 to 9000 rep. In all these cases the vessels were successfully obliterated. One of these cases had a bilateral corneal opacity following virus keratitis with superficial vascularization. A post-keratoplasty course was given to one case in this group. Two cases receiving post-graft irradiation complained of dimness of vision after the first dose, which gradually improved in the course of a week's interval. This reduced vision may have been due to reactionary dilatation of the vessels after the first dose.

Corneal vascularization may be considered generally under three categories: superficial, deep and mixed. The superficial type is most often encountered prior to keratoplasty, following keratoplasty and in corneal ulceration. It is advisable to start post-keratoplasty irradiation as early as possible; the average period in our experience has been 10 to 14 days. Dosage level should be the same whether the graft is lamellar or whole thickness. Corneal graft usually is performed 10 to 14 days after the last pre-operative dose.

This series did not include corneal ulcers. Ulcers that show superficial vascularization often heal readily when the vessels are obliterated by beta irradiation.

Deep vascularization requires higher dosage levels than superficial vessels. This type of lesion in interstitial keratitis is chiefly due to tuberculosis and syphilis. These cases are often presented for keratoplasty and the associated deep vessels must be obliterated.

Pterygia

Out of the 21 cases of pterygia referred for beta irradiation, there was one with a thin pterygium, 9 with recurrent pterygia and 11 for post-operative therapy. In this series, recurrence appeared as early as one week after the operation, while the others occurred at various intervals with an average of one to two months. The surface total dose in these cases varied between 9000 and 11,000 rep fractionated over a period of four to five weeks. The average dose for post-operative irradiation was 6000 rep. My experience with these cases indicates a routine of post-operative irradiation. The earlier the treatment is applied the better are the results with moderate doses.

All the cases treated showed good response.

Vernal Catarrh

Out of the 17 cases treated, 13 were males and 4 females. Fourteen cases were palpebral, one case was bilateral limbal and two cases involved bilateral limbar and palpebral conditions. Duration of the disease before treatment was started varied between one and ten years. Dose ranged between 6000 and 10,000 rep fractionated at weekly intervals. The single dose varied between 1000 and 1500 rep. Two cases received two series of treatments because of recurrence of the condition, in one case after three months and the other after one year. Both showed no recurrence after the second course. The first case showed an interesting condition. This 30-year-old male patient had extensive bilateral palpebral thick masses which were adequately controlled after two courses of beta irradiation. This patient was completely relieved from his long-standing allergic rhinitis which had been unsuccessfully treated over an extended interval of time. The result could be attributed to the effect of the destroyed elements and the liberation of their contents into the general circulation.

In cases of vernal catarrh, the follicles are radiosensitive and respond promptly to small doses of radiation. Usually the limbal type requires smaller doses than the palpebral variety after which the elevated gelatinous lesion responds well, leveling off promptly. Attention should be given to follicles high on the tarsal cartilage since these produce the most irritating symptoms. Long-standing cases may require surgical removal to keep dosage level at a minimum.

Tumors

Three male patients with carcinoma of the limbus were referred for beta irradiation. The first was a 60-year-old individual with a large tumor involving

about half of the limbus and encroaching upon the cornea. The tumor had been present for five years. It was removed and the biopsy report was as follows: "A squamous cell carcinoma most probably complicating an old squamous cell papilloma." Daily fractional doses were given to three fields, each field receiving a total surface dose of 15,000 rep over a period of 10 days. A mild reaction developed two weeks after the last dose, but the patient has now been free from local recurrence for two years.

The second case was that of a 70-year-old diabetic male patient who had a large conjunctival mass near the limbus of the right eye and a few enlarged, hard, deep cervical glands above on the right side. The tumor was removed and the biopsy report suggested an epithelioma. A total surface dose of 18,000 rep was delivered to each of the two fields over a period of 12 days. Regional lymphatics were irradiated with external irradiation using a beam screened by a half-value equivalent of 0.9 mm Cu. A total surface dose of 4500 was given over a period of four weeks. Local reappearance occurred four months after the treatment. The eye was removed and block dissection carried out, but the patient died a few days after the operation.

The third case was that of a 73-year-old patient who had had a pterygium for eight years. The patient noticed a sudden elevation of the corneal part of the pterygium. Surgical biopsy revealed a moderately undifferentiated squamous cell carcinoma. Estimated thickness of the tumor was 2 mm. Each of the six fields used received a total surface dose of 20,000 rep over a period of 17 days. No local reaction was noticed. The tumor disappeared and the patient has been free from local recurrence for eight months after the treatment.

Other tumors that respond to beta irradiation and reported in the literature are conjunctival and limbal papillomata. Haemangiomata of the eyelid and conjunctival surface respond well to beta irradiation. They require small doses in the range of 3000 rep. Regression begins promptly but progresses slowly. Chronic chalazion responds well to 1000 rep repeated once or twice at weekly intervals. Tuberculous sclerokeratitis responds well to an average fractionated dose of 5000 rep over a period of five weeks.

Cases of conjunctivitis that resist all other forms of therapy are reported to show satisfactory response to beta irradiation. Friedell and associates[4] have described one case of chronic conjunctivitis which had resisted other forms of therapy but which showed satisfactory response to beta irradiation. They reported that it was a case of unknown aetiology and that the conjunctival surface of the upper eyelid was thick, oedematous and velvety in appearance, with a moderate area of mucopurulent secretion. I think this may have been a case of trachoma.

Both the papillary and follicular types of trachoma respond well to beta ray therapy which cuts short the duration of the disease. Trachomatous pannus is best treated by beta irradiation designed to obliterate the superficial vascularization present and to prevent further complications of corneal ulceration and opacities.

One of my interesting cases was that of a 45-year-old teacher who had an inflammatory mass. His left eye sustained a caustic injury in the chemical laboratory at a school. He developed a traumatic granulomatous conjunctivitis one week after the trauma. The mass was oval and measured 12 by 8 mm and was 6 mm thick. Because of the radiosensitivity of such lesions, the patient was referred for beta irradiation. Two courses were given over a period of four months. Each course consisted of six treatments at weekly intervals. The single dose was 2400 rep. The large mass levelled off nicely. Such lesions respond to small doses of radiation, but because of the unusual thickness of the mass in this case, large total doses were administered.

COMPLICATIONS THAT MAY BE DUE TO BETA IRRADIATIONS

Heavy irradiation in the region of the limbus may predispose to glaucoma due to induced fibrosis around Schlemm's canal or destruction of the aqueous vein in this area.

Production of cataract must always be kept in mind. Friedell and associates reported, after four years' experience with a strontium–90 medical applicator, that they had no complications of any consequence with this applicator. The estimated dose to the surface of the lens were less than 10% of the dose delivered to the cornea and, assuming the diameter of the lens to be 3 mm, the average calculated dose to the lens was 3%. The same workers used a radon applicator for 10 years which gave larger doses to the lens due to the additional gamma rays and they state that no evidence of cataract formation was noticed. In the cases reported in this paper no complications were noticed.

In conclusion, from the physical, biological and clinical points of view, the Sr^{90} medical applicator as reported by various authors has proved to be of great value in the treatment of various eye lesions.

SUMMARY

The general principles of therapy and the physical and biological properties of beta particles have been discussed. The strontium–90 medical applicator is a useful source of radiation which has been effective in the control of some eye lesions such as corneal vascularization, pterygia, vernal catarrh, tumors of the eye and conjunctivae, and inflammatory conditions. A summary of the result of treatment of 65 cases treated in private practice over a period of four years has been given, including the methods of treatment and considerations of dosage. The value of treatment of trachomatous complications has been pointed out.

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Caesium-137 in Short Distance Radiotherapy

By Friedrich Gauwerky

Treatment of cancer by local application of radioactive substance is methodically built up in the effort to damage almost exclusively the tumor tissue by ionizing radiation and at the same time to avoid damaging the neighboring tissues as much as possible. Based on the physical, technical and anatomic conditions the following possibilities of proceeding are given.

1. *Placement into the tumor tissue itself* of radioactive substance by implantation, infiltration, micromechanical or metabolic application. These techniques are suitable for treatment of tumors of limited size located in accessible anatomic regions.

2. *Placement on the surface* of radioactive substances in applicators. This is the method of contact therapy. It is useful for treatment of relatively small tumors of limited depth where rather large differences of dose between surface and depth can be tolerated. In both Placement Methods 1 and 2, dose distribution within the growth is influenced by size and shape of applicator, and by distribution of radioactive sources within it. No dose reduction by shielding needs to be considered in gamma-ray therapy.

3. *Placement at short distance* of radioactive substances by special applicators. This method includes all types of gamma-ray therapy with source-to-skin distances of 10 to 50 mm. It is suitable for treatment of tissue volumes not too extensive, because of anatomic conditions, to be reached satisfactorily by use of the principles mentioned above. Higher depth doses can be obtained by utilization of the inverse square law. This feature has particular usefulness in connection with tumors whose precise dimensions cannot be evaluated sufficiently by conventional methods of clinical examination. Usually in these cases it is necessary to irradiate the neighboring (possible tumor bearing) tissue with relatively high doses.

Within a limited space, especially in body cavities, short distance gamma-ray therapy can be realized only by applying the radioactive source centrally. In such a case, the distribution can be modified only by (*a*) size and shape of applicator around the source, (*b*) employment of heavy metal shields close to the central source, and (*c*) use of gamma radiation of medium energy.

For practical reasons, high photon energy should not cause application of intolerably thick layers of heavy metal, but on the other hand dosage distribution should not be influenced by a noticeable degree by tissue absorption. In order to obtain definable conditions, it is desirable that only inverse square law, geometry of radiation and shielding should influence isodoses. Gamma ray energies from 300–600 kev are advisable and monoenergetic gamma radiation is preferred. A radionuclide of long half-life should be chosen. Only caesium-137 which has, through barium-137, a monochromatic gamma radiation of 0.662 Mev and a half-life of about 25 years, corresponds closely with the conditions defined above. Tantalum-182 and iridium-192, already recommended for a similar purpose, are not suitable because of their shorter half-life (117 and 170 days, respectively). Inasmuch as all caesium salts are highly hygroscopic, this easily available fission product must be used in closed tubes. Caesium-137 tubes 15 mm in length and with an activity of 50 mc have been at our disposal, and we have been able to realize the possibilities of short distance gamma-ray therapy using suitable applicators. Two types are at our disposal now: vaginal cylinder and cervix block (portioblock). They enable us to provide highly diversified yet highly reproducible tissue isodoses in a very easy way. Obtainable dosage distribution will be described.

The applicators consist of plastic, which can be boiled, lucite parts and tungsten shields up to 6mm in thickness, usable so that if necessary gamma doses can be reduced as much as one-third.

The vaginal cylinder, being the first caesium applicator employed, may bear in an axial hollow up to 6 caesium tubes. With this cylinder, the radiation can be reduced by tungsten shielding in an angle of 180 to 270 degrees to the extent mentioned above. A fastening button is connected to a metal bow which can be rotated and fixed in any position. The bow serves for fixation of the instrument to the patient. Vaginal cylinders are available in different sizes to meet the space conditions of any patient. Dose rates at the surface of the vaginal cylinders, the parts not shielded by tungsten, vary between 70 and 175 r/hr, depending on the number of caesium tubes and the diameter of the instrument. Application times are from 10 to 20 hours as required.

The second caesium applicator is called *Cervix Block*. It enables a highly variable irradiation of the uterine cervix, including its environment and excluding as much as possible the bladder and rectum (i.e., the most radiosensitive neighbouring organs). It is a brick shaped body built of material like the vaginal cylinder, in which the source, usually loaded with

350 mc caesium-137, can be centrally or paracentrally fixed. Heavy metal shields can be put into the three parts of the applicator. Consequently irradiation can be reduced as much as one-third in any desired direction.

The principle applied in modeling isodoses, by use of more or less shielding in short distance gamma-ray therapy of medium energy, realizes the effort to give higher depth doses at centimeter distances from the applicator surface. The radiotherapist, however, must keep in mind that, under the premise of desirable equal surface doses, the volume doses in patient's tissues increase with linear proportionality relative to the average distance of the applicator surface from the centrally situated source. Consequently volume doses are 2 to 2.5 times higher than from conventional radium applications when caesium treatment according to the techniques described above is used. With respect to these conditions, special aspects of clinical radiology arise inasmuch as tissue tolerance varies remarkably in different anatomic regions, even in different parts of the same organ. As known, the vaginal mucous membrane, for instance, is much more radiosensitive near the introitus than in the middle or upper third. This example indicates how important it is to increase clinical experience by a cautious and rational use of this new radiotherapeutic equipment and method.

Short distance gamma-ray therapy of small volumes by use of caesium-137, as described above, has to date proved effective in 72 cases (28 carcinoma of the cervix, 8 carcinoma of the vagina, 21 recurrent conditions of gynecological tumors, 1 chorionepithelioma, 9 cancer of the rectum, 2 carcinoma of the female urethra, 1 cancer of the anus, 1 carcinoma of the vulva, and 1 carcinoma of the pelvis) that received 135 caesium applications all together, usually with a treatment procedure in each case that combined radium, cobalt-60 and deep X-ray therapy. Clinical courses corresponded with expectations and promise satisfying results. The caesium method therefore is recommended as a valuable aid to further refinement of individualized radiotherapy.

Strontium-90 for the Treatment of Trachoma in Egypt

By Ibrahim Ahmed Mohamed, Gamal El Din Abdeen and Saad El Din El Taoudi*

Trachoma used to be practically paramount in the population of Egypt. Owing to continuous medical combat, the steady rise in standard of living and the spread of education during the last 50 years, its incidence has gradually decreased, so much so that in some urban localities the percentage of all trachoma cases (active and cicatrised) may be as low as 40%. In rural communities, the percentage is still high—75% instead of 95% or more as in the past.

PATHOLOGY

Comprehensive histologic studies made on trachoma have shown it to involve chronic inflammation in all tissues of the lid, mucous and submucous, in which the most striking features are papillary hypertrophy of the epithelium, a lymphoid infiltration of the subepithelial tissues with typical formation of follicles, and subsequent proliferation of connective tissue resulting in scar formation. In the epithelium, transformation of tissue type, degeneration, proliferation and exfoliation, are characteristic.

In the early stages of trachoma, all elements in the subepithelial tissues take part in the general hyperplastic process. A diffuse infiltration occurs and lymphocytes collect to form follicles (Stage I). Though follicle formation is characteristic, it is not invariable, for some cases may show persistent generalised infiltration without a tendency toward aggregation into follicles. At the same time, hyperaemia and inflammatory oedema in the mucosa lead to formation of vascularised papillae which become secondarily infiltrated with lymphocytes and other cells (Stage II). Healing starts in the previous 2 stages with the appearance of scar tissue (Stage III) and in time cicatrisation becomes complete (Stage IV).

A layer of newly formed vascularised tissue rich in cells, called "pannus," may invade the cornea from the limbus. Typical follicles may be formed in the pannus.

STAGES OF TRACHOMA

The ordinary course of the disease has been, for convenience, divided into 4 stages corresponding to those identified above:

Stage I: Characterised either by a generalised subepithelial infiltration of the conjunctiva, or the appearance of early tiny follicles.

Stage II: Further evolution leading to the appearance of bleb-like easily expressible excrescences (IIa), or to papillary hypertrophy (IIb).

Stage III: Characterised by beginning absorption of the follicles or papillae, and early replacement by scar tissue.

Stage IV: Characterised by complete cicatrisation.

APPLICATOR

The radioactive strontium applicator used in our series was manufactured by Tracerlab. Its surface dosage rate was 73.5 rep/sec and its capacity 50 mc.

We started using this applicator for various eye conditions by the end of 1955 and we are still using it with success in many of them.

The systematic treatment of trachoma by strontium-90 application was started in April 1957. A series of 63 cases was selected from school children between the ages of 6 and 10 years. School children were preferred because of their regular attendance and the easy follow up. Five of the cases were females and 58 were males. It is worthy of mention that the female students are usually cleaner, more tidy, and less heavily infected with trachoma than the male.

DOSAGE

The fractionation method of exposure was the one applied; 500 to 1400 rep/sec were given per sitting, delivered every other day locally on the conjunctiva of the everted upper lid with constant regular movement of the applicator from the inner to the outer canthus. The lower lid also was treated. Total dose varied from 14,000 to 21,000 rep. Treatment of the pannus was carried out by asking the child to look down then putting the applicator directly on the upper limbus; a total dose of 14,000 rep was delivered for such cases.

OBSERVATIONS

In all cases, a careful and detailed recording of the type of trachoma and pannus was done before the treatment. Only one lid was given treatment, the other one being kept as control.

Observation of the results of treatment was done at various intervals after treatment: after one, two, and three months, and then at irregular intervals up to one year. The observation and the recording of progressive notes were done by the same observer who

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did not look at the patient's record before recording the existent status of the disease.

Symptoms of the disease were not taken into account in assessing results because of the fact that trachoma is quite symptomless in uncomplicated cases.

COMPLICATIONS

During the course of treatment, no complications were encountered except for some cases of secondary infection where the child developed some oedema of the lids and a slight discharge. Smears taken from the conjunctival sac of these cases showed a Koch Weeks infection or a sterile reactionary discharge. The irradiation was then temporarily stopped, and sulphadiazine tablets were given for 3 days. When the discharge and oedema disappeared, the irradiation was resumed.

IMMEDIATE AND LATE REACTIONS

During the course of irradiation, only one case showed necrotic eschar on the surface of the conjunctiva, which bled on peeling. A smear taken from the eschar showed numerous pus cells but was negative for organisms. When the treatment was suspended for a week, the eschar disappeared and irradiation was resumed.

None of the cases showed any late pathological changes during the whole period of observation.

RESULTS

As already stated, a series of 63 cases was irradiated. In all cases the left eye was the one treated, the right being kept as control. None of the cases showed noticeable changes before one month from the end of the course of beta therapy, which lasted approximately three weeks. Analysis of the results revealed marked improvement, with the disappearance of follicles and/or papillae, and early cicatrisation in 16 cases (i.e. in 25% of all cases). The follicles or papillae melted away leaving no or only a few vestigial traces, and cicatrisation appeared. These cases could be considered on the way to complete cure.

To illustrate these results, photographs were taken at about two months after the end of treatment. These show the right eye lid with its trachoma in full bloom, while the left, which was given the irradiation, shows the disappearance of follicles and papillae and the cicatrix formation (Figs. 1, 2 and 3).

Less marked improvement was observed in 21 cases (i.e., in 33%). In these cases, the number of follicles or papillae decreased but did not disappear completely, while cicatrix formation was minimal or none at all. Figure 4 shows the remains of follicles and early scar tissue. Twenty four cases showed no improvement at all (38%), that is, in which the papillae and follicles were present just the same as before the treatment and no sign of being affected by the irradiation.

In the remaining 2 cases (4%), the condition was recorded as becoming worse on account of the appearance of fresh follicles among the preexisting and persisting simple papillae.

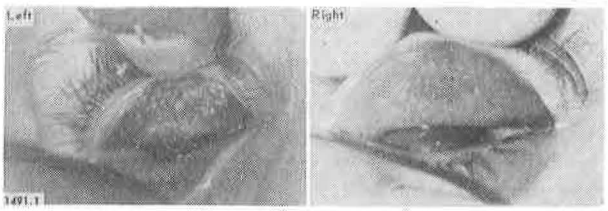

Figure 1. Follicular trachoma, Stage IIa. Right eye, control. Left eye, given a total dose of 14,000 rep in 3 weeks. Note the presence of follicles in the right, and cicatrisation with traces of follicles in the left

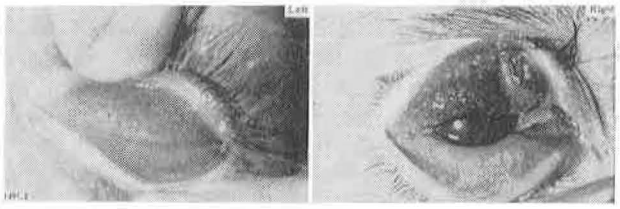

Figure 2. Follicular trachoma Stage IIa. Right eye, control. Left eye, given 14,000 rep in 3 weeks. Note the presence of follicles in the right, and the absence with total cicatrisation, in the left

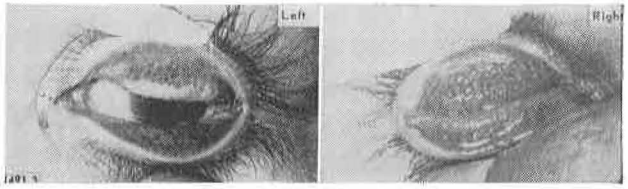

Figure 3. Papillary trachoma Stage IIb. Right eye, control. Left eye, given a total dose of 21,000 rep in 4 weeks. Note the presence of papillary trachoma in the right, and their complete disappearance and advanced cicatrisation in the left

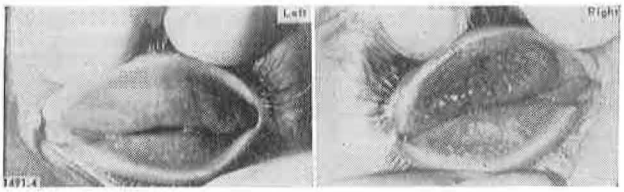

Figure 4. Right eye, control. Left eye, given a total dose of 14,000 rep in 3 weeks. Note the presence of follicles and papillae in the right, and their partial resolution and starting cicatrisation in the left

Thus, we see that 58% of the cases either were cured, or were on the way to being cured, while the remaining 42% showed no improvement.

It is noteworthy that during the long period of observation, although one eye was kept as control with its active trachoma, no reinfection was seen to reappear in the irradiated eyes which had shown amelioration or cure. Further analysis of the results shows that the follicles are more sensitive to beta rays than the papillae. This fact accounts for the greater number of cases which showed no improvement.

Pannus vessels, which with slit lamp examination were found to be present in all cases and which crossed the upper limbus for a variable distance, showed no

change after irradiation even in those cases which greatly improved.

COMMENTS AND CONCLUSIONS

The results of our experiment are encouraging as they show that pure beta ray irradiation can be used in the treatment of trachoma in all its stages, with expectation of cure in nearly 60% of cases.

One is impressed with the possibility that the remaining 40% of cases, which were mainly of the papillary type that had resisted the treatment, might have shown better results if larger doses had been given. The treatment used was a safe one with no immediate or late complications. It is easily applicable, painless and of relatively short duration. Also, no special protection of the patient's eye is needed.

One would expect difficulty in applying this method of treatment in hospitals receiving a great number of patients, such as occurs in our country; the 20 seconds application for each lid would cumulate into hours. Nevertheless, if treatment is restricted to some selected cases, it can be easily applied.

The end result of a smooth resilient lid without complications, is a sure advantage of this method of treatment, as compared with the ordinary methods being used.

SUMMARY

A brief account of the pathology and stages of trachoma is given together with a new method of treatment of the disease by means of a Tracerlab ophthalmic applicator which gives off strontium-90 pure beta rays. Doses were 14,000 to 21,000 rep, the applicator being applied on the everted lid. One eye was given the treatment, the other was left as control. One to two months after the end of treatment, about 60% of the cases, mainly of the follicular type, were considered cured. The treatment is easy, painless, and has no immediate or late complications.

Heidelberg Techniques of Contact Irradiation with Co^{60}

By I. Becker and K. E. Scheer

In 1950 and 1951 three techniques of contact irradiation by means of Co^{60} were developed in our clinic, and they have been applied to more than 1500 patients in the meantime.

BEADS OF Co^{60}

These beads were made originally of pure metallic cobalt that had been activated in a pile to about 4 mc for one bead. Each had a diameter of 6 mm and a central bore-hole 2 mm in diameter. As protection against corrosion, the surface (including the bore-hole) was coated galvanically with a layer of gold 50 μ in thickness. In applying these beads for several years, we found that coating with gold did not afford complete protection against corrosion. We therefore replaced them with beads of metallic gold of the same shape and dimensions, but containing a little ring of activated cobalt. This arrangement proved completely resistant against mechanical and chemical attacks.

Cobalt beads are used mainly for intracavitary irradiation. The required number is strung on a thread of silk which can be introduced into cavities by means of tubes with outside diameter of 8 mm. For larger cavities, for example the urinary bladder, active beads are strung alternating with inactive plastic beads of the same size and shape in order to enlarge the volume of the chain without increasing the total activity. Use of cobalt beads is indicated when natural or artificially created cavities of the body are to be irradiated—that is, tissue locations not readily accessible to treatment with outside sources of radiation. We have also used Co^{60} beads in molds for contact irradiation of extensive lesions of the skin. For this purpose, we prepare plates of foam-rubber perforated with 5 mm holes 1 cm apart. When a bead is placed alternatingly every second hole there results a rather nonhomogeneous dose distribution and an effect obtained comparable to that of grid irradiation.

PLASTOBLOCKS

This method involves a moldable inactive material in which are embedded a large number of sphere-like sources of Co^{60} measuring 2 mm in diameter. These pellets were made originally of a hard plastic but now are manufactured of metallic gold containing a core of Co^{60}. Owing to the large number of individual sources of radiation per unit volume, the mold material has always the same specific activity. To prepare a mold, the required amount of material is warmed in hot water and shaped on a radiation protected table by means of wooden tools with long handles. To avoid direct contact between the shaped mold and the patient, the mold is wrapped in wet cellophane, and for intracavitary application is put into a condom. Preparation of molds by this technique is accomplished within a few minutes. Since each mold is shaped individually to meet conditions in individual patients, it is necessary to measure the dose for each mold as used. For this purpose, an instrument with a crystal of cadmium sulfide (described elsewhere) proved satisfactory.

When comparing plastoblock with Co^{60}-bead techniques, there is a simple criterion for choice. When access to a cavity is nearly as wide as the cavity itself, we use plastoblock because it can be introduced in its final shape and easily secured. In contrast, when access to a cavity is much smaller than the diameter of the cavity, we use Co^{60} beads because they can be introduced as a straight chain by means of a tube and they fill out all the volume of the cavity by forming a pool.

For treatment of extensive lesions of the skin, we previously applied large thin plates of plastoblock shaped in the desired way. Recently these have been replaced with plates of foam-rubber filled with beads because their shape can be adapted in a better way and because they can be attached more easily.

MACROSUSPENSION

This technique is a modification of the well known method of filling rubber balloons, that have been introduced into a cavity of the body, with radioactive solutions, as applied in numerous institutes. We replaced the solution with a suspension of 2 mm Co^{60} pellets contained in an inactive jelly. With a large number of such pellets (we use 1600 per 100 ml of fluid) the resulting random distribution produces an isodose distribution which is in excellent agreement with that obtained by a radioactive solution with the same geometrical conditions. The gelatinous nature of the fluid prevents settling or rising of the pellets when there are small differences in specific weight. This macrosuspension can be introduced into rubber balloons as well as a solution, provided the diameter of the tubing enables the pellets to pass. By this approach we preserve all the advantages of the balloon-solution method but avoid the risks of radioactive contamination.

The introduction of macrosuspension into a rubber balloon takes several minutes. It is accomplished by means of a shielded storing vessel and controlled by air pressure at a distance of about 2 m which affords effective radiation protection.

Compared with the use of Co^{60} beads, the technique of macrosuspension shows an advantage when it is possible to place inside the cavity a source of radiation much larger in volume than would be possible by means of beads. Inasmuch as the depth dose that can be obtained with a source of gamma rays depends almost exclusively on the diameter of the intracavitary source of radiation, a higher relative depth dose can be obtained when applying macrosuspension. It is applicable mainly for the urinary bladder, the rectum and the sigma.

RESULTS

By means of the techniques described, we have treated more than 1500 patients from 1951 to 1957 (Table 1). Most of the patients treated had malignant

Table 1. Cases Treated with Different Techniques

Site of tumor	*Number of patients*	*Treated with*		
		Co^{60} beads	*Plastoblock*	*Macrosuspension*
Urinary bladder	497	472	—	25
Glioblastoma multiform	72	72	—	—
Maxillary antrum and epipharynx	285	99	186	—
Rectum-sigma	121	—	96	25
Female genital tract	328	74	237	17
Skin	271	26	245	—

tumors in advanced stages. Treatment by means of Co^{60} has been executed mostly as a supplement to X-ray or betatron therapy. For tumors of the brain and the maxillary antrum, the application of Co^{60} beads has always been performed in connection with an operation.

Because of wide variation in tumor localization, the state of progression of lesions and previous therapy, it is not possible to give a statistical analysis of survival time as a means of evaluating the efficiency of Co^{60} contact therapy.

However, based on seven years' observation, a series of typical indications for different forms of tumors has been elaborated.

Carcinoma of the Urinary Bladder

In most of these cases, Co^{60} beads were applied. Out of thirty-eight cases treated in 1952, five lived for more than five years. We consider the technique to be indicated for papillary and for infiltrating carcinomas. Originally we applied a surface dose of 10,000 to 12,000 r in two applications, but later we reduced the dose to 6000 to 8000 r and applications to one as the radiation reaction was found to be less with the same effect on the tumor (Fig. 1).

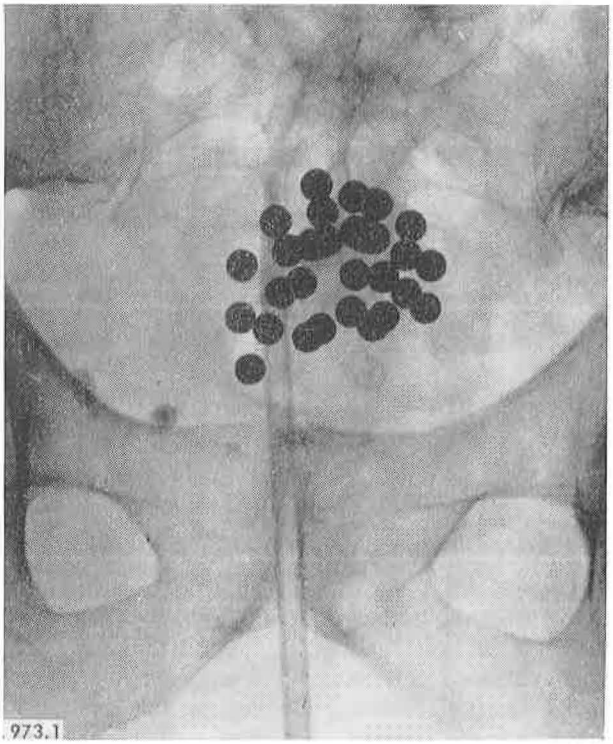

Figure 1. Twenty-six Co^{60} beads plus 26 inactive beads introduced in the urinary bladder

Brain Tumors

With a few exceptions we treated only glioblastoma multiform by inserting a chain of Co^{60} beads immediately after removal of the tumor. Out of ten patients treated in 1952, two are still alive after more than five years. The most striking observation was that no case of cerebral edema occurred in patients irradiated with cobalt. The technique has been modified in order to keep the personal dose low. During operation a rubber balloon is placed where the tumor has been removed and the filling with beads is done only when the operation has been finished (Fig. 2).

Carcinoma of the Rectum

Contact therapy is considered only as a supplement to percutaneous X-ray or telegamma therapy. In the

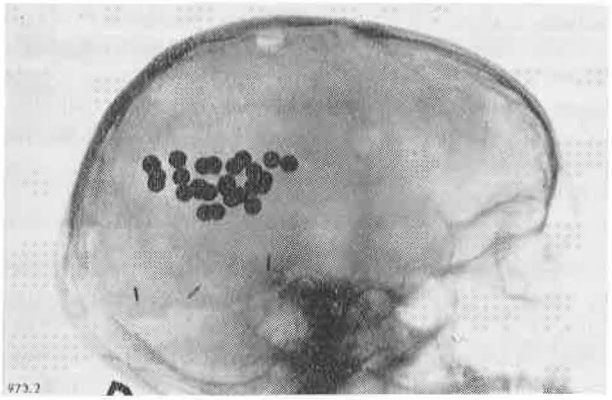

Figure 2. Twenty-six Co^{60} beads plus 26 inactive beads placed after removal of a glioblastoma multiform

rectum molds of plastoblock are applied, and in the sigma balloons filled with macrosuspension. In cases with small stenosis, macrosuspension is also applied in the rectum. The dose is between 3000 and 5000 r on the surface (Fig. 3).

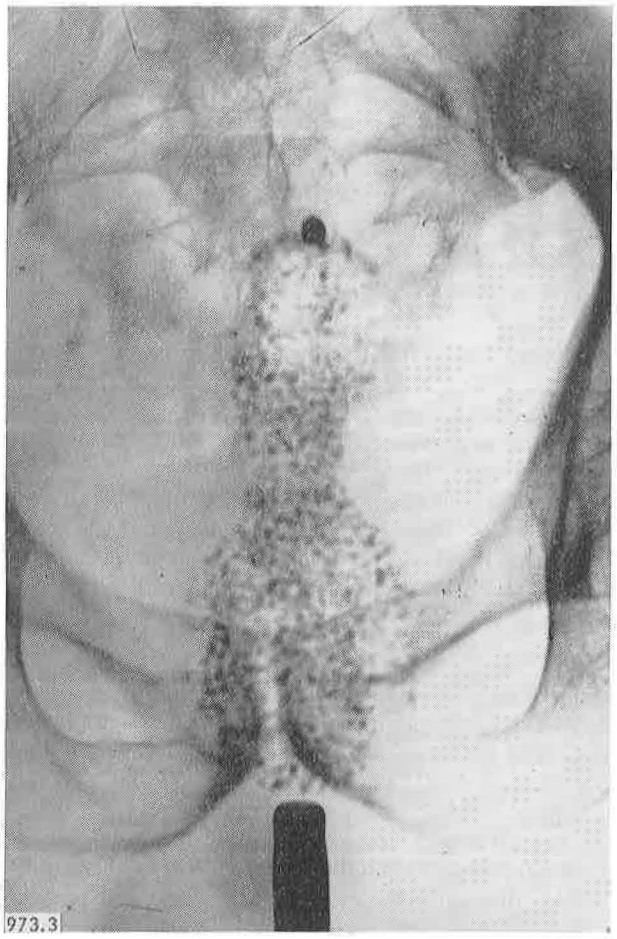

Figure 3. Rubber balloon filled with macrosuspension in a rectum

Carcinoma of the Maxillary Antrum

When the bony palate is conserved, the postoperative application of Co^{60} beads is very simple. When the bony palate is removed molds of plastoblock are applied. A dose of 10,000 r on the surface is well tolerated without reaction of the bone (Fig. 4).

Carcinoma of the Epipharynx

Fifteen to 20 Co^{60} beads are introduced in a small rubber bag after electrocoagulation of the tumor. Doses of 5000 to 6000 r on the surface are applied.

Carcinoma of the Genital Tract

For carcinoma of the corpus, the Co^{60}-beads method corresponds in principle to the packing technique of Heyman. An advantage of the beads is that less than one minute is taken for application. Accordingly, the personal radiation dose is kept very low. For cancer of the neck we think it justified to fill also the uterine

Figure 4. Mold of plastoblock in a case of sarcoma of a maxillary antrum

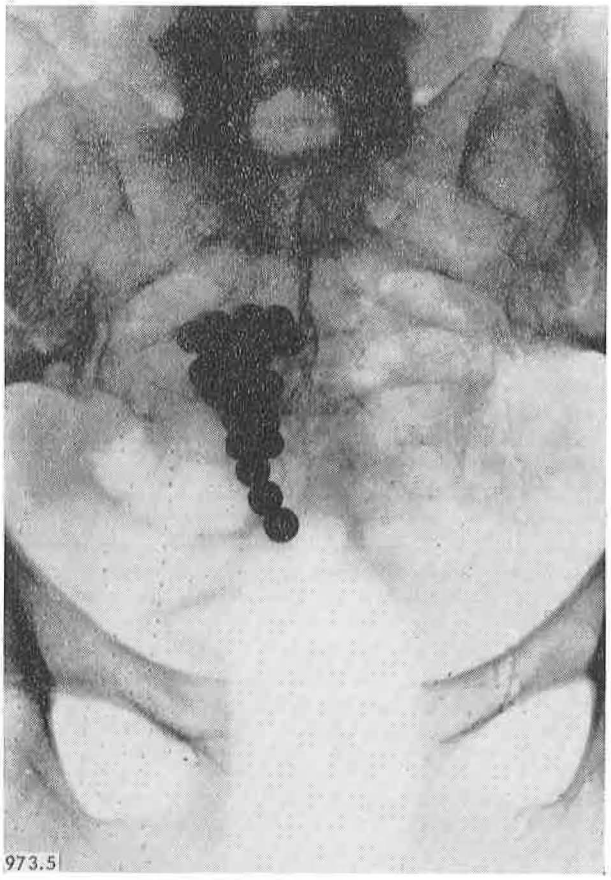

Figure 5. Uterus filled with 26 Co^{60} beads

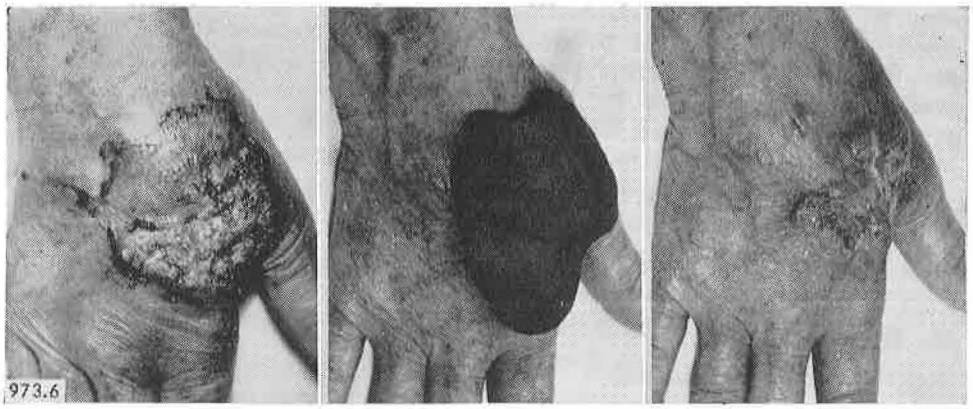

Figure 6. Spindle cell carcinoma of the back of the hand. Left: before treatment; middle: mold of plastoblock in position; right: two months after treatment

cavity with Co^{60} beads in connection with a mold of plastoblock fixed in contact with the petiole. The dose applied is the same as is usual for radium. For carcinoma of the vulva, we rejected contact therapy by means of molds of plastoblock and apply now electron beam radiation with a betatron (Fig. 5).

Skin Tumors

For tumors of the skin, therapy with molds is indicated in special cases only. There may be extensive carcinomas on the head where large areas of bone are lying immediately under the tumor. Preservation of bone is assured by Co^{60} mold therapy more than by any other form of radiation treatment. For benign lesions such as hemangiomas on children we were not satisfied by the results and therefore rejected it. We feel that extensive lymphangitis carcinoma after a cancer of the breast is very suitable for contact therapy with Co^{60} molds. Intracutaneous metastasis disappears when irradiated with rather small doses in the order of 2500 to 3000 r. By irradiating strips about 5 cm in width, further spreading of metastasis can be stopped. Since X-ray therapy of large areas as in lymphangitis carcinoma requires much time, the mold technique is advantageous (Fig. 6).

The indications listed above for contact therapy by means of Co^{60} have proved satisfactory and the techniques described can be considered as valuable supplements to conventional or supervoltage radiotherapy.

SUMMARY

Three techniques of contact irradiation by means of Co^{60} have been described: Co^{60} beads, molds of plastoblock and macrosuspension. These have been applied to more than 1500 patients during seven years. A series of typical localized tumors proved suitable for radiotherapy by means of these techniques. Typical indications were presented and discussed. Within these indications, the methods described are considered to be a valuable supplement to other forms of radiotherapy.

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Strontium-90 in the Treatment of Cystic Glandular Hyperplasia of the Endometrium

By P. Czerniak,* E. Rabau† and K. Rikower‡

The treatment of cystic glandular hyperplasia of the endometrium[1–4] demands: anatomical and functional safeguarding of the uterus in young patients who want to bear children, a quick and effective treatment in cases of prolonged menometrorrhagia which may cause serious anemia, a gynecological and histological diagnosis, and a carefully planned treatment. The treatment may be endocrine,[5,6] surgical[7,8] or radiological. The latter utilizes X rays,[9] radium[10–13] and lately radioactive isotopes.[14,15]

It is desirable to use ionizing radiations which will penetrate the hyperplastic mucosa of the uterus without affecting the other pelvic organs. Such a radiation is β radiation as, e.g., emitted by Sr^{90}. The results of studies with Sr^{90}, initiated in 1956, are presented in this paper.

MATERIAL AND METHODS

Ten cases studied are summarized in Table 1.

Use was made of radioactive Sr^{90} in Monel tubes of 0.2 mm wall thickness and containing 10 mc each. Sr^{90} (half life 25 years) emits soft β radiation (0.54 Mev) and turns into Y^{90} (half life 2.45 days), which emits hard β radiation (2.35 Mev) and yields stable Zr^{90}.

The treatment consisted of placing two to three Czech applicators (Fig. 1) into the uterine cavity after dilatation of the cervix. The applicators contained 60 to 90 mc of Sr^{90} and were left in place from five to twelve hours. The radiation doses given and the clinical results are summarized in Table 2.

It is very important to estimate the radiation doses reaching the mucosa of the uterus, the tissues beneath, and the nearby organs. It is reported by Friedell[16] and Müller[17] that 50% of the β-radiation of Sr^{90} penetrates 1 mm of tissue, while the effective range is 4.4 mm. Under similar conditions, the intensity of β-radiation from Sr^{90} and Y^{90} is 2.1 times stronger than that from radium.

In our work we used Sievert chambers, a Kondiometer and a Bomke dosimeter to measure the radiation dose emitted from 50 mc Sr^{90}. They were placed inside the uterine cavity of a corpse. It was found that: (1) the uterine mucosa received from 550 to 700 mc hr, while the middle portions of the uterine cavity received more than the cervical and fundal areas; (2) the ovaries, urine bladder and rectum received only a fraction of a roentgen per hour, or 2 to 4 roentgens during a complete treatment of 10–14 hours; (3) areas external to the body received only nominal radiation. The radiation penetrating outside the uterus was not due to the β-emission of Sr^{90}, but to Bremsstrahlung (Fig. 2).

RESULTS OF TREATMENT

Follow-up of the cases included histological and clinical examinations. The histological one consisted of checking the changes that took place in the uterine mucosa by the use of endometrial biopsy before and after 15, 70, 115 and 150 days of treatment with 630–720 mc hr of Sr^{90}. The changes are represented in Figs. 3–9.§

Two weeks after treatment necrotic material with epithelial residues in it was observed, while 150 days after treatment (Fig. 9) the material contained fibrous and collagenous tissue, with a few inactive epithelial cells.

A smaller dose of radiation (560 mc hr) apparently permitted active epithelial regeneration with reappearance of menstruation. A larger dose (840 mc hr) resulted in complete damage of the uterine mucosa and partial damage of the myometrium (Fig. 10).

Clinical examination indicated that in two cases hyperplasia was accompanied by large myomas; bleeding followed the radiological treatment, and hysterectomy was performed. There was another case of a woman, who was treated 3 years earlier by endometrial electrocoagulation. Bleeding reoccurred 50 days after radiological treatment, and the enlarged and soft uterus was removed.

The other seven cases of straight hyperplasia showed good condition. Bleeding stopped two weeks to two months after Sr^{90} treatment and no complications appeared. In the case of the young woman, menstruation reappeared, while the six older cases showed persistent amenorrhoea.

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§ The examinations were carried out by Dr. Reif and Dr. Rosin of the pathological Departments of the Asaph Harofe and Tel-Hashomer Government Hospitals.

