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OAK RIDGE INSTITUTE OF NUCLEAR STUDIES PERIODIC PROGRESS REPORTS OF THE MEDICAL DIVISION JUNE 1950 - DECEMBER 1954 MIDYEAR JULY 1 - DECEMBER 1958

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INSTITUTE OF NUCLEAR STUDIES

Medical Division.

Progress Report

of the

Medical Division

June 1, 1950 - June 1, 1951

Operating Under Contract
with the
UNITED STATES ATOMIC ENERGY COMMISSION

P. O. Box 117
Oak Ridge, Tennessee

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HISTORICAL STATEMENT

In March of 1948, the Atomic Energy Commission requested the Oak Ridge Institute of Nuclear Studies to call together representatives from the Southern Medical Schools to organize a clinical research program in Oak Ridge. A Medical Advisory Panel (formerly known as the Board of Medical Consultants) was elected by the Board of Directors from nominations submitted to it by this group and during the year of 1948 developed the basic plan of a Medical Division of the Institute. During 1949 and early 1950 the medical program consisted primarily of the development of facilities. A hospital and accompanying laboratories were designed and constructed. A research and medical staff, nursing staff, technicians, and shops were brought together and set into operation. In May 1950, somewhat before completion of the facilities, the first patient was admitted to the hospital. Preliminary animal testing had been under way for some time. The present report covers the period from June 1, 1950 to June 1, 1951.*

I. GENERAL PROGRAM DIRECTIVE

The Medical Division has been directed to make use of the special facilities of Oak Ridge as they relate to the study and therapy of neoplasms and allied diseases using radioactive materials and radiation in the fields of clinical medicine. Without permanently fixed limitations, the program has concentrated on the following matter:

1. A study of the therapy of neoplastic and allied diseases using radioisotopes and newer methods of applying radiation.

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* Because this is an activities report to participating medical schools only Institute activities are mentioned. Space prohibits the detailed acknowledgement of ideas and help received from outside sources.

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2. The study and development of processes and procedures involving radioisotopes which can be done outside of AEC facilities only with diffi or which are not being done elsewhere.

3. Special methods of measurement and safe handling of radioisotope in hospital-type operations.

4. Providing of facilities for clinical training in the use of radioisotopes.

5. Assistance in making the facilities of Oak Ridge available to participating medical schools.

II. MEDICAL STAFF ARRANGEMENTS

Close relations have been developed with the participating medical schools. On the recommendation of the Medical Advisory Panel, and with the assistance of the University Relations Division, a plan has been devel which allows members of the faculty and residents from these schools to jo the staff of the Institute for work in the general field of isotope therap Here they can carry out special problems which for various reasons cannot b investigated in their own laboratories. This is essentially a response to a demand from the Institute's member institutions.

1. The Permanent Staff of the Medical Division

The total staff of the Medical Division has changed as the program has been built up. At the present time, there are 16 persons on the scientist level, three on a half-time basis, and two on a one-third time basis. Six members are on the senior full-time staff and five members on the junior staff. There are currently five full-time permanent employees on the technician level and one Oak Ridge Hospital employee who is supervised by the

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Medical Division and does work for both the Oak Ridge Hospital and the Medical Division. There have been five trainees on the technician level, usually for periods of three to five months. The seven research participants and twenty-four resident physicians have been present for periods ranging from three months to seven months. There are presently eight administrative workers. The current nursing staff consists of nineteen nurses and aides, maids, and orderlies, but this number fluctuates with the patient census. The technicians and administrative people have been asked to do a large amount of overtime work in order to keep up with the accumulation of work.

2. The Medical Consultant Program

One of the methods of strengthening close relationships with the Medical Schools and of implementing the flow of patients to the Medical Division is through the appointment of consultants. Most have visited Oak Ridge at least once; some have taken a very active part. This list of consultants has a slow but steady turnover as the staffs of the medical schools change. The current list is shown in Appendix 1.

Each of the consultants is under a contract with the Institute which allows payment of travel expenses. No fee is included. Each is encouraged to visit the Medical Division at least once for inspection of the facilities of Oak Ridge and to get a better idea of the types of patient problems being studied. In a number of patients very extensive thoracic surgery was indicated and surgeons from the consultant list were called in to perform the operations. On some occasions there have been anesthesia, EENT, genito-urinary, and other problems which were taken care of by consultants who performed much of the work. Operations have been performed at the medical schools by consultants primarily to fit the patient for a specific problem of therapy in Oak Ridge. Much of the follow-up work has been done at the medical schools and reported to the Medical Division staff.

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3 The Resident Physician Program

Another method of integrating the medical schools with the Oak Ridge Program which follows the directive to provide clinical training in the use of radioisotopes is the acceptance of residents on a three or four month basis. It was decided that five residents was the ideal size staff, although as many as 12 physicians have been on the resident staff at one time. The training and field of interest of the individual resident determine his activities in Oak Ridge. For example, one of the surgical residents became interested in the biological distribution of hafnium. He began rat distribution studies and is continuing this work at his medical school. Another surgical resident was interested in the deposition of colloidal radiogold following intra-arterial injection. Both of these studies have been published. Another resident in genito-urinary surgery was interested chiefly in the clinical side of the program and development of autoradiographic methods within his own field. Another undertook a problem in sulfur metabolism and another studied the incorporation of radiophosphorus in nucleoprotein of lymphosarcoma. Other subjects studied were: the deposition of radioindium, the toxicity of colloidal gold, beta radiation from ruthenium plaques, external calibration and detection of radiation. On the other hand, some of the residents have spent most of their time working on clinical problems with patients. Whenever their interests fitted into the studies already under way within the Medical Division, residents were taken into full collaboration.