DISCUSSION

Radiological Problems

1. Which is the sufficient and the optimum dose of radiation to treat a case of endometrial hyperplasia? Malpas[18] recommends 2000 mg hr of radium (about 16,000 r to the mucosa) to achieve 98% recovery. Barr[19] uses 1500 mg hr of radium in a silver tube (12,000 r to the mucosa) with 91% recovery. Czech[20] started with 400 mg hr radium in a Monel tube, then, because of numerous relapses, increased the dose to 600 mg hr with 90% recoveries. We achieved good results‖ with 560 to 840 mc hr of Sr^{90} (6000–9000 r to the mucosa). It further appears that the radiation dose may be tailored to fit clinical requirements. Thus 500–560 mc hr of Sr^{90} (6000 r) is the right dose for young cases (anatomical and functional regeneration remaining possible). Older cases, preclimacteric and climacteric, should receive 700–750 mc hr (this brings about necrosis of the mucosa, fibrosis and inactive epithelial residues). The maximum dose of 800–850 mc hr causes complete necrosis of the mucosa, and sometimes infiltration of the myometrium plus secondary complications. This dose should be given only in cases of polyposis of the endometrium, and when the uterine cavity is over 10 cm long.

‖ With the exception of the two cases with myomata and the one unusual case after coagulation.

Figure 1. Three applicators with 7 tubes of Sr^{90} inside the uterus

2. What amount of radiation reaches the other pelvic organs? The use of Sr^{90} insures negligible radiation leakage outside the body (Fig. 2). The pelvic organs receive only minute radiation doses, as is apparent from Table 3. Thus during treatment with Sr^{90} the ovaries receive less radiation than from straight X-ray treatment of the pelvis and even less than from pyelography or tomography of the pelvis.

3. What is the probable genetic damage, if pregnancy is to follow the radiological treatment? Based upon a human genetic doubling dose of 50 r, the probable genetic damage from radiation treatment with Sr^{90} should be insignificant. A similar treatment

Table 1. Cases Treated with Sr^{90}

Age			*Clinical diagnosis*		*Histological diagnosis*	
Under 30	*30–50*	*Over 50*				
1	6	3	Meno-metrorrhagia, uterus normal	8	Cystic glandular hyperplasia	3
					Glandular hyperplasia with evidence of cyclic changes	6
			Meno-metrorrhagia, uterus enlarged	2	Polyposis of endometrium	1

Table 2. Radiation Doses and Clinical Results

No. of cases	*Details of Sr^{90} treatment*			*Clinical follow-up*	
	Strength of source (in mc)	*Duration of treatment (in hours)*	*Dose received (in mc hr)*	*Length of follow-up (in months)*	*Results*
1	80	7	560	20	Menorrhagia disappeared. Menses reappeared after a few months
3	90	7	630	12–24	Meno-metrorrhagia stopped Menopausal disturbances appeared in one case
3	70–80	9–10	700–720	12–22	In 2 cases menorrhagia stopped, in 1 case myoma and hysterectomy
3	60–90	8–14	810–840	2–16	In one case menopausis, in a second myoma and hysterectomy, in a third endometritis and hysterectomy

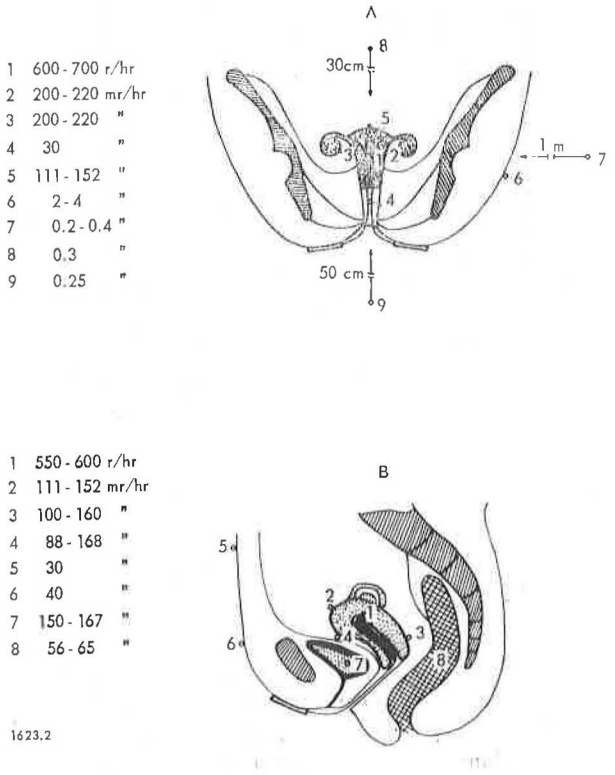

Figure 2. Intensity of ionizing radiation of various points in and near the pelvis, resulting from the application of Sr^{90} to the uterine cavity. Applicators with 50 mc of Sr^{90} used. A = anic-posterior view. B = lateral view

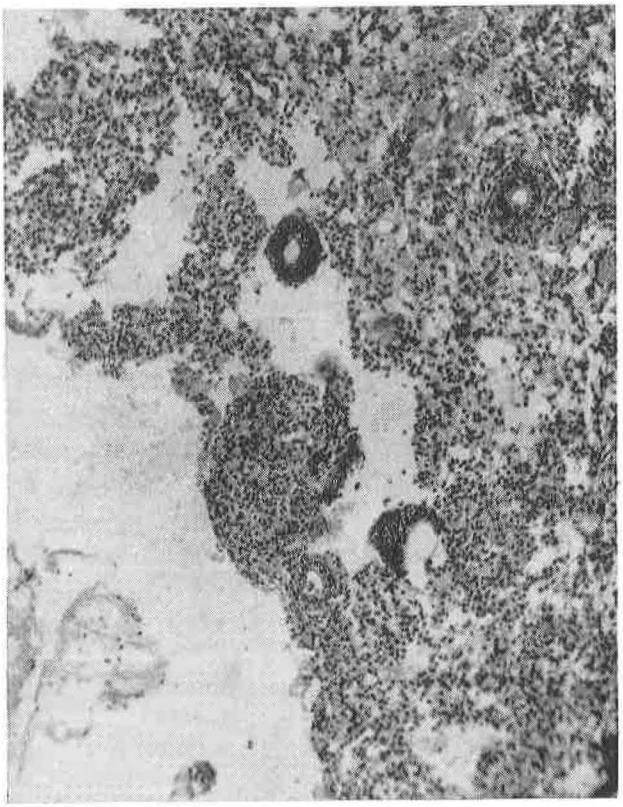

Figure 4. Endometrial biopsy of same patient (L.E.) 15 days following treatment with Sr^{90} (630 mc hr). Necrotic substance and several small specimens from the external part of the endometrium

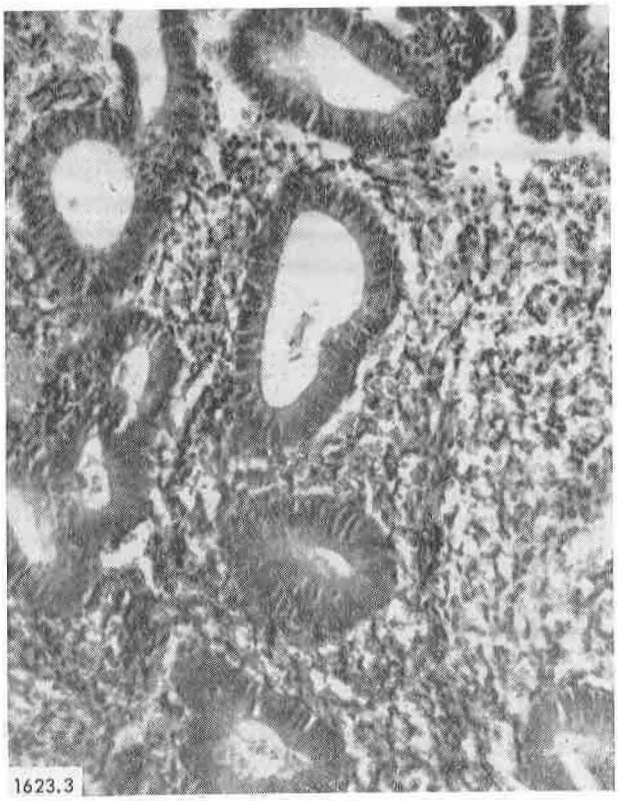

Figure 3. Endometrium of patient L.E. before treatment with Sr^{90}. Glandular hyperplasia

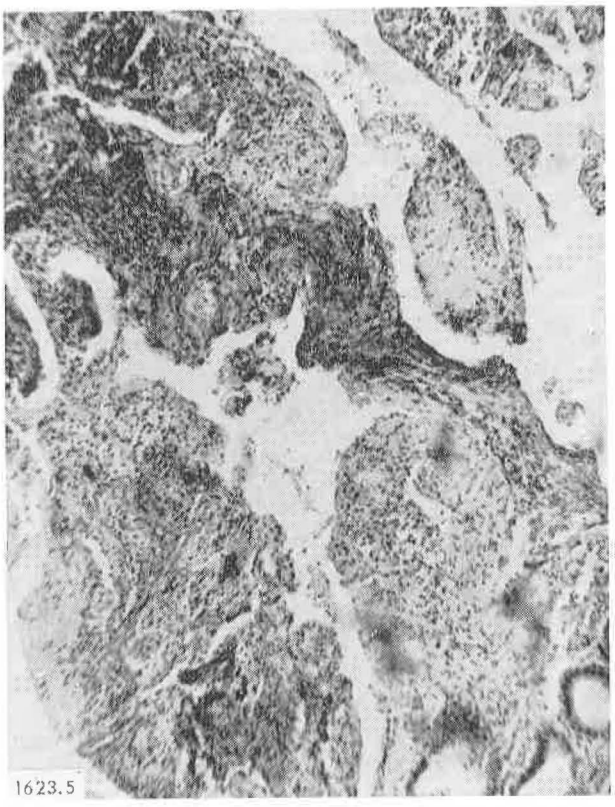

Figure 5. Endometrial biopsy of same patient (L.E.) 75 days following treatment with Sr^{90}. Few glands are perceived in the endometrium, which is mostly fibrotic

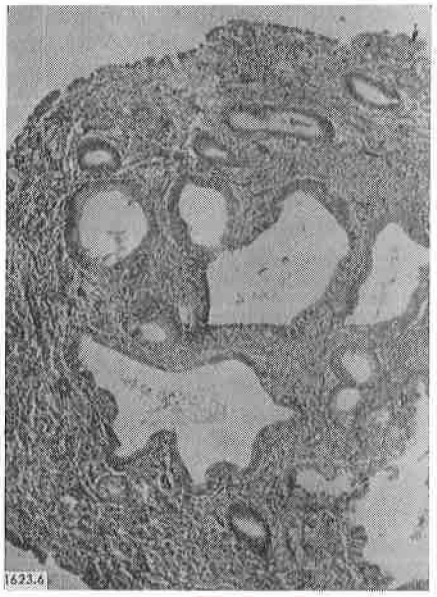

Figure 6. Endometrium of patient T.N. before treatment with Sr^{90}. Cystic glandular hyperplasia

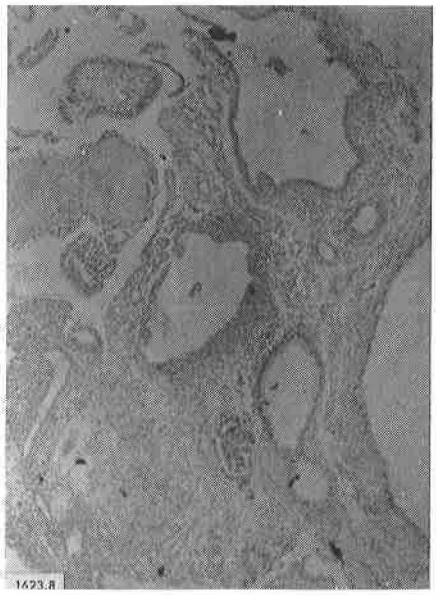

Figure 8. Endometrium of patient S.C. before treatment with Sr^{90}. Endometrial hyperplasia

with radium may involve much greater risk due to its gamma emission (Barr).[19]

4. What is the probability of a radiological cancerization of the uterus? There is a divergence of opinion. Barr reported 3 cases of cancer of the uterus among 850 patients with 25 years follow-up who received radium treatment. Corscadden,[21] on the other hand, noted 32 cases of cancer among 1150 who received non-radiological treatment. Radiation very probably destroys the epithelium and thus eradicates potential malignancy or a precancerous state. Nowak states that 24.3% of the cases of adenocarcinoma of the uterus were actually hyperplasia of the endometrium, and Kottmeier[22] claims that in 20.7% of the cases the endometrium polypi was responsible for cancerization. Schröder,[23] however, thinks that there is little connection between carcinoma and hyperplasia of the uterine endometrium. In any event, the elimination of this hyperplasia is possible by surgical means or by destruction of the endometrium by β-radiation.

Gynecological Problems

Treatment of the hyperplasia of the endometrium with Sr^{90} is essentially a radiological curettage. The radiation completely destroys the mucosa of the uterine cavity, and metro-menorrhagia ceases. The pros and cons of such radiological curettage should be

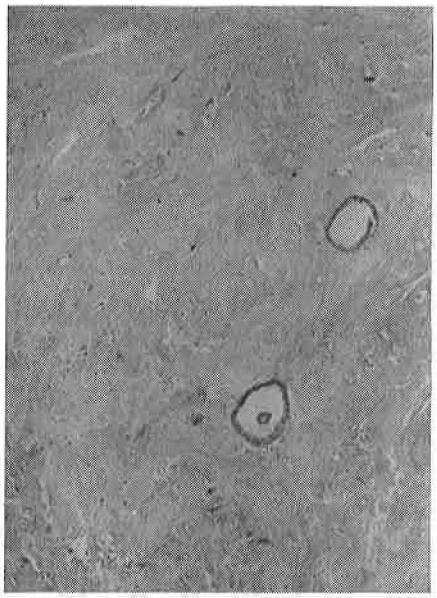

Figure 7. Endometrium of same patient (T.N.) 115 days following treatment with Sr^{90} (720 mc hr). Few glands are perceived. Cylindrical epithelial cells with vacuolar protoplasma. Few mitoses. Much fibrous and collagen tissue

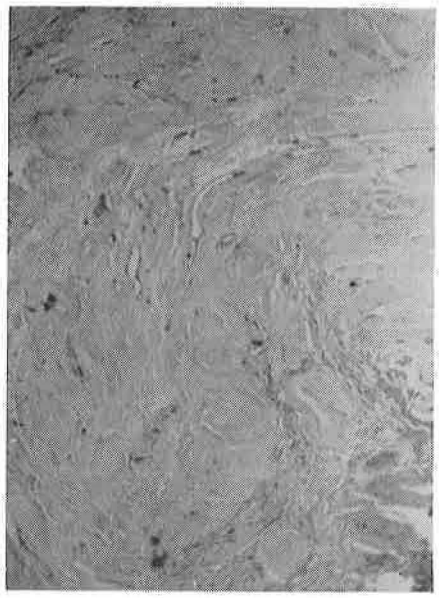

Figure 9. Endometrium of same patient (S.C.) 150 days following treatment with Sr^{90} (630 mc hr). Collagenous changes, few inactive epithelial cells

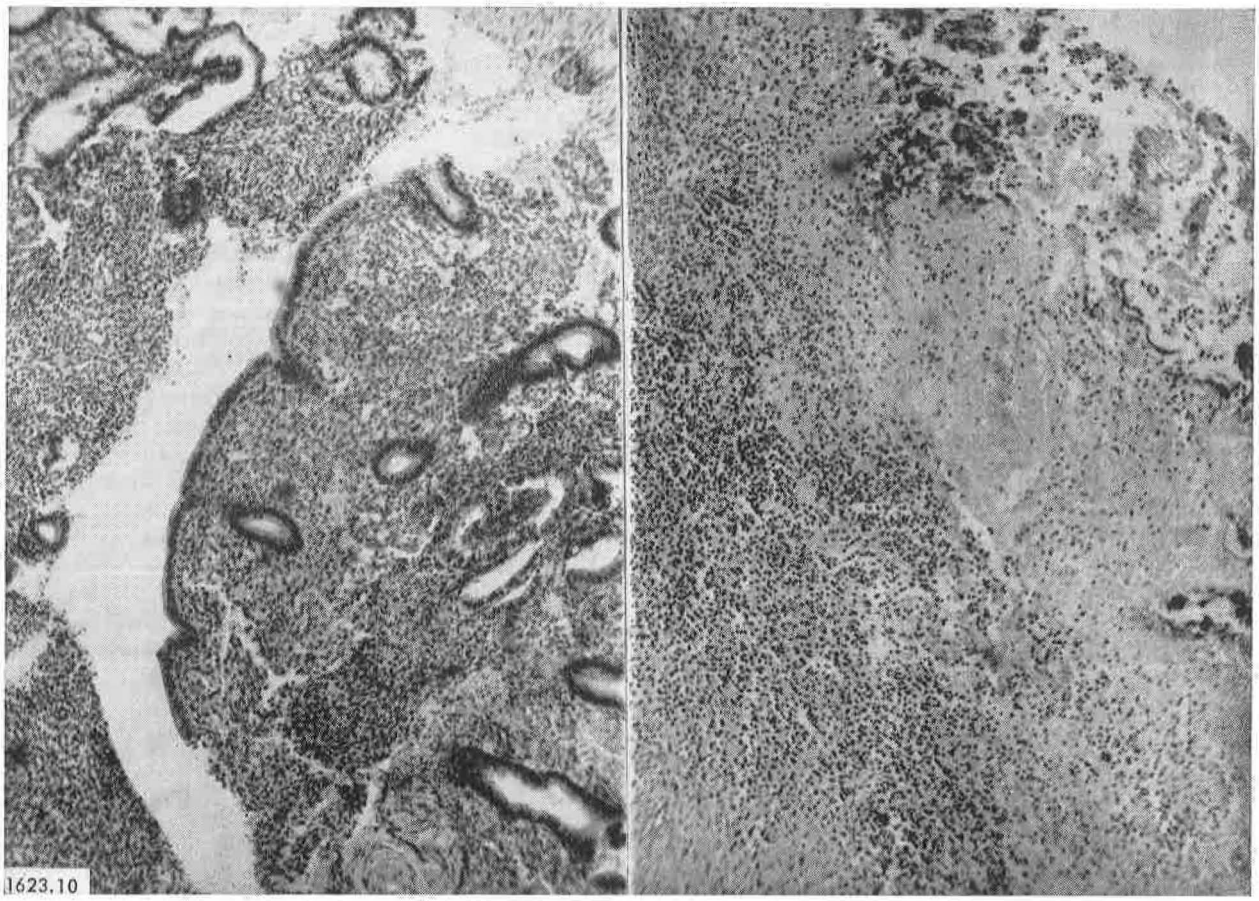

Figure 10 (left). Endometrium of patient T.C. before treatment with Sr^{90}. Endometrial hyperplasia. (Right) Microscopy of uterus of the same patient (T.C.), operated 55 days following treatment with Sr^{90} (840 mc hr). Few deteriorated endometrial residues. Pyogenic infiltration—necrotizing pyogenic endometritis

Table 3. Radiation Doses Received by the Pelvic Organs during some Radiological Procedures

Treatment	*Duration of treatment*	*X-ray dose in uterine mucosa (r)*	*Gamma or X-ray dose in r*		
			Ovaries	*Rectum*	*Urine bladder*
1500 mg hr Ra (Barr)	30 hours	12,200	200	130	160
600 mg hr Ra (Linden)	6 hours	7000	40–70	30–40	35–50
X ray of pelvis (applanate)	sec.	1	1.5	0.6	1.1
X ray of pelvis (lateral)	sec.	4	3.7	0.55	0.6
630 mc hr Sr^{90}	8 hours	7700	2–4	0.9	2.2

evaluated. Hyperplasia of endometrium is usually treated by hormones, followed by one or two curettages. If no recovery is achieved, radiological curettage with Sr^{90} (or other β-emitters) or hysterectomy should be considered. It appears that the treatment with radium, X rays or gamma sources should be discarded.

In the following cases, radiological curettage is indicated:

1. Hyperplasia of the endometrium in young girls who wish to bear children.
2. Cystic hyperplasia in preclimacteric and climacteric women when there is no indication of malignancy.
3. Repeated bleeding in seriously anemic cases when operation is out of the question.

In the following cases, radiological curettage should be excluded:

1. Prevalence of subserotic myomata or large polyps which prevent the free access of the β-radiation to the uterine mucosa.
2. Indication of malignancy.
3. Bleeding due to general or hematological causes.

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A New Treatment of Brain Glioblastoma by Intracerebral Applications of Cobalt-60 Followed by Telecobalt Sessions (Cobalt Bomb)

By Albert Jentzer*

From the therapeutic standpoint, the chapter on brain glioblastoma still remains most disappointing to the neurosurgeon. Some progress has been made however by combining surgery with X-ray therapy, but today the treatment of these tumors by a surgical procedure followed by an application of cobalt-60 within the bed of the tumor and then by sessions of telecobalt therapy, appears to give us, if no actual cures, what on the whole are unexpected successes with respect to survival. We actually had a patient who, while he had been comatose prior to therapy, was able to resume 50% of his activities for many months, and one pregnant woman who delivered a perfectly normal baby. Physiological development of this child (both somatic and intellectual) showed that the cobalt-60 therapy does not appear to have deleterious effects on descendants.

TECHNIQUE ADOPTED

A. *General localization of tumor.* Biopsy to obtain precise anatomical-pathological diagnosis; access for biopsy by selecting a bone section centered over tumor; after partial or total excision of bone enabling biopsy, closure of dura mater with care and suture of bone flap which is outlined by trephine holes used for freeing the bone section.

B. *Radiograph of cranium.* Selection on radiograph of trephine opening which best corresponds with circumscribed tumor mass.

C. *Treatment procedure.* Anesthesia: pentothal intubation; incision of skin (1 to 1.5 cm) above trephine hole chosen and then of dura; enter brain with Kocher forceps approaching center of tumor.

D. *Application.* By means of the prepared approach mentioned, insertion 3 to 4 cm into brain the special graduated metal rod containing radioactive cobalt; attachment of the device to skin by 2 gut threads. Duration of treatment: 39 to 40 hours for a load of 100 mc of cobalt-60. In general, we gave doses of 5500 to 6000 r.

E. *Removal of cobalt rod.* As for the first operation, the dura mater is closed with care in relation to the galea and subcutaneous cellular tissue to avoid formation of fistula which may be fatal. In the last 3 patients in whom we allowed for these factors, a healing was achieved *per primam.* Whether dealing with steps D or E, they are nearly bloodless and they require only 20 to 30 minutes to be carried out. They are so harmless we have not provoked any anatomical lesions in healthy cerebral tissue.

F. *Cobalt teletherapy.* Beginning when the wound is approximately healed, the patient may undergo thirty to forty treatments with cobalt teletherapy, four to five treatments per week, total dose 4000 to 6000 r per tumor.

G. *Intravenous injections.* Arfonad at the beginning of treatment to protect against edema, then Pendiomide *per os* (50 to 100 drops per day).

CLINICAL OBSERVATIONS

Among the 5 cases treated in 1956 and 1957 by the new method, let us describe one of the most typical (Mrs. Z. H., born 1913).

Disease: Since the end of March 1956, more violent headaches, marked fatigue. Neurologically, on June 7, we noted a left pyramidal hemisyndrome (Mingazzini); on the left, over-all reduction of muscular strength; left sided Babinsky; pseudo-cerebellar hemisyndrome on the left; drunken gait; dysmetria; asynergy; dysdiadokokinesia; hypotonia on the left; superficial and deep sensory disturbances; poor tactile discrimination on the left; very bad tactile localization on the left; disturbance of position sense on the left; left astereognosis; zone of hyperesthesia and paraesthesia on the left. On May 28, concentric reduction of the visual field on the left; beginning of papillary stasis of the right eye. Radiograph: finger-shaped impressions. Spinal tap: pressure to 36 cm of water. Auditory examination: vestibule affected, central type hypoacoustica. EEG: truly abnormal tracing, hemispheric asymmetry, pain at the right temporal crossing. Arteriography: lowering of the aqueduct of Sylvius as well as of the right anterior cerebral artery.

Diagnosis: Right parietal tumor, in all probability malignant (glioblastoma).

Operation June 8, by Werner, Associate Neurosurgeon. Right fronto-parietal trephining, extirpation of a parasagittal tumor which was affecting the ventriculum, of the dimension of an orange, neither solid nor cystic, very epidural; superficially it seemed well

Original language: French.
* Geneva.

delimited, but in depth there was no longer a cleavage plane. At the time of operation the patient had been pregnant 31 weeks.

Anatomical-pathological diagnosis: June 12 (Prof. Rutishauser): glioblastoma.

On June 20, cobalt-60 was inserted intracerebrally. Twelve hours after removal (2½ days after placement), pariesis of the left arm until June 28; progressive development of a total left motor hemiplegia. On June 27, cobalt teletherapy was begun. Following a conference with Prof. Watteville, patient was transferred July 23, to the maternity ward. On July 24, this colleague carried out a prophylactic cesarean section which enabled delivery of a boy normal from every standpoint (9 months and 2 weeks). During the procedure sterilization technique was according to that of Lieppmann-Labhardt. No subsequent fever. Immediate weaning. Boy 3440 g, 51 cm, artificial feeding.

On the sixth day after delivery, July 30, patient transferred again to the surgical ward. During this confinement, several Jacksonian seizures. Teletherapy 38 sessions (dose 5000 to 6000 r on the tumor) June 27 to August 29 (Prof. Sarasin). At the beginning, vomiting and Jacksonian seizures; thereafter, marked improvement with respect to these symptoms. September 1, physiotherapy (Dr. Blanc). Patient with good appetite. September 10, we noted that she moved the left arm and leg and on September 22 made movements at the level of the elbow and knee. September 24, she was placed in an easy chair, and on September 26 she took a few steps with the aid of a tricycle dragging left leg. September 29, slight epileptiform seizure. October 4, massages and walks with a tricycle continued. October 11, menstruation began again. October 15, patient left ward and went to Beau-Sejour where kinesitherapy was continued. October 18, patient doing well. She remained at Beau-Sejour until the end of January, 1957, when she went home satisfied, walking

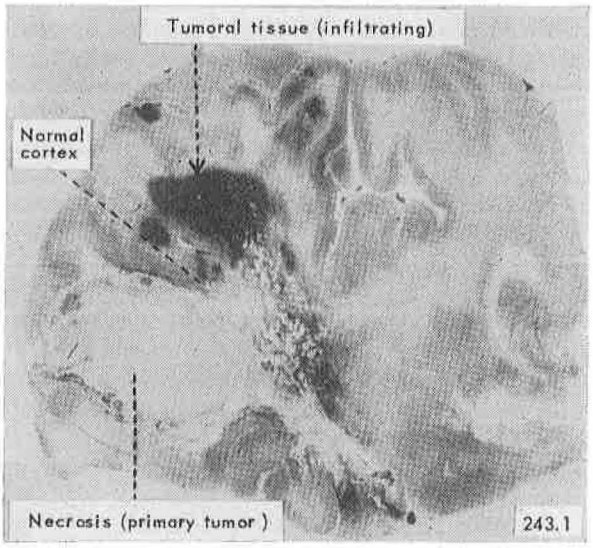

Figure 1. Fronto-temporal area; ovoid necrosis below the upper frontal cortex; presence of tumor tissue some distance from main tumor mass under the cortex of F2 behind second frontal convolution. Celloidin-20; Nissl. stain; normal magnification

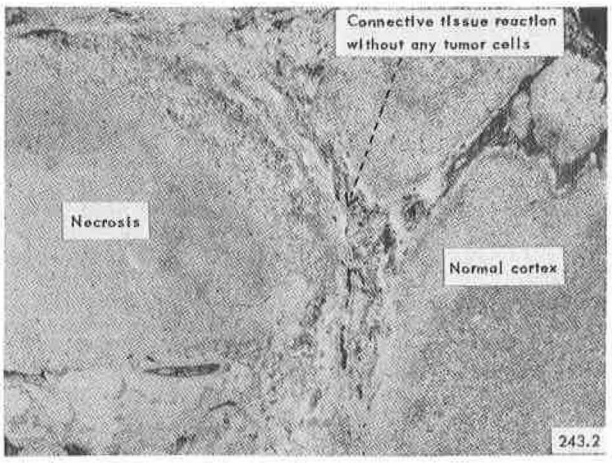

Figure 2. Left: Necrosis surrounded by minimum fibrosis and vascular reaction. Right: normal cortex, absence of any tumor tissue between the necrosis and normal tissue. ×8.5

without a cane. Resumed household work with pleasure (3 children). Her condition remained good until June, 1957, at which time there was a recurrence which obliged her to return to the hospital. On August 19, she passed away.

DISCUSSION

Since on June 7, 1956, the patient was 31 weeks pregnant, we wondered whether the trephining would cause premature delivery and whether a cesarean section should be done. Following an exchange of opinions, we considered it advisable not to deal with the pregnancy, but rather to concentrate efforts on the mother's condition. The brief episode of hypotension during the operation had no pernicious effects. Regarding the hemiplegia, what impressed us (and this is why at no time we made a firm prognosis) was that neither deep sensitivity nor superficial sensitivity of the whole left side was ever affected. The hemiplegia which was developing out of the pyramidal hemisyndrome on the left (mentioned May 26, 1956) appeared to be due to development of the tumor rather than to introduction of the cobalt-60. This impression was corroborated by developments, since on September 10, 1956, the patient began to move first the left leg and then the left arm, and she was able to return home at the end of January, 1957.

AUTOPSY—No. 495, 1957

August 19, the brain was placed in formalin. On September 21, Dr. Wildi (Pathology Institute, Director: Prof. Rutishauser) conducted a macroscopic and microscopic examination of the brain.

Macroscopic examination: No arteriosclerosis at the base. Levelling of the gyri on both sides, but mainly on the right. At tumor center on the right, tissue firm and quite fibrous. Fibrosis is of connective tissue type in continuity with internal surface of the dura. Third ventricle virtually intact. Left foramen of Monroe slightly more dilated than the right; appears com-

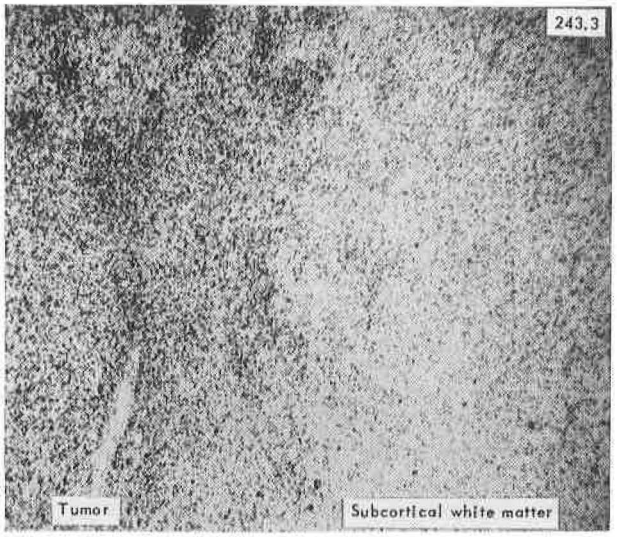

Figure 3. Left: Tumor. Right: white subcortical matter, diffuse infiltration. ×25

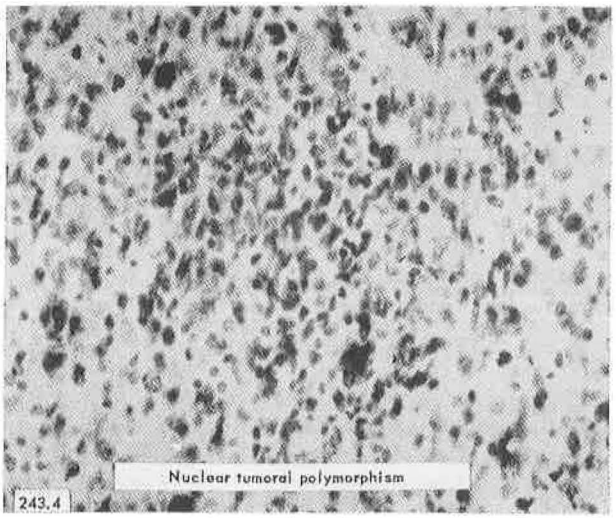

Figure 4. Tumor histology: nuclear polymorphism and hyperchromia; multiplicity of giant cells. ×210

pressed in part by the tumor. Latter straddles internal and external surface of cuneus and extends 1 cm along tail of corpus callosum which appears not infiltrated.

Anatomical diagnosis: Tumor of right hemisphere, large, extensive, right-parietal, subcortical, necrotic scar adhering to dura. Hemorrhagic infarcts of right hippocampal-calcarine region. Herniation of right corpus callosum, uncus and right hippocampus. Three tissue specimens taken from the right hemispheric region.

Microscopic examination: The most striking finding is the extent of necrosis. For the most part, it was localized at the center of the tumor, where there was no tumor tissue—a finding not normally seen. Many microscopic sections were made, from which we have selected four of the most typical specimens (Figs. 1 to 4).

CONCLUSIONS

1. Therapy of glioblastoma with cobalt-60 (internal and external) is from many points of view better than other types of therapy.

2. By such therapy we have obtained survival of about 1 year; this is regarded as worthwhile since it stimulates patients' desire to live, and enables them to do accustomed partial work. By other methods, survival-time is hardly six months, most often under lamentable conditions.

3. The very real improvement in physical condition is accounted for on the basis of microscopic examinations. We noted that in place of tumor tissue which ordinarily is present surrounding necrosis, there is a layer of cerebral tissue containing normal cells, and some infiltrations, beyond which there is normal cerebral tissue. It would seem in this specific case, the dose of cobalt-60 was inadequate to destroy simultaneously the tumor center and the extensions.

4. By using a greater dose of cobalt-60, we should not affect the governing cells of the brain, since according to our experiments on the rabbit brain, these cells withstand much larger doses. It should be understood from our earlier studies of human brains affected by cerebral tumor, cobalt-60 does not cause bone necrosis and it destroys the pyramidal and other healthy cells far more slowly than the tumor cells.

Intracavitary Administration of Radioactive Gold in the Treatment of Ovarian Cancer

By J. H. Muller*

The author started the intraperitoneal and intrapleural administration of artificial radioactive isotopes in the form of colloidal suspensions in 1945[1] and 1949.[2] These procedures have since gained indisputable practical importance, colloidal gold being used mainly. Intracavitary administrations were initiated because we were distressed about our many hopeless cases of cancer of the ovaries having effusions in the abdomen, in some cases also pleural effusions. I had thought that it would be logical to attack by this means the tumor cells floating in such malignant effusion liquids as well as the neoplastic deposits on the large serosal surfaces. It soon became apparent that such intracavitary administrations of radiocolloids, which are now a therapy accepted and in use all over the world, yield satisfactory results for the palliative treatment of such malignant effusions, particularly when they originate from true diffuse carcinomatosis of the peritoneal and pleural serosa without very large tumor masses.

It occurred to me then that such isotope administrations would be likely to contribute curative results also if performed early enough. In 1949 I initiated the intraperitoneal injection of colloidal Au^{198}† together with an artificial hydroperitoneum, and we started, with E. Held, the routine intraperitoneal (and intrapleural) application of colloidal radioactive gold in all cases of ovarian cancer,‡ following exceptional presurgery in combination with conventional radiotherapy, including deep X-ray therapy (200–400 kv), vaginal and, when possible, intrauterine radium therapy. This paper gives the first account of cures obtained 5 years after such treatment in an unselected group of patients with ovarian cancer.

METHODS

The method of intracavitary radiocolloid administration has been described previously by the author in a number of original papers and book chapters;[1–6] many other investigators have reported on their experience with this method which, owing to its particular mode of action, is undoubtedly fitted for efficiently combating early serosal and lymphogenic metastasizations.

The statement about successful therapy is supported not only by the clinical data given below, but also by the physical radioassay of distribution and "paraselective" concentrations of the intraperitoneally administered colloidal radiogold. It is important to emphasize in this respect that experiments on animals, as well as experimental investigations on human beings, by means of radiocolloids in tracer doses are unreliable for the assessment of specific tissue radiation dosage, a feature which becomes of increasing clinical significance. Only studies made on human patients and on specimens obtained therefrom after application of a regular isotope treatment, at full clinical dosage, can supply adequate and accurate information about distribution of the particulate radioactive material in the organism, as well as about the radiation dosage thus realized and the corresponding radiobiological effects.

The author's studies thus made on autopsy material collected from a few patients with advanced abdominal carcinomatosis, whose unrelated intercurrent death occurred about 1–2 weeks after the radiogold had been administered intraperitoneally, have established that secondary concentrations of the colloidal radioactive material of a highly desirable type are indisputable facts. Dosage assessments of the beta radiation based on autoradiograms and on neutron activation analysis, first employed by the author for precise medical dosimetric studies,[7,8] show that after intraperitoneal administration of 150 mc of colloidal Au^{198},§ diluted with about 400 milliliters of physiological saline (which corresponds to our standard technique), the following figures (extrapolated for full decay of the Au^{198}) are obtained: at least 4000 rads for the peritoneal serosa, about 6000 rads for the omentum, and a certified average of 7000 rads (with probable maxima up to 10,000–30,000 rads) for all the retroperitoneal and mesenteric tissues, including (and this is quite important) for the paraoesophageal and paratracheal mediastinal lymph nodes. The actual "spilling" of the colloidal radiogold

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† The isotope Au^{198} ($T_{½}$ = 2.69 days) is prepared from pure gold Au^{197} by a neutron-gamma reaction, which has a very high capture cross section (100 barns) for slow neutrons, whence the production of Au^{198} is quite economical. The disintegration scheme of this isotope involves mainly a strong beta emission, with final production of extremely small amounts of Hg^{198}. The latter is without any practical significance.

‡ Except for a limited number of cases of Stage I, Grade A.

§ The specific activity of Au^{198} should be maintained at about 1 c/g of gold.

into the reticuloendothelial system of the liver and spleen contributes only 170 rads and 250 rads respectively, and, for the kidneys, about 30 rads, as shown by neutron activation analysis. About 750 rads of diffuse penetrating gamma radiation must be added, as we have estimated by calculation,[3] for the intra-abdominal structures. Correspondingly high active deposits were also found after intrapleural administration, within the pleural serosa and the mediastinal lymph nodes. Tumor cells floating (and perhaps multiplying) in ascitic or pleural effusions, or scattered about in early dry serosal disseminations are also submitted to a very efficient radiation bombardment.

The findings, quite reliable in their order of magnitude, are definitely of practical significance since they are well within the range of therapeutically efficient radiation effects. It can thus be admitted quite readily, both from the standpoint of dosimetric data and our clinical experience, that such isotope therapy, owing to the "paraselective" mode of distribution and concentration following the same pattern as regional and systemic distribution of tumor cells and particles—leaving aside hematogenic generalization—is in a position to destroy efficiently early serosal and lymphatic disseminations in very extended areas. However, it is quite evident, with respect to the limited range of beta radiation, that this "paraselective" action of the radiocolloid therapy will be insufficient or fully impaired when the metastatic deposits have already reached the advanced stages of gross node formations. Hence the intracavitary colloidal Au^{198} therapy does by no means replace surgery and conventional deep radiotherapy in their well established classical indications; instead its essential advantage is to supply an efficient blockade and sterilization of the early stages of neoplastic microdisseminations, even when these have extended substantially beyond the local and regional action range of conventional procedures. In this respect, colloidal isotope administration is to be considered a true progress (not a merely technical advance) in the field of radiation therapy.

As shown by the results of routine adminstration for postoperative management of ovarian cancer, the intracavitary colloidal Au^{198} therapy is particularly satisfying for the surgical therapist since it reduces considerably the disappointing losses among operable "good" cases. On the other hand, the results indicate clearly the value of performing the utmost radical removal of all grossly visible and palpable tumor masses that is reasonably possible in abdominal cancer surgery; this is in order that the isotope therapy can be administered under conditions most favorable for controlling the micronodular and microscopical residual deposits. The true significance of this new therapeutic procedure must thus be understood both from a technical and a tactical point of view.

As far as the technique of intraperitoneal and intrapleural administration of colloidal Au^{198} is concerned, many devices were developed for injecting the isotope material with minimal radiation hazard to personnel. Simple techniques are most suitable, since they allow a better reduction of the time required for the administration of the radiocolloid. If ascitic (or pleural) fluid is already present, the liquid must be first withdrawn, leaving enough of it (several hundred milliliters) for the final dilution of the colloidal gold, given with some added saline. Such applications are thus easy to perform. In cases without previous effusion, that is, almost all the cases with operable primaries (Stage I, II and III, see below) a very careful administration is mandatory, since the radioactive material must be administered intraperitoneally together with an artificial hydroperitoneum of 300–400 millilitres. In our experience of about 10 years, we have found that the best way to proceed is to perform paracentesis by means of a rather thin special trocar with a horizontal supporting part, adjustable for insertion to convenient depth. A piece of polyethylene tubing is then introduced through the trocar about 10 cm deeper into the abdominal cavity and the trocar gently withdrawn. A flask of physiological saline is then attached to the tubing in such a way as to enable intravenous perfusion. If the liquid flows continuously by gravity into the abdomen under low pressure, one can be certain that the polyethylene tube is properly placed within the free abdominal cavity. After administration of about 200 ml of saline, the injection of the colloidal gold, diluted with saline, is administered, and finally saline is again given for final dilution and dispersion of the radiocolloid within the abdominal cavity. In several cases we have also added some anesthetic, as used for local anesthesia of the abdominal wall.

As soon as the intraperitoneal injection is completed, the polyethylene tube is removed and the puncture quickly dressed, whereupon the patient is directed immediately to turn in bed in such a way as to ensure even distribution of administered colloid within the abdominal cavity.

The author, as well as other workers, has thus consistently found[3] that intraperitoneal and intrapleural administration of colloidal Au^{198} is a safe procedure and by no means hazardous for the patient or the operator, if carefully performed. Cases with marked abnormal loculations of the abdominal cavity from adhesions, however, are not suitable for this therapy.

The dosage of colloidal Au^{198} administered to the patients is indicated below, together with definition of the different stages of the disease. The majority of patients were treated first by surgery and then by supplementary intraperitoneal colloidal radiogold, together with the standard postoperative radiation therapy, as used for many years.[9] The latter consists of fractioned roentgen therapy resulting in a total depth dose of about 3000 to 4000 r within the pelvic cavity and the lower abdomen, and of 1000–2000 r within the upper part of the abdomen. No such penetrating radiation, however, is dispensed upon the subphrenic structures. Most of the patients received also a vaginal radium application from 1000 to 1800 mg hr, but since the great majority had either supravaginal or total hysterectomy, only a few intrauterine radium treatments were performed.

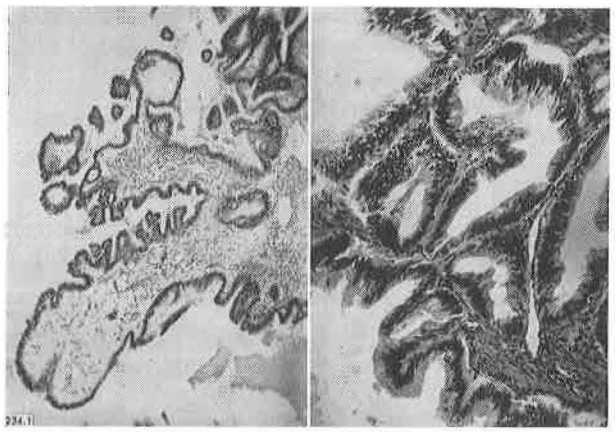

Figure 1 (left). Highly differentiated proliferative papillomatous ovarian blastoma of the serous type, Grade A. Figure 2 (right). Highly differentiated proliferative adenomatous ovarian blastoma of the pseudomucinous type, Grade A

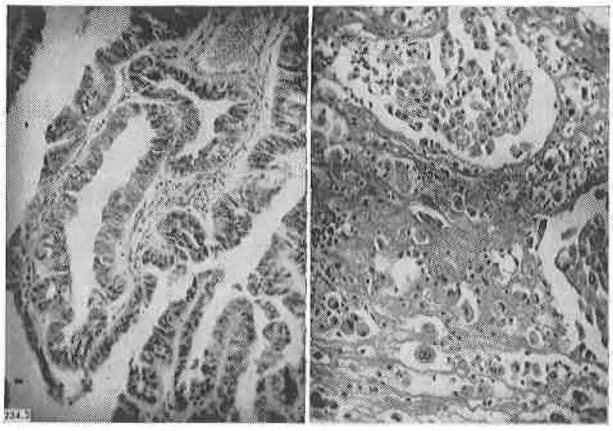

Figure 3 (left). Moderately differentiated ovarian adenocarcinoma, Grade B. Figure 4 (right). Poorly differentiated solid ovarian carcinoma, Grade C

As an important complement to previous publications we will now give a first account of cures observed 5 years after the combined treatment in an unselected group of 51 patients. All radiation treatments of these patients were performed by the author, and autopsy findings on the deceased have become available. This series pertains to ordinary ovarian cancers only. The cases presented are defined also with respect to histologic differentiation grade and to anatomical extension stage of the ovarian neoplasms.

Histopathologic Grading

Histopathologic grading was done along the lines indicated in the author's previous paper on this topic[10] as follows:

Grade A. Highly differentiated proliferative adenomatous and papillomatous growths of disputable histological malignancy, but clinically aggressive and metastasizing within the abdominal cavity.

Grade B. Moderately differentiated adenocarcinomas and papillary carcinomas.

Grade C. Poorly differentiated solid carcinomas.

Compound borderline cases of Grades B and C were classified in accordance with the predominating cancer type.

In order to illustrate the histopathologic grading used, micro-photographic examples of the different types of ovarian tumors are shown in Figs. 1–4.

Staging of the Cases

The staging of cases, as indicated below, was worked out carefully by the author during the last 6 years and has been found in his experience adequate for a correct evaluation of therapeutic results obtained from both surgery and radiotherapy, with special consideration of routine intraperitoneal radioactive Au^{198} administration. Staging of ovarian cancer has not yet been established along internationally accepted rules, but we believe that our classification could be considered a valuable suggestion in this respect, as follows:

Stage I. Cases with unilateral ovarian tumors, in which radical surgery is possible.

Stage II. Cases with bilateral ovarian tumors; cases with doubtful radical removal by surgery or in which metastatic deposits were already found in the pelvic cavity, the latter being at least partially resectable; and cases in which a partly cystic neoplasm ruptured before operation, with effusion of carcinomatous materials.

Stage III. Cases with resectable primaries as in Stages I and II, but with metastatic disseminations in the great abdominal cavity, the metastatic nodes being not larger than 2.5 cm in diameter.

Stage IV. All other cases with diffuse abdominal and pleural carcinomatous extensions or metastases within the liver, in which no surgery or only a palliative removal of some tumor parts was possible.

Treatment

As far as the dosage of colloidal gold is concerned, we proceeded along the following lines. As a rule, except some cases of Stage IV with ascitic abdominal carcinomatosis, we started by giving fractioned X-ray therapy during periods of 1–3 weeks. This approach has the advantage that exceptionally late postoperative complications will appear before the gold is administered and, on the other hand, allow the organism to become somewhat adapted to radiation; general reactions from radiogold application then are as a rule minimal. In order to avoid undue stress on the patient we never administered single doses of more than 150 mc to larger patients, or of 100–120 mc to smaller. A second and even third application followed in some instances at intervals of not more than 4 to 5 weeks. Exceptionally, and in cases of Stage IV only, a fourth and even fifth treatment with radiogold was sometimes administered. No rigid rules can, however, be established as far as these radiocolloid administrations are concerned, since recovery rate and other complex factors, which play an important part in clinical radiotherapy, must be evaluated in each case.

In this series, the cases of Stage I received as a rule 1 treatment only; the dosage varied from 70 to 150 mc. A single case received 2 treatments totaling 225 mc.

Table 1

Stage	*No. of cases*	*Grade A*	*Grade B*	*Grade C*	*Alive without symptoms after 5 years*	*Deceased from carcinoma before 5 years*	*Deceased from intercurrent disease*	*Stages III and IV Valid palliation at least 6 months' life prolongation*
I	10	4	6	0	10 (100%)	0	0	—
II	13	2	10	1	9 (70%)	2	2	—
III	10	1	9	0	4 (40%)	6	0	6
IV	18	1	11	6	0	18	0	15
I–IV	51	8	36	7	23 (45%)	26	2	21 (75% of Stages III and IV)

With respect to the Stage II group, all cases of this series received 1 treatment only, with a dosage of 70 to 150 mc.

With respect to Stage III, 4 cases received 1 treatment only of 60 to 150 mc, 5 cases received 2 treatments with a total of 130 to 290 mc, and 1 case received 3 treatments with a total of 400 mc. In the latter case the Au^{198} was administered prior to surgery.

With respect to Stage IV, most patients (except 7 cases) received multiple Au^{198} treatments, mostly intraperitoneal but in some instances intrapleural administrations also, the total dose in exceptional cases reaching as high as 800 mc.

In more recent years, our procedural trend has been to administer 1 treatment to the cases of Stage I, 1 to 2 treatments to the cases of Stage II, and 2 to 3 treatments to those of Stage III; for the cases of Stage IV, inasmuch as they appeared incurable, both the dosage and the number of colloidal gold administrations have tended to vary greatly, since our aim has been to obtain prolongation of life span with as little discomfort as possible.

RESULTS

The therapeutic results thus obtained in the series for 51 cases are summarized in Table 1.

DISCUSSION

These results clearly show that routine administration of colloidal Au^{198} must be welcomed as true progress in the treatment of ovarian cancer. The figures of 100% and of 70% 5-year cures in Stage I and Stage II, respectively, despite the limited number of cases, are undoubtedly much higher than those hitherto obtained by means of surgery and conventional radiation therapy alone. Leaving aside the most favorable cases of Stage I, Grade A, we have had in a previous series[10] 23 cases of Stage I, Grades B and C, treated with surgery and conventional radiotherapy without colloidal Au^{198}, only 14, or 60%, of which survived 5 years after treatment. This figure compares quite well with other published data. Moreover, the cases of Stage III, of which 40% were saved in this series, were heretofore seldom controlled. However, the fractioned administration of even large amounts of colloidal gold (up to about 800 millicuries) did not save any case of Stage IV, though many of the unfortunate patients obtained substantial palliation therefrom (up to 4 years of extra life span). Despite this state of affairs and the relatively high incidence of Stage IV in this series, the over-all 5-year cure rate of 45% obtained is about double the figure found hitherto for comparable unselected groups of patients.

The routine intraperitoneal Au^{198} administrations were performed without any mortality related to the treatment. Thus, if correctly applied, intracavitary administration of colloidal Au^{198} is a safe procedure. All patients that suffered from terminal ileus had recurrent cancer.

It is quite clear that ovarian cancer remains primarily a "surgical" disease, for the treatment of which, however, the routine intraperitoneal administration of colloidal radioactive gold, even if often apparently "prophylactic," is in fact an important additional curative procedure, owing to the well known high incidence of early macroscopically invisible microdissemination throughout the abdominal cavity, which may already have occurred in about 50% of the operable cases. This conclusion finds confirmation in the study by H. B. Elkins and W. C. Keetel[11] who made cytologic examinations of peritoneal washings which had been centrifuged and the sediment stained with Papanicolaou's stain. In 50% of the operable cases of ovarian cancer with no breakthrough of the ovarian capsule and no evidence of neoplasm outside the ovary, these authors found tumor cells in the peritoneal washings. It is interesting that this percentage parallels closely the number of cases which did not survive 5 years despite radical surgery. In contradistinction thereto, all cases of the corresponding group of our own series, which were treated additionally with colloidal radiogold, have survived 5 years.

This indicates further that the results obtained by means of routine administration of the colloidal Au^{198} are significant.

SUMMARY

A report is presented on the first 5-year results of routine intraperitoneal and intrapleural administration of colloidal radioactive gold (Au^{198}) for the treatment of ovarian cancer in an unselected group of 51 patients. The results indicate that such isotope administration is a true advance in this field of cancer therapy, since it does at least double the salvage rate of ovarian cancer patients with surgically resectable primary tumors.

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Distribution of Intraperitoneal Radiocolloids

By P. V. Harper and K. A. Lathrop*

The frequent use of colloidal gold-198, yttrium-90 and chromic phosphate for the treatment of tumor ascites and destruction of tumor cells seeded at operation has led us to investigate in more detail the distribution of such substances in the peritoneal cavity. Considerable information[1-4] is available on the movement of radio active colloidal material out of the peritoneal cavity, and on the concentration of isotopes in various intra-abdominal organs following intraperitoneal injection. Radioautographic studies[5,6] have indicated a tendency for these materials to become deposited irregularly upon the serosal surfaces within the peritoneal cavity. To the best of our knowledge no systematic studies have been carried out on the variations in distribution upon peritoneal surfaces as influenced by various controllable experimental factors. We became interested in this problem through our work in the prevention of intraperitoneal tumor implants with intraperitoneal installation of radioactive colloidal material, such as radioactive gold[7] and yttrium.

METHODS

Radioactive colloidal gold and radioactive yttrium chloride were injected intraperitoneally into 250 g rats under various circumstances. When an animal was sacrificed, the abdominal wall and viscera were laid out on a sheet of filter paper, sealed in a polyethylene envelope and then layed on photographic film to obtain gross radioautographs of the actual organs. Ten-minute exposures to the film were adequate when the rat had received approximately 100 μc of Y^{90}. The factors which were studied were time, carrier level, nature and volume of solvent, and presence of inflammation.

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RESULTS

The radioautographs from these various preparations give a qualitative but strikingly graphic demonstration of the intra-abdominal distribution of the radioactive material.

A comparison of Fig. 1(a), (b) and (c) reveals the intra-abdominal distribution at 1, 3, and 6 days following the injection of 1 mg of carrier Y as YCl_3 at pH_6 in 1.0 ml of 0.9% NaCl. There is marked uptake in the omentum and in the lymphatics and lymph nodes of the mesentery, and with this level of carrier a moderate parenchymal uptake in the liver and spleen is visible. It is possible to distinguish easily in these preparations between the activity deposited on the surfaces of the

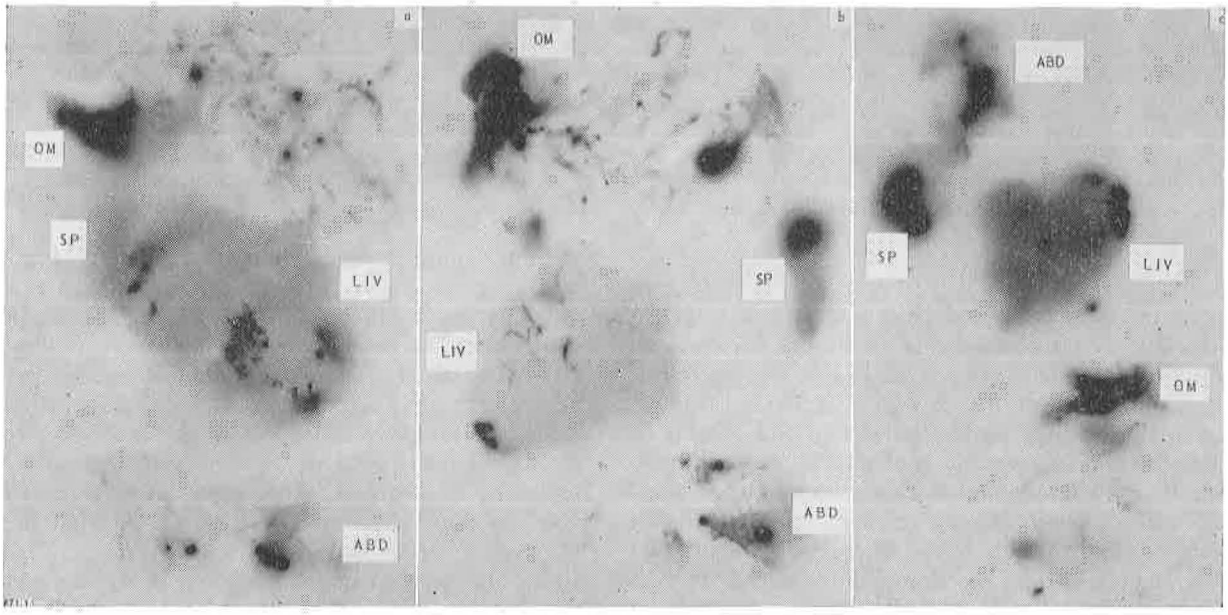
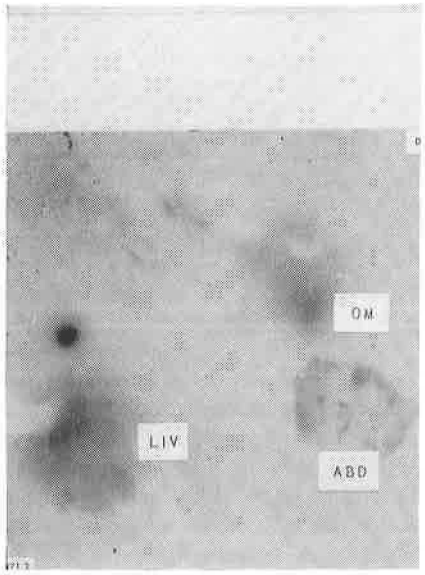


Figure 1(a). Gross radioautographs of intraabdominal organs of rats following intraperitoneal injection of $Y^{90}Cl_3$ in 1 ml of 0.9% NaCl with 1 mg of Y^{+++} carrier; one day following injection. Marked uptake is evident in the omentum and in the lymphatics and lymph nodes of the mesentery and there is a moderate parenchymal uptake in the liver and spleen which becomes more marked with time. Localization in the abdominal wall is not marked. LIV liver; SP spleen; OM omentum; ABD abdominal wall. (b). Same, 3 days following injection. (c). Same, 6 days following injection



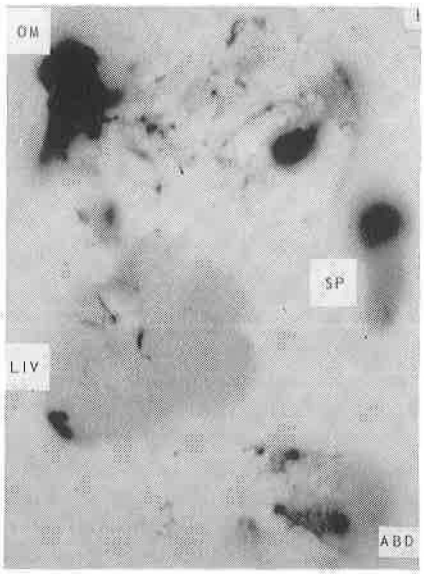


Figure 2(a). Gross radioautographs showing effect of carrier Y^{+++} on intraperitoneal distribution (material injected in 1.0 ml of 0.9% NaCl) carrier-free; 24 hours. Increasing the amount of carrier reduces the amount of parenchymal localization in the liver evident with carrier-free yttrium and 1 mg of carrier Y. Further^{+++} increases of carrier level result in patchy distribution of isotope on surfaces in areas of localized fibrinous peritonitis. Figure 2(b). Same, 1 mg carrier Y^{+++}; 72 hours.

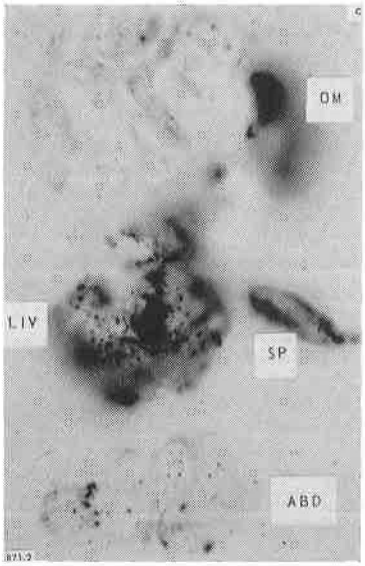


Figure 2(c). Same, 3 mg carrier Y^{+++}; 72 hours

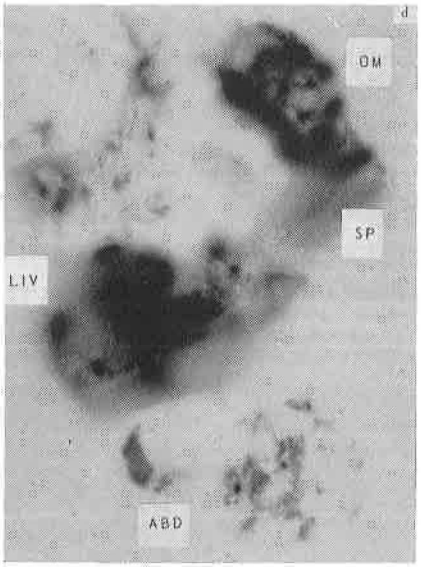


Figure 2(d). Same, 10 mg carrier Y^{+++}; 72 hours

organs, which form dark irregular patches, and the parenchymal uptake, which gives a diffuse even darkening of the film. Darkened areas that appear to be engorged lymphatics are readily discernible. There is no dramatic difference between the 1- and 3-day preparations, but at 6 days there is evident a marked translocation to the liver and especially to the spleen. In studies at shorter intervals (not shown), the same pattern of uptake in the omentum and lymphatics is present within one-half hour or less, and subsequent changes are relatively slow, since the one-half and 24-hour preparations are almost indistinguishable.

In Fig. 2(a), (b), (c) and (d) is shown the effect of varying the amount of carrier yttrium with other factors remaining constant. The isotope was injected in 1 ml of 0.9% NaCl at pH_5. In Fig. 2 (a) (carrier free) the most marked localization is in the liver, but the whole picture is less distinct. In contrast, 1, 3 and 10 mg of carrier produce a decreasing tendency to parenchymal localization, and a greater tendency to localize on peritoneal surfaces, especially of the liver. The gross appearance of the specimens is consistent with the radioautographic results, white patches of yttrium hydroxide being evident on the peritoneal surfaces, especially of the liver. With 10 mg of yttrium, there was a substantial chemical peritonitis, with patches of fibrinous exudate on the peritoneal surfaces. The activity appeared to be incorporated in these areas as may be seen in the radioautograph of the abdominal wall in Fig. 2(d). The effect of local peritonitis was studied further as shown in Fig. 3. Experimental animals were subjected to laparotomy one-half hour be-

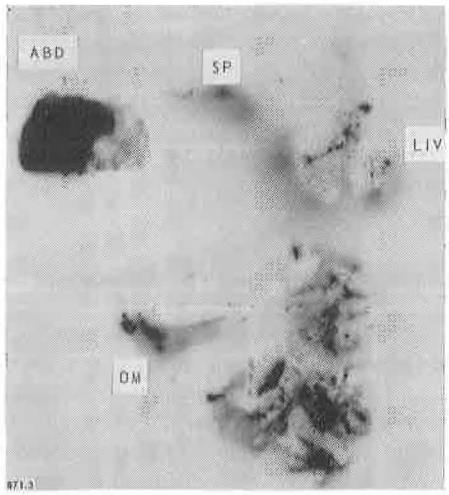


Figure 3. Radioautograph showing marked localization of activity in region of laparotomy wound of rat following intraperitoneal injection of 1.0 ml of 0.9% NaCl containing Y^{90} plus 3.0 mg carrier. Injection made one-half hour following closure of wound. Animal sacrificed 24 hours following injection

fore injection of the Y^{90} with 3 mg of carrier Y^{+++} in 1 ml of 0.9% saline. A very marked localization of the isotope in the abdominal wall, in the region of the fresh laparotomy wound, as contrasted with Fig. 2(c), is evident.

Increasing to 6 ml the volume of the solution in which the yttrium was injected had the remarkable effect shown in Fig. 4, which we can only interpret as

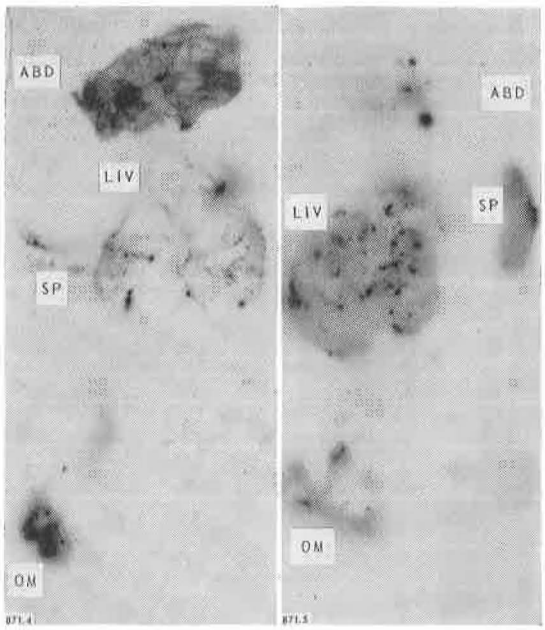


Figure 4 (left). Marked localization of Y^{90} in anterior abdominal wall of rat 24 hours after intraperitoneal injection of Y^{90} plus 3.0 mg of carrier in 6.0 ml 0.9% NaCl

Figure 5 (right). Radioautograph 24 hours after intraperitoneal injection of Y^{90} plus 3.0 mg of carrier in 6.0 ml of human serum. Contrast this with Fig. 4. There is marked parenchymal localization in the presence of serum protein which is almost completely absent when the isotope is dissolved in 0.9% NaCl. This is probably due to chelation of the carrier yttrium by the protein

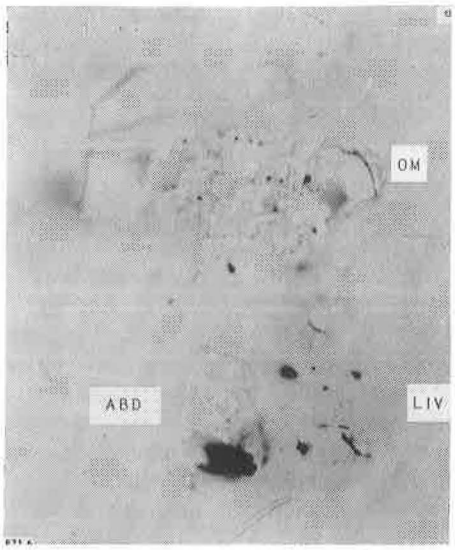


Figure 6(a). Radioautograph at 24 hours following intraperiotoneal injection of 0.2 ml colloidal gold (Aurcoloid, Abbott). Contrast these with the animals injected with Y^{90}. Note translocation of isotope into liver after 72 hours.

evidence that yttrium hydroxide precipitate had collected in the most dependent portion of the abdominal cavity, with resultant translocation of isotope into the adjacent abdominal wall lymphatics to outline the muscle fibers as shown. Injecting the isotope dissolved in 6 cc of serum gave the picture shown in Fig. 5. There is a very substantial increase in the parenchymal localization as compared with Fig. 4, and the localization in the abdominal wall is completely absent. This experiment was designed to simulate treatment of tumor ascites, and the result is probably caused by chelation of the injected yttrium with the serum protein.

Figures 6(a) and (b) show the effect of 0.2 ml radioactive gold colloid (Aurcoloid). Here there is a rather different pattern of distribution, with some activity still in the peritoneal fluid at 24 hr, and a conspicuous absence of omental uptake. At 72 hours, the paren-

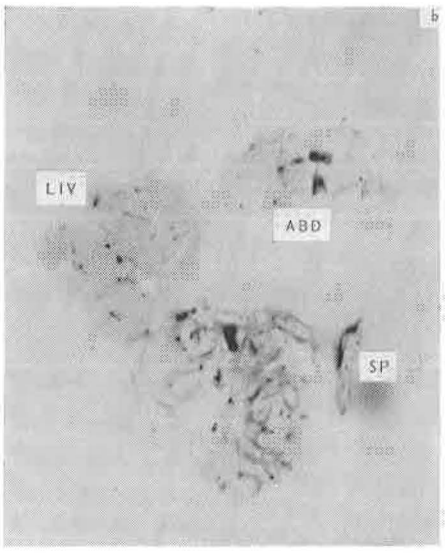


Figure 6(b). Same at 72 hours

chymal uptake in the liver is evident. These differences are probably a function of particle size since India ink injected intraperitoneally gives the same type of localization as the yttrium.

DISCUSSION

The localization of intraperitoneal colloidal and particulate material evidently depends on a number of factors, the most important of which appear to be the nature of the material, its quantity, and the presence of inflammatory reaction. The marked localization of yttrium chloride in the omentum, mesenteric nodes, and in the laparotomy wound follows the pathway of other particulate material such as carbon particles, and indeed, of tumor cells. Walker 256 sarcoma injected intraperitoneally into rats localizes exactly in these areas. This phenomenon makes it appear that the use of yttrium chloride should prove effective in suppressing the growth of tumor cells seeded at operation. On the other hand, the behavior of yttrium in serum suggests that its use in tumor ascites in which there is a fairly rapid protein turnover might lead to extensive translocation of the isotope unless very large amounts of carrier are used. Radioactive gold-198, which is non-reactive chemically, should therefore be preferable to yttrium chlorides in the treatment of tumor ascites.

SUMMARY AND CONCLUSION

Gross radioautographs of intra-abdominal structures following intraperitoneal injection of yttrium-90 chloride and gold-198 colloid show that the intraperitoneal distribution is influenced markedly by carrier level, volume of injected material, nature of suspending medium, inflammatory reaction, and nature of radioactive material. The relevance of these factors in the treatment of tumor ascites and implants is indicated.

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Transsphenoidal Hypophyseal Destruction with Radioactive Yttrium

By R. D. Moseley Jr., W. M. S. Ironside and Paul V. Harper*

This report concerns the technique of pernasal transsphenoidal of Y^{90} implantation into the pituitary using biplane fluoroscopic image intensifier control. Some preliminary results of destruction of the hypophysis in a group of 40 patients with metastatic breast or prostate cancer are being presented. Theoretical considerations leading to the development of this technique, the present status of the technique itself, and the incidence of complications will be discussed in detail. Brief reference will be made to comparative results obtained by other methods of hypophysectomy.

Because of work by Huggins[1] and others, the endocrine influence on metabolism of certain neoplasms, notably those arising in the breast and prostate, has become well established. Luft, Olivecrona, and Sjögren[2] introduced surgical hypophysectomy as an endocrinologic method for the control of breast cancer. There can be no doubt that this procedure will produce remissions in some cases.[3,4] Several methods for introducing radioactive materials into the sella turcica for destruction of the pituitary have been described.[5–7] There is evidence that ablation of the hypophysis can be obtained with relatively high doses of externally administered proton-beam radiation,[8] but sufficiently high doses of radiation to the pituitary cannot be achieved with ordinary external roentgen therapy.

Because of the difficulty of achieving complete surgical removal of the gland,[3,6] it was felt that the destructive action of radioisotopes might offer more complete ablation. Because the use of radon[5] involves the gamma irradiation of numerous important structures in close proximity to the pituitary, the employment of discrete sources of beta radiation, such as those described by Kisilleski, Svihla and Brues,[9] was elected. Due to dosimetric considerations, the number of discrete beta sources was set at 6 to 10 rather than the smaller number used by others;[7] the mechanical introduction of more than this number of localized sources presents practical problems. Inhomogeneity in dose is greatest from localized beta-particle sources if the volume occupied by the localized sources is small while size of the source is large.[10]

Because the minimum beta-particle dose may be much smaller than the average when the localized sources are far apart, it is obligatory for good dosimetry to introduce as many small pellets as practicable. Although the ideal technique would be the injection of radioactive colloidal material, such as Au^{198} or $CrP^{32}O_4$, it is not possible to ensure that such materials will remain at the site of injection; if the particles simply remained in the needle tract, the technique probably would not achieve a more homogenous distribution than multiple discrete sources. Because of the operative risk in patients with extensive metastatic disease, as well as the difficulty of achieving adequate distribution of radioactive pellets, the transcranial route[11] has now been supplanted by the pernasal transsphenoidal approach performed with biplane fluoroscopic image intensifier control.

Y^{90} has many characteristics which make it one of the most suitable isotopes for this technique. It has a strong beta radiation (E_{max} 2.3 Mev), short half-life (62 hr), and Y^{89} has an adequate activation cross section for thermal neutrons (1.24 barns). Small cylindrical pellets (17 gauge), weighing approximately 4 mg, are produced by compressing $Y^{89}{}_2O_3$ powder in a mold and then sintering the pellets in an alumina crucible at 1650°C for one hour, converting them to solid ceramic material. Activities of 1 to 2 mc per pellet are obtained by placing them in a thermal neutron flux of 3×10^{13} N/cm²/sec for 4 to 5 hours. The activity is determined by dissolving a test pellet in nitric acid and counting an aliquot under conditions of known geometry. Since the pellets are not radioactive during the process of fabrication, many manufacturing difficulties are avoided.[9] While the maximum range of the beta particles from Y^{90} in tissue is about 1 cm, a significant radiation dosage is not encountered farther than 4 or 5 mm from the pellet.

TECHNIQUE

Following premedication with Seconal (150 mg) and Demerol (100 mg), local anesthesia of the nasopharynx is induced with 10% cocaine with adrenalin. Radiopaque markers are placed on the patient's chin and on the vertex of the skull in order to facilitate alignment of the skull under fluoroscopic control. The field is draped without the use of metallic clips which might interfere with fluoroscopic visibility. Two mobile Phillips image intensifier units (Surgex) are positioned so that the radiologist can view the posterior nasopharynx, the sphenoid sinus and the sella turcica on

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the lateral screen, and can visualize the base of the skull in a projection 90° from lateral on a screen placed at the vertex of the skull. The operator loads the Y^{90} pellets into cartridges under water (11 mm of water offers complete shielding against the beta particles).

The needle, a strengthened 17-gauge spinal needle, is passed into the left nostril and guided to the medial part of the anterior wall of the sphenoid sinus. Under fluoroscopic image intensifier control, the position of the tip of the needle and its direction are checked before it is advanced into the sphenoid sinus. Penicillin-Topical Thrombin (1.5 cc of a solution containing 10,000 units of penicillin and 200 units of thrombin per cc) is introduced into the sinus. The tip of the needle is then advanced under fluoroscopic control into the posterior portion of the sella turcica medially. A posterior pellet is deposited and the needle tip withdrawn 4 mm for placement of the anterior pellet. The needle is then withdrawn into the sphenoid sinus directed approximately 4 mm laterally and again introduced into the posterior part of the sella turcica. Posterolateral and anterolateral pellets are deposited. The procedure is repeated via the right nostril with depositions into the right half of the gland. Variations in the size of the sella and in the accuracy of placement determine the total number of pellets (6 to 11) required to achieve adequate distribution. Individual variations in size and position of the nasal and sphenoidal septa may result in modification of the planned approach but do not preclude accurate deposition. Following placement of the implant, radiographs are obtained for dosimetric determinations.

Determinations of the dose of X rays received by the operator's hands during the fluoroscopic control of these procedures indicates that an average of approximately 400 millirads can be expected. Because of the international recommendations of 1500 millirads/week maximum for such exposures, an individual operator is limited to three operations per week.

RESULTS

Only preliminary conclusions regarding the method are justified at this time due to the short period of observation and the small number of cases. Analysis has been made of the results from 42 cases treated by means of pernasal transsphenoidal Y^{90} implantation of the pituitary.

Of the 42 patients, 7 were male (6 with metastatic prostatic carcinoma and 1 with metastatic breast carcinoma) and 35 were female (33 with metastatic breast carcinoma and 2 with ovarian neoplasm). There were no operative mortalities.

Four of the 6 patients with prostatic neoplasm survive to date (seven, five, five and three months following operation). One patient died four months and another six months after operation from progression of neoplastic disease.

The one male with carcinoma of the breast has not yet presented objective evidence of remission but shows no evidence of progression and is alive six months after the procedure.

Both patients with carcinoma of the ovary died—1 twelve days after the procedure, the other three months after operation—both from progression of the disease. In neither case was there evidence of the effect of hypophysectomy.

Fourteen of the 33 female patients with carcinoma of the breast are dead and 19 survive. Seven of the 14 deaths occurred in patients who were obviously moribund at the time of surgery and who died within one month from progression of the disease. There were no operative deaths. Seven of the patients now dead lived longer than one month (two to five months) and, with one exception, also died of progression of their disease. One patient died two months after operation of meningitis; she had developed rhinorrhea as a complication.

One of the 19 survivors had a subsequent surgical hypophysectomy in another institution. Three of the 19 still survive but show evidence of progression of their disease. Seven of the 19 show at this time no evidence of advancement of their lesions. The concept of "arrest" of breast neoplasm after such a short observation interval is not considered valid because of the well-documented variability in the natural life history of this disease. Four patients have subjective (relief of pain etc.) but no objective evidence of improvement; 4 patients demonstrate both subjective and objective (improvement in appearance and size of lesions, decrease in effusions and ascites, reossification of bony metastases, etc.) evidence of beneficial effect of hypophysectomy.

COMPLICATIONS

There were 21 instances of significant complication in the 42 patients. Fourteen of the 42 patients had no complication; 28 had one or more. Seven of the 28 had diabetes insipidus as the only postoperative difficulty. The validity of including this phenomenon as a complication at all is open to some question. Certainly it represents a problem which must be medically managed in the postoperative period but, by the same token, so is panhypopituitarism a "complication." Diabetes insipidus in 17 of the 28 patients occurred postoperatively, in ten instances in combination with more significant complications.

There was one instance of third cranial nerve damage, two cases of paresis of the fourth cranial nerve, and three cases of sixth nerve involvement. Combined nerve damage (III and IV) occurred in 8 patients, and in one case there was bilateral paresis of III and IV. In only 1 patient was there evidence of damage to the second cranial nerve (constriction of the visual field of one eye). Thus, in 15 of 42 patients there was evidence of radiation effect in nerves adjacent to the sella.

Cerebrospinal rhinorrhea occurred as a complication in 12 patients. Meningitis occurred in 3 and in one instance (previously mentioned) was apparently the

cause of death. One of the three meningitis cases occurred not as a result of the original procedure but, rather, after a successful transsphenoidal repair of a defect that produced the rhinorrhea. Both this patient and the patient in whom it occurred as a primary complication have responded to treatment for meningitis.

In one patient during the operative procedure, three Y^{90} pellets entered the arterial circulation at the base of the brain and embolized one of the small branches of the middle cerebral artery on the opposite side from that of insertion and also two small branches of the anterior cerebral artery on the same side. There were neither immediate nor long-term detrimental effects or symptoms as a result of this accident.

PATHOLOGY

Histologic sections made serially through the glands removed at autopsy demonstrate considerable variability in the extent of destruction of the pituitary by this method. There have been instances of 100 per cent destruction; some cases show as little as 75 per cent destruction. Based on an estimate of the area of destruction evidenced by the placement of the radioactive sources, it is apparent that some of the survivors have less than 100 per cent destruction of the hypophysis (average estimate 80 per cent). Despite this evidence, there are indications that beneficial effects are being achieved in their cases. Evaluation of this problem requires a longer period of observation and more material for study.

DISCUSSION

It is, of course, much too soon to make final evaluation of the clinical results of hypophysectomy by this method. However, certain preliminary conclusions seem valid.

The morbidity and mortality of craniotomy make the transcranial approach for either surgical or radiation hypophysectomy less acceptable for both patient and physician. As a matter of fact, many of the patients who withstood without difficulty the transsphenoidal approach would not have been accepted for transcranial surgery because of their age and general condition.

There can be no doubt that hypophysectomy will produce palliation in cases of endocrine-sensitive tumors. The problem is how to accomplish ablation of the hypophysis in the surest, safest manner. The lack of operative mortality by the transsphenoidal Y^{90} implantation technique recommends this approach; the complication rate is distressing but compares favorably with the complication rate of transcranial approaches. Moreover, because of recent modifications in distribution of the pellets and great attention to avoid placing the pellets too far laterally, there has been no cranial nerve damage in the last twelve patients of the series. This favorable result has been accomplished without compromise in obtaining distribution of the radioactive pellets that should produce destruction of the gland.

Complete destruction of the pituitary gland was the aim of this method; it is apparent that this objective is not uniformly accomplished. On the other hand, there is evidence of favorable response, both in these cases and in those cases of prostate cancer reported by Fergusson,[7] without complete destruction of the gland. Moreover, it is probable that the extent of destruction is at least as great as the extent of removal possible by transcranial surgical techniques.

SUMMARY

The technique of transsphenoidal Y^{90} implantation of the pituitary under biplane fluoroscopic image intensifier control has been described. Principles of dosimetry, nuclear chemistry, and surgical and fluoroscopic techniques were considered. Preliminary estimates of clinical response have been presented, and the types of complications and their incidence given in detail. The method promises to be a most innocuous and effective method of hypophyseal ablation.

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Pituitary Ablation with Radioactive Seeds

By Frank Ellis, George Jackson, Charles L. Lewis, Anthony Nias and Raymond Oliver*

Illingworth and his group at Glasgow[1,2] described a method for insertion of radioactive sources into the pituitary fossa using an apparatus which enabled them to insert a cannula without an open operation. The aim was to give a sufficient dose of radiation to the pituitary gland without overdosing surrounding structures, and at the same time to destroy the function of the pituitary gland in the hope of influencing the growth of carcinoma of the breast or its metastases. They were followed by others who, using intensifying screens and inserting the seeds under direct vision, or by using a similar instrument, attempted the same procedure. The results in otherwise hopeless cases were sufficiently encouraging to justify development of the method.

At a lecture in Oxford, 14 March 1955, Illingworth suggested that yttrium, with its long-range high-energy beta particles and with adequate dosage, would offer the possibility of effective destruction of the pituitary gland involving less danger of what seemed to be the chief complication, namely the destruction of vision by overirradiation of the optic chiasma. This suggestion of the use of yttrium was followed at Hammersmith[3] and in other centres. The problem of maintenance replacement therapy, following such destruction of the pituitary gland, was less of a problem than might have been supposed. Such therapy is less troublesome than that of replacement therapy after adrenalectomy and requires only a relatively small dose of cortisone or of hydrocortisone and a small dose of pitressin for patients who develop diabetes insipidus.

INDICATIONS

The indication for ablation treatment exists in patients who have widespread metastases and are not amenable to other treatment. In these types of patients, hormone therapy by stilboestrol, testosterone or both has usually been tried and in most cases, especially in premenopausal patients, when ovariectomy should have been used. Hormone therapy can often cause great improvement by itself and it indicates whether or not the patients are likely to be hormone-sensitive. In our experience, the existence of large liver metastases causing jaundice is an indication that hormone treatment is very unlikely to be successful in relieving the patients of their symptoms.

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The aim of ablation treatment is to destroy the pituitary gland by delivering to the whole of the gland a sufficient dose of radiation to destroy the secreting tissue. According to investigations carried out by Young[4] relating the post-mortem histology of pituitary glands treated and the doses received, it is necessary to give a minimum dose of 70,000 rad to all parts of the pituitary gland to ensure that the histological appearance becomes incompatible with secretion.

Whether or not smaller doses, while still leaving distinguishable histological appearances of viable pituitary cells, will be compatible with normal secretion to any extent is unknown.

Another aim must be that the patient is not subjected to complications that are dangerous to life, dangerous to vision or intolerable to his comfort.

COMPLICATIONS

The immediate complications likely to appear on carrying out the procedure for ablation are as follows:

Haemorrhage. While this may be troublesome in patients who have the pituitary fossa exposed by operation (as in our first series), it is usually of no significance in connexion with the method at present being used.

Diabetes insipidus. Not infrequently this complication follows insertion of the seeds and is an indication that damage or a high dose of radiation to the posterior part of the pituitary has interfered with the secretion by this part of the gland. It is corrected by the use of pitressin snuff, or, in patients who have painful spine or rib metastases, by use of an intramuscular injection of pitressin tannate. Such patients find the use of pitressin snuff (which may cause sneezing) painful because of the jarring of the metastases. It is possible to stop the administration of pitressin in most cases after a relatively short time of a few weeks.

Leakage of cerebro-spinal fluid. This implies a fistula through the bone, putting the nasal cavity in communication with the subarachnoid space, a step which causes constant anxiety because of the possibility of infection of the meninges from the nasal cavity. When leakage occurs, it is likely to continue for a long period, and there is the possibility that administration of cortisone or Prednisolone, which is the necessary replacement therapy for pituitary functions, will mask possible infection.

Long-term complications may be due to the proce-

dure adopted or to the irradiation. The most important complication that may develop as a result of the procedure is infection and continued leakage of cerebrospinal fluid. The most important complication due to the radiation is possible loss of vision, due to overdose to the optic chiasma. Loss of vision occurred completely in one patient and partly (one eye) in another in our series. In these cases, the estimated dose at the region of the upper margin of the pituitary fossa was 40,000 rad in the first case and 19,000 rad in the second. A possible complication due to irradiation is bone necrosis, but this we have not seen. In a patient examined at autopsy a small aneurysm close to the carotid artery was seen; this was considered by neurosurgeons to be due possibly to damage of the internal carotid caused by mechanical injury to the wall at the time of insertion of the seeds. It is not a complication which can occur in connexion with our present method.

Following the lecture given by Professor Illingworth, and in conjunction with the ear, nose and throat surgeons, we treated a series of cases in which the pituitary was approached by operation through the nose by making a small hole in the floor of the sella turcica and implanting radioactive gold grains into the sella through this hole. The method involved making X-ray checks in the operating theatre, and the procedure was sometimes very time-consuming. Haemorrhage was a feature and infection occurred in a few cases. Malplacement of grains was not uncommon and the results expected were not as good as we felt they should have been. Because of this, one of us (FE) designed a method for attempting to place the seeds into the pituitary fossa with precision using the nasal route, but taking less time and causing less trauma both to the bone in getting in to the sella turcica and to the structures inside in attempting to find the exact position at which to deposit the seeds.

METHOD

Principles of the method involved the following: (*a*) placing marks on the patient's skin to provide external reference points relative to the centre of the pituitary gland; and (*b*) using a suitable framework fixed to the skull, to place the centre of the arc of a circle at the centre of the gland so that a drill followed by a cannula may reach exactly this centre along any convenient radius and in order that radioactive sources may be deposited in a known position relative to the centre (Fig. 1).

The method as carried out at present is as follows:

1. Marks are made at points on the skin just in front of and above the pinna to correspond roughly with marking for the pituitary fossa.
2. Centred on each of these marks, clock-faced markers are affixed to the skin using a plastic solution (Fig. 2).
3. A lateral X-ray film then is taken.
4. A point is chosen on the X-ray film at which it is intended to centre the end of the cannula.

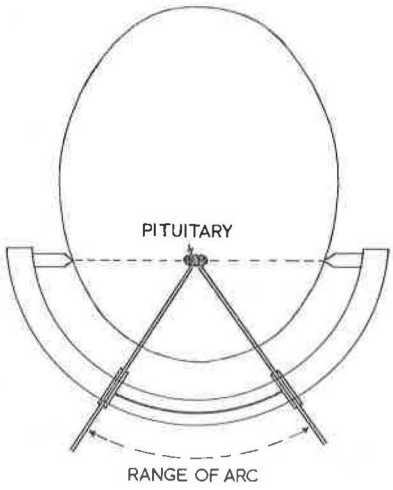

Figure 1

5. The coordinates at this point, relative to the markers, are read off (e.g., 12—6.30 and 3—8.20).
6. With the patient lying with the head flat (no pillow), marks on each side of the head are placed on the skin corresponding to the coordinates; differences in the markers enable one to know to which side each marker corresponds.
7. Hair is shaved from the head over the region of the mastoids to permit the set screws of the framework to which the arc is attached to be screwed into the skin (with sterile precautions).
8. At this point, the patient is given a general anaesthetic.
9. The vestibule of each nostril and the areas of skin into which the set screws are to be inserted are sterilised.
10. The rigid framework is fixed to the skull, taking care not to distort the skin, since this would otherwise change the positions of the marks relative to the pituitary gland.
11. The adjustable pointed screws are brought into correct position by sliding along the framework so as to be collinear with the axis of the arc which is to be put in position later; the axis thus passes through the marks made on the skin and the point decided on in the pituitary fossa; the adjustment procedure involves two steps: (*a*) the position in an anteroposterior direction is first decided upon on each side, using a device which is illustrated in the film; (*b*) the position in an angle in a vertical direction is then fixed.
12. After the screws have been adjusted so as to touch the skin lightly, the arc is fitted into sockets in the ends of the screws (Fig. 3).
13. Measurements are then made which enable adjustment of the position of the arc so that its centre is at the point chosen in the pituitary fossa; two points are thus used, each 2 mm to one side of the midline, so that one is in the left half and the other in the right half of the pituitary gland.
14. A drill is then inserted through a guide which passes into the nostril and the drilling is carried out to the depth desired in the pituitary fossa (Fig. 4).

Figure 2

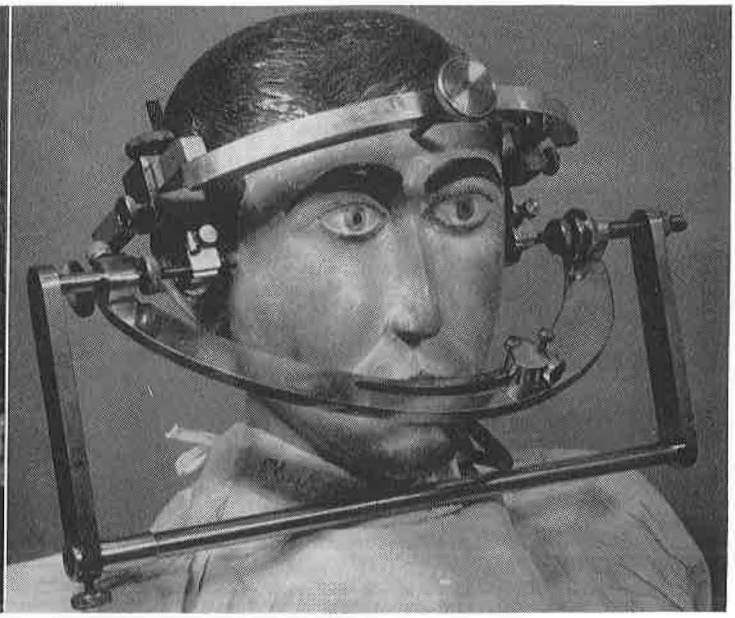

Figure 3

15. The drill is removed and replaced by a cannula into the distal end of which a little penicillin-sulphonamide emulsion has been introduced.

16. The radioactive seed is then inserted (Fig. 5).

17. The position of the centre of the arc is then adjusted so as to correspond to the point in the other half of the pituitary and the procedure repeated.

18. The apparatus is then dismantled.

19. Finally, an X ray is taken to demonstrate the position of the seeds in the pituitary fossa (Fig. 6).

[The above procedure is demonstrated by a film.]

The greatest difficulty we have had has been to make certain that the seeds were precisely placed. There has been no difficulty in ensuring that the seeds were correctly placed relative to the midline, but there was a tendency for them to be too high, in which case there is danger to the optic chiasma, or too low, in which case the pituitary is not sufficiently irradiated.

Important steps in development of the technique have been as follows. Until we were certain of precision of the method, strength of the sources was kept relatively low, since it was felt that in a patient who might survive for some time, the development of blindness would be a most depressing result. Because of this, two 20 millicurie gold grains were inserted. These gave at the margin of the pituitary gland a dose of approximately 18,000 rad. In July, 1957, one patient had as a trial three 20 millicurie gold grains, the dose in her case being 37,000 rad at the pituitary fossa margin. So far, this patient has not developed any visual complications, except that for a short time after the insertion of the seeds she did complain of slight blurring of vision. We decided, as a result of our experience in this case, to use two 30 millicurie seeds in each case. With respect to the patient mentioned, we had not started the technique of putting one seed in each lateral half of the pituitary fossa and all the grains were in the middle of the gland. We now feel it is safe to put 30 millicuries laterally in each half of the pituitary gland.

The most important development to ensure precision is one we probably should have thought about previously. In the process of drilling, the drill first of all comes against the wall of the sphenoidal sinus at a distance of approximately three centimetres before it reaches the final position. After going through the wall of the sphenoidal sinus the drill passes through no bone until it reaches the floor of the sella turcica. It is possible at this stage to estimate how much further the drill must go before the stop on it prevents going further, also to decide just how much further the drill should go to place the seeds precisely in a vertical direction.

The next important development has been in connexion with the cerebro-spinal fluid. We attempted to put in a small plug of fibrin foam to produce a clot which we hoped would block the fistula. This, however, did not prove satisfactory and since February, 1958 we have been using a method of inserting dry agar powder into the hole after each seed has been inserted, and since doing this we have had much less leakage.

The gold grains which we have used are platinum sheathed, 2.5 × 0.5 mm, of the type described by Sinclair.[5] These are obtainable from Harwell at two days' notice. Recently, due to some reorganisation at Harwell, it has not been possible to obtain these grains and we have used radon seeds instead. The grains will soon be available again, but meanwhile we are having yttrium seeds prepared for insertion into each half of the pituitary gland, using a cannula with a hole placed at the side and a flexible trocar.

RESULTS

The results of the treatment so far have not been impressive statistically; however it must be remembered that all the patients treated had reached the stage at which no more benefit could be expected from

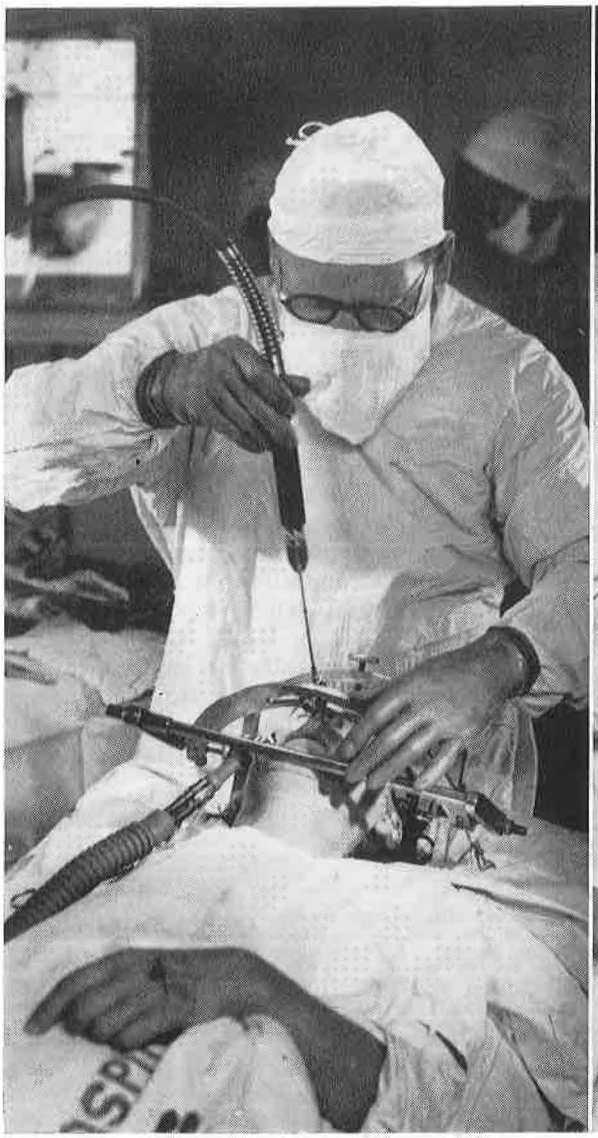

Figure 4

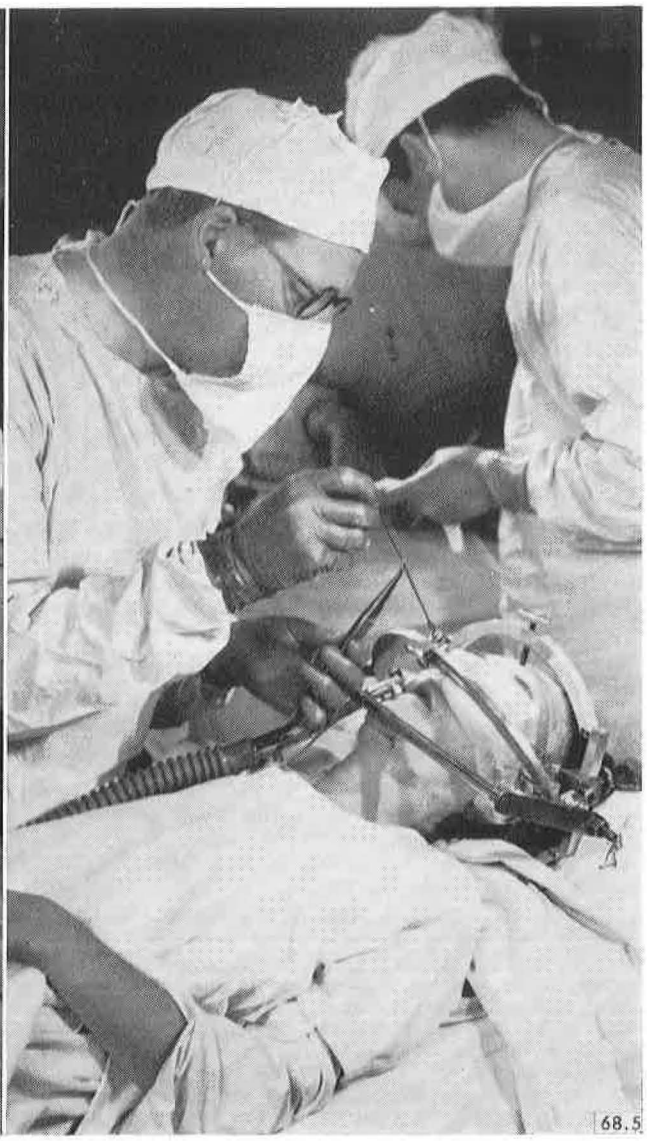

Figure 5

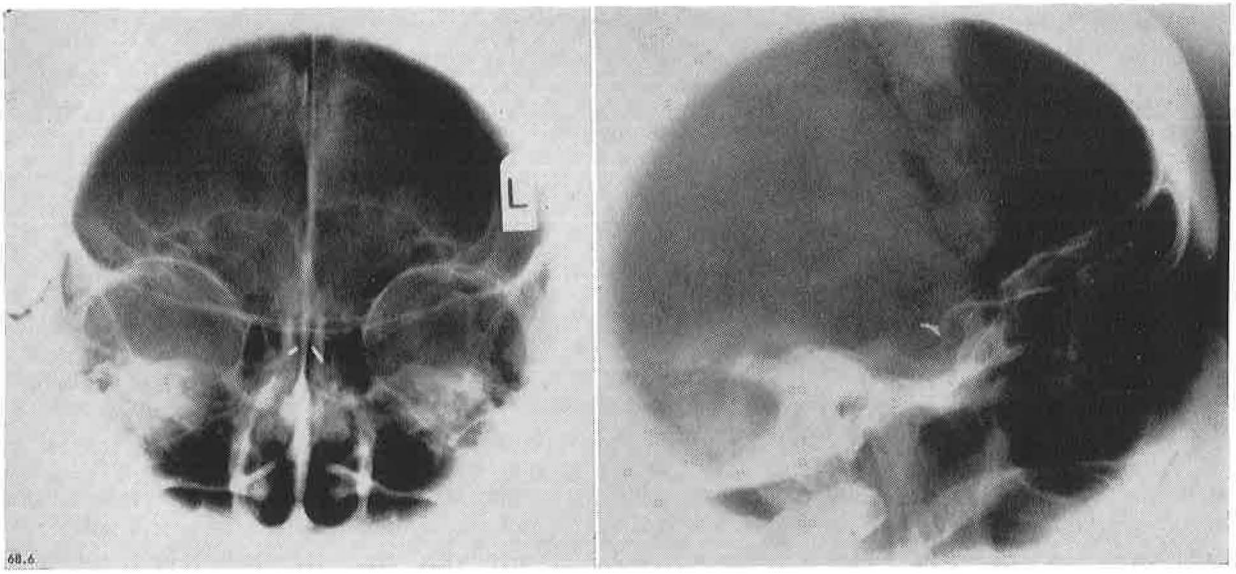

Figure 6

any other treatment, the possibilities of local irradiation, surgery and hormone therapy all having been exhausted. Thus any improvement in the patient's condition is sheer gain and the considerations to be taken into account are chiefly the risk and discomfort of the actual procedure of pituitary ablation and the risk and discomfort of complications, set against the likelihood, duration and extent of improvement.

Risk of the procedure as carried out by us is small. No patient has as yet died as an immediate consequence. The discomfort immediately following the operation consists chiefly of headache and slight sickness for two or three days and, less constantly, of diabetes insipidus.

The long-term results are shown in the accompanying appendices. Of 42 patients, 15 have shown improvement. Eleven of these are alive, but only 6 have survived for more than three months. Estimates of mammatrophic hormone content in the urine and of thyroid function have been carried out, and recently estimates of cornification indices to check oestrogen activity have been made.

The mammatrophic hormone estimations were a section of a larger series covering several centres which were carried out by Dr. Stretton Young in the laboratory of Professor Hadfield at the Imperial Cancer Research Fund. The rationale has been described by Professor Hadfield.[6] In our cases, the following points are worthy of being noted:

1. Meaningful estimates have not been obtained on patients undergoing hormone therapy.
2. The mammatrophic hormone content of the urine fell to a very low value following the treatment in those cases in which it had previously been high, with one exception.
3. The patients with the highest initial hormone content were most favourably affected.

The radioiodine uptake tests have not demonstrated any consistent effect on thyroid function.

Three patients died in less than one week. All of these had obvious liver metastases with jaundice and were recognised as deteriorating rapidly at the time of implantation. Recently a note has been published from Belfast[7] on packing the sella turcica with a wax paste mixed with powdered yttrium-90. This is a means of completing destruction of residual elements of the pituitary gland at the time of surgical hypophysectomy. They report 16 improved cases out of 25 operated upon. Operative mortality was 20%. We feel this method may offer more than the method of implantation of radioactive material into the gland and are intending to run a comparable series on patients suitable for hypophysectomy using yttrium seeds in one series and yttrium plus wax following surgical ablation in the other. Patients unfit for hypophysectomy will be treated by implantation only.

Our results to date are summarised in Appendices 1 and 2.

Appendix 1. Current Data on Pituitary Patients (old method)

Case no.	*Age*	*Length of survival after operation*	*Better, static, worse or dead*		*Iodine T.R.F.*		*Mammatrophic index*	
			½	*Current*	*Pre-op*	*Post-op*	*Pre-op*	*Post-op*
1	47	18 months	S°	B°	—	0.04	11	0.6
2	50	6 weeks	S	D	—	—	4	—
3	61	17 months	S°	S°	—	—	3	0.2
4	70	4 months	S	D	—	—	—	—
5	42	16 months	S°	W°	0.08	0.16	0	0
6	41	1 month	S	D	0.1	—	0	—
7	68	10 months	B°	D	—	—	7.95	0.2
8	52	2 months	W	D	—	—	—	—
9	40	1 week	D	D	—	—	—	—
10	49	4 months	B^s	D	—	—	1.0	0.1
11	59	3 months	B^s	D	0.03	—	2	0.5
12	54	6 weeks	W	D	0.085	0.09	1.5	0.08
13	47	Inhaled blood post-op	D	D	0.115	—	—	—
14	63	2 months	B	D	0.065	0.06	7.35 14.4	0.023
15	48	11 months	B°	B°	0.11	0.08	2	0.175 Negligible
16	56	2 months	B	D	0.17	0.065	0	—
17	36	8 months	W°	D	0.0005	0.0005	0	0
18	53	6 weeks	W°	D	0.05	0.102	Killed mice	—
19	59	5 months	S	D	0.045	—	Very high	Very, very high
20	70	3 months	B°	D	0.01	0.07	—	0

° Objectively.
^{s} Subjectively.

Appendix 2. Current Data on Pituitary Patients (new method)

Case no.	Age	Length of survival after operation	Better, static, worse or dead		Iodine T.R.F.		Mammatrophic index	
			½	Current	Pre-op	Post-op	Pre-op	Post-op
1	77	7 days	D	D	0.025	—	Low 0.36	—
2	60	2 months	S°	D	0.1	0.08	Killed mice	Very low
3	44	2 months	S°	D	0.28	0.12	Very low	0
4	56	4 months	B*	D	0.09	0.07	Killed mice	—
5	54	3 months	B*	D	0.04	0.015	Negligible	Killed mice
6	71	8 months	B	B	0.04	0.01	Negligible	Negligible
7	61	5 months	B*	D	0.07	0.065	Negligible	Negligible
8	48	2 months	W	D	0.065	0.049	Killed mice	0
9	40	4 months	B*	D	0.105	0.105	0	Very low
10	47	2 months	S°	D	0.06	0.077	0	—
11	63	3 months	W	D	0.10	—	0	—
12	56	4 months	S	D	0.055	0.015	Low 1.4	Negligible
13	50	3 weeks	D	D	0.088	—	3	—
14	56	6 weeks	W°	D	0.046	0.036	High	Killed mice
15	58	5 months	B*	B*	0.08	0.04	Nil	Nil
16	62	5 months	S°	S	0.20	0.11	Nil	Negligible
17	55	5 months	B*	D	0.04	—	Killed mice	Negligible
18	61	4 months	S°	W°	0.04	0.05	Doubtful	Negative
19	35	3 months	W	D	0.013	—	Nil	—
20	45	1 day	D	D	0.02	—	Doubtful	—

° Objectively.
* Subjectively.

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Mr. Ellis presented Paper P/68, above, at the conference and demonstrated his clinical and radiological procedures by motion pictures.

Stereotaxic Placement of Radioactive Isotopes in the Brains of Laboratory Animals and Man: A Study Directed Toward the Alleviation of Parkinsonism

By J. B. Campbell, H. H. Rossi and S. Boyesen*

Partial destruction of the globus pallidus, a deeply seated nucleus in the brain, is believed to be followed by amelioration of artificially produced dyskinesia in monkeys[1] and the tremor and rigidity of man suffering from Parkinsonism.[2] The clinical and laboratory results of attempts to destroy subcortical structures have been variable because of difficulties in producing a precisely delineated lesion by interruption of blood supply, electrocoagulation, or necrosis induced by mechanical, thermal, and chemical methods.[3] Failure to accurately localize and reach the site selected for application of these destructive agents may also have contributed to inaccuracy of the technique. In fact, because of these uncertainties, doubts have been raised whether it is the destruction of the globus pallidus rather than of some neighboring structure that has been responsible for the favorable results that have been obtained.

The availability of artificially produced radioactive isotopes which are sources of beta rays, provides the opportunity to create lesions of predicted volume in deeply seated centers by implantation via a guiding trocar. Such lesions can be expected to be sharply limited because of the finite range of the beta particles in tissue. Experiments carried out in the brains of cats have shown that stereotaxic implantation of 0.86 mm sources of beta radiation can be relied upon to accomplish this end.[4] Figure 1 shows a 7.5 mm diameter lesion in the feline preoptic area 21 days after implantation of a 0.4 mc Y^{90} source incorporated in a ceramic matrix.[5] The extent of the lesion is visualized by supravital staining (intravenous 4% Evans blue dye W761-1). This volume of radionecrosis at the site caused no detectable physiological disturbance whereas smaller electrolytic lesions in this area have led to profound physiological disturbances and death in Heath's experiments.[6] Microscopic examination of such a lesion two weeks after implantation of the source shows an approximately spherical volume of cell breakdown to the point of liquefaction, which is separated from normal tissue by a 700 micron zone of partial destruction.[4] Approximately one year after implantation, similar lesions produced by Pd^{109} in the caudate nucleus consist of a cyst filled with watery clear fluid contained within thin walls with a yellowish tint. Microscopic examination reveals that the boundary between absolute destruction and normal tissue has narrowed to 300 μc.[7]

These data accumulated from 250 animal experiments indicate that with respect to acute and chronic tissue reactions, the method merits clinical application. In preliminary clinical trials carried out in conjunction with Walker,[8] attempts were made to place 0.4 mc Y^{90} sources in the globus pallidus of five individuals with Parkinsonism by means of a trocar oriented in accordance with serial roentgenograms. Successful delivery to the globus pallidus has not been demonstrated since none of these patients has come to autopsy. Nevertheless, three of them have been improved.

These results were sufficiently encouraging to warrant further efforts. However, it was believed that successful application of the technique required refinement in localization of position of the globus pallidus in the individual brain, and in delivery of the source. Therefore, a stereotaxic manipulator was designed and constructed which is a modification of the instrument developed by Leksell.[9] One of the major changes is the mode of fixation to the skull. Stainless steel plugs screwed into the skull support the machine in the manner of Wycis[10] and serve as points of reference in obtaining coordinates for the globus pallidus. After fixation of the screw plugs and test mounting of the machine, pneumoencephalography is performed. Antero-posterior and lateral roentgenograms are obtained with the head immobilized in a frame which supports two film cassettes at right angles to each other. By modifications of a method developed at this institution,[11] it is possible to convert the resulting radiographic images into orthogonal projections. Using the anterior commissure as a reference point and utilizing its established spatial relationship to the globus pallidus,[12] the distances between the latter and the screw plugs are determined graphically from the orthogonal projections. The tip of the trocar may be adjusted for the calculated site of delivery by three mutually perpendicular motions of its support along calibrated scales. The scale readings required for positioning of the tip of the trocar at the required distances from the screw plugs may be determined by simple formulae which have been derived for this purpose. While these

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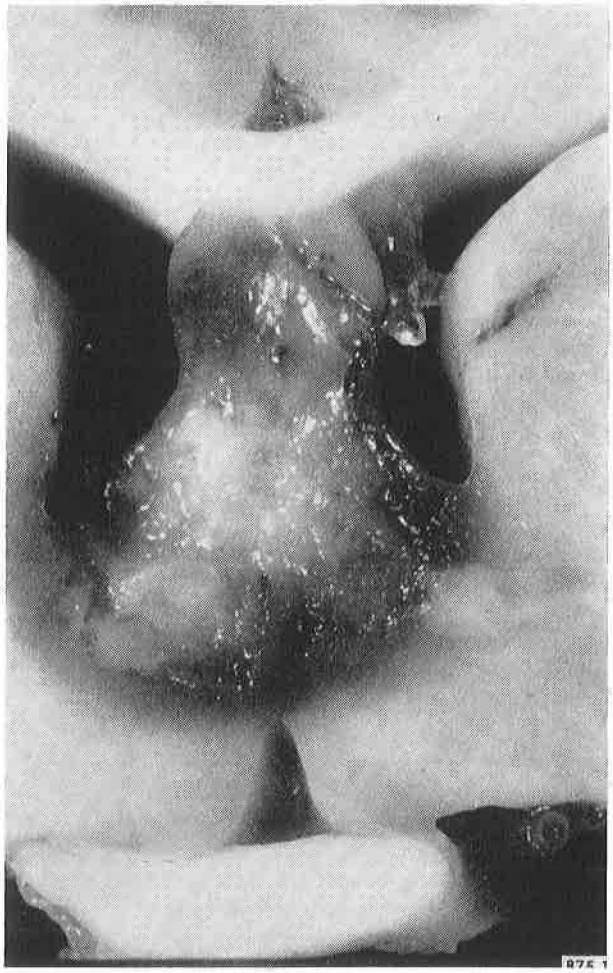

Figure 1

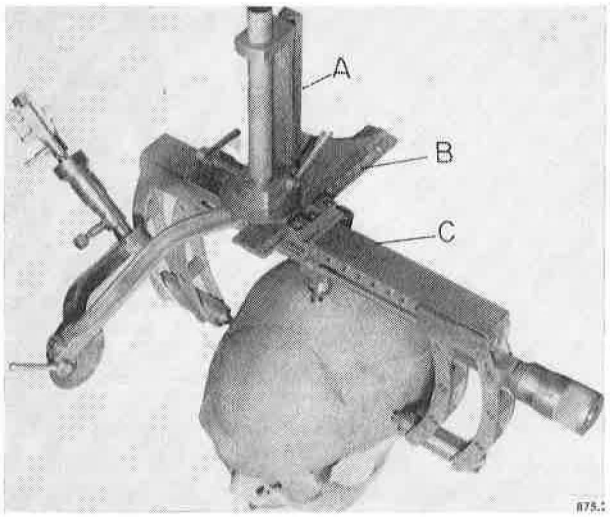

Figure 2. Stereotaxic manipulator mounted on a skull: A, B and C, scales for rectilinear motions determining site of delivery

adjustments uniquely determine the site of the delivery, the route to this point can be selected according to surgical considerations, making it possible to avoid damage to cortical blood vessels and sensitive subcortical structures, and loss of the sources within the ventricular system. This freedom of delivery is achieved by provision of two pivoting motions which keep the tip of the trocar at the same point but permit arbitrary angulation.

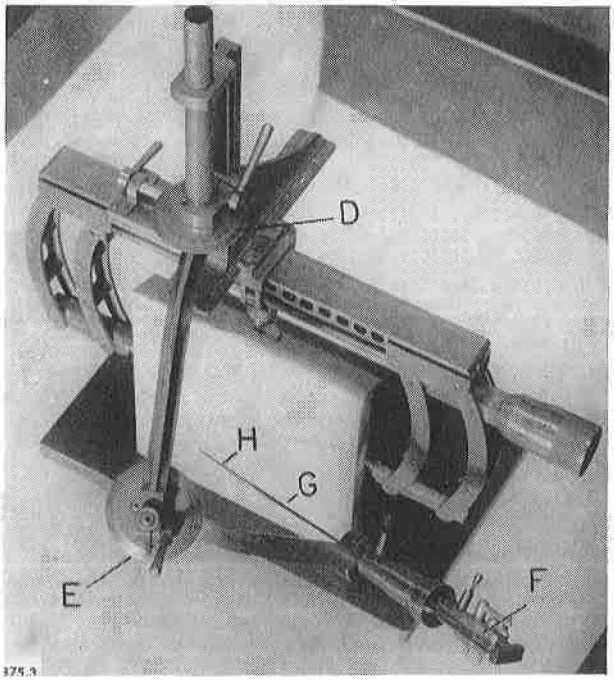

Figure 3. Stereotaxic manipulator mounted on a test block: D and E, protractors for rotational motion determining route of delivery; F, aluminum cartridge for radioactive source; G, guiding trocar; H, finely tapered stylet

Figures 2 and 3 show the stereotaxic manipulator adjusted for similar sites of delivery using two entirely different routes of approach.

The radioactive seed is contained within an aluminum cartridge of sufficient wall thickness to absorb all beta particles. Delivery of the seed is accomplished by pushing the Y^{90} sphere by means of a finely tapered stylet out of its container and down to the tip of the trocar which has been passed to the calculated site through a burr hole. With the stylet remaining fixed, the trocar is withdrawn, leaving the seed surrounded by neural tissue on its entire surface except for the point of contact with the stylet. Subsequent withdrawal of the stylet completes the procedure.

This technique evolved by experimentation on cats and human cadavers is now ready for clinical trial.

ACKNOWLEDGEMENTS

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Experimental Intralaryngeal Injection of Radioisotopes

By J. J. Pressman, A. H. Dowdy, R. L. Libby, M. Fields, M. B. Simon and K. Hand*

This report is concerned with the experimental injection of $CrP^{32}O_4$ and $Cr^{51}P^{32}O_4$ (radioactive isotopes) into the submucosal spaces of the larynx. Observations were made of the local effects of the radiation from P^{32} on the larynx and the distribution of $CrP^{32}O_4$ within this organ. These observations have expanded our knowledge of the anatomy and physiology of the larynx, and have proved helpful in understanding the natural history of certain diseases of the larynx.

Ability of the normal larynx as a whole and of its component parts to tolerate injected radioactive material has been observed, and the way has been opened for a clinical trial of radioisotopes in the treatment of certain cancers of the vocal cords. It has likewise been established that if radioisotopes are to be used for the treatment of cancer of the larynx, injection should be made in accordance with the anatomical details which have been observed in the course of these experiments.

Studies of spread and distribution of injected radioisotopes have supplemented observations made using a colloidal dye (4% Direct Sky Blue, Wyeth)[1] and have provided further identification of submucosal compartments of clinical importance originally described by Hajek in 1891[2] and elaborated upon in our previous reports.[1,3] The pattern of lymphatic flow, ordinarily considered to be as illustrated in Fig. 1, has been further identified in the experimental animal and in observations on humans.

Radioactive chromic phosphate is useful in these anatomical observations by reason of its being identifiable over longer periods of time than dyes or radiopaque contrast media. Observations within the larynx by the latter methods are possible for only a few hours or days at the most, but by the use of radioisotopes the period of observation has been extended in our experiments for as long as eight weeks, which by no means exhausts the time limit of usefulness.

The $CrP^{32}O_4$ was prepared by a modification of the method of M. E. Morton.[4] Particle size was determined by electronmicroscopy and was found to vary from 0.25 to 0.5 μ. The final solution for injection was prepared by suspending the particulate $CrP^{32}O_4$ in a medium containing 10% by volume of hyaluronidase (Wydase) and 1:100,000 epinephrine. A small amount of Evans Blue dye was added as a visual aid to detect leakage from the injection sites and to observe its spread within the laryngeal tissue. $Cr^{51}P^{32}O_4$ was prepared in a similar manner. Chromium-51 was employed in these experiments so that its gamma emission might be utilized for external scanning of the larynx and the cervical region post injection.

In order to properly introduce radioisotopes into the submucosal structures of the larynx, a special automatic injector is required (Fig. 1) capable of delivering exact amounts of the colloid. The Gamble-Libby[5] unit is excellent for this purpose and has been used in these experiments. This is an electromechanical leakproof injector activated by a foot switch, capable of delivering fixed amounts of fluids through a 3 to 5 foot section of flexible tubing into a needle the orifice of which is located a few millimeters proximal to the tip. Specially prepared curved needles with a 60° to 90° offset have proved most practical. The amount of fluid delivered by the automatic injector can be varied from 0.065 to 0.4 ml. For these experiments the 0.065 ml injection volume was used.

TECHNIQUE OF STUDY

Studies were carried out upon human cadaver larynges, living dogs, living pigs and living humans. Injections of dyes preliminary to the use of radioisotopes were made into cadaver larynges at various sites, and gross observations made of the limit of spread taking place prior to rupture of the anatomical structures from pressure of the injected fluid.

Two humans prior to laryngectomy, each having unilateral carcinoma of such limited extent as not to interfere with the normal anatomy, were selected for observation. One-half ml of dye was injected through a direct laryngoscope in several fractions in and about the true vocal cord of the uninvolved side and the laryngectomy completed four hours later. Gross observations of the spread of the dye were made. The experiment was repeated in living dogs and pigs, using dyes for preliminary study and radioisotopes for longer term observations. Experiments were conducted both with larynx split in the midline anteriorly and with the larynx intact.

The dogs utilized in these experiments were prepared under general anesthesia and with sterile sur-

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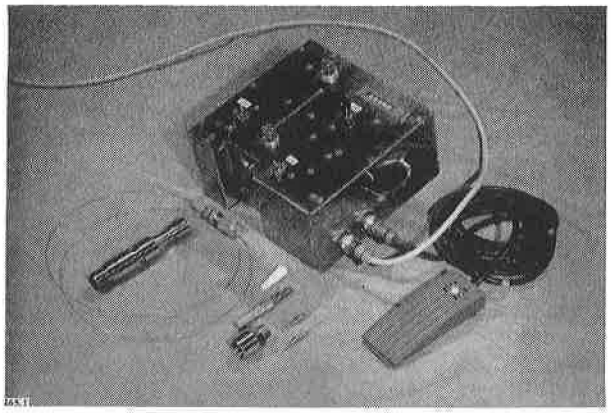

Figure 1. The Gamble-Libby Automatic Injector

gical techniques. The interior of the larynx was exposed through an anterior midline incision of the thyroid cartilage. The various compartments of the larynx were identified as indicated in Fig. 2. The Gamble-Libby automatic injector, Fig. 1, was employed to deliver 0.065 ml of the radioactive material to each of 8 to 10 injections to one or both sides of the exposed larynx. In these experiments the amount of radioactivity varied from 25 to 70 μc per injection.

Scintigrams of all larynges of dogs injected with doubly labelled $Cr^{51}P^{32}O_4$ were made at selected periods up to eight weeks. At sacrifice the laryngeograms were superimposed upon the larynx and photographed. Micro and gross radioautographs of the larynges and cervical nodes were made subsequent to autopsy.

Gross observations following the injection of dye into the larynx were made of the associated lymphatics to determine the spread of the dye by lymphatic channels. When radioisotopes were used, counts were made of blood samples, and of all organs including adjacent and distant lymphatics, to determine the degree of radioactivity present. Excreta were examined to determine loss of radioactive substance by these channels.

ANATOMICAL OBSERVATIONS

Relationship between Opposite Sides

If $CrP^{32}O_4$ (radioactive isotopes) or colloidal dyes are injected into one side of the larynx at any point above the lower level of the cricoid cartilage, the spread of the material by the lymphatics will be such that there is, with exceptions to be described, no cross-over to the opposite side. This conforms to the pattern of lymphatic distribution, the intralaryngeal lymph channels forming collecting lymph vessels which converge and ascend parallel to each other along the midline. Observations concerned extended to twelve days in the instance of the dye, after which it could not be any longer identified, and to eight weeks in the instance of the radioisotopes, representing the longest period over which observations have been made. It is believed that the degree of isolation of one side from the other has not previously been demonstrated.

Two exceptions were noted. In the instance of pigs, dye injected submucosally 1.0 cm below the level of

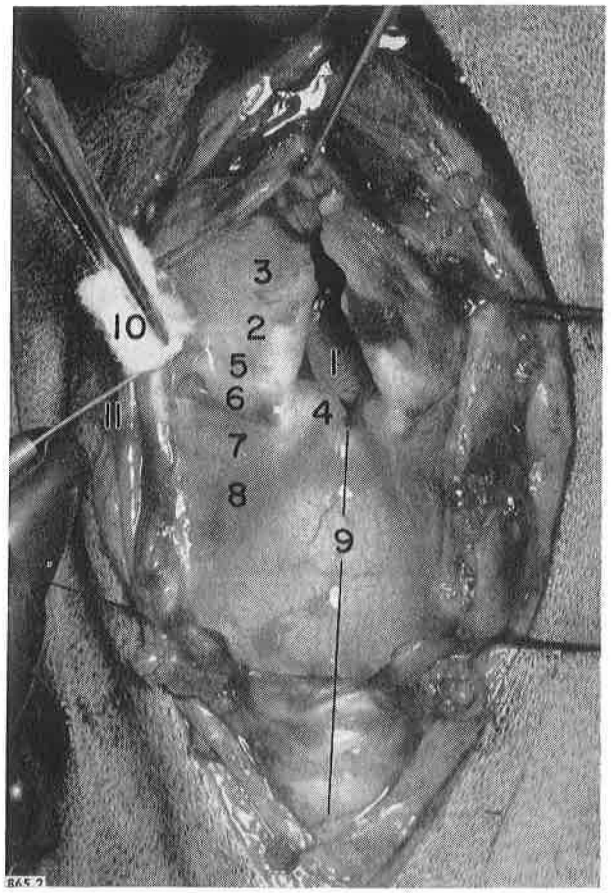

Figure 2. Interior of larynx surgically exposed. Vertical line represents midline of posterior wall of larynx passing through posterior commissure. 1. Posterior wall pharynx; 2. right aryepiglottic fold; 3. right half of the epiglottis; 4. right arytenoid; 5. right false cord; 6. right ventricle; 7. right true cord; 8. intrinsic muscle on right; 9. mucosa over cricoid cartilage; 10. cotton sponge; 11. injection needle

the vocal cord passes upward, fails to enter the margin of the vocal cord, and reappears on its superior surface. The dye stained the wall of the saccule and crossed the midline at the anterior commissure to spread as a thin band along the superior aspect of the opposite cord. The second exception was observed in the cadaver larynx of dogs. Dye forcibly injected into the ventricle appears in two lymphatic channels one immediately above and the other immediately below the ventricle. These converge anteriorly forming a single channel which crosses the anterior commissure. The channel then splits into two surrounding the ventricle on the uninjected side. No cross-over to the isolated side was noted at any other level, including injection of the epiglottis.†

In the living human, prior to laryngectomy, dye injected in and above the true vocal cord spreads diffusely staining the entire homolateral side including the arytenoid cartilage and extending to its posterior

† Attempts have been made to repeat this observation in humans and in the dog. It has not been possible in any subsequent experiment to demonstrate these lymphatic pathways. Attempts to observe them by the injection of dyes in the living dog have likewise been unsuccessful.

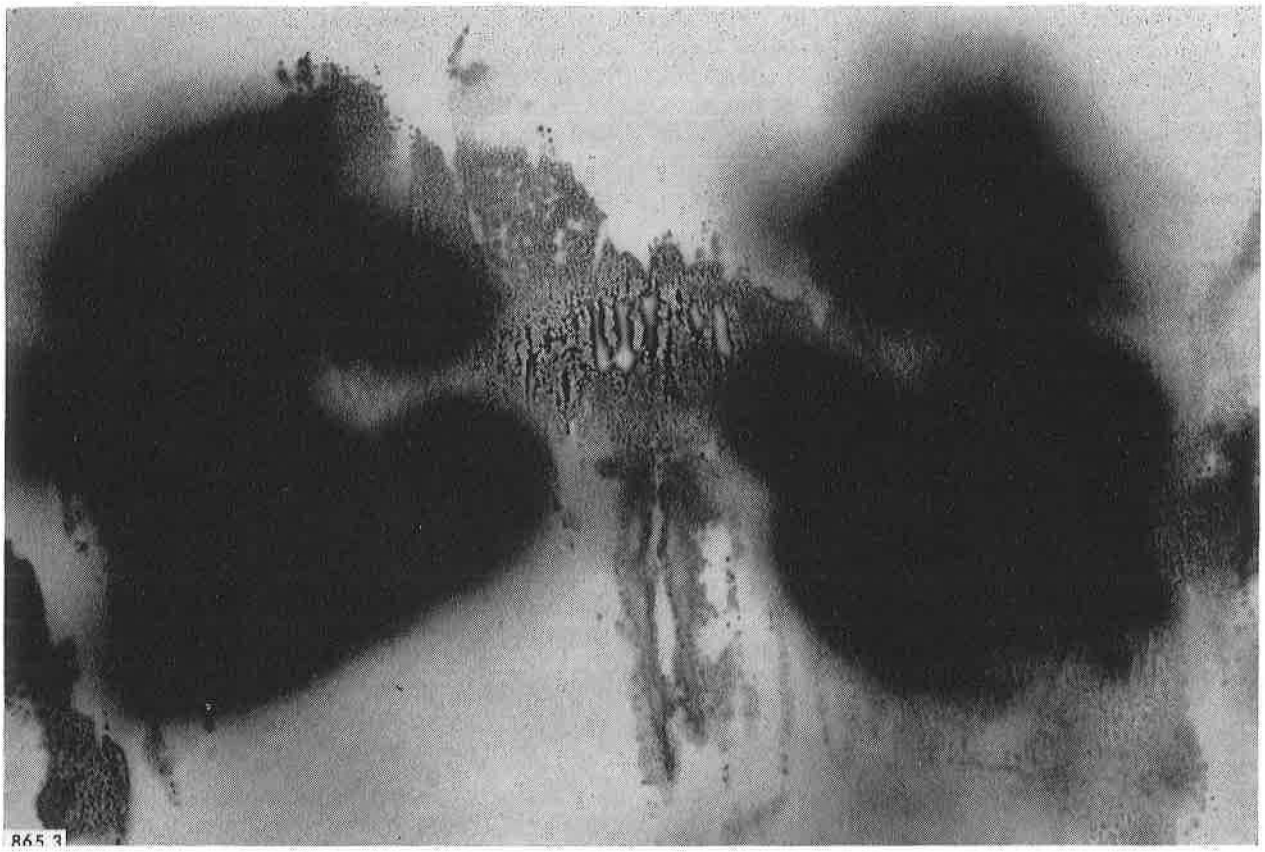

Figure 3. Radioautograph of larynx following injection of $CrP^{32}O_4$

surface to enter the pyriform sinus area. No cross-over beyond the midline occurs at any point, the midline itself being sharply delineated. The lower limit of spread is at the lower border of the cricoid cartilage. This is likewise sharply delineated, representing the separation of the lymphatic bed of the larynx from that of the trachea. This is likewise of the greatest practical importance. This finding is discussed in detail.

Since conclusions concerning the spread of dye depend upon visual observation alone and there is no opportunity to learn of its ultimate fate, or its area of dissemination prior to sacrifice, this method of observation can be considered only as a preliminary study requiring the use of radioisotopes for confirmation and for observation of details.

Corroborative observations upon possible cross-over beyond the midline after an extended period of time were made upon living dogs using radioactive isotopes. Three dogs were used in similar experiments and the findings were alike. Ten submucosal injections of 0.065 ml containing 37 μc of $Cr^{51}P^{32}O_4$ were made on the right side of each larynx. The injections were made at various sites throughout the larynx including the subglottic area, the free margin of the vocal cord, the ventricle, the aryepiglottic folds and the epiglottis. With the injector needle vertically placed, one injection was made in each area just lateral to the midline. The dogs were sacrificed eight weeks later. There was by scintiscanner no demonstrable cross-over beyond the midline. The injected side, however, remained markedly radioactive. The lymph glands of the neck were scanned, radioactivity being demonstrable only on the side of the injection while nodes on the opposite side remained free of radioactivity.

The Vocal Cord Bursa

Preliminary observations following the injection of dye below the level of the cord indicates that the dye passes upward, staining the internal surface of the saccule, but after five hours fails to enter the lymphatics of the free margin of the vocal cord, this area representing the vocal cord bursa which remains free of dye. These preliminary findings were augmented by experiments using radioisotopes. Ten injections of 37 μc each (0.065 ml per injection) were made $\frac{1}{2}$ cm below the level of the vocal cords. Following sacrifice eight weeks later radioautographs were made of the entire larynx. The findings obtained by dye studies were confirmed, no evidence of radioactivity being demonstrable in the area corresponding to the level of the vocal cords (Fig. 3).

The vocal cord bursa, therefore, from the standpoint of lymphatic distribution as demonstrated by the injection of radioisotopes as well as dye, is isolated from the remainder of the larynx. With dye studies this applies to the human cadaver larynx as well as to the living dog. The reverse situation, however, does not apply invariably. It has been noted that dyes injected within the bursa, particularly in dogs, sometimes enter

the saccule, distending it and staining it, but this does not occur in every instance. Studies under way of the fate of radioisotopes injected directly into the laryngeal bursa are expected to clarify this point but have not yet been completed.

Lower Limit of Distribution of Laryngeal Lymphatics

Determination of the lower limit of spread of the laryngeal lymphatic plexus is of the greatest practical importance and in large measure needs to be considered the limiting factor in performing certain partial resections of the larynx. Additional experiments have therefore been carried out in an attempt to establish this lower level with certainty. These consist of observations following the injection of doses of radioactive isotopes in sufficient strength to produce widespread necrosis. The level of radionecrosis is invariably sharply demarcated at the lower level of the cricoid cartilage, amounting in some instances to almost complete destruction above this level with normal trachea wall remaining below (Fig. 4). It is apparent therefore that radioisotopes introduced into the lymphatic circulation of the larynx do not extend below the lower limit of the cricoid cartilage, corresponding with the previously described separation of laryngeal lymphatic channels above this level from the tracheal lymphatic circulation immediately below. This finding, representing isolation of the larynx above from the trachea below, has been confirmed visually by use of dye in the living human, and in the living dog. (The former has been mentioned parenthetically in the paragraph having to do with ipsolateral distribution of injected dye.) When dye is injected in and above the vocal cord in the human four hours prior to laryngectomy it fails to cross to the opposite side and a sharp line of demarcation occurs at the lower base of the cricoid cartilage. This observation has been repeated in dogs. Dyes injected in minute amounts between the level of the vocal cord and the lower border of the larynx spread on the injected side upwards and downwards, the latter distribution terminating abruptly in a straight line at the lower border of the cricoid cartilage. This finding, as evidenced by all methods of observation, is rather startling in that one could consider the larynx and trachea to be a continuous tube with free communication of lymphatics between them, but such evidently is not the case.

Figure 4. Extensive necrosis of interior of larynx 36 days post injection of 50 μc $CrP^{32}O_4$ per each of 20 injections. Note ulceration limited inferiorly to lower border of cricoid cartilage

ANATOMICAL FACTORS INFLUENCING RADIONECROSIS FOLLOWING INJECTION OF RADIOISOTOPES

At least two factors contribute to the increased sensitivity of certain areas of the interior of the larynx to radionecrosis following the injection of $CrP^{32}O_4$. One is the close adaptation of the mucosa to the cricoid cartilage in the subglottic area and the other the confluence of lymph channels at the midline near the upper level of the posterior commissure (Fig. 5). If radionecrosis does occur, it is most apt to be in the mucosa closely adapted to the cartilage, particularly

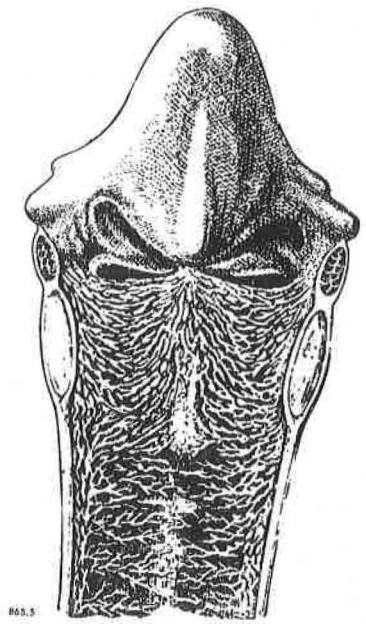

Figure 5. Schematic representation of lymphatic of interior of larynx with convergence of lymph channels at the midline near the upper level of posterior commissure

Figure 6. Small ulceration posterior over cricoid cartilage below posterior commissure

near the midline (Fig. 6). The point of greatest susceptibility seems to lie posteriorly just below the posterior commissure at which site small ulcerations are frequently found. This corresponds to the confluence of a greater number of lymphatic channels than is to be found at any other site (Fig. 5). Radionecrosis is least apt to be found overlying the intrinsic muscles of the larynx and is seldom seen in the ventricle or aryepiglottic folds. With massive dosage no area is immune.

FATE OF INJECTED $Cr^{51}P^{32}O_4$ AND $CrP^{32}O_4$

The clinical experience of Mumma with cancer of the oral cavity[6] and animal experience[7] indicates radioactive chromium phosphate prepared as described and injected into muscle or lymph nodes remains at the local site of injection in sufficient quantities to be cancerocidal. When injected into mucosal or submucosal areas it is distributed to the regional lymph node bearing areas. The interior of the larynx with its paucity of muscular substance and its semi-compartmentalization affords a unique opportunity to study the effects and fate of certain colloidal or particulate radioactive materials when injected into its various compartments.

In a series of 10 dogs the following redistribution and losses of $CrP^{32}O_4$ were found:

1. A small amount of $CrP^{32}O_4$ escapes into the venous circulation at the time of injection. This was observed by examining the blood for radioactivity. This small amount of initial radioactivity is rapidly removed by the liver and spleen.

2. Due to the nature of the structure of the laryngeal tissue it was found that 22.8 $\pm$ 6.0% of the injected dose was lost by oozing from the injection site. This was determined by measuring the radioactivity collected on sponges.

3. During the first 24 hours following injection, it was found that 20.9 $\pm$ 6.5% of the initial radioactivity in the neck was lost to other organs in the body. The details of this loss are given in 6 below.

4. Over a period of from one day to two weeks after the injection about 21% of the radioactivity found in the larynx at 24 hours is redistributed into the regional lymph nodes (Fig. 7).

5. Of the original calculated dose only approximately 50% remains at the sites of injection within the interior of the larynx because of the above losses.

6. The distribution of the $CrP^{32}O_4$ that is lost from the sites of injection (3 above) was studied in 11 dogs. It was found that the radioactivity in the liver accounted for from 0.0 to 8.2% of the loss, the spleen 0.0 to 2.2%, intestines 0.0 to 6.0%,‡ the stomach none, the kidneys 0.0 to 1.3% and the lungs 0.0 to 0.05%. Counts of the feces and urine showed little or no radioactivity.

By this technique it has been possible to deliver to the interior of the larynx an average of from 13,380 to 27,230 reps per gram of tissue when utilizing 25 or 50 μc of $CrP^{32}O_4$ per each of the 18–20 injections into the mucosal areas of the interior of the larynx of the dog.

CLINICAL IMPLICATIONS

One cannot fail to be impressed with the clinical implications of the above study. The isolation of one half of the larynx from the other (except by the demonstrated cross-over of lymphatics at the ventricles) corresponds to the known behavior of many cancers of the larynx in which enormous tumors occupy one side of the larynx without involvement of the other. Similarly there appears to be very great resistance to the extension of laryngeal tumors from above to the trachea below corresponding to the sharp delineation between the two as demonstrated in the destruction of the larynx by radioisotopes. Further detailed studies not herein described demonstrate that certain laryngeal compartments identifiable by dye and radioisotope studies correspond to the observed behavior of spread of many intralaryngeal neoplasms. These findings will be reported upon in subsequent communications.

The importance of bearing in mind observations reported herein as they apply to the surgery of the larynx can hardly be overestimated. Surgical procedures for cancer need to consider the likelihood of routes of spread of these tumors in which the anatomical details

‡ This may be the result of the ingestion of material coughed up from the larynx and swallowed.

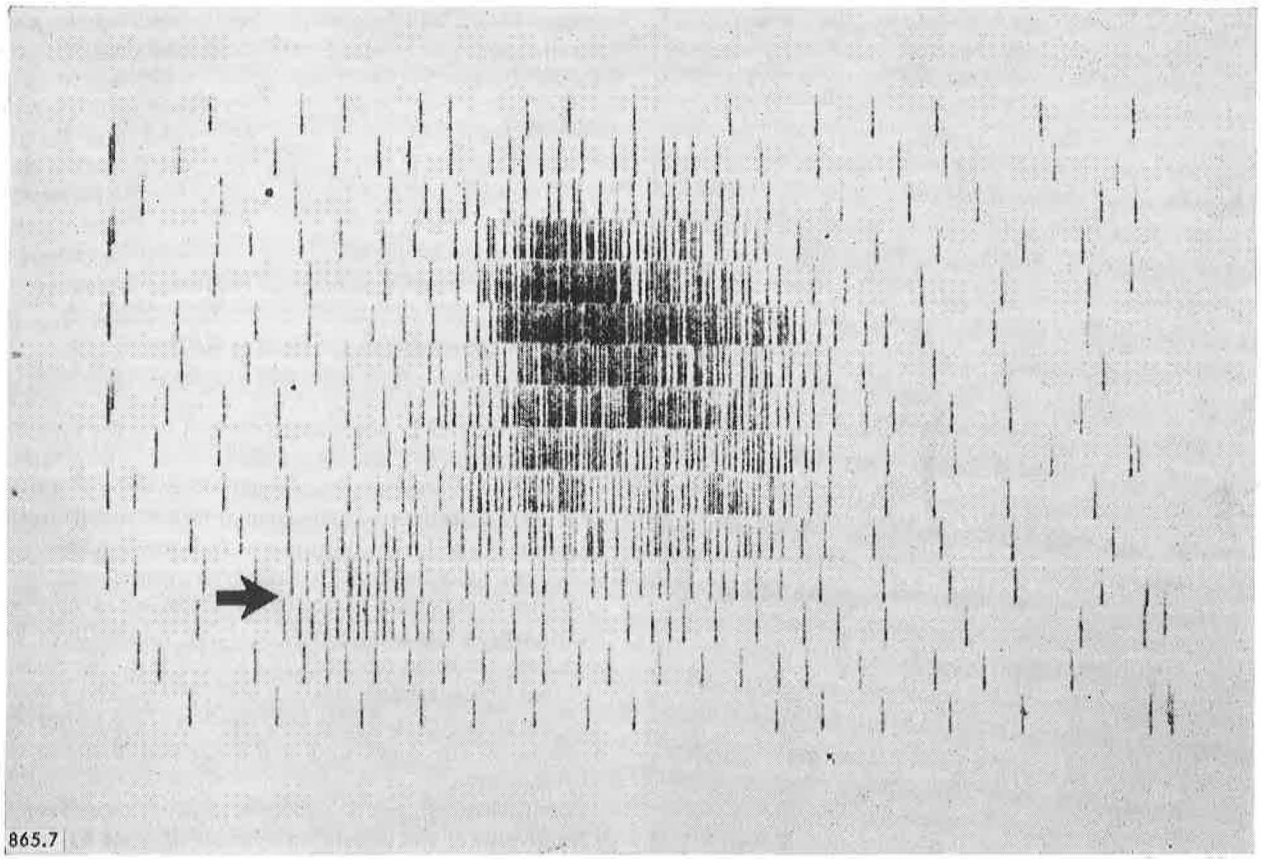

Figure 7. Scintigram of cervical region of dog whose larynx had been injected with $Cr^{51}P^{32}O_4$. Note activity in cervical lymph node

of lymphatic flow are of the foremost importance. With these observations in mind one can almost venture to predict the route of spread of these lesions in deciding upon the technical surgical procedures to be followed and can be guided accordingly. A subsequent communication will present the details of this correlation, the anatomical details and surgical indications. It has likewise been established by these observations following experimental intralaryngeal injection of radioisotopes that the latter remain within specific areas of the larynx long enough and in sufficient dosage to be considered of therapeutic value and that methods for the injection of radioactive isotopes into the larynx are feasible and practical.

A further report on the tolerance of the larynx to varying doses of radioactive isotopes is in preparation.

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Isotopes Decaying by Electron Capture: a New Modality in Brachytherapy

By P. V. Harper, K. A. Lathrop, L. Baldwin, Y. Oda and L. Kryshtal*

A number of ways have been devised for reducing radiation hazard to the operator during handling of radioactive source material in performing an implant. These problems are particularly great in connection with surgical procedures during which the surgeon's hands must remain in the radiation field for a substantial period of time.

One approach in circumventing this difficulty is to use, as a radiation source, an isotope that decays by electron capture, emitting instead of the usual hard gamma rays, soft characteristic fluorescent X rays. A number of considerations limit drastically the choice of radioactive material. In the first place, the physical and chemical properties must be suitable. In addition, the atomic number must be within a certain range. The characteristic K radiation of high Z elements overlaps the lower end of the gamma-ray range, and one loses the principal advantage of the soft X rays, which is ease of shielding. On the other hand, the low Z elements have very soft characteristic X rays that are absorbed in tissue in much the same way as beta radiation, and have no obvious advantage over this type of source. These considerations limit Z to values between approximately 45 and 70. It seems desirable to limit the half-life of the material used to something less than 2 or 3 weeks and something greater than 2 or 3 days. The isotope chosen must have no additional undesirable radiation of significant intensity, or undesirable activities produced by daughter isotopes. The factors involved in the production of the isotope are, of course, of primary importance. The natural abundance of the precursor isotope should be sufficient to avoid the necessity of using an enriched target material, and for financial reasons it would be desirable to use reactor-produced rather than accelerator-produced isotopes, so that the cross section for thermal neutrons should be sufficiently large and the cross sections of accompanying isotopes of the same element must be sufficiently small to avoid serious flux depression.

Within these many limitations, two isotopes whose production and use appear feasible are cesium-131 and palladium-103. While both require for production the availability of a high thermal neutron flux, it appears that continued development in reactor technology should make this possible in the near future, so that production can be economically as well as experimentally practical at multicurie levels. The present report deals with the preliminary work on such production together with the development of methods for calibration, and also the preliminary dosimetric and pathologic studies.

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CESIUM-131

Although cesium-131 does not form any suitable insoluble compounds that can be used for interstitial irradiation, it may be used in solution in applicators such as those described by Harper *et al.*[1] The isotope decays by electron capture to xenon-131 with a half-life of 9.7 days, emitting the characteristic fluorescent radiation of xenon, the principal components of which, the K alpha and K beta lines, have energies of about 30 kv. The gamma-ray dose-rate constant for this radiation is 0.8 r/hr at 1 cm, and its half-value depth in water, calculated from the true absorption coefficient, is about 5 cm, thus the dosimetry in an implant of this isotope should not differ radically from that of a conventional implant with a gamma-ray source, and the quantity of isotope necessary for a large implant can be estimated at 200 to 300 millicuries. The principal difference between using cesium-131 and gamma-emitting isotopes is in the shielding characteristics, 0.2 mm lead giving virtually complete shielding of the soft X rays, avoiding heavy clumsy equipment and greatly facilitating handling procedures. The only other radiation from cesium-131 is the very weak inner bremsstrahlung.[2]

Cesium-131 is produced by neutron irradiation from the naturally occurring barium-130 which captures a neutron, becoming barium-131. This then decays with a 11.5 day half-life to cesium-131, which subsequently decays with a 9.7 day half-life to stable xenon-131. The natural abundance of the precursor barium-130 is low (0.101%). A value of the thermal neutron cross section for the reaction Ba^{130} (n, γ) Ba^{131} of about 30 millibarns was reported by Yaffe.[3] This was at first generally accepted[4–6] although an earlier report by Katcoff[7] gave a much higher value of 6 barns for this cross section. Katcoff based his estimate of the cross section on the assay of cesium-131 by measuring the K radiation, assuming a counting efficiency of 1%. A soft component of the radiation was interpreted by Katcoff as L radiation, and no evidence of gamma-ray activity was found. The smaller cross section found by Yaffe was based on the earlier observations of Fu-Chun Yu *et al.*[8]

that the soft component of the radiation of cesium-131 represented conversion electrons from a highly (97%) converted 145 kv gamma ray. Basing his assay on this decay scheme and apparently measuring the soft radiation on the assumption that it was conversion electrons, he found a cross section smaller by a factor of 200 than that of Katcoff. A detailed analysis by Cork *et al.*[9] of the decay scheme of barium-131, using an enriched barium-130 sample for activation, revealed no evidence whatever of the 145 kv gamma ray found by Fu-Chun Yu. A report by Kondaiah[10] indicates that the conversion electrons believed to originate in the cesium-131 actually came from the parent barium-131.

Our measurements were performed on a cesium-131 sample separated from barium nitrate irradiated with thermal neutrons at Oak Ridge Laboratory (Oak Ridge Catalog, barium-131 irradiated unit). The barium was removed by precipitation as the sulfate, and the supernatant containing the cesium was evaporated to dryness. Measurements of radioactivity were made with a thin window Geiger tube. The absorption curve in aluminum (Fig. 1) was almost identical with that published by Yaffe. The soft component has a mass absorption coefficient in aluminum that corresponds to a wave length of about 3 Å. The absorption coefficient of this component in polyethylene sheeting (86% carbon) corresponds to a wave length of 2.7 Å (Fig. 2). This observation can be explained only on the basis

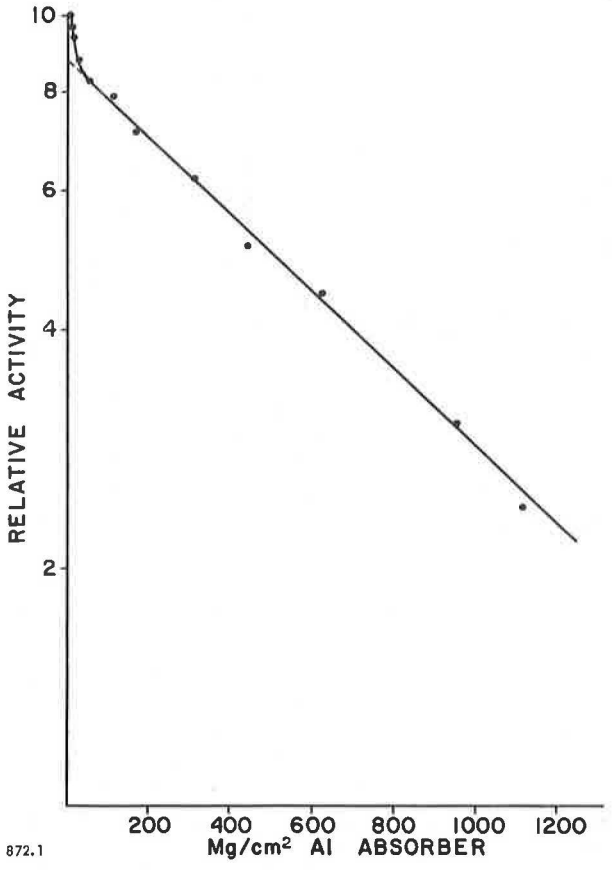

Figure 1. Aluminum absorption curve of radiation from Cs^{131} source using thin window, helium filled G-M tube (Tracer-Lab TGC-2)

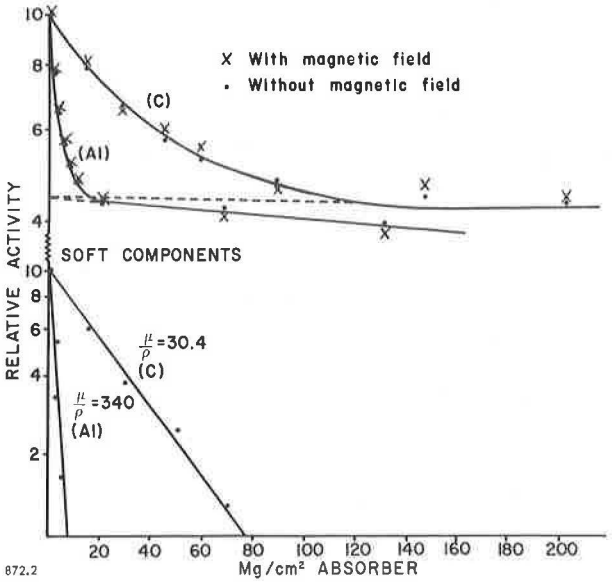

Figure 2. Aluminum and carbon absorption curves of radiation from Cs^{131} source using thin window argon filled G-M tube (Tracer-Lab TGC-3A). Note that relative counting efficiency of soft component is several times greater than with helium filled tube. Passing radiation through 3000 gauss magnetic field has no appreciable effect

that the radiation is electromagnetic rather than conversion electrons. The characteristic L radiation lines of xenon lie between 2.3 and 2.6 Å, which is in fair agreement with the absorption measurements. Passing the radiation from the cesium-131 sample through a 3000-gauss magnetic field (Fig. 2) did not alter the soft component of the radiation, again indicating that the soft component is electromagnetic in nature and not composed of conversion electrons. The conclusion seemed inescapable that the 30 millibarn cross section was incorrect and the 6 barn cross section more nearly right. Using the latter figure, the activation of a mole of natural barium for 4 weeks in a flux of 2×10^{13} neutrons per cm^2 per second, should produce about a curie of cesium-131. The absorption cross section of natural barium is sufficiently low, 1.38 barns, to avoid serious flux depression even with this large mass of material, and no other noxious isotope is formed in significant quantities. Thus, the production of the isotope appeared practical.

Since the radiation from cesium-131 as seen by a thin-window argon-filled Geiger tube appeared to consist almost solely of K and L radiation, it seemed feasible to use K, L coincidence measurements as a method of assay. The L radiation is completely separated from the K radiation by 20 mg per cm^2 of aluminum, while the mica window of the tube shields out M and N radiations and Auger electrons. It was necessary to make additional corrections since only K alpha photons are accompanied by coincident L photons. K photons are extraneous, and a number of extraneous L photons arise from L capture (14.6%) and from the Auger transitions involving the L shell. The relative strengths of these transitions have been measured[11] so these corrections can be made, and thus absolute assay of cesium-131 samples of the order of 1 μc can be carried

out. It was possible to confirm measurements made in this way by measuring directly the ionization produced by the K radiation, using 100–200 μc quantities of cesium-131. The sample was placed in the center of an open air chamber modified to increase the sensitive volume as shown in Fig. 3. Corrections were made for

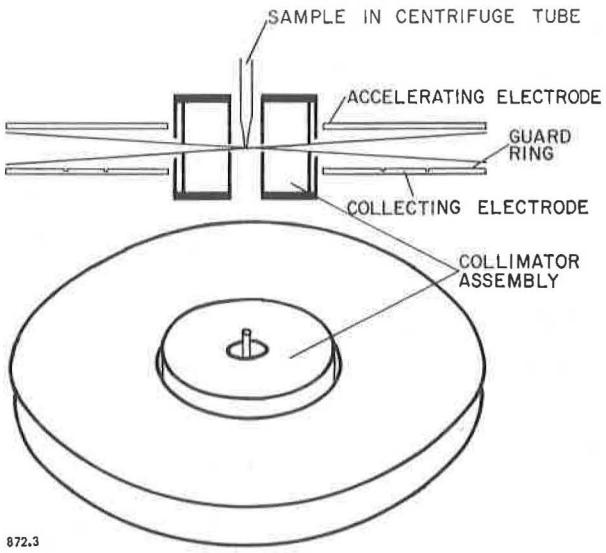

Figure 3. Modified open air chamber for measuring Cs^{131} K radiation. Modification preserves standard geometry and increases sensitive volume approximating 100 fold

self-absorption in the source, L capture and fluorescence yield. Although these measurements fall 30% above the coincidence measurements, the order of magnitude of the activity appears to be firmly established. Using these methods of assay, the cross section of barium-130 for pile neutrons lies between 5 and 10 barns.

The production of cesium-131 in curie quantities presented some problems in the processing of hundred-gram quantities of barium. It was found possible to accomplish this without using elaborate facilities by irradiating the barium in the form of the metal and then distilling off the daughter cesium in an inert atmosphere. The barium was first prepared by melting it in a steel pipe, one end of which was welded shut. Helium was bubbled through the molten barium and carried with it volatile impurities. The barium slug was then removed from the pipe, sealed in aluminum and irradiated. Following irradiation it was placed in a distillation apparatus as shown in Fig. 4. The vessel was purged with helium, and distillation was carried out at 850°C. The distillation proceeded very rapidly, being complete in an hour. Experiments were carried out with a barium magnesium alloy that has a eutectic melting point at 380°C.[12] This worked fairly well, but significant amounts of magnesium distilled over with the cesium and caused some handling difficulties. It was necessary to use helium for the inert atmosphere during the distillation, as argon produced considerable convection. It was found convenient, however, to substitute the heavier argon for helium in the distillation chamber after it had cooled before opening the chamber in order to reduce access of air to the reactive barium metal. The cesium together with some barium that condensed as a white deposit was removed by washing the cold finger in a large lead glass test tube containing dilute nitric acid. Carrier cesium was added and then the cesium activity was precipitated with perchloric acid and ethanol. In view of the explosive nature of perchloric acid it seems desirable perhaps to use another method of separation at this point. The cesium perchlorate precipitate was then reduced to the chloride by heating, in which form it was ready for assay or use.

Because of the very large scattering coefficient in water for the 30 kv X rays, it was felt that it would be of considerable interest to measure dose ratios in air and water at various distances from a small source of cesium-131. These were carried out using small cylindrical lucite ionization chambers with aquadag electrodes. The results are shown in Fig. 5 and are compared with similar measurements on radium.[13] The marked effect of back-scatter is clearly evident, which has the net result of increasing the localization of the radiation field surrounding the point source.

Substantial implants using cesium-131 were prepared in experimental animals with plastic applicators.[14] The ease in handling the isotope as compared with similar procedures using gamma-emitting isotopes was very impressive as far as radiation exposure to the operator was concerned. As far as the dosimetry is concerned for small implants of the order of 2 cm or so in greatest dimension, no modification of conventional dosimetry seems necessary. For larger implants modification might be desirable in order to maintain an even radiation field in the volume implant.

In the event of an accident with this isotope in which the entire contents of an implant might be distributed throughout the body, even in the worst possible case where the isotope remained within the body until complete decay, the radiation dosage to the entire body would not approach dangerous levels.

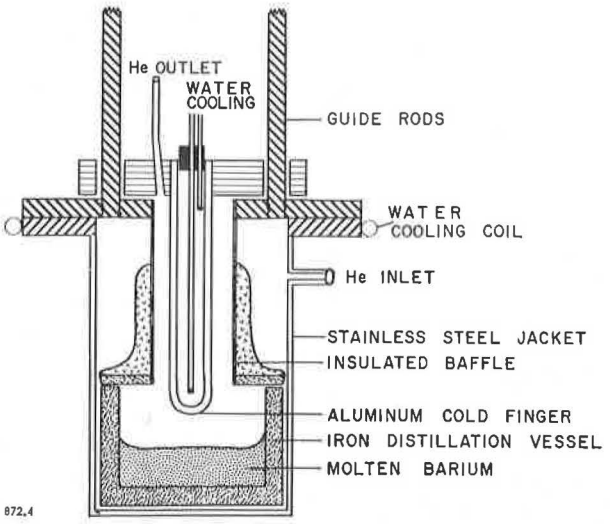

Figure 4. Apparatus for recovering daughter Cs^{131} from melted barium metal by distillation at 850°C

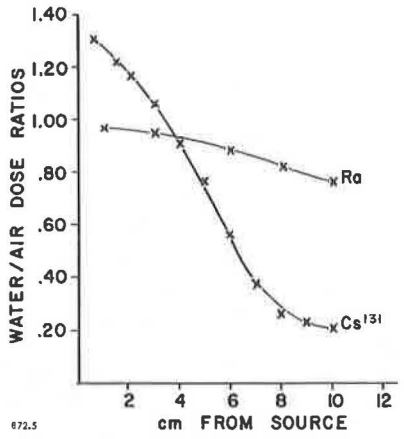

Figure 5. Water/air dose ratios at various distances from small sources of Ra and Cs^{131}

PALLADIUM-103

The other isotope under consideration, palladium-103, has a half-life of 17 days, decaying entirely by electron capture. This is accompanied by a number of very weak gamma rays with intensities of 10^{-3} to 10^{-6} photons per disintegration[15] which are negligible from the point of view of radiation dosage. The daughter rhodium-103 has a 54-minute metastable state emitting a 40 kv gamma ray that is almost completely converted in the L shell, so that for practical purposes the only radiations of significance are the characteristic 20 kv radiation of rhodium and the 37 kv conversion electrons whose range in tissue is approximately 30 μ.

The 20 kv X rays have a half-value depth in tissue of approximately 1 cm and the photoelectric absorption cross section, unlike the radiation from cesium, is much greater than the scattering cross section, so that the true absorption coefficient gives a good approximation for attenuation.

Palladium-103 is produced by irradiation of palladium metal. The precursor isotope palladium-102 has a natural abundance of 1.0%, and the cross section for thermal neutron activation is 4.8 barns.[16] Other activities that are induced in the palladium are the 13.6-hour palladium-109 and the 22-minute palladium-111 which decays to 7.5-day silver-111. Thus before using irradiated palladium, it is necessary to allow the 13.6-hour activity to decay and to separate chemically the silver activity. In addition to this, particular attention must be paid to impurities of the platinum group, especially that of iridium which has a long half-life and a high cross section for thermal neutron activation. We have found that even when using palladium of the highest commercial purity available (99.95%), it was still necessary to carry out glyoxime precipitation from neutral solution in order to remove traces of iridium activity from the final product. This is better done prior to irradiation. Removing the silver activity presents no great difficulty. The irradiated sample is dissolved in warm *aqua regia*, diluted and then scavenged with repeated small quantities of silver nitrate. The silver-111 is carried down with the silver chloride precipitate leaving the final solution free from detectable silver activity.

Assay of the palladium has been carried out by determining the silver-111 content after separation from the palladium, using geometrical beta counting and then calculating the palladium activity from the cross sections.

APPLICATION

In using palladium-103 therapeutically it seems unlikely that it will be possible to obtain a sufficiently high specific activity to use the material in plastic applicators in which very small volumes of solution are required. However, palladium can, with ease, be precipitated as palladium black, which can be injected into tissue as a suspension. If the suspension is sufficiently coarse it should remain more or less where it is placed similar to the pigment in a tatoo, so that the location of the radiation field should be adequately controlled. Preliminary experiments in which suspensions of palladium black in gelatin were injected into experimental animals (Fig. 6a, b and c) indicate very little reaction of the tissue to the injected material, and while there appears to be some migration, it is slow.

In considering the radiation dosimetry of palladium-103, each disintegration releases into the surrounding medium 17 kv of energy as characteristic K X rays, and about 40 kv of energy as conversion electrons, principally the 37 kv line. Other radiations such as the L X rays and the very weak gamma rays are ignored in these considerations. In a continuous distribution as with the isotope in solution the 37 kv conversion electrons may not be ignored, but with the isotope distributed as discrete sources through the tissue the range of the conversion electrons (about 30 μ) becomes negligible.

If we consider a very large implant, there will be a region in the center in which radiation leaving the region will be replaced by radiation from the surrounding regions, so that dose calculations may be carried out in the same way as for an evenly distributed beta source. On this basis, a uniform distribution of palladium with an isotope density of 1 mc/cm^2 would give a radiation dosage of approximately 20,000 rads per mc destroyed. In order to achieve this isotope density it would be necessary to have 2 or 3 mg of palladium distributed per cc of implant. If we consider a very small implant in which the absorption in tissue becomes negligible, then 3 to 4 times as much isotope per cc are required to produce the same dosage from soft X-ray radiation as in the central region in the very large implant. These are the limits between which we must work in establishing dose distribution for various size implants, and the upper limit appears to be within the range of practical possibility.

These calculations are based on a uniform distribution for the large implant, Paterson-Parker distribution for the small implant. When the distributed sources are condensed into discrete sources placed in a

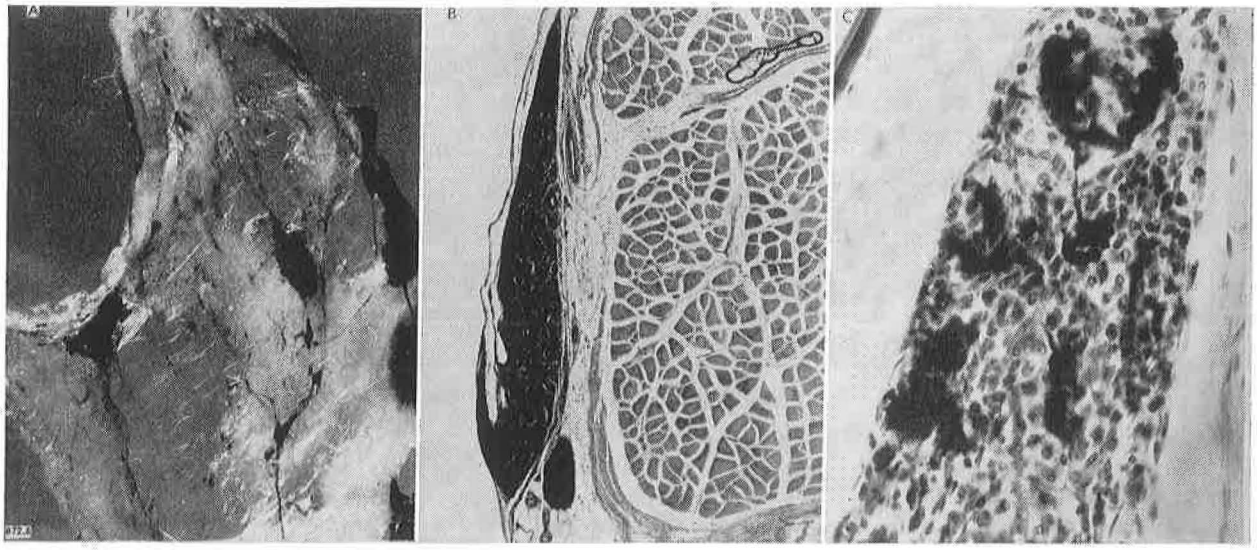

Figure 6. A. Inert palladium-black suspension in 6% gelatin injected into rats 100 days previously. Omentum (× 3) showing slow migration in large lymphatics. B. Inert palladium-black suspension in 6% gelatin injected into rats 100 days previously. Serosal surface of abdominal wall showing nature of granuloma formation around palladium (× 25). C. Inert palladium-black suspension in 6% gelatin injected into rats 100 days previously. Serosal surface of abdominal wall showing nature of granuloma formation around palladium (× 200)

1 cm lattice, the radiation field at the lowest point in the lattice drops about 40%. Thus, a more or less even dose distribution is maintained in such an implant in sharp contrast to that produced by a beta emitter under similar circumstances, where the dose distribution varies by many factors of 10.

It must be remembered that palladium has a mass absorption coefficient of about 10 for the 20 kv X rays, so that there may be considerable self shielding within the implant. In a continuous distribution this becomes negligible. With discrete sources this is not necessarily true. In order to test this, cylindrical implants in gelatin were made 12 cm in diameter and 6 cm high. One of these contained 1 mg per cc of palladium in solution, the second contained a similar amount of palladium in an even suspension as palladium black, and in the third the palladium suspension was placed in the gelatin in 0.1 cc volumes arranged in a 1 cm lattice. Photographic measurements of the radiation field at the cylinder ends were made by way of comparison. The solution and evenly distributed suspension gave equal readings. The reading for the lattice distribution was 60% of this, indicating no appreciable self absorption in the palladium under these conditions.

DOSAGE

While the 20 kv X radiation from palladium-103 is in a range not usually considered satisfactory for film dosimetry because of energy dependence of the film, we felt that it might be possible to use film to measure relative dosages because of the monochromatic nature of the radiation. The scattered radiation should not be degraded appreciably as the change in energy in Compton scattering is very slight at this wavelength. In order to test this, radiation from a palladium sample was recorded with a 256 channel Argonne type pulse height analyzer, and then without changing the geometry otherwise, 6.4 cm of lucite were placed between the source and the scintillation head which reduced the radiation to 3% of its original intensity. Shift in energy was very slight (Fig. 7).

These investigations of the dosage problems involved in use of palladium-103 indicate that it should be possible to use the material clinically and have a reasonably certain idea as to the radiation dosage being administered. Figure 8 shows the effect of a palladium-103 implant in subcutaneous tissue of a rat. Injection of the material into the retroperitoneal tissues in the pelvis of a rabbit resulted in only traces of activity in the liver after 2 weeks (0.002–0.004% of injected dose/g).

THERAPY

Our first thought in clinical application of this material was in connection with carcinoma of the cervix and prostate. Infiltration of the parametria[17] and prostate[18] with radioactive gold has been carried out, and while dose calculations under these circumstances have been made, assuming uniform distribution, we are not convinced that they represent the facts, since distribution for a beta emitter must be at a cellular level in order to be truly effective, as in the thyroid gland. We feel that a suspension of palladium-103 should give a much more even and more effective radiation field in the regions under consideration than gold-198 colloid, as well as avoiding the disadvantages of dealing with gamma radiation. Extension of this type of approach to inoperable tumors of the abdominal and chest cavities becomes much more feasible using palladium-103 because of the reduced exposure and handling problems.

In order to confirm calculated radiation dosages, measurements are desirable. Absolute dose measurements of soft X rays present special problems. A very promising method appears to be the use of the $Fe^{++} - Fe^{+++}$ system stabilized with benzoic acid as described

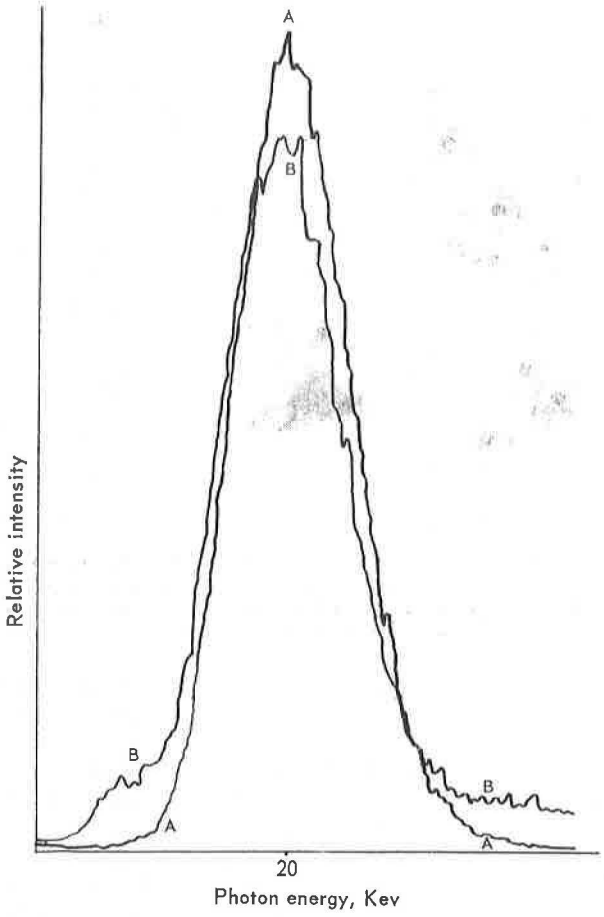

Figure. 7. Rh^{103} K radiation before and after traversing 6.4 cm lucite absorber. Curve A: Pd^{103} source recorded for 1 minute without absorber. Curve B: Same source and geometry; recorded for 24 minutes with 6.4 cm lucite absorber. Note only slight shift in energy with 97% attenuation. (Argonne type 256 channel pulse height analyzer)

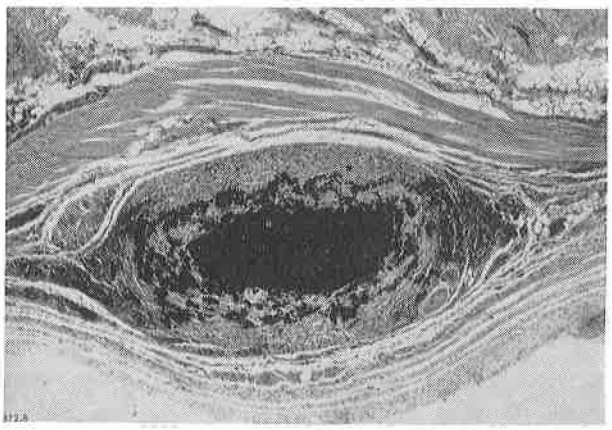

Figure 8. Pd^{103} implant in subcutaneous tissue of rat. 2.5 mg Pd, 180 μc Pd^{103}, 56 days (× 9). Note difference in character of granuloma as compared to inactive palladium (loss of cellularity and fibrosis)

by Adams and Balkwell.[19] This is several times more sensitive than the conventional $Fe^{++} - Fe^{+++}$ system, and we have been able to show, using Grenz rays, that the lack of energy dependence characteristic of the conventional system is retained in the benzoic acid system down to radiation with a half-value depth in water of 0.7 mm (30 kv unfiltered).

SUMMARY

We thus appear to have in our hands all the tools necessary to make substantial use of K-capture isotopes for implant work. The advantages of this in institutional practice at least seem far to outweigh the disadvantages, and the prospects for establishing this approach as a routine as well as an experimental procedure appear excellent. The properties of cesium-131 and palladium-103 and their respective radiations are discussed from the viewpoints of production, calibration, dosimetry and therapeutic use.

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An Instrument Permitting a Rapid and Homogenous Administration of Radioactive Fluids in the Treatment of Malignant Tumors

By Kåre Myhre*

The success of treating malignant tumors with intratumoral injection of radioactive fluids is dependent upon the degree of an adequate and uniform radiation. The main obstacle has been uniform distribution of the radioactive fluid, older procedures requiring time and exposing the operator to undesirable amounts of radiation.

The instrument to be described offers the following advantages: (1) an even distribution in the pathway of the needle; (2) an adequate amount of fluid not exceeding the capacity of the canal formed by the needle; (3) a minimum amount of radiation to the operator.

Principal Features

An even distribution is achieved in the following manner: A syringe is mounted on the top of a pistol-like instrument. The needle on the syringe is pushed to the deepest point of the tumor. By means of a "trigger," the syringe with the needle is forced back against the fixed piston. In this way the amount of fluid expelled per cm withdrawal of the needle is constant.

The canal formed by the needle will ordinarily not allow for more than 0.2 ml/cm of canal. Superfluous fluid is drained towards the skin. By using an ordinary tuberculin syringe, 5 cm long and containing 1 ml of fluid, withdrawal of the needle will cause 0.2 ml to be expelled per cm of withdrawal.

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Between the syringe and the needle, a valve is mounted. By turning the crane of the valve in either of two directions, the fluid is either expelled through the needle or may be sucked into the syringe through a polyethylene catheter, the end of which is inserted into the container arriving from the atomic pile; in this way only the amount of radioactive fluid to be used at a single point is present in the syringe, thus obviating unnecessary radiation to the operator.

The sucking of fluid into the syringe is semiautomatically arranged by means of a coiled spring. This spring is compressed when the "trigger" of the pistol is pulled back. By releasing pressure on the "trigger," the spring will force the syringe forward, thus creating a negative pressure in the space which then is rapidly filled with fluid from the container.

A handle on the pistol assures a proper distance from the syringe to the operating hand, thus reducing the radiation dose to the hand. Three screws serve the adjustment for: (1) different amounts of fluid in the syringe; (2) different sizes of the commercially available tuberculin syringe, and (3) the stopping of injection at different distances beneath the skin (Fig 1).

SUMMARY

The instrument offers the following advantages:

1. Even distribution of radioactive fluids in tumors.
2. Very rapid handling of the cases with consequent low risk of radiation to the operator.

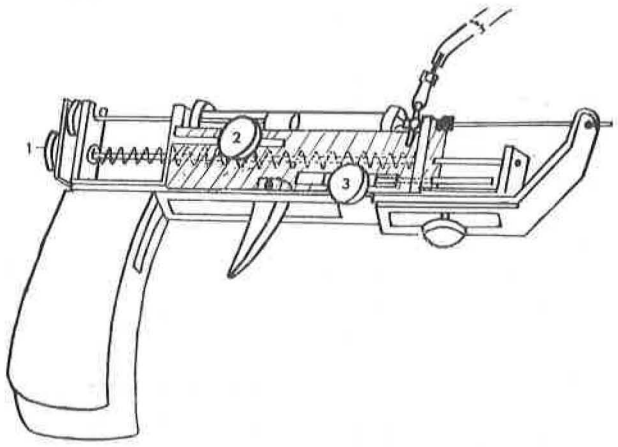

Figure 1. 1—Adjustment for syringes; 2—adjustment for fluid; 3—adjustment for depths beneath skin

New Method for the Preparation of Very Active Chromium Radiophosphate for Therapeutic Use

By Constant Burg and André Chevallier*

Since the last Geneva conference at which we presented our first results[1] we have continued our investigations on the preparation and use in medicine of colloidal chromium radiophosphate.

This product has not been studied or used as widely as gold-198 in cancer therapy. However we have continued our investigations since we believe that the advantages of chromium radiophosphate over gold are so important (high-energy beta rays, absence of gamma rays, sufficiently long half-life) that it was worth while trying to overcome the fundamental obstacle, namely the difficulty of making a satisfactory preparation.

As far as we know until now everyone who has prepared chromium radiophosphate,[1–7] including ourselves, has done so by precipitation. All the methods used were similar to that used in our early studies and are described below.

To a solution of P^{32}, in the form of phosphoric acid, about 10^{-4} M of H_3PO_4 are added as carrier and also a stoichiometric amount of a violet salt of chromium, preferably chromium nitrate. The pH of the solution is brought to 4.6 at a temperature of about zero, with vigorous stirring. An abundant violet precipitate of chromium phosphate is formed ($CrPO_4 \cdot 6H_2O$) which is centrifuged and washed with ice water, and then with alcohol.

This compound cannot be used directly as it hydrolyzes rapidly in the tissues and gives rise to soluble phosphates. Therefore, it is first dehydrated between 140 and 400°C. Then it is ground in a quartz tube with quartz balls in the presence of distilled water for from one to eight days. Colloidal particles of suitable size are separated by fractional centrifugation and the colloidal solution which is thereby obtained is made stable with gelatin.

There are many disadvantages in preparing the active compound by this method. It is time consuming and requires many operations involving very active solutions. Moreover, the yield in specific activity is relatively low because of the solubility of chromium phosphate in water.

The question of specific activity is fundamental for upon it depends adequate local and lymph node diffusion. For this reason we have tried to overcome the disadvantages of the precipitation method by the use of another method based upon an entirely different principle. We were finally successful in developing such a method, the details of which are given below.

PRINCIPLE OF SYNTHESIS BY REDUCTION

The new method is based upon the reduction of chromic acid in an anhydrous medium in the presence of radioactive phosphoric acid at a temperature above 110°C which produces the required dehydration. Ascorbic acid, hydrazine, hydroxylamine, etc., can be used as reducing agents but ethyl alcohol gave the best results.

Any organic solvent, such as glycol, glycerol, the higher alcohols, etc., whose boiling point is sufficiently high and in which phosphoric acid is soluble can be used as the reaction medium; however we found normal butanol the most satisfactory solvent for the production of stable colloidal solutions.

The synthesis of the colloidal chromium phosphate we are now using has three distinct phases: (*a*) purification of commercial P^{32}; (*b*) synthesis and dehydration of $CrPO_4$; and (*c*) elimination of adsorbed soluble phosphates.

Purification of P^{32} solution

Phosphorus-32, the raw material, should be in the form of a solution of phosphoric acid containing no carrier. To this solution is added a small quantity, say from 1 to 8×10^{-6} M of inactive H_3PO_4 and 1 cc of hydrochloric acid.† The solution is heated to 80–90°C for 5 to 10 minutes to hydrolyze any pyrophosphates and polyphosphates that may have formed and to liberate the phosphoric acid as a salt. This solution is then evaporated to dryness at a temperature of 50°C in an infrared oven in the presence of metallic sodium. The dry residue is taken up in distilled water‡ and the solution is passed through an anion resin exchange column. We used Amberlite IR 45.

The adsorbed phosphoric acid is washed with 40 cc distilled water, then eluted with 0.5N HCl. The eluate is collected fractionally in tubes of approximately 10 cc

Original language: French.

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† The hydrochloric acid is pure commercial acid redistilled in an apparatus made entirely of glass.

‡ The water used during this synthesis is redistilled in a quartz still.

capacity. The fractions containing almost all the radioactivity rarely exceeds a total of 20 cc. The loss in the course of this operation is less than 10%.

This fraction is evaporated to dryness under infrared as described above. The residue is taken up in a small amount of distilled water and the solution is then passed through a cation exchange column. We used Permutite 50.

The column is washed with 30 cc distilled water and the entire eluate collected in a 500 cc distilling flask with side arm. This solution is evaporated to dryness under infrared as before.

Synthesis of Chromium Phosphate

The dry residue is dissolved in 1 cc of water. After a few minutes 50 cc absolute alcohol and then 50 cc of benzene§ are added. The distilling flask is equipped on top with a thermometer and on the side with a water suction pump. The temperature is raised slowly until the solution just begins to boil. Heating is interrupted and 1 cc of an aqueous solution of chromic acid is added all at one time and the mixture stirred vigorously. The concentration of the acid is calculated so as to add a 20% excess of chrome with respect to the phosphorus carrier introduced at the beginning of the synthesis.

Heating is resumed and allowed to rise rapidly while the solution is distilling. The liquid level in the flask is maintained by the addition of normal butanol (freshly distilled over 2% Na) introduced alongside the thermometer. The operation is terminated when the temperature reaches 115°C and the yield is verified by paper chromatography according to the method of Ebel.[8]

In verifying the yield, the following solutions may be used as solvents: isopropanol 75 cc, water 25 cc, trichloroacetic acid 5 g and ammonia (22°B) 0.3 cc; or, isopropanol 40 cc, isobutanol 20 cc, water 39 cc and ammonia (22°B) 1 cc. Under these conditions chromium phosphate remains at the starting spot whereas phosphoric acid, which did not enter into the reaction, migrates with an RF of 0.79 or 0.36. The yield of a normal synthesis varies from 80 to 95%.

Elimination of Adsorbed Soluble Phosphates

In principle we assume that a solution of chromium phosphate for therapeutic use should not contain more than 5% free phosphate which may be estimated chromatographically according to the method described above.

In order to eliminate excess free phosphates the colloidal solution is filtered through a sugar column, preferably lactose. The column is made as follows: 3 g of lactose are ground carefully in 20 cc absolute alcohol in a Potter tube. The solution is filtered through a column 40 cm long and 2 cm in diameter having at its lower end a highly porous fritted glass filter.

§ Absolute alcohol and benzene were freshly distilled after addition of 2% Na. Absolute amounts as well as the ratio of the two solvents can be changed widely.

At the moment when most of the alcohol solution has passed through the filter, the solution of chromium phosphate is passed through the column, after previous cooling of the solution and the addition of 1 g of hot lactose. The solution is carefully shaken and poured onto the column in small amounts at a time. With the aid of a suction flask a small vacuum, which should not exceed 5 cm of mercury, may be applied. The chromium phosphate is held on the column as a large green band.

The column is then washed with 40 cm^3 of a solution having the following composition: 75 cc isopropanol, 25 cc water, 5 g trichloacetic acid, 0.3 cc ammonia at 22°B and 0.025 g orthophosphoric acid. This is followed by a second washing with 40 cm^3 of a solution containing: 40 cc isopropanol, 20 cc isobutanol, 30 cc water, 1 cc ammonia at 22°B and 0.025 g orthophosphoric acid. Final washings were carried out with 20 cc absolute alcohol containing 0.1% KOH and finally with 10 cc absolute alcohol. The solutions used for washing were previously saturated with lactose.

Control chromatography made upon the different filtrates should not reveal any significant proportion of phosphate provided that the lactose column has been carefully prepared.

The lactose column is then dissolved in a hot 5% solution of gelatin (edible gelatin treated with boiling alcohol for 3 hours then passed through anionic resin followed by passage through cationic resin, according to Kumagawa). The suspension of chromium phosphate so obtained is refrigerated for preservation. At a low temperature it forms a gel which provides the best condition for maintaining stability.

Before use enough water is added to produce a solution with the proper osmotic pressure for introduction into living tissues, i.e., a concentration which will lower the freezing point from 0.50 to 0.60°C approximately.

CHARACTERISTICS OF THE COLLOIDAL SOLUTION OF CHROMIUM PHOSPHATE

The suspension of chromium phosphate prepared in the above manner has excellent colloidal stability. The particle size varies depending upon the conditions of precipitation. Under the conditions in which we work it is probably in the neighborhood of 100 to 150 Å. It has a very high specific activity which is proportional to the high activity of the initial P^{32}. Starting with 200 millicuries of P^{32} the specific activity varies from 4×10^{-8} to 5×10^{-9} M of $CrPO_4$ per millicurie of P^{32}, this depending on the quantity of phosphoric acid-carrier added at the beginning of the operation. Other than a very slight Tyndall effect, such suspensions exhibit practically no visible turbidity. The chemical stability is excellent. Chromatography performed after one month does not show any appreciable hydrolysis.

These chromium phosphate solutions will undoubtedly be used in cancer therapy for interstitial radiotherapy by injection either into the tumor itself or into the lymphatics in the area invaded by the tumor. Part of the injected chromium phosphate migrates into the

lymphatic vessels as well as into the nodes. The principal advantage of radioactive colloidal solutions lies in the possibility of producing radiation dosages sufficient to destroy metastatic lesions which may have escaped surgery.

Migratory Properties of the Solution

It is difficult to obtain exact measurements of the migratory properties of colloidal solutions because it is impossible to reproduce in animals those conditions which obtain in man. However, it is possible to effect experimental conditions which will allow a comparison of the "migratory" properties of different colloidal solutions. In earlier reports we suggested measuring the activity obtained in the lumbar nodes of the rat after injection of the suspension into the thigh muscles on the same side. We also showed the need to use a rather small volume having an activity of about 10 millicuries.

However, since perfecting the method of producing chromium phosphate by reduction, we have become aware that the migration phenomena it produces are much greater than with preparations made by precipitation. Therefore, in order to understand this phenomenon better we modified our original technique by trying to determine the nodal concentration in two nodes in the same drainage system. To do this we chose as the site of injection the plantar sac of the hind leg of the rat. The first node into which the lymph drains from this point is the popliteal node which in turn drains into a homologous lumbar node. In comparing different homozygous strains of animals we have found that the same colloidal solution brought about very different lymph node concentrations, all other experimental conditions being the same. It is therefore very important to carry out migration tests on animals of the same pure strain and in our investigations we used inbred rats of the Wistar strain.

Each paw may be used for injecting. This permits either double the number of injections for testing the same solution, or comparison of two different solutions on the same animal. The volume of the test solution and its activity should always be the same. We have used in our investigations 0.05 cc and 10 microcuries, respectively.

Forty-eight hours after injection, the absolute activity in the paws, in the popliteal and lumbar nodes, and in the liver are determined after ashing. Table 1 shows in per cent of the injected dose the limits of concentration for ten different solutions of chromium phosphate prepared according to the method described above.

Table 1

Organ	*Max conc* %	*Min conc* %
Paws	81.0	49.0
Popliteal nodes	6.0	0.8
Lumbar nodes	6.8	0.19
Liver	2.5	0.2

The amount of activity remaining in the foot after 48 hours is a valid measure of the amount of chromium phosphate which has migrated by way of the lymphatics. However, we emphasize that these experimental findings do not give any information on the proportion of the suspension which migrates in a particular case when applying this therapeutic procedure in man. In migration, local conditions such as greater or lesser invasion of the lymphatics by the cancerous process, the importance of local drainage depending upon the region, etc., are determining factors. However, in a certain number of cases where we have used the solution therapeutically, the migration effects were much more significant than those indicated in the rat experiments. The value of the latter, therefore, lies solely in permitting comparison of different suspensions.

ACKNOWLEDGEMENTS

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Importance of Thyroid Weight Determination and Clinical-biological Factors Involved in the Treatment of Hyperthyroidism with Iodine-131

By W. Clode, V. Sobral, A. M. Baptista, M. A. Perez Fernandes, M. Susa Martins, L. Btelho, M. Freire Da Vruz and F. Magalhães Colaço*

It will be the purpose here to review the results of hyperthyroidism treatment with I^{131} in our laboratory since introduction of the "Pneumothyroid Method" for evaluation of thyroid weight,[1–3] and to correlate results with the physical, clinical and biological factors involved.

The patients with hyperthyroidism treated with I^{131} were 20 to 40 years of age who had suffered a setback after thyroidectomy, who had revealed recurrence or grave symptoms after treatment with antithyroid drugs, who had hyperthyroidism simultaneously with cardiac disease, diabetes or neoplasms, and who had refused surgical treatment. Patients over 40 years of age were treated not only for reasons similar to the younger age group but also for severe hyperthyroidism without previous therapy.

PROCEDURE

After decision for treatment on the basis of clinical and laboratory evidence, the uptake curve was obtained with carrier free I^{131} in the usual way[4] about one or two weeks before administration of the therapeutic radioactivity.

The activity to be administered A (mc) required to deliver an absorbed dose D (rad) to the thyroid gland of weight M (g) was calculated from the uptake curve as described previously,[1]

$$A = \frac{MD}{1.05 \int_0^{t_n} p\,dt + 1.52 p_n T_e} 10^{-4} \text{ mc} \qquad (1)$$

where T_e is the effective half-life of I^{131} in the gland which we have assumed to be t_n days after administration of the radionuclide, and p_n the fraction of activity remaining in the thyroid gland t_n days later. Integration gives

$$\int_0^{t_n} p\,dt = \sum_{i=1}^{i=n} p_i \qquad (2)$$

where p_i is the average fraction of administered radioactivity existing in the gland during the ith day. This formulation and development is based on assumptions as follows: a uniform distribution of radioactive material in the gland, a 10% gamma ray contribution, and a beta ray energy of 0.187 Mev, yielding, of course, an average dose for the gland.

After administration of the radioactivity A, the uptake curve was determined in order to calculate the effective absorbed dose delivered to the gland.

Aside from biological features, the more important factor for accurate dosage determination is thyroid weight evaluation. Until recently only two methods have been used for this purpose. One was palpation of the gland by an experienced person—called by Loevinger, "method of calibrated fingers." The shortcomings of this method are obvious. Weight of the thyroid gland has been determined also with radioiodine and a collimated detector. With an "image" of the gland the area can be determined utilizing an empirical formula, and with the gradient in isocount lines thickness can be estimated. The method utilizing a collimated scintillation detector has been much used.[5–7] It is more objective than the first method, which we have criticized,[3] and we shall refer to it again later.

Our laboratory has devoted special attention to the important problem of determining thyroid gland size. An effort will be made to summarize the results obtained.

As is known, the thyroid gland capsule is surrounded by elastic tissue. By using gas contrast, it is possible to obtain an X-ray photograph which shows a distinct outline and dimensions of the gland. A visualization technique for the thyroid gland is thus available comparable to that used for retroperitoneal organs, and it is called the "Pneumothyroid Method."

The procedure is as follows. The patient is asked to lie on his left side, thus diminishing the possibility of a gaseous emboly. The skin in the midline of the infrahyoid region is anaesthetized with novocain, and a 0.7 mm needle is then inserted until resistance of the midcervical fascia is overcome and the fascia perforated. The patient is asked to swallow, which by up and down movements of the needle indicates whether it is properly located. The oxygen insufflation used for contrast purposes is performed with an apparatus like that used in pneumothorax procedures. Connected

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with the rubber tube attached to the needle is a syringe which allows verification of whether a blood vessel has been reached, and a manometer which measures the pressure used in insufflation. Pressure is kept as low as possible, usually 2 to 3 cm Hg. The volume of injected oxygen varies with case needs, but on the average is about 300 cm³.

After insufflation, a series of radiographs and tomographs is taken, using different positions. The method has been used in about 150 cases without ill effects and therefore is not regarded as dangerous. By means of the radiographs and tomographs, the thyroid volume is determined by comparing each lobe with a scalene ellipsoid with semi-axes a, b and c that can be measured directly in the X-ray pictures, corrections being made as necessary when the X-ray source is not indefinitely far away.

The volume is given by

$$V = \tfrac{4}{3}\pi abc$$

This provides a simplifying approximation since it is known that the thyroid gland presents variable and irregular outlines and shapes.

Figure 1 shows a pneumothyroid tomograph which is especially interesting since it enables one to visualize an intrathoracic goiter, to understand the problems involved, and to determine the dose of I^{131} required. Figure 2 shows the scintigram obtained for the same case. In Fig. 3 are two tomographs of pneumothyroids which show the gland before I^{131} treatment (a), and seven months after treatment (b), gland weights being 83 and 30 g, respectively.

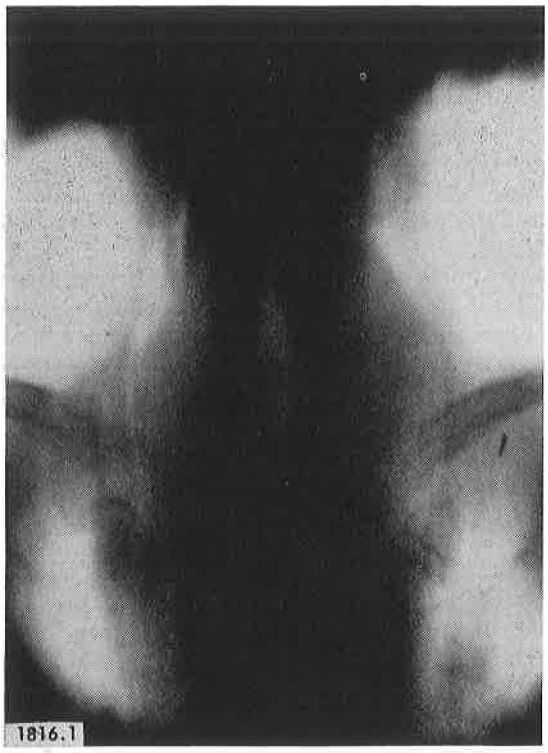

Figure 1. Pneumothyroid tomograph showing an intrathoracic goiter

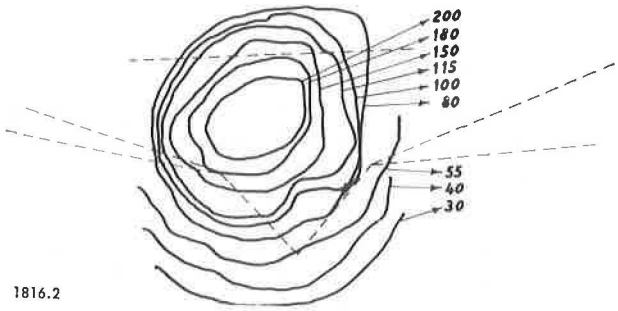

Figure 2. Scintigram corresponding to the intrathoracic goiter of Fig. 1

In our opinion, it is possible to obtain more accurate gland weights using a model made from the radiographs and tomographs, which we have tried in a few cases but which we find to be a time consuming procedure.

It is worth noting that the tomographs are especially helpful in determining the normal axes since in some cases the lateral radiograph does not allow a clear evaluation due to overlapping of the two lobes.

Of interest is the comparison of results obtained by different workers in order to establish an empirical relation between estimated weight, length, projected areas, scintigrams, actual weights and sizes obtained at surgical removal or necropsy, and now the pneumothyroid results.[3] Figure 4 shows the contours of glands obtained with pneumothyroid procedures in 44 cases.

Allen and Goodwin[6] assuming the relation between volume V, projected area S and length L to be

$$V = kSL \tag{3}$$

from scintigrams of 10 cases, obtained $k = 0.32$. Himanka and Larson,[8] on the basis of measurements made on thyroid glands removed at necropsy, and assuming two relations, the empirical formula (3) and that

$$V = K\sqrt{S^3} \tag{4}$$

in a study of 44 cases obtained comparative values $k = 0.27 \pm 0.06$ and $K = 0.33 \pm 0.06$.

In our study, adjusting numerical values to the following equations

$$V = kSL + v_1 \tag{5}$$

$$V = K\sqrt{S^3} + v_2 \tag{6}$$

we obtained figures (that of course do not have physical meaning) as follows:

$$k = 0.31 \pm 0.05 \qquad v_1 = 5.8 \text{ cm}^3$$

$$K = 0.37 \pm 0.04 \qquad v_2 = 7.4 \text{ cm}^3$$

It is remarkable that the figures show such agreement; however, it is necessary to note that deviations in all the studies are sufficient to make use of an empirical formula not accurate enough. For instance, Kelly,[9] from scintigrams in 15 cases, found a maximum deviation of 105% with an average of 49%, using $k = 0.32$. We obtained deviations of 107% with an average of 25% using equation (5), and about 60 and

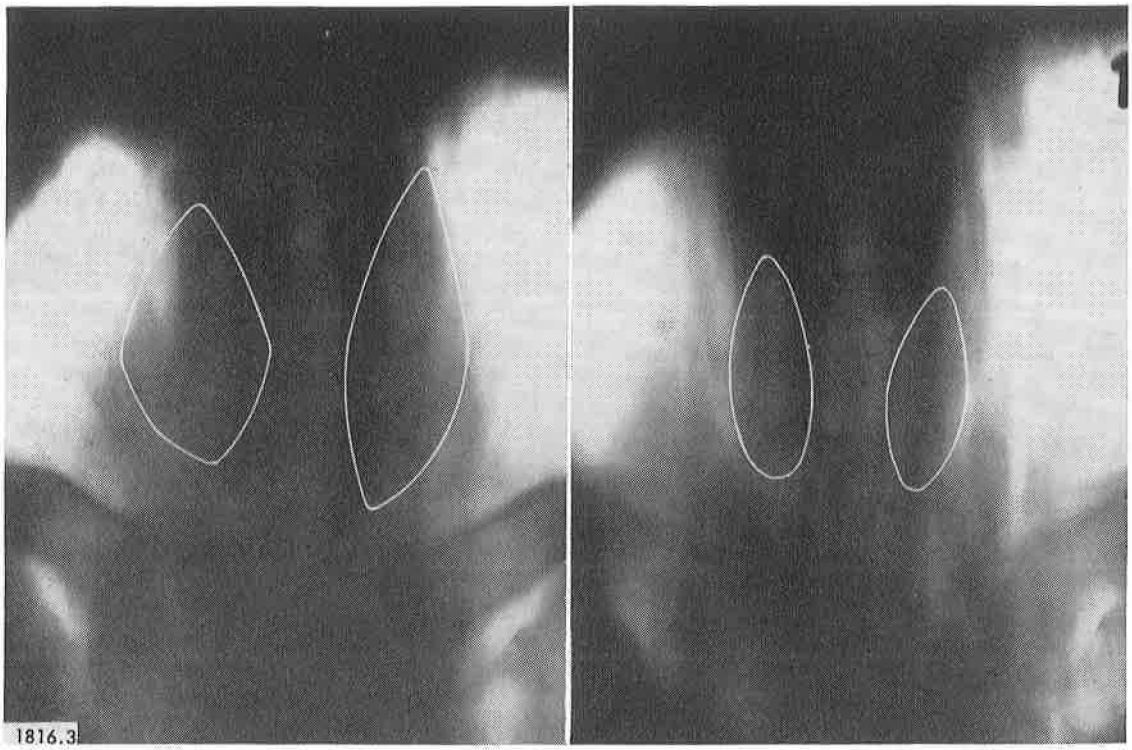

Figure 3. Two pneumothyroids with tomographs showing reduction of the volume of the gland after treatment with I^{131}. The gland weight was 83 g before treatment (a) and 30 g after (b)

24% using equation (6). Needless to say, changing collimation of the detector causes changes in values obtained.

RESULTS

The patients we wish to consider are those who were treated between September 1952 and September 1957; their post-treatment is more than nine months. Although 140 were treated, 129 of which were females, we shall consider only 117 as the others did not return for observation after treatment. Of the 117 patients, 110 (94%) were women and 7 (6%) were men. Ages ranged from 25 to 80 years, the majority being in the fourth and fifth decades of life. The interval between onset of illness and treatment varied from 1 to 29 years, the greatest number having an interval of less than 5 years.

From the clinical standpoint, the patients were divided into three classes: grave 52 (44%), moderate 56 (47%), and mild 9 (7%). Seventeen had complications: heart disease 9, diabetes 6, vertigo 1, and malign exophthalmos 1. Forty-five patients had exophthalmos of different kinds as follows: very intense 1, intense 2, moderate 29, and slight 13. With respect to the thyroid gland, 26 patients were without goiter and the remaining 91 had: diffuse goiter 74, nodular goiter 14 and multinodular goiter 3.

All patients were treated with I^{131} according to the scheme already presented. When this method of treatment was started, the prescribed dose varied according to the clinical cases, and on the average was 9600 rad (12,000 rep). However, as lower doses seemed more useful, we began to give doses of 8000 rad (10,000 rep). The majority of our patients received doses between 5000 and 14,000 rad, and the radioactivity administered varied from 1.5 to 40 mc.

Figure 5 shows the percentage deviation of dose received with respect to dose prescribed. It is seen that the greatest frequency of deviation occurs in the range 0 to 10% and that many cases had a deviation not more than 30%.

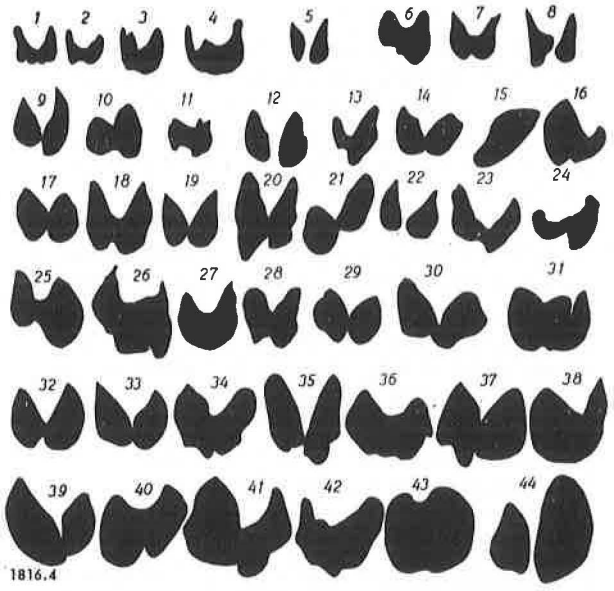

Figure 4. Thyroid gland contours obtained from pneumothyroid tomographs (Baptista and Franco[3])

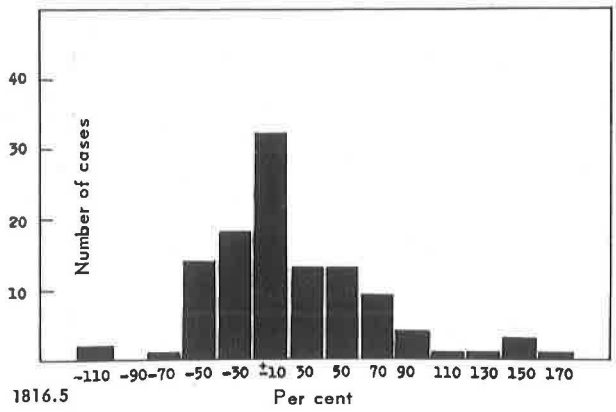

Figure 5. Percentage deviations of the administered doses relative to the prescribed doses

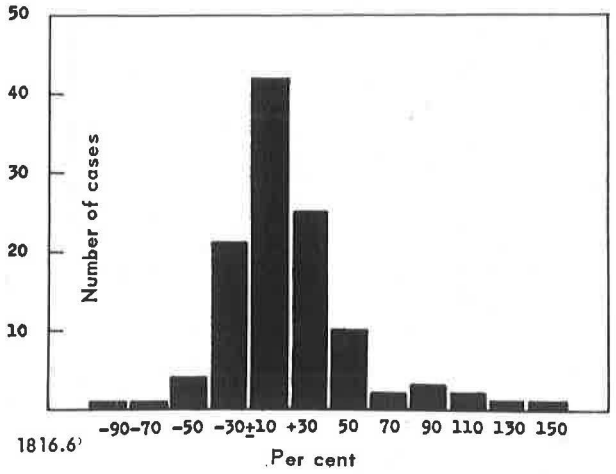

Figure 6. Percentage deviations of the effective half-life before treatment and during treatment

Similarly, Fig. 6 shows the deviation of effective half-life with respect to calculated half-life. Here it is seen that a great number of cases varied within 30% also.

The differences between prescribed dose and the dose received may be due to variations in tracer uptake, thus yielding inaccurate uptake curves, and to variations in uptake of therapeutic radioactivity. It is not easy to find a reasonable explanation for the discrepancies.

In order to avoid variation in behavior of the thyroid gland, the interval between pretherapeutic tests and therapy was kept within two weeks, except in a few cases. With the same problem in mind, any drug or other therapy that modifies thyroid metabolism was suspended for at least one month before I^{131} pretherapy. Despite such precautions, however, we have found some glands to have an unsteady behavior sufficient to account for some of the deviations in doses administered. In our series of cases, we did not find any relation between uptake and half-life variation with respect to age of the patient, evolution time of disease, seriousness of illness or physical characteristics of the thyroid including weight of the gland. Although in principle we could accept the view that therapeutic radiation affects rate of uptake of I^{131}, it is difficult from the data available to see any correlation.

In order to analyze results, the patients were divided into four groups: those that showed remission, those that showed improvement, those that showed recurrences and those with hyperthyroidism. Selection was based on clinical and laboratory data, including those obtained with the I^{131} tests. Each group was divided into two subgroups to distinguish those palpated for thyroid mass from those on whom the pneumothyroid procedure was used for the same purpose. For this analysis, only the patients receiving one therapeutic treatment were considered. Comments will be made later about recurrences. The findings are shown in Fig. 7, based on 76 cases diagnosed by pneumothyroid and 41 by means of palpation. As may be seen, the percentage of remissions was greater in patients diagnosed with pneumothyroid procedures (70%) than in those merely palpated (45%), and correspondingly, there was a lesser percentage of improved patients (8%), with recurrences (17%), and with hypothyroidism (5%) in the pneumothyroid diagnosed group than in the palpation diagnosed group in which the percentages were, respectively, 15%, 27.5% and 12.5%.

It seems important to point out that inasmuch as hypothyroidism is the least desired result of therapy, the lower figure (5% as compared with 12.5%) obtained for cases on which pneumothyroid procedures were used may be pointed out as of interest. The percentage becomes still better if two pneumothyroid pa-

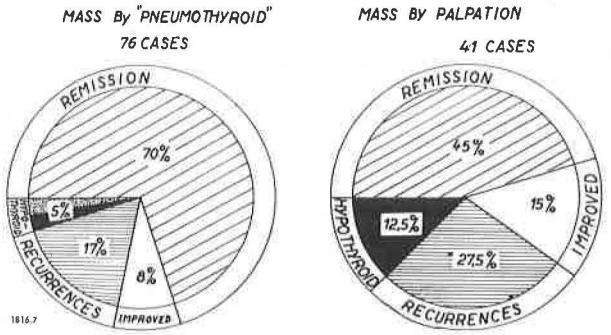

Figure 7. Graphs summarizing the results of treatment of hyperthyroidism with I^{131} in two groups of patients for which thyroid weight was estimated by pneumothyroid and by palpation

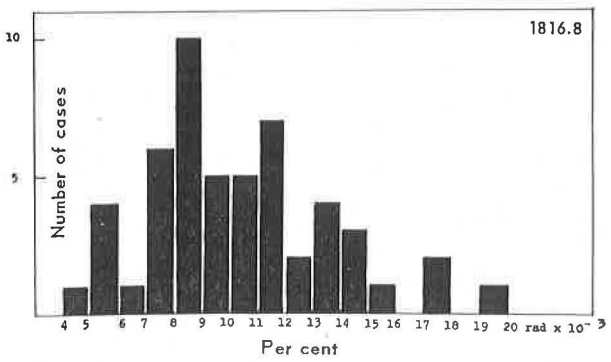

Figure 8. Absorbed dose in rad effectively delivered to patients in which remission was obtained after treatment with I^{131} and whose thyroid weight was estimated by pneumothyroid

tients believed to be transitory hypothyroid cases are not considered. When these are disregarded the percentage of hypothyroidism drops to 2.5%.

Two patients who had slight hypothyroidism are now with remission, returning to normal within two to three years after therapy.

The radiation doses received by cured patients who had undergone pneumothyroid were calculated according to the methods described, and they are shown in Fig. 8. As seen they varied between 4400 and 20,000 rad, the majority being between 8000 and 9000 rad. The number of patients in improved, recurrent and hypothyroidism groups is too small with respect to the different doses administered to give significant results.

In Tables 1, 2 and 3, we show our patients with improvement, recurrences and hypothyroidism and the doses received by each. It is to be pointed out that of the 9 hypothyroid patients, 6 got doses higher than 10,450 rad, and that of the 24 patients with recurrences, 11 got doses lower than 7000 rad. The patient who received 174 rad had an accidental saturation of the thyroid.

It is difficult to explain how a patient that received 30,500 rad got a recurrence and how one that received 4350 got hypothyroidism—both having had pneumothyroid.

Of the recurrent group patients, 3 did not receive repeated treatments, whereas 3 of the pneumothyroid group received repeated I^{131} treatments with success.

The weight of the thyroid gland, calculated by means of pneumothyroid procedures, was again considered. In Table 4 a summary of the data is presented. Five patients underwent radioiodine therapy three times. One that had received pneumothyroid showed absence of disease just before the third treatment; another got hypothyroidism, still another got a remission, and the other two did not return to our laboratory. Among 13 patients whose thyroid gland weight was guessed on the basis of palpation, we got 3 with hypothyroid and 6 with remissions, no information being obtained on the other four.

We were not able to show that age of patient or duration of the illness had any influence on therapeutic failures, inasmuch as the number cured and not cured was essentially the same. We compared the clinical results obtained with patients having thyroid characteristics (without goiter and with diffuse and nodular goiter) and having different degrees of illness. Subgroups were formed to separate out the patients that received pneumothyroid. The results are shown in Table 5, where it is seen that the most favorable responses were obtained in the patients for whom thyroid gland weight was computed on the basis of pneumothyroid procedures.

SUMMARY AND CONCLUSIONS

From the results obtained with 117 hyperthyroid patients treated with I^{131}, 77 of whom received pneumothyroid (a thyroid gland weight determination procedure originated in our laboratory in 1953), and 40 of

Table 1. Recurrences

Case	*Rad dose*	*Pneumothyroid*	*Palpation*
130,715	174	x	
121,859	628		x
92,602	946		x
98,116	1,985		x
102,943	5,730	x	
93,599	5,770		x
100,816	6,000	x	
100,831	6,200		x
129,637	6,230	x	
90,492	6,700	x	
137,882	6,750		x
110,154	7,670	x	
136,722	7,740		x
144,180	7,800	x	
115,745	8,000		x
100,889	8,540		x
116,138	9,660		x
108,285	10,000	x	
92,403	12,450	x	
40,129	13,350	x	
103,075	13,850	x	
131,433	17,750	x	
130,856	30,500	x	

Table 2. Improved

Case	*Rad dose*	*Pneumothyroid*	*Palpation*
99,374	4,810	x	
109,460	5,310	x	
145,320	6,220		x
106,305	6,630	x	
112,551	7,820		x
144,427	8,660	x	
123,330	9,540	x	
125,350	10,000		x
112,706	10,900		x
131,530	12,500	x	
104,442	13,950		x
136,648	14,800		x

Table 3. Hypothyroidism

Case	*Rad dose*	*Pneumothyroid*	*Palpation*
146,765	4,350	x	
145,492	6,560		x
150,139	10,450		x
115,096	10,450	x	
97,336	10,650		x
117,190	12,500		x
139,641	12,600		x
123,457	13,700	x	
129,675	15,650	x	

Table 4. Patients Who Received a Second Treatment Involving Pneumothyroid

1st		*2nd*	
Weight	*Dose*	*Weight*	*Dose*
120	6,700	30	9,300
70	6,230	30	6,300
83	30,500	30	13,100

Table 5. Relationship between Characteristics of the Thyroid Gland and Seriousness of Illness

	Remission				*Improved*				*Recurrence*				*Hypothyroidism*				*Total*	
	Pn[a]		*Pa*[b]		*Pn*		*Pa*		*Pn*		*Pa*		*Pn*		*Pa*		*Pn*	*Pa*
	No.	%	*No.*	%	*No.*	%	*No.*	%	*No.*	%	*No.*	%	*No.*	%	*No.*	%	*No.*	%
Diffuse goiter	29	60	13	50	5	10	4	15	10	21	6	23	4	8	3	12	48	26
Nodular goiter	8	89	1	13	—	—	2	25	1	11	5	63	—	—	—	—	9	8
Without goiter	16	84	5	71	1	5	—	—	2	10	—	—	—	—	2	29	19	7
Hyperthyroidism																		
Grave	19	60	6	30	3	10	1	5	9	28	10	50	1	5	3	10	32	20
Moderate	33	79	8	57	2	5	5	35	4	9	—	—	3	7	1	7	42	14
Slight	3	—	3	—	1	—	—	—	—	—	1	—	—	—	1	—	4	5

[a] Pneumothyroid. [b] Palpation.

whom were palpated to determine gland size, it can be concluded:

1. Remissions were seen in 70% in the pneumothyroid group and 45% in the other.
2. In the pneumothyroid group, post-therapeutic hypothyroidism was observed in only 5% (except for 2.5% which were mild), whereas 12.5% was seen in the other group.
3. Recurrence in the pneumothyroid group was 17%, while in the other group it was 28%.
4. In the pneumothyroid group we observed improved cases in 8% of the patients against 15% in the other group.
5. No correlations were found between the clinical and biological factors such as age of patient, duration and seriousness of illness, and gland characteristics (type of goiter, mass of gland).

In conclusion it may be said that definitely the determination of thyroid weight by the pneumothyroid method enables a more correct dosimetry in therapeutic application of I^{131} to hyperthyroidism and has led to better clinical results, although it should be said that the differences between prescribed and effectively delivered dose deserve further consideration and study.

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Radiation Thyroiditis after Treatment with Radioactive Iodine—Clinical and Laboratory Investigations

By P. Czerniak and A. Harell-Steinberg*

There are known and unknown causes, which may bring about acute, sub-acute and chronic thyroiditis.[1] Known causes include various ionizing radiations, such as α, β, γ and X rays and neutrons,[2–4] whether acting externally or internally (through implantation or resorption of the radioactive substance); they may result in thyroiditis, known as radiation thyroiditis. In such cases, the dose of radiation rather than its type is the controlling factor.

The histology of the gland affected by radiation thyroiditis was studied by animal experimentation[5–8] and by examination of human patients.[9,10] It was found that in direct proportion to the intensity and length of radiation, infiltration of the struma and damage to the epithelium takes place, similar to that caused by other agents in acute and sub-acute thyroiditis.[11,12]

Finally, changes of the serum protein-bound iodine in experimental animals[13,14] and in patients[15] have been examined and several clinical observations of radiation thyroiditis have been made.[16,17] The number of cases of radiation thyroiditis is on the increase due to increased treatment with radioiodine. Both a review of the literature and our own observations on patients who received I^{131} for radiothyroidectomy, indicate that this treatment may cause complications, which are mainly trivial and temporary, but which may become acute or even fatal. Our aim has been to gather clinical and laboratory material on patients suffering from radiation thyroiditis.

MATERIAL AND METHODS

Three hundred sixty patients were treated with radioiodine during the last four years, several of them manifesting mild to serious radiation thyroiditis. The present report pertains to twenty one of these who were available for reexamination at any desired time. They included (Table 1): seven patients with thyrotoxicosis without evident goiter, seven with thyrotoxicosis and goiter, and seven with heart disease but normal thyroid function. Each patient received as a first treatment from 5 to 10 mc of I^{131}. Dosage was determined, taking into account diagnosis, size of the gland, biological half-life and uptake of I^{131}, and age of the patient.[18–21]

Four radiological factors were evaluated in each case: (1) I^{131} uptake after 24 hours,[22] (2) concentration of I^{131} per gram of thyroid tissue,† (3) β and γ radiation-dose which each gram of the thyroid receives during treatment, according to the equations of Marinelli,[23,24] and (4) biological half-life of I^{131}, which averages six days.

The clinical and laboratory changes caused were checked periodically according to the schedule presented in Table 2. Barker's method[25] was applied to check PBI, Westergreen's to examine BSR. The clinical observations were classified according to five or six main symptoms.

RESULTS

Tables 3 to 7 and Figs. 1 to 3 summarize our clinical and laboratory observations.

THE CLINICAL SYMPTOMS

Clinical symptoms appear in thyrotoxic cases on the sixth and in cardiacs on the second day after treatment and last for 10–15 days. This period is longer with thyrotoxic patients, who usually receive larger doses of radiation (see Tables 3, 4 and 6). Clinical symptoms may be mild or severe, the latter occurring mostly in cardiac cases, and requiring rest or hospitalization after treatment. Our group of 21 patients included eight cases who had to remain in bed for one to ten days. However, the total group of 360 patients treated included cases which had to be hospitalized: three due to cardiac asthma (recurring twice in one patient), two due to severe arythmia and one because of acute cor pulmonale. In patients with angina pectoris an increased demand for nitroglycerin occurs during the first few days following I^{131} therapy and continues for a period up to 3 weeks (Table 5). Nocturnal anginal attacks appeared in 2 cases. Bed rest reduced considerably the frequency of the anginal attacks.

LABORATORY RESULTS

1. The serum PBI of patients after I^{131} treatment increases from 50 to 300%.‡ The increase begins 1 to

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† It was estimated that the normal thyroid gland weighs 25 grams, while the weight of goiters was evaluated by a rough clinical external method. The largest goiter in the group weighed 75 grams.

‡ A PBI change of 1γ% is considered to be insignificant.

Table 1. Data on 21 Patients Treated with Radioactive Iodine

No. and sex of patients		*Age of patients*			*Clinical diagnosis and number of cases*		
F.	*M.*	*Below 50*	*50–60*	*Above 60*			
12	2	8	2	4	Thyrotoxicosis	With goiter	7
						Without evident goiter	7
1	6	2	2	3	Euthyroid patient with	Angina pectoris	5
						Other heart disease	2

12 days (average 5§) after treatment, reaches a peak after two weeks and decreases to minimal levels after 55 to 60 days (Table 7 and Fig. 1). The relative increase is sometimes greater in euthyroid than in hyperthyroid cases since the initial blood level of PBI is higher in cases of thyrotoxicosis.

2. The changes in BSR are similar to those in the PBI, but differ in time and amplitude. These changes are more striking in cardiac cases, reaching a peak 10 days after I^{131} treatment in the thyrotoxic and 5 days in the cardiac patients. Return to normal occurs 60 and 40 days later, respectively (Table 7 and Fig. 2).

3. The cholesterol level is usually lowered during the first month after I^{131} treatment and becomes normal again 2–3 months later (Fig. 3).

The reaction to repeat therapy is clinically and biochemically less pronounced.

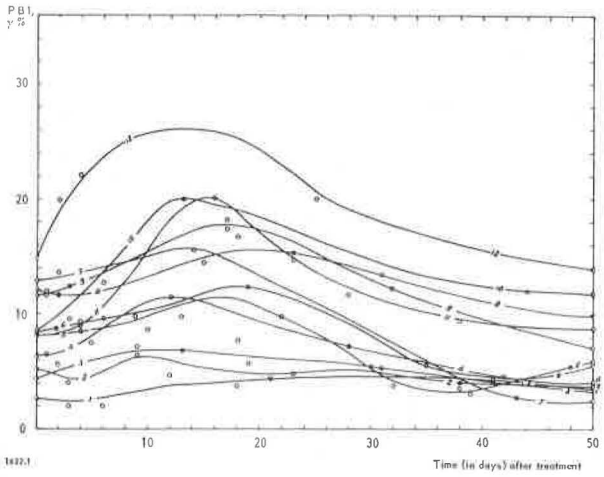

Figure 1. Changes of PBI after treatment with radioactive iodine

DISCUSSION AND CONCLUSIONS

The etiological, pathological and clinical observations enable us to define the features of radiation thyroiditis.

1. The syndrome appears in a certain percentage of patients after receiving I^{131} treatment and is largely caused by β rays, which account for 90% of the radioiodine radiation.[26] From our material it can be concluded that in the case of thyrotoxic patients a radiation dose of 15,000 rep/g of gland and in cardiac patients a dose of 6000 rep/g may cause clinical changes. Experimentation on animals[27] suggests that a dose of 2800 rep/g of thyroid gland would not cause morphological, and hence neither clinical nor laboratory changes. Similarly, histological examination of glands receiving higher radiation doses reveals changes in the struma, epithelium and colloid, which is followed by entry of thyroid hormone into the blood stream[28,29] and by the appearance of clinical symptoms.

2. The clinical picture of radiation thyroiditis may be either mild or severe. If mild ("unpleasant signs"[30]), they may be local or general and consist of pressure or aching pain in the region of the neck, dry throat, nervousness, weakness, poor sleep, sweating, palpitations, precordial sensitivity, etc. If severe, they result in increased thyrotoxic manifestations and even in a thyroid crisis,[31] in temporary mental disturbances in patients with cerebral arteriosclerosis and in cardiac complications, such as: pulmonary edema, cardiac asthma, arythmia, anginal crises and also myocardial infarction.[32–34] The latter complications may be fatal, as in the cases reported by Freedberg[34] (one week after

§ In the case of cardiac patients, the increase of PBI, as indicated by laboratory examinations, occurs a short time after the appearance of clinical symptoms; the reverse is true for thyrotoxicosis.

Table 2. Schedule of Clinical and Laboratory Tests

Group types	*Clinical tests*		*Laboratory tests*	
	Details of tests	*Time after I^{131} treatment*	*Type of test*	*Days after treatment*
Thyrotoxicosis	*Thyroid region:* size of gland, sensitivity, voice, swallowing	First week: twice	PBI	1, 3, 6, 10, 15, 20, 30, 40, 60, 90
	Thorax: condition of heart and lungs, pulse	Second week: once	BSR	
	General: excitability, perspiration, weight, blood pressure, etc.	Second and third month: twice	Cholesterol	1, 15, 30, 60, 90
Euthyroid with angina pectoris	Number of angina attacks and dose of nitroglycerine	Daily for one month	ECG	Few times

Table 3. Results of Clinical and Laboratory Examination of Thyrotoxic Patients after I^{131} Treatment

No. of case	Patient, age, sex and diagnosis[a]	*Radiological data*				*Laboratory changes*				*Clinical changes*							
		% I^{131} uptake in 24 hrs	Per gram of thyroid		Biol. half-life in days	PBI γ %		BSR mm		Days before onset	Symptoms[b]					Days duration
			uc I^{131}	rep (β + γ)		Before therapy	Peak value	Before therapy	Peak value		1	2	3	4	5	
1	A.S. 48, f (A)	95	95	12,500	6.0	7.5	9.6	—	—	—	−	−	−	−	−	—
2	T.H. 40, f (B)	52	104	12,500	6.5	7.8	15.0	4/15	20/44	—	−	−	−	−	−	—
3	R.R. 49, f (A)	85	142	12,900	3.5	8.2	9.8	1/2	45/72	—	−	−	−	−	−	—
4	H.L. 56, f (B)	66	156	13,600	3.0	7.2	26	100/123	99/120	2	−	+	−	+	−	10
5	N.P. 62, f (A)	83	133	14,900	5.0	11.7	17.2	7/22	11/37	4	±	+	−	+	−	15
6	F.S. 46, f (A)	85	170	15,100	4.0	8.9	26	16/28	20/50	5	+	+	−	−	−	21
7	F.E. 64, m (B)	59	132	15,900	10.0	7.0	—	2/5	6/10	—	−	−	−	−	−	—
8	S.S. 33, f (A)	73	175	16,400	4.5	13.7	15.5	30/41	39/70	14	+	+	−	−	+	10
9	G.E. 55, f (B)	64	144	17,300	6.0	13.4	—	0/1	40/70	4	±	−	−	+	−	14
10	A.B. 47, f (B)	60	144	17,400	6.0	8.8	15.7	3/7	10/45	5	−	+	−	+	−	14
11	J.S. 64, f (A)	85	170	20,500	6.0	14.6	26	15/42	30/62	3	+	+	−	−	+	10
12	G.R. 70, f (B)	75	170	20,600	7.0	6.5	11.4	8/20	13/36	7	+	+	−	−	+	14
13	F.P. 42, f (A)	80	185	22,700	6.0	8.3	14.0	—	—	12	+	+	+	+	−	18
14	K.L. 44, m (B)	75	210	23,500	5.5	5.9	9.9	1/2	35/61	5	+	+	−	+	−	30
Mean values		74	152	16,800	5.6	9.2	16.3	16/26	30/56	6	8	9	1	6	3	16
Range		52–95	95–210	12,500–23,500	3.–10.	6.5 14.6	9.6 26.0	0/1–100/123	13/36–99/120	2–14	No. of each symptom in this series					103–0

[a] A = Thyrotoxicosis with goiter.
B = Thyrotoxicosis without evident goiter.

[b] 1 = Pressure in the neck, redness, heat, dryness of mouth.
2 = Tachycardia, palpitations.
3 = Disturbances of respiration—attacks of dyspnoea.
4 = Nervousness, exacerbation of fatigue.
5 = Rest or hospitalization.

Table 4. Results of Clinical and Laboratory Examination of Euthyroid Cardiac Patients after I^{131} Treatment

No. of case	Patient, age, sex and diagnosis[a]	Radiological data				Laboratory changes				Clinical changes							
		% I^{131} uptake in 24 hrs	Per gram of thyroid		Biol. half-life in days	PBI %		BSR mm		Days before onset	Some symptoms[b]						Days duration
			uc I^{131}	rep ($\beta + \gamma$)		Before therapy	Peak observed	Before therapy	Peak observed		1	2	3	4	5	6	
1	W.J. 70, m (A)	22	44	6,400	7	8.6	9.1	11/30	13/51	1	−	+	+	+	−	+	19
2	A.Ch. 52, f (B)	55	72	9,500	6	8.0	7.9	20/46	45/74	3	−	+	−	+	+	−	14
3	M.B. 48, m (A)	40	80	9,700	6	5.6	6.8	12/27	14/30	2	−	+	−	+	±	+	17
4	W.A. 46, m (A)	45	90	10,800	6	2.8	4.8	23/39	80/120	5	−	−	−	+	+	+	16
5	M.S. 58, m (A)	54	140	12,500	4	2.0	5.8	0/1	35/55	1	−	+	−	+	+	+	10
6	A.Z. 62, m (B)	36	72	12,500	9	3.9	4.1	2/4	55/—	3	−	+	+	+	±	+	14
7	D.K. 68, m (A)	46	110	15,300	8	5.7	11.4	20/56	20/46	1	−	+	−	+	−	+	7
Mean values		42	87	10,900	6.5	5.1	7.1	10/29	37/63	2	−	6	2	7	6	6	14
Range		22–55	44–140	6,100–15,300	4–9	2.0–8.6	4.1–11.4	0/1–20/56	14/30–80/120	1–5	No. of each symptom in this series						7–19

[a] A = Euthyroid patients with angina pectoris.
B = Euthyroid patients with other heart disease.

[b] 1 = Pressure in the neck, redness, neat, dryness of mouth.
2 = Tachycardia, palpitations.
3 = Disturbances of respiration—attacks of dyspnoea.
4 = Nervousness, exacerbation of fatigue.
5 = Rest or hospitalization.
6 = Increase in amount of nitroglycerine.

Table 5. Anginal Pains, Nitroglycerine Requirement and Laboratory Findings in Cardiac Patients after Radioiodine Therapy

Patient, age, diagnosis and treatment	*Clinical and laboratory observations*	*Days after radioiodine treatment*[a]																														
		1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*	*15*	*16*	*17*	*18*	*19*	*20*	*21*	*22*	*23*	*24*	*25*	*26*	*27*	*28*	*29*	*30*
D.K., 68,	Anginal pains	2	1	3	4	4	0	1	1	1	1	0	1	1	0	1	0	1	0	1	1	2	1	1	0	0	0	0	0	0	0	
Anginal syndrome	Nitroglycerine	3	1	?	3	4	0	1	0	0	1	0	0	0	0	1	0	1	0	1	0	2	0	2	0	0	0	0	0	0	0	
6 mc of I^{131} =	PBI			5.7				6.8					11.4											7.4								6.2
15,300 rep/g	BSR		10/36	20/46				19/35																15/28		11/30						8/12
D.K., second treatment	Anginal pains	0	0	0	4	0	3	0	0	0	2	1	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
5 mc of I^{131}	Nitroglycerine	0	0	0	3	0	2	0	0	0	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
A.Z., 62,	Anginal pains	0	0	2	3	3	2	3	?	3	5	m	m	4	2	?	3	4	2	0	2	1	2	0	2	1	2	2	0	0	0	
Anginal state, arteriosclerotic H.D.	Nitroglycerine	0	0	m	m	4	2	m	?	3	m	m	m	3	1	?	2	m	2	?	1	1	1	0	?	1	1	1	0	0	0	
5 mc of I^{131} =	PBI	3.5		5.8				3.9		7.2		6.2		4.8						4.1				2.6					3.3			
12,500 rep/g	BSR (1h)	35		29				35		21		19			52						38								24			
W.J., 70,	Anginal pains	1	1	4	2	1	0	1	1	6	1	1	1	1	2	1	1	1	3													
Intractable angina	Nitroglycerine	1	1	4	2	1	0	1	1	6	1	1	1	1	3	1	1	1	2													
pectoris, myocardial infarctions	PBI	8.6		9.1					8.7			9.0																				
																									dead							
5 mc of I^{131} =	BSR (1h)			8				11								15																
6,400 rep/g																																

[a] m = multiple

Table 6. Summary of Clinical Changes due to Radiation Thyroiditis after I^{131} Treatment

Diagnosis	Time of appearance of symptoms (days)			Numbers of cases with symptoms due to radiation thyroiditis					
	Evaluation	Onset	End	Evaluation	Number symptom	General	Local	Cardiac	Others
Thyrotoxicosis	Mean	6	16	No. of cases	4	6	8	9	3
	Range	2–14	10–30	%	30	40	60	65	20
Euthyroid cardiac patients	Mean	2	14	No. of cases	0	6	0	6	2
	Range	1–5	7–19	%	0	85	0	85	30

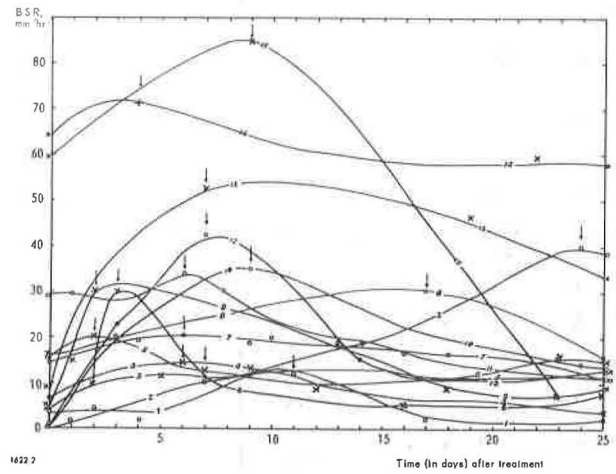

Figure 2. Changes of Blood Sedimentation Rate after treatment with radioactive iodine

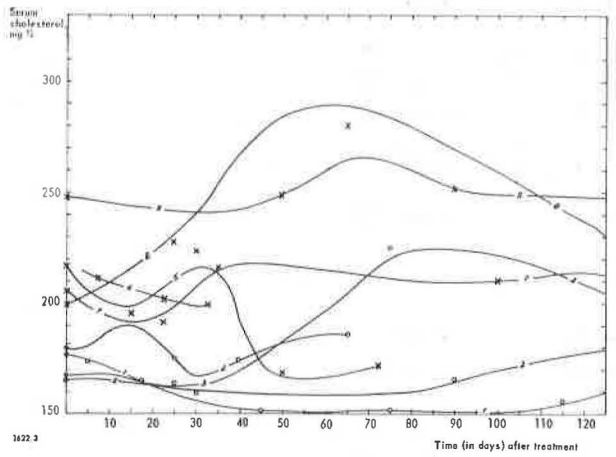

Figure 3. Changes of serum cholesterol after treatment with radioactive iodine

receiving from 15,000 to 70,000 rep/g of thyroid). Among all our cases we had one fatality—a patient, 70 years old, suffering from intractable angina pectoris and old myocardial infarctions. He died 19 days after a radiation dose of 6400 rep/gm of thyroid. No laboratory changes were noted with this patient except increased BSR (Table 5). Other patients who received a dose of 12,000 rep/g showed no clinical symptoms but revealed changes in PBI and BSR. Hence, one may differentiate between clinical and laboratory radiation thyroiditis. The increase in PBI alone may not be significant, since it has been demonstrated that only a portion of the PBI which appears after the destruction of the thyroid is active thyroxine, the rest consisting of thyroglobulin, diiodotyrosine, etc. Therefore the butanol fraction of PBI may need to be checked in order to elucidate the question.[35]

3. Diagnosis of radiation thyroiditis is easy, as the causative connection between it and the treatment with I^{131} is, as a rule, obvious. It should be differentiated from radiation sickness and subacute thyroiditis.[36,37]

4. The treatment of radiation thyroiditis depends on severity of the symptoms. Pressure, pain or swelling of the thyroid are treated by putting cold compresses on the neck, and nervousness by sedation. More severe cases necessitate consultation with an internist or cardiologist and they require complete rest in bed or even hospitalization up to 10–15 days. This is particularly important in cardiac cases, as evidenced from our 8 cases (cases 8, 11, 12 in Table 3 and cases 2, 3, 4, 5, 6 in Table 4).

A comparison of clinical and laboratory results of this investigation leads to the following conclusions:

1. The time of appearance and the degree of severity of radiation thyroiditis differ in thyrotoxic as opposed to cardiac patients. Thyrotoxics who received over 15,000 rep/g suffered less than cardiacs who received less than 10,000 rep/g.

2. Parallelism between clinical and laboratory changes is not necessary. Thus it is possible to distinguish clinical and laboratory radiation thyroiditis.

3. There is no necessary parallelism in the same

Table 7. Summary of Laboratory Changes (PBI and BSR) due to Radiation Thyroiditis after I^{131} Treatment

Diagnosis	Evaluation	Time (days) of PBI changes			Time (days) of BSR changes	
		Onset	Peak	Minimal value	Peak	Minimal value
Thyrotoxicosis	Mean	5	15	63	10.5	59
	Range	2–9	9–25	27–118	4–24	20–111
Euthyroid cardiac patients	Mean	5	13	54	5.5	41
	Range	1–12	3–25	15–97	2.11	10–70

clinical group between radiation dose and severity of the complications. Perhaps sex of the patients plays a role, for the two males in our series showed less reaction to therapy than females (Cases 7 and 14, Table 3).

4. The radiation dose to be applied should be determined, taking into account not only I^{131} uptake, biological half-life, size of thyroid and age of patient, but also his cardiac condition.

5. To avoid severe complications due to radiation thyroiditis, the radiation dose should not exceed 10,000 rep/g of thyroid for a single treatment in cardiac cases. A time lag of at least 20 days between consecutive treatments is required. In noncardiac patients the dose may reach 20,000 to 25,000 rep/g of gland.

6. To avoid serious and even fatal complications, cardiacs and severe thyrotoxics should rest and be hospitalized for a few days after treatment with I^{131}.

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Clinical Experience with Radioactive Iodine in the Treatment of Thyrotoxicosis

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Radioactive iodine is now used extensively for the study of thyroid function because of its selective absorption by the gland. Radioiodine tests of thyroid function generally depend upon measurement of radioactive iodine excretion in the urine, uptake in the thyroid gland, level of I^{131} in the blood, or on various combinations of these measurements.

The 24-hour uptake of I^{131} is the routine method used in our unit. In some cases the protein bound iodine and the conversion ratio were determined as well. The uptake test was carried out in 2000 cases comprising normals, diabetic cases, patients with hyperfunctioning thyroids, patients with malignant thyroids and patients suspected of aberrant thyroid tissue or functioning thyroid metastases. In our hospital the usual tracer dose administered is 20 mc. Our experience has been that uptake values greater than 55% of the administered tracer dose indicate hyperfunction of the gland; normal values range between 15 and 55% while hypothyroid individuals show values less than 15%. The urinary output of I^{131} is often a valuable check on the radioiodine retained by the gland. Keating, *et al.*, found the urinary excretion values of I^{131} at 48 hours to be 40 to 86% for euthyroid subjects, 3 to 54% for exophthalmic goiter and 60 to 90% for myxoedematous subjects. Some workers maintain that the ability of salivary glands to concentrate iodine is also of diagnostic significance, particularly in diagnosis of hypothyroidism.

The urinary excretion of I^{131}, the 24-hour uptake of the gland, and the serum protein bound iodine determinations are liable to inaccuracies due to the following factors:

1. In our practice, the I^{131} urinary excretion test was found to be impractical because of incomplete collection of urine specimens over a long time, mainly due to loss of urine by the patient at the time of defecation. A delay in renal excretion of I^{131} may also occur owing either to reduced renal function, common in Egypt as the result of bilharziasis, or to failure of normal circulation.

2. Thiouracil derivatives or other antithyroid drugs change the total amount of uptake. Potassium iodide reduces the uptake of I^{131} to very low values which are unrelated to the basal metabolic rate, an effect which may last as much as seven weeks after cessation of administration of the drug. Organic iodine compounds used as contrast media in diagnostic radiology, as for cholecystography, myelography and pyelography, have the same effect in producing low thyroid uptake and high urinary excretion values. Thyroid extract medication and diets rich in iodine as well as iodoxyquinoline compounds used in the treatment of amoebiasis and chronic colitis may also diminish the uptake to misleadingly low figures.

3. The conversion ratio gives unduly high figures in areas of deficient iodine intakes.

In selecting our cases of hyperthyroidism for radioiodine therapy, we set the following criteria: (1) uncomplicated cases of hyperthyroidism in patients over 35 years of age; (2) cases with persistent or recurrent hyperthyroidism following a previous surgical thyroidectomy; (3) cases that fail to respond to antithyroid drugs; (4) cases that refuse surgical or other therapy; (5) cases having surgical contraindications such as severe heart failure or myocardial infarction of less than one year's duration, laryngeal palsy, severe emotional disturbances, severe hypertension, severe lung disease and renal and liver disease, and (6) cases of hyperthyroidism with malignant exophthalmos at any age because surgical treatment in such cases frequently results in progression of the severity of exophthalmos (radioactive iodine therapy of these cases being considered the safest practical method of rendering the patient euthyroid).

Our contraindications to radioiodine therapy were: (1) patients below 35 years of age; (2) cases of toxic nodular goiter, unless the nodule is proved to be a hyperfunctioning adenoma; (3) pregnancy and lactation; (4) severe hyperthyroidism (this being considered a temporary contraindication in order to prevent death from thyroid crisis or acute congestive heart failure due to the rapid dumping of the thyroid hormone into the blood stream); (5) nontoxic nodular goiter, and (6) nontoxic diffuse or simple goiter.

Determination of the dose of radioactive iodine and its method of application varies according to several workers. Two methods of dosage administration are usually used. The single dose method consists of giving the predetermined dose to relieve the thyrotoxicosis completely in one application. The fractionation method consists of several applications of repeated

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Table 1. Distribution of Type of Goiter with Respect to Age and Sex

	Diffuse				*Nodular*				*Recurrent*			
Age.....	35–40	41–50	51–60	61–70	35–40	41–50	51–60	61–70	35–40	41–50	51–60	61–70
Female....	7	16	8	2	7	11	6	3	3	3	1	0
Male.....	6	3	5	2	1	5	4	1	0	0	0	1

small doses at relatively frequent intervals over a long period of time. The average dose is usually 10,000 rep and the amount of I^{131} necessary to deliver this dose is calculated according to the estimated thyroid weight, per cent uptake of the gland from the administered tracer dose of radioactive iodine, and biological half-life of the radioactive material. In addition, due consideration is given to the nature of the gland, for it is well known that a diffusely hyperplastic gland responds better than any other type of toxic goiter.

We have treated 95 cases of hyperthyroidism with radioactive iodine at the University Radioisotope Laboratory since its opening in June 1955. About half of the cases have lived in Cairo for the past five years; the remaining cases came from upper and lower Egypt with a slight preponderance from lower Egypt. Table 1 shows the distribution according to type of goiter, age, and sex. From this table it may be seen that the female cases constituted 70% of the total; 49 cases (51.5%) were of the diffuse type, 38 cases (40%) were of the nodular type, and the remaining 8 cases (9.5%) were of the recurrent type.

Diagnoses were made on the basis of clinical signs and symptoms, the basal metabolic rate, and the 24-hour I^{131} uptake. Cases that were clinically euthyroid and showed an uptake in the hyperthyroid range were discarded. Four, that were clinically hyperthyroid and had high metabolic rates while their I^{131} uptaken was 35, 39, 25 and 10.9%, respectively, were treated with radioactive iodine on clinical grounds. The second of these four had been on iodine until three years previous to radioiodine therapy. The third and fourth had taken iodine recently. In all of the cases it was difficult to be sure that no iodine containing drugs had been taken before. There was a fair degree of correlation between basal metabolic rate and uptake in the remaining cases. In all cases the patient's uptake, B.M.R., blood picture, weight, neck circumference, chest film, blood cholesterol, measurement of degree of exophthalmos when necessary, and other investigations were carried out to assess results of treatment.

DOSAGE

Table 2 shows the distribution of cases that received one dose in relation to type of goiter and the result of treatment. Table 3 shows the same kind of information cases that received more than one dose.

Out of the 54 cases that received a single dose, 34 (62%) showed marked improvement, 9 (17%) showed slight improvement but did not require any further radioiodine treatment, 2 showed no improvement and did not report for completion of their treatment, 8 did not attend for their follow up, while the last case, that had received 10 mc, developed persistent myxoedema. The maximum dose in this group varied between 20 and 25 mc while the minimum dose varied between 3 and 5 mc with an average of 10 mc.

Of the 41 cases that received several doses, 39 received two doses, one received 3 doses, one 4 doses and one 6 doses. Maximum doses were given to 2 cases in this group. The first was that of a nodular toxic goiter that received 40 mc, and the second was of the diffuse type that received 55 mc. These two cases were interesting. The first was a male, 46 years old, who reported to us, complaining of tremors, nervousness, palpitation, marked loss of weight, and hyperhidrosis of five months duration. His pulse was 124, blood pressure 145/90, the thyroid gland was three times the normal size and was finely nodular, the B.M.R. was plus 90%, and the 24-hour I^{131} uptake was 54.4%. Table 4 shows details of the doses given during a period of four months and the progress of radioiodine therapy. Although the laboratory investigation showed slight but definite improvement after the first two doses, the general condition did not coincide with the laboratory findings, and the nervousness increased to such an extent that we thought the treatment was hopeless. With further detailed study of his radioiodine uptake, we noticed that this patient had a very rapid turnover of radioiodine which, together with the clinical effects, disappeared promptly. This led us to give further fractionated doses at weekly intervals to keep radioactivity in the gland at an efficient level. The patient responded clinically to this new method of administration, and he is now hypothyroid.

The second case was a male, 65 years old, with diffuse toxic goiter and angina pectoris. The gland size was six times normal, B.M.R. plus 80%, and a 24-hour uptake, 70%. A large initial dose of 20 mc was given to control his anginal symptoms. This was

Table 2. Cases that Received One Dose of I^{131}

	Marked improvement	*Slight improvement*	*No improvement*	*No follow up*	*Myxoedema*	*Doses*		
						Max.	*Min.*	*Av.*
Diffuse.....	19	4	1	3	0	25	4	9
Nodular.....	11	4	1	5	1	20	5	10
Recurrent.....	4	1	0	0	0	25	3	10.6

Table 3. Cases that Received Several Doses I^{131}

	Marked improvement	Slight improvement	No improvement	No follow up	Myxoedema	Doses		
						Max.	Min.	Av.
Diffuse	13	8	1	0	0	55	4.5	15
Nodular	8	6	2	0	0	40	11	17
Recurrent	3	0	0	0	0	30	5.5	17

followed by further doses amounting to a total of 55 mc over a period of two years. The patient was completely relieved of his thyrotoxicosis with complete disappearance of the gland and no relapse of his anginal pains. His uptake is now in the euthyroid range (46.8%).

Table 4. Doses Given to Case No. 34

Date	BMR	% uptake	Dose in mc
9.9.57	+48	54.4 at 24 hrs	0
30.9.57	+48	48 at 24 hrs	0
2.10.57			5
22.10.57	+44		
7.11.57			10
31.12.57	+60	69.4% 2 hrs 49.9% 24 hrs	
7.1.58			5
14.1.58			10
Total			40

RELATION OF THE TYPE OF GOITER TO THE EFFECTIVE DOSE

Table 5 shows the distribution of cases in relation to various types of the disease and the dosage level. It will be noticed that the diffuse toxic goiter requires less than the toxic nodular goiter for adequate control of the symptoms.

RESULTS OF TREATMENT AND SOME OBSERVATIONS

The cases that showed marked (61%) or mild improvement (24%) added weight. The controlled cases showed complete disappearance of the clinical manifestations except for exophthalmos which was present in 7 cases. Some cases showed very slow improvement and the others were referred for pituitary irradiation. In no case did exophthalmos become malignant. All cases are now in the euthyroid range except one which is hypothyroid and another one which developed myxoedema after one dose of 10 mc. Menopausal symptoms appeared in some female climacteric patients, only after control of the thyrotoxicosis with I^{131}, and they were referred to the endocrine clinic for hormone therapy. This finding suggests a study of the possible inhibition of gonadotrophin release by a hyperfunctioning thyroid.

One of our cases, who was 35 years old and had a diffuse toxic goiter, was completely controlled after one dose of 4 mc. She complained of a 15-day delay of her menses in addition to the toxic manifestations. This result was thought to be due to thyrotoxicosis. She proved later to be pregnant, and was delivered of a normal baby who is still living and healthy after two years.

Cramps appeared in one case, and tetany in another. Both are now euthyroid. Follow-up was impossible in 8 cases and it is a possibility that they did not return due to improvement of their condition.

SUMMARY AND CONCLUSIONS

Although the number of treated cases is small and the maximum period of observation is only about three years, we have reached general conclusions which fit in with the findings of other workers over longer periods of time, especially with the early work done in this field by Hamilton and Lawrence (1942) and Hertz and Roberts (1942).

Our small group of patients consisted of 95 cases of diffuse, nodular and recurrent thyrotoxicosis who were treated by radioactive iodine; 61% of these showed marked improvement and 24% showed moderate improvement. All of these (85%) are euthyroid except one who is hyperthyroid. The method of administration of the dose and of determining dosage level are described. Myxoedema developed in one case that was given a comparatively small dose.

Table 5. Results of I^{131} Therapy Relative to Dosage Level and Type of Goiter

Goiter type	Diffuse			Nodular			Recurrent		
Improvement	Marked	Slight	No	Marked	Slight	No	Marked	Slight	No
Below 10 mc	16	7	3	6	4	2	3	2	0
11–15 mc	8	3	0	7	5	0	1	0	0
16–20 mc	5	1	0	2	1	0	1	0	0
21–25 mc	1	0	0	1	1	0	1	0	0
above 25 mc	1	1	0	0	1	0	0	0	0
Total cases	31	12	3	16	12	4	6	2	0

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Studies on Neutron Capture Therapy

By Gordon L. Brownell and William H. Sweet*

A limitation in the use of radioactive isotopes in tumor therapy is the low whole-body radiation dose required to produce marked radiation effects as compared to the tumorcidal dose. As a result, large ratios of isotope content in tumor tissue to normal tissue are required for a successful therapeutic procedure. One method for achieving these ratios is the use of a colloidal substance injected locally at the site of the tumor. Although this technique has had marked success in certain applications, it lacks one of the potentially powerful features of isotope therapy in that it does not employ the physiological properties of the radioelement. One of the few applications employing the physiological properties of the substance administered is the treatment of certain types of thyroid metastatic carcinoma with radioiodine.

Administration of a stable isotope possessing a high neutron capture cross section and subsequent irradiation with thermal neutrons offers two advantages. First, the whole-body dose can be decreased as only a selected portion of the body is subjected to the neutron flux. Second, certain capture reactions such as (n, p), (n, α), and (n, f) reactions produce ionizing particles of very short range. Thus, if tumor cells can be made to concentrate the stable isotope, the possibility exists of irradiating small groups of tumor cells even if surrounded by normal tissue.

The possible application of slow and thermal neutrons to radiation therapy was recognized as early as 1936 by Locher,[1] and in 1940 Kruger[2] reported on observations of neutron capture of boron-10 (B^{10}) in mouse mammary carcinoma, lymphoma, and sarcoma *in vitro*. In the same year, Zahl, Cooper and Dunning[3] reported on *in vivo* studies of neutron irradiation of boron and lithium compounds in mouse sarcomas. Later Zahl and Cooper[4,5] reported studies of lithium and lithium compounds in mouse tumors. In 1948, Tobias, Weymouth, Wasserman and Stapleton[6] observed biological effects induced in animals by thermal neutron radiation following administration of uranium. Conger and Giles[7] reported in 1949 on genetic studies in *tradescantia* irradiated with thermal neutrons. In this study, boron capture in the normal *tradescantia* accounted for a considerable proportion of the radiation effect.

From theoretical considerations, neutron capture therapy would appear to have a promising role in the treatment of brain tumors. Conventional radiation therapy has had limited success with these tumors and surgical treatment is followed by a high percentage of recurrences. The short range of particulate radiation following some neutron capture reactions suggests the possibility of preferentially irradiating small groups of tumor cells or even single tumor cells in normal brain. Thus, the possibility exists of destroying the tumor remnants following operation which lead to recurrence. A further characteristic of brain tumors which makes them particularly suitable for this technique is the peculiar property of normal brain to exclude or admit slowly many substances introduced into the blood. This "blood–brain barrier"[8] is broken down in areas of tumor or other abnormality and many elements and compounds introduced intravenously achieve marked concentrations in brain tumor compared to normal brain. This phenomenon has been the basis of a practical method of brain tumor localization.[9–11]

Sweet and Javid[12] demonstrated in 1952 that usable concentrations of boron could be administered to humans and that useful ratios of boron content in tumor to normal brain existed for some 30 to 40 min after injection. In the same year, Javid, Brownell and Sweet[13] presented calculations of radiation dosage in normal and neoplastic brain. These studies have been followed by clinical trials of neutron capture therapy in patients with glioblastoma at the nuclear reactor at the Brookhaven National Laboratory in collaboration with Dr. Lee Farr and others of the Medical Department.[14–16]

In this paper, some considerations of the physical aspects of neutron capture therapy will be presented without regard to a specific therapeutic problem. However, certain aspects obviously apply to the use of B^{10} in the therapy of brain neoplasms as this technique is the only one to have actual clinical trial in humans. This technique will further be the first to be attempted at the medical therapy facility of the reactor at the Massachusetts Institute of Technology now under construction. However, the unusual features of neutron capture therapy would warrant careful consideration of its application to other therapeutic problems.

THERMAL NEUTRON DOSE CALCULATIONS

In a region irradiated uniformly with thermal neutrons (v = 2200m/sec, E = 0.025 ev), the product of neutron density and velocity, nv, will be a constant.

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Table 1. Radiation Dosage Resulting from Neutron Capture in Normal Tissue Constituents ($\phi = 10^{10}$ n/cm² sec)

Element	*Weight per cent*	σ_a, *barns*	*Radiation*	*E, Mev*	*f*	*R, rad/min*
O	70.1	<0.0002	γ	4.10	0.050	<0.01
C	13.4	0.0032	γ	4.95	0.048	0.05
H	9.9	0.330	γ	2.23	0.058	24.3
N	4.1	1.88	P	0.624	1.	19.8
Cl	0.13	31.6	γ	8.57	0.046	2.6
Others			γ			0.13
					Total R =	46.9

This quantity is called the thermal neutron flux, ϕ(n/cm² sec). Thermal neutrons are lost in a moderator by capture within the nucleus of the various materials making up the moderator. This capture may be accompanied by emission of a heavy particle such as a proton or alpha particle or by emission of a gamma ray, and the reaction invariably results in the liberation of kinetic energy (exothermal). The resultant nuclide may be a stable or radioactive species. The probability of a reaction taking place is given by the absorption cross section, σ_a, expressed in barns (10^{-24} cm²).

The rate of energy dissipation within a uniformly irradiated region is given by:

$$P = 1.60 \times 10^{-30}\phi \sum_i N_i \sigma_{a_i} E_i \text{ ergs/cm}^3 \text{ sec} \quad (1)$$

where N_i is the number of nuclei of the ith substance per cc and E_i is the energy in Mev of the resultant radiations. To calculate the radiation dose rate in a region of finite extent, some assumption must be made as to the fraction of the energy produced which is absorbed in the region. This fraction will be called f and will be unity for heavy particles such as protons, alpha particles, or fission fragments. The dose rate, R, will then be:

$$R = \frac{1.60 \times 10^{-30}\phi \sum_i \sigma_{a_i} N_i f_i E_i}{100} \text{ rad/sec} \quad (2)$$

N_i is given by the expression:

$$N_i = \frac{N}{A_i} P_i \quad (3)$$

where N is Avagadro's number, P_i is the fraction by weight and A_i is the atomic weight of the ith element. One rad is defined as 100 ergs/g of tissue.[17] Combining equations 2 and 3 and converting, one finds:

$$R = 5.77 \times 10^{-7}\phi N \sum_i \frac{\sigma_{a_i} E_i f_i P_i}{A_i} \text{ rad/min} \quad (4)$$

Table 1 gives the dose rate resulting from neutron capture in various constituents of lean tissue for $\phi = 10^{10}$ n/cm² sec. The weight percentages for lean tissue have been taken from Siri[18] and are essentially the same as for normal brain and brain tumor.[13] The capture cross sections have been taken from the compilation of Hughes and Harvey[19] and the reaction energies have been taken from the table of nuclear disintegration energies by Van Patter and Whaling.[20] Calculation of the fraction of gamma-ray energy absorbed in the region requires some assumption as to the volume irradiated. In this computation, f has been set equal to $\mu_a L$ where μ_a is the true absorption coefficient for γ rays in tissue and L is the diffusion length of the neutrons in tissue (2.5 cm). This quantity is the ratio of the dose rate at the center of a uniformly irradiated sphere of 2.5-cm radius to the dose rate in an infinite medium, and obviously serves only as an estimate of the contribution of gamma rays to the total dose. A more detailed calculation would require further data as to the dimension of the radiation portal and the tissue configuration.

It is seen from Table 1 that H and N account for about 95% of the radiation dose rate in normal tissue. These two elements produce approximately the same dose although H accounts for 85% of the total captures. The smaller contribution of H to the dose rate results from the penetration of γ rays outside the region of interest. Although the relative biological effectiveness (RBE) of the various radiations will be discussed later, it should be noted that the linear energy transfer (LET) of the γ rays and protons are markedly different. The average LET for high-energy γ rays in water or tissue is about 0.25 kev/μ.[21] The range of the 0.66-Mev protons from nitrogen capture is 12.2μ in tissue[22] giving an average LET, $\langle \text{LET} \rangle_{av}$, of 24 kev/$\mu$. The recoil C^{14} nucleus has an energy of 0.13 Mev and will have a much greater $\langle \text{LET} \rangle_{av}$.

Four radionuclides are produced by neutron capture in normal tissue constituents: C^{14}, Na^{24}, P^{32} and C^{38}. The dose rates resulting from these nuclides is small compared to those in Table 1 because of the small concentration of the capturing substance or, in the case of C^{14}, because of the long life of the nuclide. These nuclides are of interest, however, because of their possible application to dosimetry in capture therapy. The total dose resulting from these radionuclides following therapy is complicated by the physiological distribution and excretion of these elements, but estimates indicate that this dose will be comparatively insignificant.

Table 2 lists the properties of various substances with large capture cross sections which might be used in neutron capture therapy. Values of σ_a and ϵ have been taken from the references cited for Table 1. The energy of the emitted particle is $E\left(\frac{A_R}{A_P + A_R}\right)$

Table 2. Concentration of Various Neutron-capturing Nuclides Required to Produce 100 rad/min ($\phi = 10^{10}$ n/cm^2 sec)

Nuclide	*Normal abundance, per cent*	σ_n, *barns*	*Radiation*	*E, Mev*	*E(radiation), Mev*	*Range, μ*	$\langle LET \rangle_{av}$ *radiation, kev/μ*	$\langle LET \rangle_{av}$ *recoil, kev/μ*	*f*	*Concentration of nuclide to produce 100 rad/min, μg/g tissue*
He^3	0.00013	5400	P	0.76	0.57	12	48	160	1	12.6
Li^6	7.52	945	α	4.80	2.08	13	160	120	1	22.9
B^{10}	18.8	4010	α	2.79	1.78	11	160	—	1	15.4
O^{17}	0.037	0.5	α	1.6	1.25	8	160	—	1	3.68×10^5
Cd^{113}	12.26	20,800	γ	9.05	9.05	—	~0.25	—	0.043	241
Sm^{149}	13.84	50,000	γ	7.89	7.89	—	~0.25	—	0.044	150
Gd^{155}	14.73	70,000	γ	~6.6	~6.6	—	~0.25	—	0.046	126
Gd^{157}	15.68	160,000	γ	6.6	6.6	—	~0.25	—	0.046	56
U^{235}	0.714	580	fission	180	84	30	2800	—	1	39

where A_P and A_R are the atomic numbers of the emitted particle and the recoil nucleus. The $\langle LET \rangle_{av}$ is estimated from the particle energy and range. The quantity f has been calculated as in Table 1, and the concentration of the isotope required to produce 100 rad/min from its capture radiations in a flux of 10^{10} n/cm^2 sec is given. The first four reactions, occurring in light nuclei, result in proton or α particles of short range. Neutron capture in He^3 produces protons of 0.57 Mev and a $\langle LET \rangle_{av}$ of 48 kev/μ and tritons of 0.19 Mev and a $\langle LET \rangle_{av}$ of about 160 kev/μ. Li^6 produces α particles of 2.08 Mev and a $\langle LET \rangle_{av}$ of 160 kev/μ and a recoil triton of 2.32 Mev and a $\langle LET \rangle_{av}$ of 120 kev/μ. B^{10} and O^{17} produce α's with similar $\langle LET \rangle_{av}$'s. The estimate of the $\langle LET \rangle_{av}$ of the heavy recoil nuclei is complicated by lack of information on electron stripping, but these particles will have a greater $\langle LET \rangle_{av}$ than the tritons. The four heavy nuclei, Cd^{113}, Sm^{149}, Gd^{155} and Gd^{157}, with large capture cross sections undergo (n,γ) reactions and so have low $\langle LET \rangle_{av}$'s. Finally, the neutron-induced fission of U^{235} produces large amounts of kinetic energy. This energy is divided into 168 Mev per fission received by the two fission fragments, 5 Mev to the fission neutrons, 7 Mev emitted as β radiation of resultant radionuclides and 20 Mev of gamma radiation emitted instantaneously on fission, in capture reactions, or by radionuclides. Only the energy of particles has been included in the present calculation because the absorbed energy due to γ rays will be small. The range of fission fragments is about 30μ in tissue, and as, on the average, each fragment will have 84 Mev, the $\langle LET \rangle$ will be about 2800 kev/μ.

Of the nuclides listed, Li^6, B^{10} and U^{235} have received the most study. He^3 would appear to have promise in situations where a gas could be introduced into the desired region. Extremely small quantities of these substances are required to produce significant radiation dose rates. Further, the short ranges of the radiations limit the biological effect to within one or two cell diameters of the nuclide. O^{17} has been included because of the possibility of introducing highly enriched oxygen gas into a body cavity. Figure 1 shows the total radiation dose rate in tissue as a function of He^3, Li^6, B^{10}, or U^{235} concentration for a flux of 10^{10} n/cm^2 sec.

The nuclides undergoing (n, γ) reactions may be useful in certain applications. However, the long range of the γ rays precludes preferential irradiation of tumor cells. The use of these materials might be analogous to the infusion of tumors with a γ-ray-emitting colloidal substance.

One of the problems in the use of neutron-capturing materials is the chemical toxicity of substance administered. B^{10} and Li^6 can be administered intravenously in quantities sufficient to produce usable concentrations in normal and neoplastic brain tissue. The chemical toxicity of uranium introduces more serious limitation. Local administration of certain compounds may aid in the toxicity problem.

THERMAL NEUTRON DISTRIBUTION

With the exception of small objects placed in thermal columns, a uniform thermal neutron distribution

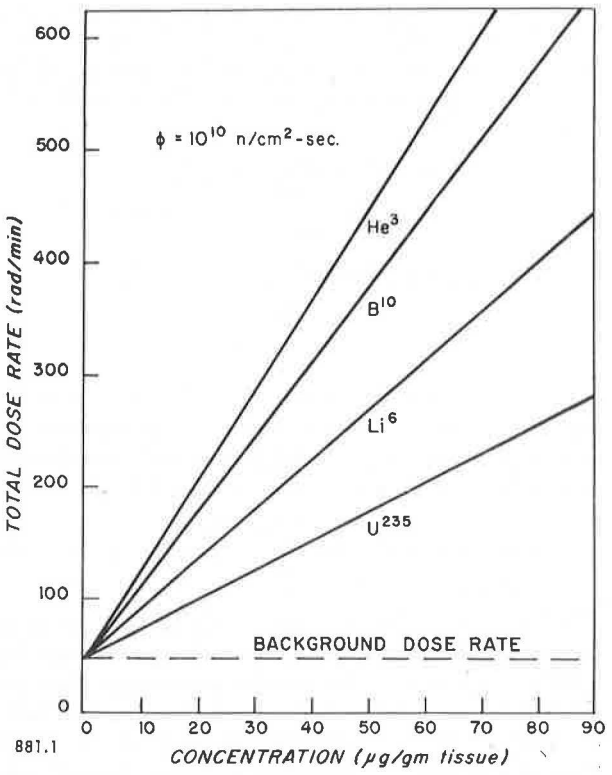

Figure 1. Total radiation dose rate in tissue as a function of concentration of neutron-capturing substances

cannot be achieved. Thermal neutrons incident on a moderating substance are readily scattered and subsequently diffuse into the moderator until they re-emerge or are captured. In hydrogenous material such as tissue or water, hydrogen produces most of the scattering and most of the captures.

The basic diffusion equation for thermal neutrons in a moderator[23] is:

$$D\nabla^2\phi - \Sigma_a\phi + S = \frac{\partial n}{\partial t} \tag{5}$$

where

D = diffusion coefficient
$\Sigma_a = \sum_i N_i\sigma_{ai}$
S = neutron source
n = neutron density

This equation states that the change in the neutron density in any small volume element equals the gain or loss by diffusion less the loss by capture plus the gain due to the neutron source. In the steady-state case, $\partial n/\partial t$ is zero. If it is assumed that a current of neutrons, j n/cm^2 sec, is incident on a large slab of tissue-like moderating material and that neutrons are scattered isotropically in laboratory coordinates, the source function, S, might be represented as:

$$S = j + \Sigma_s e^{-\Sigma_s x} \tag{6}$$

where Σ_s is the macroscopic scattering cross section and x is distance into the moderator. The differential equation may readily be solved, and yields the following expression for the neutron flux:

$$\phi = Ae^{-x/L} + Be^{-x/\lambda_s} \tag{7}$$

where

$$A = \frac{5}{\left[1 + \frac{2\lambda_s}{3L}\right]\left[1 - \left(\frac{\lambda_s}{L}\right)^2\right]}$$

$$B = \frac{3}{\left[1 - \left(\frac{\lambda_s}{L}\right)^2\right]}$$

and

$$L^2 = \frac{\lambda_s\Lambda}{3}, \qquad \lambda_s = \frac{1}{\Sigma_s} \qquad \text{and} \qquad \Lambda = \frac{1}{\Sigma_a}.$$

The results of diffusion theory are not valid near surfaces, but this equation gives results for thermal neutron flux in plane slabs essentially in agreement with the calculations and measurements of Smith and Tait,[24] Snyder,[25] and Snyder and Neufield.[26] Figure 2 shows the variation of flux with depth into a thick slab. The distribution reaches a peak within a few mm and then falls rapidly, decreasing to $1/e$ in a diffusion length, L. The addition of B^{10} increases Σ_a but changes Σ_s only slightly. Figure 2 shows the effect of B^{10} on the flux distribution. Although the addition of B^{10} affects the flux, the effect is not comparable to the marked increase in dose rate at the same concentrations. One μg of B^{10} is equivalent to 0.22 μg of He^3, 4.0 μg of Li^6, 163 μg of U^{235} in its effect on the flux distribution.

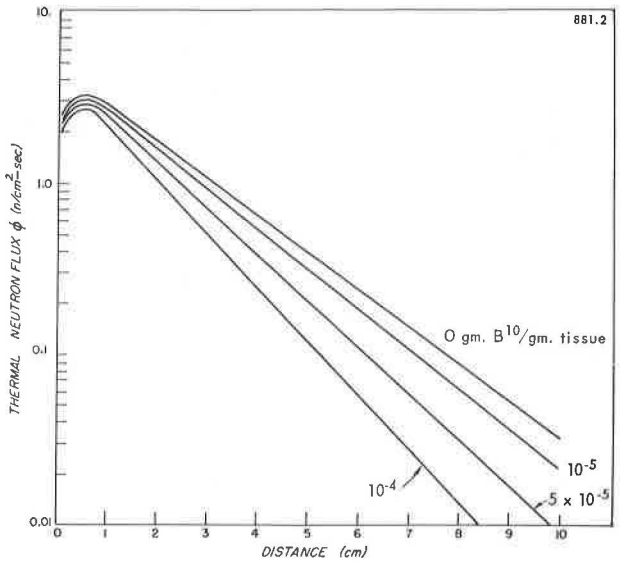

Figure 2. Thermal neutron distribution in tissue for different B^{10} concentrations. Calculations based on a thermal neutron current of 1 n/cm^2 sec incident on a large block of tissue-like material

The problem of determining the flux distribution in regions of the body is much more complicated and may be approached most readily by direct measurement in phantoms. Stickley[27] has observed the flux distribution in a tissue equivalent phantom.

The rapid decrease in thermal neutron flux with depth into tissue makes it difficult to selectively irradiate deep tumors even if an adequate ratio of neutron capture substance exists. One solution is to expose the area to be irradiated and use only the peak of the flux distribution. This is particularly suitable in the treatment of brain tumors as the major portion of the tumor may often be excised and the problem is to destroy the remaining tumor cells infiltrating into surrounding normal brain.

A second possibility is the use of incident epithermal neutrons. These neutrons are moderated in tissue with relatively little biological effect and produce thermal neutrons at a depth within the tissue. The improvement in thermal neutron flux can be estimated from diffusion theory on the conservative assumption that an epithermal neutron becomes an isotropic thermal neutron after one scattering event. Such calculations have been performed using the scattering cross sections of epithermal neutrons in hydrogenous material observed by Melkonian,[28] and the results are shown in Fig. 3. Neutrons with energy as low as 0.1 ev result in a marked improvement in thermal neutron distribution. The Monte Carlo calculation of Snyder and Neufield[26] for incident neutrons of higher energy shows even more pronounced improvement in thermal neutron distribution, although at these energies the fast neutrons produce a considerable radiation dose. It is interesting to note in Fig. 3 that the area under the

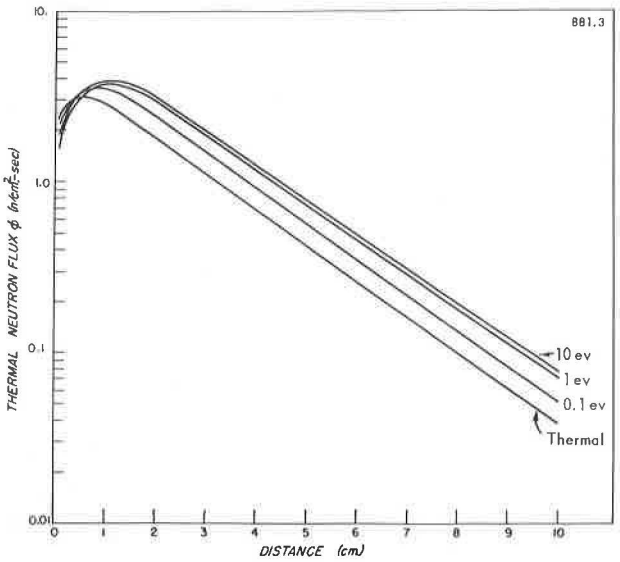

Figure 3. Thermal neutron distribution in tissue for incident neutrons of thermal, 0.1 ev, 1 ev, and 10 ev. Calculations based on a neutron current of 1 n/cm² sec incident on a large block of tissue-like material

thermal neutron distribution is greater for the case of incident epithermal neutrons. The total number of neutrons absorbed in the moderator per second, A, is:

$$A = \Sigma_a \int_0^\infty \phi \, dx \tag{8}$$

For an incident current of 1 n/cm² sec, this gives the fraction absorbed, and this quantity varies from 0.19 for incident thermal neutrons to 0.29 for incident 10-ev neutrons. The thermal neutron figure corresponds to the observed "albedo" or the fraction backscattered of 0.82 for thermal neutrons on a hydrogenous material. The net result is that a greater fraction of epithermal neutrons incident on a moderator is absorbed within the moderator.

A major problem in the use of epithermal neutrons is the production of sufficient intensities in this energy range. A study is planned in connection with the calibration period of the MIT reactor to investigate the flux distribution and other problems in neutron diffusion. A crystal spectrometer is to be used for neutron energy studies.

USE OF EPITHERMAL NEUTRON-CAPTURE PEAKS

The very large resonance cross sections exhibited by certain nuclides for neutrons above thermal energy suggests the possibility of their use in neutron capture therapy. The ideal situation would be to irradiate tissue containing the capture substance with neutrons of exactly the resonance energy. However, the possibility of obtaining sufficient neutrons in a small energy range is very remote, and a more likely possibility is the injection of neutrons of energy greater than the resonance energy. These neutrons might then be captured as their energy passes through the resonance peak. The probability of capture of a neutron in passing through a resonance peak in a hydrogenous material is given by the approximate expression:

$$P = \frac{\Sigma_a}{\Sigma_s + \Sigma_a} \frac{\Gamma}{E} \tag{9}$$

where E is the resonance energy and Γ is the width of the resonance peak. By increasing the concentration of the epithermal capture nuclide, Σ_a may be increased and the probability of capture increased. However, it is seen from Equation 9 that even with large values of Σ_a only a fraction Γ/E will be captured. The reason for this is that in hydrogenous materials the energy loss is not continuous but takes place in large discrete steps on collision with hydrogen nuclei. Below 10 Mev, the energy loss takes place by the process of elastic scattering. For hydrogen scattering, the probability of a neutron entering an energy interval at a lower energy is uniform for all energy intervals. Thus, the probability of a neutron with energy above the resonance peak entering the resonance peak through elastic scattering is Γ/E. Once a neutron has entered the resonance peak, its probability of capture rather than rescattering to a lower energy is given by $\Sigma_a/\Sigma_s + \Sigma_a$. The concentration at which 90% of the neutrons entering a resonance peak are captured is called the saturation concentration.

Table 3 lists 5 nuclides having large epithermal capture peaks with values of σ_a, saturation concentration, and Γ/E. The saturation concentrations are seen to be extremely large, ranging from 3 to 14% by weight. Concentration of this order of magnitude could only be achieved by local administration. Further, the values of Γ/E for peaks above 1 ev are small. The two nuclides Cd^{113} and Sm^{149} with low-lying resonances offer the most promise as these peaks extend into the thermal region and the values of Γ/E are relatively large. The cross sections for these peaks correspond predominantly (>90%) to neutron capture with subsequent γ-ray emission. In the case of Ag^{109}, In^{115}, and Au^{197}, the resultant nuclide is radioactive. The large saturation concentration of the nuclide, the emission of γ rays rather than particulate radiation, and the problems of achieving substantial epithermal neutron fluxes indicate the limited application of epithermal neutron capture.

BACKGROUND RADIATION

Any source and moderator of thermal neutrons will produce some extraneous radiation. The design criteria will be set primarily by the dose rate in normal tissue resulting from thermal neutron capture.

The calculations of Snyder and Neufield[26] may be used to estimate the limit to the fast neutron flux. From their calculations, an incident current of 2.5-Mev neutrons, typical of pile fast neutrons, incident on a tissue-like substance produce a maximum dose rate due to recoil nuclei of 3×10^{-7} rad/min. If 10 rad/min is considered the tolerance level, the permissible fast neutron flux would be about 3×10^7 n/cm² sec. Two factors modify these considerations; the dose from the fast neutrons will be distributed over a much

Table 3. Saturation Concentration of Various Nuclides Having Epithermal Neutron-capturing Peaks

Nuclide	*Normal abundance, per cent*	*Peak energy, ev*	*Peak σ_a, barns*	*Radiation*	*Saturation concentration, μg/g tissue*	*Γ/E*	*Comments*
Ag^{109}	48.65	5.12	24,700	γ	91,000	0.029	Ag^{110} has a 25 sec ½-life
Cd^{115}	12.26	0.18	65,200	γ	36,600	0.635	
In^{115}	95.77	1.46	30,000	γ	79,000	0.049	In^{116} has a 54 min ½-life
Sm^{149}	13.84	0.096	116,000	γ	25,500	0.677	
Au^{197}	100.	4.9	30,000	γ	135,000	0.025	Au^{198} has a 2.7 day ½-life

larger volume than that due to thermals, and fast neutrons have been reported to be particularly effective in producing skin destruction and cataracts. As a result, most design considerations are based on values much lower than 3×10^7 fast n/cm² sec. As tissue containing no capture substance will have a dose rate of about 50 rad/min in a flux of 10^{10} n/cm² sec, an added dose of 10 rad/min would have little effect. For most sources of thermal neutrons, the reduction of the γ-ray dose rate to this figure or below is comparatively simple. The dose rate due to fast neutrons is perhaps a more important consideration, particularly if epithermal neutrons are to be employed to improve the thermal neutron distribution.

RELATIVE BIOLOGICAL EFFECTIVENESS

The important question of the relative biological effectiveness, RBE, of the various radiations has not yet been discussed. Qualitatively the high RBE of α rays and other heavy charged particles would enhance the biological effect of the nitrogen protons and the capture reactions producing protons or alphas or those resulting in fission. However, the quantitative data on this point is far from complete. Boag[29] has reviewed the experimental data yielding RBE's and finds values ranging from 3 to 30 for the RBE of fast neutrons and α particles on lethality in mice and effects on particular organs. Tobias *et al.*,[6] found an RBE of 27 for fission fragments from U^{235}. However, recently Bond and others[30] at Brookhaven have observed values of RBE as low as 1.6 for B^{10} capture, 2.5 for the B^{10} α's alone, and 3.8 for thermal neutrons alone in the degree of spleen and thymus weight depression 3½ days after exposure. Although the importance of the RBE factor cannot be minimized, it seems fruitless at the present time to introduce detailed values into the previous dose considerations. Certainly a great deal more work is indicated in evaluating this important quantity.

CONCLUSIONS

Neutron capture therapy would appear to offer many of the advantages of both external and internal radiation therapy. For those reactions yielding protons, alpha's or fission fragments, biological concentrations on a cellular level may be employed for preferential irradiation. Those reactions yielding γ rays are not as promising but may have application. The use of epithermal capture peaks is the least promising approach.

The rapid attenuation of the thermal neutron flux is a major disadvantage of this technique, but this may be overcome by direct irradiation of the tumor tissue or by the use of incident epithermal neutrons to produce an enhanced thermal neutron distribution.

The concentration of many substances yielding energy absorption in excess of that resulting from normal tissue constituents appears to be in an attainable range. For B^{10} and Li^7 in therapy of brain neoplasms, usable concentrations have already been achieved.

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ADDENDUM

Dr. Albert Soloway of the Massachusetts General Hospital has been successful in preparing three boron compounds which show tumor to brain ratios in mice of 5 to 8:1 in comparison to 2 or 3:1 for borax. These compounds are triisopropanolamine borate, p-carboxyphonyl-boronic acid, and m-carboxyphenylboronic acid. These compounds appear promising in preliminary studies in man. Dr. Soloway is also studying boron compounds which might show antimetabolic or carcinostatic activity. He has also been successful in tritiating one of these compounds and Dr. Derek Gordon and Mr. William Ellett are carrying out radioautographic studies on its distribution.

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Recent Advances in Neutron Capture Therapy

By L. E. Farr, J. S. Robertson, E. E. Stickley, H. J. Bagnall, O. D. Easterday and W. Kahle*

Since the report given at Geneva in 1955 we have further developed theory, potential application and practice of neutron capture therapy. The literature and Brookhaven experience to a recent date have lately been summarized by Farr.[1] While neutron capture therapy still remains an unproved approach to control of malignant diseases, no evidence has yet been uncovered which is incompatible with such a goal. Physical principles are quite well understood but the physiological principles have been only partially outlined and remain in a state of flux. Therefore during the past two years we have endeavored to develop studies which will elucidate further the physiology of the systems concerned in this manipulation. In part for this reason we have limited our use of capture element to boron-10 but in part also because data we have obtained and as yet unpublished suggest we can control boron toxicity more satisfactorily. Other interested physicians have reported data obtained on patients with brain tumors in studies on partition of uranium injected intravenously.[2] No experimental data were obtained by them with subsequent neutron exposure nor have we. Also from the Massachusetts General Hospital group is a paper dealing with suitability of lithium based on calculations and certain assumptions.[3] Our own experience with lithium has not indicated any clear-cut superiority for this element over boron.[4] This is discussed in greater detail in another publication by Bond and Easterday soon to appear.[5] The very complicated systems studied under biological conditions make exact comparisons between various capture elements most difficult. Until the physiology and kinetics of these substances are better known, empirical approaches must be the basis of selection.

HYPOTHESES

A very brief review of the major hypotheses of neutron capture therapy as it has been developed at Brookhaven is provided by a quote from the first paper cited. "Neutron capture therapy is a therapeutic system so organized that by providing particles, e.g. neutrons, of low energy, penetration of a vital organ can be accomplished without significant tissue response to this component of the therapy. It must be pointed out that nervous tissue tolerance to thermal neutrons remains to be satisfactorily established. These neutrons pervade the space concerned fully, promptly, and in a predictable manner. Since neutrons can be measured fairly accurately, if the number entering the tissue volume be known, a reasonable approximation of distribution can be calculated from a limited number of measurements made under varying conditions. At the same time or immediately prior thereto it is also possible to load the neoplastic tissue of interest with a high cross section capture element, in this case boron, and this loading can be accomplished without significant toxicological risk.

"The interaction of thermal neutrons and boron-10 is accompanied by a very significant release of energy, 2.3 Mev divided between two heavy particles and 0.48 Mev gamma rays in 92% of the events. The total energy is transmitted entirely in 8% of the events together by the lithium 7 atoms and alpha particles which result from the disintegration of the boron atom after thermal neutron capture. The distribution of the particle energy is sharply limited to approximately the dimensions of a sphere some 14 μ in diameter or roughly just slightly larger than one red cell diameter. Therefore the destructive effects of the reaction are confined to cellular dimensions. By limiting the distribution either of thermal neutrons or of capture element atoms a type of specific localization can be accomplished. In practice up to this time it appears more satisfactory to restrict the region which may be exposed to neutrons thereby gaining risk advantages as well as selectivity and to circumscribe the local regional effects of the reaction by a knowledge of boron distribution. Free regional diffusion of neutrons has certain advantages in removing from the procedure geometric restrictions in relation to the tumor that otherwise would be very troublesome. By application of knowledge obtained, under ideal conditions not yet realized a differential effect to destroy neoplastic tissue and preserve normal tissue could be utilized selectively to eliminate the neoplasm."[1]

The present discussion will be limited to a very brief resume of the procedural variations used during the past two years; to the experimental verification of the principles used for biological selectivity of cellular structures; and to a review of data obtained by study of the patients actually receiving this therapeutic maneuver. In the clinical field, we are still applying the procedure only to glioblastoma multiforme although in a few instances other closely allied malignancies of the central nervous system were treated when longevity was not a point at issue. The results discussed

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in this communication were all obtained with the original large Brookhaven graphite air-cooled reactor of about 30 Mw thermal power.

PREVIOUS TREATMENTS

The first series of patients treated and previously reported[6,7] showed the possibility of using the procedure as well as demonstrating a number of practical difficulties. The second series of patients treated demonstrated that significant changes in neutron exposure might result in unexpected complications. It was this series at that time still uncompleted that was reported upon at the first Geneva Conference. End results have been tabulated in a later report by Farr.[8] Subsequently, we have begun treatment of a third series of patients to develop and utilize procedures which will prevent, eliminate or circumvent the complications which were too often incident to the procedure used in the second series of patients. The most serious and vexing of these complications was the development of a spreading necrosis of the skin not limited to the area immediately confronting the port of the facility and which was indolent in its genesis with a complete failure to heal, though a tough eschar provided a protective coating satisfactory for many practical purposes. The mechanisms producing this vexing complication were at first unresolved but during the course of time between treatment of patients in series two and three a fairly complete understanding evolved from extensive animal and instrumental experimentation. Despite this complication the average longevity of the patients treated in series two was greater than that in series one. In every instance efforts were made to keep the groups comparable. In series two nearly all patients had their neoplasm in the non-dominant hemisphere but otherwise no general selection factors operate that were not used in series one except to be more certain that a highly invasive neoplastic lesion was involved.

A comparison of results between series one and series two shows that average survival beyond the treatment date for series two was 186 days as compared to 108 days for series one. The true significance of these data lies in negative qualities rather than in positive affirmations. These data strongly indicate that by increasing the boron dosage administered from 26 to 42 mg/kg no significant adverse clinical effects resulted. Since originally the dose of 26 mg/kg was believed close to the maximum tolerance dose of human beings the significance of this increase without adversity is large. This was accomplished by administration of glucose in a boron-glucose molar ratio of 2:1.[9] Subsequently it will be noted significant increases even in this very large dose are possible. Secondly, it will be noted that the average number of thermal neutrons applied to the skin surface (and therefore an important parameter of the total tissue exposure) was increased in the second series by 50% and reached a thermal neutron exposure alone approximating an LD_{50} value for whole body exposure of mice. Each of these factors alone might have been expected to cause an adverse effect on normally functioning structures yet such it appears was not the case. While one must be very cautious in interpreting the increase in average longevity from 108 to 186 days as an affirmation of effectiveness of the therapeutic procedure, one can with emphasis point out that under the conditions of treatment no adverse effects were seen in series two as compared with series one. Since the selection of patients was more rigid in series two than in series one, it can be said that the results are significant also as indicating a position one step closer toward the beginning of effective therapy.

In both series one and series two, the boron was administered as sodium tetraborate or borax and was administered intravenously in the ante cubital vein and over an interval of less than one minute. Thereafter no fluid administration was given to the patient until subsequent to the neutron exposure and then only if after several hours there had been a failure to take fluids orally.

SPECIAL STUDIES

Easterday at Brookhaven showed with mice that a new empirically derived compound of boron, sodium pentaborate, $Na_2B_{10}O_{16}$, had markedly lessened toxicity and therefore in terms of boron given could be safely administered to animals in doses over 135% larger than could be done with the tetraborate compound. Therefore in designing procedures for series three, since we could not at this time increase the neutron exposure within the time limitations imposed, we made every effort to increase the boron dosage. The development of the pentaborate compound was one step in this direction.

During the interim between series two and series three, a number of animal experiments carried out by members of the Brookhaven Medical Department and designed primarily as extension of studies on relative biological effectiveness of energetic particle radiation had conclusively shown for the first time that the baffling skin complication could be entirely due to the capture reaction occurring in the skin.[10] Subsequently studies carried out on a patient with serial skin biopsies showed that in human beings as in animals the rate of accumulation in skin while still very rapid was slower than in neoplastic tissues. Partly for this reason and partly to achieve a very much higher perfusion concentration than toxicological effects permit in the systemic circulation, it was decided that for series three the administration of sodium pentaborate would be through a catheter inserted into the internal carotid artery in the same side of the head as the tumor. Further, it was decided to expose the tumor to neutrons while perfusion was still taking place so that a maximum loading of neoplastic tissue could be achieved and maintained. To do this, it was necessary to design and construct infusion equipment incorporating remote control which pumps into the vascular system a solution of desired composition while varying at will

the rate of administration by manipulation of the central consol. Further it permits perfusion with either of two solutions as desired or needed. The interim report here will be amplified in more detail elsewhere.[11]

LIMITATIONS

Before progressing to a discussion of this procedure it would be well to review limitations with the equipment at hand on the basis of our present theoretical concepts. It became increasingly apparent as we studied material to be discussed later and as we evaluated animal data that the present facility at the large Brookhaven graphite air-cooled reactor was incapable of providing the very high flux of thermal neutrons necessary for complete destruction of the neoplastic cells. The marked attenuation of neutron flux as it penetrated tissue resulted in a very sharp decrease in thermal neutrons. Estimates suggested that beyond a depth of 3 to 4 cm, this had decreased to an extent that would be inadequate therapeutically. The animal tumor experiments were designed to determine what boron dosage was necessary to render a transplantable tumor non-viable when total neutron exposure approximated $10^{12}/cm^2$. Because of the accumulation of boron in the skin of patients it was necessary to limit the time of exposure to a maximum of eleven to twelve minutes after beginning the boron infusion. Within this period using the large graphite reactor the total neutron exposure of the tumor could not even closely approximate the indicated requirement on the basis of our animal work.

There was another weighty consideration which also resulted in an alteration of procedure from that previously followed. It is desirable to obtain maximum concentration of capture element in the neoplasm as rapidly as possible. From data at hand it may be surmised that the movement of the boron from the vascular spaces to tissue water occurs with almost unbelievable rapidity in certain tissues notably the tumor. Therefore a large concentration advantage might be obtained by increasing concentrations of boron in the blood perfusing the neoplasm. However, the total dose must be held within tolerable limits and this can be accomplished best by injecting the boron containing solution into the arterial system feeding the tumor. In practice this was approximated by catheterization of the internal carotid artery on the same side as the tumor and then with a statistical estimate of cerebral blood flow, adjusting the rate of injection of boron solution so that the perfusate mixture has the desired boron concentration and yet within the total injection time will not exceed the allowable dose of boron. Fortunately by the use of fluorescein and ultra violet light it is easy to check on the placement of the catheter.

Using this test for placement, a solution of glucose could be injected slowly until time for treatment when first the rate of injection could be adjusted to the desired minute volume followed by a switch from glucose to the appropriate boron containing solution. The design and development of the device permitting distant control of rate of injection and transfer from one solution to another together with heaters and jackets for maintaining the solution at the proper temperature made this procedure possible. Because of the previous frequency of harassing skin complications, patients in the current series were selected for treatment initially only when believed to be near terminal status although the latest patients were treated in an earlier state. This was done, however, only after gaining confidence in the safety of the procedure. It must be emphasized that the third series of patients were treated to evaluate procedural changes alone and therefore cannot properly be compared with the patients of series one and two for longevity following treatment. The time of critical saturation of skin with capture element could be finally determined in patients only by observation of a skin complication or its avoidance. Accordingly, such a series of observations was set up and it was quickly ascertained that if a ten minute injection period was used to perfuse the neoplasm that exposure during the final nine of these ten minutes plus one or two additional minutes resulted in no skin lesions but that exposure beyond fifteen and to twenty minutes resulted in skin lesions. Therefore, it was decided that in the remainder of the patients the procedure would be in general to infuse with boron solution for a total period of ten minutes. This infusion was started one minute before beginning neutron exposure which would be limited to a ten minute interval at the maximum flux obtainable.

RESULTS OF THERAPY

Through March 1957 a total of nine patients was serially treated by intra carotid infusion of a glucose-borate solution over a ten minute interval coexistant with a thermal neutron exposure of the head. All nine patients had previously been operated upon so that diagnosis could be confirmed by biopsy or operative excision of part of the neoplasm. Three patients had received X-ray therapy following their operation and prior to neutron irradiation. The facility for neutron exposure was that previously used for series two. The neutron flux averaged 0.8×10^9 thermal neutrons per cm^2/sec. A 10×10 cm port was used in all. Through a technical failure one additional patient received no boron injection but did receive a full neutron exposure.

The results from this series of patients show that by limiting the neutron exposure to ten minutes under the conditions described the skin complications can be eliminated. Further, internal carotid infusion of a boron-glucose mixture in a molar ratio of 2:1 can be safely carried out at rates of injection from 179 up to 407 mg of boron per minute or 1026 to 2328.5 mg of sodium pentaborate (Table 1). When the new Brookhaven Medical Research Reactor comes into operation, it will be possible to introduce an adequate charge of thermal neutrons in much less than half the present exposure time. No adverse, neurological or systemic effects were noted in the patients which clearly resulted from the procedure itself. We believe that some

Table 1. General Data Relating to Patients Treated with Neutron Capture Therapy

Series	Boron-10 dose		Thermal neutrons exposure per treatment $\times 10^{12}/cm^2$	Minutes exposure time per treatment	Days survival time after first treatments
	Mg/kg body weight	Mg/treatment			
Average	25	2060	1.03	35	108
Median	26	2020	0.93	35	97
Range[a]	16–43	1470–2120	0.44–1.93	17–40	43–185
Average	42	2630	3.30	20	186
Median	42	2520	3.38	20	147
Range[b]	32–50	1960–3380	2.34–3.84	17–21	93–337
Average	48	3000	0.80	10	97[d]
Median	50	3030	0.72	10	96[d]
Range[c]	25–60	1830–4050	0.39–1.5	6–20	29–158[d]

[a] Ten patients treated in this series through a 10 × 5 cm port. Five patients received multiple treatments to a maximum of 4. One patient developed skin lesion.
[b] Nine patients treated in this series through a 10 × 10 cm port. Two patients each received two treatments. All nine patients developed skin lesions.
[c] Thus far nine patients treated in this series through a 10 × 10 cm port. One patient received two neutron exposures but only one treatment. Skin lesion developed only in patient receiving 20 minute exposure.
[d] One patient still alive at time of compilation 1 April 1958. Days survival times are not comparable with Series 1 and 2 since in Series 3 only late terminal phase patients were initially selected.

retardation in neoplastic growth was obtained in most instances excepting the case in which for technical reasons boron administration failed. It is noteworthy that no complications were seen in the three patients who had received X-ray therapy following the operative procedure and prior to neutron capture therapy. Specimens obtained from seven patients at autopsy are now being suitably prepared for histological study of whole brain sections for later evaluation.

OTHER ANIMAL STUDIES

At the time these clinical, physical and pharmacological studies were being carried out we were endeavoring experimentally to determine the conditions of neutron exposure and boron concentration necessary to render a highly invasive, transplantable animal tumor not viable. In this instance a methyl-cholanthrene induced tumor of the central nervous system was used which for eight years had been transplanted serially in mice by intracerebral inoculation. This tumor is highly invasive and while its cell type originally suggested a glioblastoma multiforme, it is now more compatible with a spindle cell sarcoma. Since we are interested in it for its invasiveness rather than its cell type, it continues to serve admirably for certain test purposes. Tumor bearing mice were used to determine parameters of exposure to neutrons and boron under conditions approximating whenever possible those obtaining with patient therapy. These experimental results are to be presented in detail elsewhere.[12] However, a brief summary of the findings can be discussed here.

The data summarized in Table 2 suggest that a thermal neutron exposure of 10^{12} neutrons per square centimeter must be closely approximated with boron dosages used to obtain effective results. This is on the basis of the test system used which requires ten

Table 2. Effectiveness of Selected Boron Dosages and Neutron Exposures on Viability of a Test Neoplasm of the Central Nervous System by Transplant Trials. Each Test Neoplasm Transplanted to Ten Host Animals for Viability Trial

Mice with neoplasm treated	Boron-10 dose[a] mg/kg	Incident thermal neutrons per treatment $\times 10^{12}/cm^2$	Ratio of tumors killed to tumors treated	Tumors killed (%)	Ratio of tumor transplants taking to transplants made (all tumors treated)	Take transplants (%)	Ratio transplants taking to transplants made (viable tumors only[b])	Take transplants (%)
20	—	0.87	0/20	0	188/195	95	188/198	95
16	—	0.13	0/16	0	154/160	96	154/160	96
10	150	—	0/10	0	96/100	96	96/100	96
10	175	—	0/10	0	98/100	98	98/100	98
11	200	—	0/11	0	101/110	92	101/110	92
13	150	1.3	7/13	54	16/130	12	16/60	26
12	175	1.3	3/12	25	23/120	19	23/90	26
16	200	1.3	6/16	37	24/158	15	24/98	24
9	150	0.87	1/9	11	17/90	19	17/80	21
10	175	0.87	0/10	0	61/100	61	61/100	61
10	200	0.87	1/10	10	31/100	31	31/90	33

[a] Boron dose rapidly injected intravenously. Calculated on basis of observed body weight.
[b] These data obtained by removing transplant trials of non-viable tested tumors after performance. Data show reduced take ratio in viable test specimens.

transplants from each tumor for effect valuation. Only when none of the transplants is viable is the tumor assumed to be "killed."

SURVEY

A combined topographical and histopathological survey of brains in which neutron capture therapy had been administered for glioblastoma multiforme is currently being continued and extended. Observations to date will be summarized and detailed reports will be forthcoming.[13–15] We believe that the project requires the entire brain to be studied in a fashion such that all spatial relationships can be clearly visualized. Dr. Yakovlev† provides the laboratory and supervises the procedures utilizing coronal, horizontal or sagittal sections cut from whole brain blocks previously embedded in celloidin. A variety of stains are utilized to demonstrate specific cellular and tissue structures. Such a technique offers three principal advantages, namely (1) an opportunity to compare host to neoplasm relationships in nonirradiated as well as irradiated cases thereby increasing our knowledge of the natural history of the disease; (2) an opportunity to establish the effects of radiation or lack of them on the neoplasm; (3) an opportunity to establish the effects of neutron capture procedures on the entire remainder of the brain with particular reference to the nuclei and tracts.

The evaluation of material so prepared is difficult to make because of several cogent reasons. As a basis for comparison of any alterations due to irradiation of the neoplasm, it would be desirable to use already catalogued, detailed histologic features of a progressively growing glioblastoma or of any transient regressive changes, and the impact of such a neoplasm upon surrounding structures. Unfortunately, no reported study available to us or brought to our attention has been developed in such fashion that these questions can be answered and in the study for the design of the present project it became very clear that unless the whole brain section technique were used the results probably would be equivocal. The effects on histological findings of possible additional events occurring, as an operative procedure or, for example, a significant period of anoxia, must be kept in mind. Perhaps even more difficult to establish are the criteria for recognition of effects direct and indirect, immediate and delayed, from any form of irradiation.

Pertinent to this present study in regard to the last point is the need to determine if irradiation effects do occur, what the sequence of events might be and whether any evidence exists of nonhomogeneity of distribution of target element within specific cell types or structures particularly those not involved by the neoplasm such as specific nuclei or fiber tracts. The need for this is demonstrated by keeping in mind observations which have, at least in part, been established.[16–24]

The neuropathological and topographical survey on sixteen cases of glioblastoma multiforme in series one and series two treated with neutron capture therapy and studied topographically by the whole brain section method is proceeding with assistance from and consultation with Dr. Yakovlev on neuroanatomy and Dr. Haymaker‡ on the neuropathology. In the neoplasm and possibly in immediately adjacent areas, but not elsewhere in hemispheres, nuclei or tracts, certain vascular changes were noted that are compatible with the established criteria for minimum irradiation effects on central nervous system tissue. In addition, giant cell formation in excess of expectations may again suggest the procedure as a causative mechanism. In some tumor regions intense and widespread necrosis is found and may be more than that which might be expected to occur spontaneously. These changes are correlated with those regions of the tumor receiving a maximum neutron exposure. No specific changes were noted in non-neoplastic tissues or in the contra lateral normal hemisphere which could be charged to the therapeutic procedure tested. While numerous changes have been noted in normal structures in these specimens, comparisons made and being extended in specimens from untreated patients show that the neoplasm itself may have profound architectural effects of this type. As previously noted this material will be published in detail with photomicrographs showing the tissues on which the statements are based.[13–15]

SUMMARY

This discussion may be summarized as follows: (1) intracarotid administration of a boron salt can safely be carried out for neutron capture therapy; (2) when the intracarotid injection route is used, no radiation skin lesion develops when boron dosage is given within a ten minute interval and neutron exposure does not extend over a time more than twelve minutes after beginning boron administration by the procedure previously noted;[1] (3) data have been obtained on the kinetics of boron distribution in human skin; (4) results are summarized to date on treatment of nine terminal patients treated in the above manner; (5) animal experiments with a transplantable invasive tumor show that an exposure of approximately 10^{12} thermal neutrons per cm^2 and a boron dose of 150 mg/kg body weight resulted in a reduction of tumor viability by transplant test from *circa* 95 to 46%.

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Record of Proceedings of Session D-18

Use of Isotopes in Medicine, Part II

WEDNESDAY AFTERNOON, 10 SEPTEMBER 1958

Chairman: Mr. M. Roche (Venezuela)

Vice-Chairman: Mr. S. M. Lee (China)

Scientific Secretaries: Messrs. C. Garavaglia and G. Strelin

PROGRAMME

P/2056 Clinical applications of radioisotopes.....A. V. Kozlova

Discussion

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Discussion

The Chairman: I hereby declare open the session on the uses of isotopes in medicine. Although isotopes have not completely solved the problem of cancer, they have undoubtedly made a very great contribution to its treatment.

Some isotopes, such as iodine-131, act on cancer through physiological localization; others, such as collodial radioactive gold, can be implanted in the site of the cancer by mechanical means; still others are high energy emitters—the last category includes radioactive cobalt and cesium, which can be used for the external treatment of cancer and which have the added advantage of being relatively cheap.

Lastly, it will be extremely interesting to hear of the progress that has been made in the technique of neutron capture. This, as you know, is based on the

use of boron which has a very high cross section and is taken up preferentially by cerebral tumor tissue.

But I think I should make way for the speakers who are to present papers. I therefore call upon Dr. Kozlova, who is to speak on the "Application of Radioisotopes in Clinics for Diagnosis and Treatment."

DISCUSSION OF P/2056

Mr. G. L. BROWNELL (USA): Mme Kozlova, the question of biological effects of tracer doses is one of great importance. Could you indicate the level of tracer doses used for thyroid uptake and other diagnostic tests in the USSR?

Mrs. A. V. KOZLOVA (USSR): We use a dose of 1 or 2 microcuries of radioactive iodine for the diagnosis of thyroid disease.

Mr. J. C. F. MACDONALD (Canada): May we know the dosage levels used in the treatment of malignant melanoma by gold-198, and the activity per cubic millimetre of the colloid?

Mrs. KOZLOVA (USSR): We used a solution with a specific activity of 2 to 5 millicuries, and in treating small tumours we introduced 1.5 to 2 millicuries per cubic centimetre of the tumour. In the case of large tumours we reduced the dose to 1.5 millicuries per cubic centimetre.

DISCUSSION OF P/2403, P/579, P/67

Mr. K. E. HALNAN (UK): This question is addressed to all three speakers. If there were no difficulties of cost or availability of cobalt-60, cesium-137, or other isotopes, which would you choose for teletherapy, and why?

Mr. M. BRUCER (USA): Without respect to any consideration of cost, as was specified in the statement, I would choose cesium-137, primarily because it is supervoltage therapy for everybody except Dr. Paterson, and also because there is so much less shielding necessary.

Mr. J. BAARLI (Norway): Well, if you are to choose between cesium-137 and cobalt-60, you have to know what you are going to use the radiation for. If I were going to choose, I should choose cobalt-60 for the treatment of cancer located deeper in the organism and cesium-137 for cancer located closer to the skin. The reason for this is as follows: if you compare the physical properties of cesium-137 with those of cobalt-60, you find that for cobalt-60 you get a very high specific activity, and accordingly a very small source of penumbra and a well-defined beam. With cesium-137 you will find the source quite big and you will have a very large penumbra, which complicates things.

If you compare with X rays, you will find cobalt-60 favoured for use in deep therapy and cesium-137 for cancer located closer to the skin surface.

Mr. R. PATERSON (UK): I see I have trailed my coat with some effect with Dr. Brucer, intentionally. My whole paper was meant to be an answer to that question, even to making the points that cobalt-60 is so superior and that economics—in view of the fact that we are dealing with human lives—do not enter into the argument. Stating the reasons why cobalt-60 and cesium are different would involve a detailed argument, but basically cesium lacks the quality of penetration; it lacks a comparable force. As far as close distance therapy is concerned, I had intended my paper to answer that point, indicating that the wedge plan had superceded the need for the short distance plans.

Mr. J. MEWISSEN (Belgium): Dr. Paterson, differential absorption in various tissues is practically equivalent at voltage levels of cobalt-60 and cesium-137. What is the main advantage of cobalt-60 over cesium-137 as far as super voltage is concerned?

Mr. PATERSON (UK): I had reversed the statement that the main advantage lies in cobalt. I do not think that, as far as the bone is concerned, the superiority is very large; it is somewhat better.

Mr. G. R. NEWBERY (UK): Could Dr. Paterson say what is the importance of the large zone of tissue raised to 50%–75% tumour dose in the three-field technique, particularly from the point of view of fibrosis?

Mr. PATERSON (UK): There is no question of fibrosis involved. The fundamental principle is that we want to irradiate the block of tissue of our choice, and then as little additional tissue as possible. That technique which gives you minimal additional necessary radiation raises your ability to irradiate tumours and raises your cure rate.

Mr. M. WEINBREN (Union of South Africa): I understood Dr. Paterson to say that he did expect improved cure rates. All other speakers have the general opinion that the improved cure rates are not to be expected. In what regions does Dr. Paterson expect the improved cure rates? One always expects better cure rates in deep seated tumours, but the reports of his results indicate that his 4 Mev linear accelerator has not given any improved cure rates in the oesophagus, nor has the 8 Mev linear accelerator at the Postgraduate Hospital in London given any better results. In what regions, then, are we to expect improved cure rates?

Mr. PATERSON (UK): The main fields in which we should expect them—and I think the indications are already clear that we shall get them—are those fields in which the figures for cure were previously high, such as tumours of the mouth and the fairly superficial ones I mentioned. All the deep seated tumours, such as tumour of the bladder, for example, are almost certainly going to be much more quickly cured. Publications to that effect already exist. The trouble at the moment is that, with the need to wait for five-year results, no final results can come out for a few years. Unpublished results from centres with which we have contact make it quite clear that the provisional results, in one or two years, are going to show improvement.

In Manchester we have experiments under way which in three or four years' time will give us an answer that is irrefutable.

DISCUSSION OF P/874, P/68, P/973, P/234

Mr. K. E. SCHEER (Fed. Rep. of Germany): Dr. Harper, do you consider histologically complete destruction of the gland to be essential for a therapeutic effect? Secondly, what mechanism do you consider to be the cause of rhinorrhoea?

Mr. P. V. HARPER (USA): The reason for rhinorrhoea I presume to be the holes we punch in the anterior wall of the sella turcica and which heal with difficulty in the presence of a high radiation field, as was suggested by Dr. Ellis. Whether or not complete destruction of the gland is essential, I think it probably is not, as demonstrated by our colleagues who have been using gamma radiation. They have shown microscopic sections in which there was still recognizable pituitary tissue left. However, we think it makes a better experiment to destroy the gland completely, and I think we must still consider the work as in the stage of experimentation.

Mrs. P. CAMBEL (Turkey): This question is directed to both Dr. Harper and Dr. Ellis. Have differential counts of hypophyseal cells (eosinophil, basophil) been made as well as Golgi apparatus preparations which would permit differential counts of chromophobe mother cells? If so, how were these related to the clinical picture of post-hypophysectomy?

Mr. HARPER (USA): These were not done in our case, I am afraid.

Mr. F. ELLIS (UK): They were not done in our case either.

Mr. FITTING (Fed. Rep. of Germany): My question is also addressed to both Dr. Harper and Dr. Ellis. Have you had any experience with the therapeutic effect of isotope irradiation of the hypophysis in patients with malignant progressive exophthalmos? Dr. Harper has not, I see.

Mr. ELLIS (UK): We do not use this method for a relatively benign condition which we know is easily treatable by conventional X rays.

Mr. ELLIS (UK): Dr. Scheer, have you any evidence that all parts of the bladder wall are in contact with the cobalt beads used for treating bladder carcinoma?

Mr. SCHEER (Fed. Rep. of Germany): Yes, I think so. After the insertion of a chain of beads, a catheter is put in to drain the urine and we make one or more X-ray pictures afterwards. We may also inject diluted contrast matter directly into the bladder, and we are convinced that in most cases a good contact between the bladder wall and the beads is obtained for the bladder as a whole.

Mr. M. TUBIANA (France): Dr. Harper, do you consider that the hypophysis occupies the whole of the sella turcica?

Mr. HARPER (USA): We are forced to assume that it occupies the whole of the sella turcica as this is our only landmark.

Mr. ELLIS (UK): I think that the sella turcica usually is not completely occupied by the pituitary gland; it is mostly low down and rather anteriorly rather than up above posteriorly.

Mr. ELLIS (UK): I would like to congratulate Dr. Muller on his good results and also ask the following questions. First, how much fluid do you use to produce the artificial hydroperitoneum in cases of ascites?

Mr. J. M. MULLER (Switzerland): First, so far as the results are concerned, I would like to add that in the previous series with the gold, we had about 60 per cent cures in Stage I with the same therapies. There were many other results, as for instance, those of the First Clinic of Vienna, where the result was 47 per cent instead of the 100 per cent we now obtain. For production of the artificial hydroperitoneum, I found an average of 350 to 450 millilitres of the physiological saline to be enough and to be quite right.

Mr. ELLIS (UK): What dose is received at the paraortic glands from the gamma radiation of the gold in such cases?

Mr. MULLER (Switzerland): There are two components, one of which is the emission from the lymph node itself which collects the gold and the other is from the sphere (assuming it is a sphere) of the whole abdomen. The sphere of the abdomen, assuming it is a sphere, would be about 500 rad of gamma on this superficial structure, and from the node itself it is likely that you would have about 2000 roentgens more gamma, since we have an average of 4 to 6, or 10,000 rad of beta.

Mr. M. WEINBREN (Union of South Africa): Dr. Muller, is the gold introduced at operation and, if not, at what period post-operatively?

Mr. MULLER (Switzerland): This is an important question. From experience I do not advocate the use of the gold immediately after operation by implanting polythene tubes before closing the abdomen. Since ovarian cancer patients are very often badly shocked and ill, we allow them to recover for at least two to three weeks and then start with roentgen therapy first in order to avoid any late-operative complication and also to get the patient used to radiation. When the patient has received a depth dose of about 1000 roentgens within the pelvis we perform the radiogold operation by means of parasynthesis and we introduce the polythene tubing about 10 centimetres deep in the abdomen and start with the production of the artificial hydroperitoneum. When the fluid drips evenly with very small gravity pressure one is very sure to be free of the peritoneal cavity.

Mr. BATEMAN: Perhaps Dr. Muller could comment on the incidence of abdominal fibrosis following intracavitary colloidal gold.

Mr. MULLER (Switzerland): We have not observed abdominal fibrosis after radiogold treatment when it

is properly done. One of our young men prepared his thesis on the fifty-one cases I mentioned and studied all the aspects of treatment. We have only one case in which unquestionably the gold could be held responsible for the production of fibrosis.

The CHAIRMAN: Now there is a question to Dr. Ellis and Dr. Harper from Dr. Venanzi of Venezuela, who has himself shown that inorganic phosphorus of the serum is frequently elevated in cancer patients—an effect which is found also by growth hormone and acromegaly. He would be interested to know if either of the authors have measured serum inorganic phosphorus, and, if so, what is the effect of hypophysectomy upon this matter? Dr. Ellis indicates that he has not done this, nor has Dr. Harper.

DISCUSSION OF P/881

The CHAIRMAN: I wonder if I could ask a minor question of Dr. Brownell? I am not sure I interpret rightly the studies of Dr. Farr, but I believe he has shown that there is no such thing as a blood–brain barrier in the case of borax. In other words, what happens is that borax penetrates the tumour at a much faster rate than it does the brain, but eventually both concentrations become equal, and if you put neutrons in at the right moment you will have a much higher concentration of radiation in the tumour tissue. Is that a correct description?

Mr. G. L. BROWNELL (USA): Yes, I believe that is correct. Borax differs from most of the radioisotopes we have studied in brain tumour tissue. It is for this reason that we feel that virtually any compound would be preferable to borax; certainly some compounds appear to be preferable.

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