4 The USAF Resident Program

With the recent expansion of the Armed Forces the supply of residents decreased. Offsetting this, a cooperative program with the Air Surgeon's Office was instituted. Air Force medical officers can serve on temporary duty with the Medical Division for four months to become familiar with isotope

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and radiation problems. The training period was organized somewhat differently from the activities developed for the residents of the medical schools. Each Air Force resident spends (a) one month taking the basic course in radioisotope techniques given by the Special Training Division; (b) approximately two weeks in routine health physics; (c) two weeks in survey and radioassay work on human tissues; (d) approximately one month in purely clinical study of patients undergoing both internal and external radiation therapy; (e) approximately one month personally handling various isotopes in minor experiments on animals. The program involving experimental work in animals was not necessarily planned to yield publishable results but rather is devised to give experience in handling radicisotopes, assaying tissues, calculating dosages, and applying the principles of radiation protection.

Thus far eleven Air Force residents have participated. Although this program takes up more time of the staff than was first contemplated, it has more than paid for itself in the assistance these residents have been in clinical work. For example, most of the biopsy studies and minor surgical procedures performed during the past quarter have been done by Air Force residents. A major portion of the routine roentgenographic surveys, many of the admission examinations and work-ups have been done by Air Force residents. The minor problems which have been set up primarily for training purposes have added to the data being collected on toxicity of radiogold and radiohafnium.

5. Medical School Staff Participation

In keeping with point 5 of the program outline, viz., to make the facilities of Oak Ridge available to the medical schools, a staff participation program has been developed which has proven very useful. With cooperation of the University Relations Division, staff members of the medical schools are appointed

as Oak Ridge Research Participants and assigned to the Medical Division. The first of these was Dr. John Wood, University of Tennessee, Department of Biochemistry, who spent the summer of 1950 with the Medical Division. During his stay he worked out a bio-synthesis of sulfur-labeled yeast proteins and amino acids. In addition to his animal work, his preparation was used in one patient to study the metabolism of organically bound sulfur by tumor cells. A paper on the methods in this study is in publication.

Dr. Robert S. Ingols of Georgia Institute of Technology worked six months on the problem of evaluating radioactive and stable gallium toxicity using Warburg tissue respiration techniques. A number of reports have been given and are in preparation for publication.

Dr. Betty M. Cooper, University of Texas, Anesthesiology Department, spent four months during the summer of 1950 modifying a clinical method for the assay of stable gallium in tissues with relation to the question of gallium toxicity. The surprising hypersensitivity of dogs to gallium was first recognized in her work and led to a modification of the procedures followed in patients. Dr. Cooper has since rejoined the Medical Division staff and will continue the same work.

Dr. Walter Cargill, Department of Physiology, Emory University, joined the staff in January for a three month period to study the distribution of Carbon^{14} labeled dextran. His residence has been extended to six months because of the difficulties involved in setting up radiocarbon analyses. His program will be continued when he returns to Emory University Medical School.

Dr. Etta Macdonald, University of Texas, Department of Bacteriology, has recently joined the staff to work on the problems involved in the auto-sterilization of radioactive compounds prepared for intravenous and intra-cavitary injection.

Dr. James W. Archdeacon, Department of Physiology, University of Kentucky, will be with the staff of the Medical Division for a period of approximately seven months. The problem he has selected concerns the selective uptake and excretion by the liver of radioactive compounds injected intravenously. The problem involves a very complex instrumentation in artifical organ perfusion.

In addition to the residents and staff members, Ph. D. candidates and technicians in basic medical sciences have been accepted to work with the Medical Division. Mr. Duane Sparks of the Department of Radiology, the University of Kansas spent two months working on the preparation of radioisotopes for human usage. Mr. Robert Gardier, Department of Pharmacology, University of Tennessee, worked on the effect of pituitary hormones on sodium transport. Mr. Joe Nash, Department of Pharmacology, University of Texas, worked on the metabolism and distribution of chelated gallium. A list of the residents and research participants is attached as Appendix II.

III. ORGANIZATION OF THE HOSPITAL PROGRAM

One of the outstanding benefits of close cooperation with medical schools lies in the procurement of patients for study in the Medical Division. Since the entire research program is directly pointed toward the therapeutic use of radioisotopes, obtaining suitable patients is one of the most important administrative problems. In general the plan of having all patients referred through participating medical schools has been followed. However, a few patients have been accepted upon the recommendation of non-participating medical schools, from other AEC installations, and from the Navy Medical Center at Bethesda, Maryland. Two patients have been admitted directly from the Oak Ridge area and some from the medical group of the University of Tennessee in Knoxville.

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1 Summary of the Clinical Program

The clinical program continues to emphasize specific therapeutic problems. One of these is the use of radiogallium. The data already collected bears out the preferential distribution of this metal in areas of bone formation or destruction. While the clinical results of treatment of primary and metastatic bone tumors have not been encouraging, neither have they been sufficiently discouraging to warrant a slackening of effort. Clinical observation suggests further trials in primary osteogenic sarcoma and extension to the study of additional types of bony metastases.

The use of intraperitoneal or intrapleural colloidal radiogold has been used as palliative treatment in intractable pleural effusions and ascites due to neoplasms. The results suggest that the study should be greatly expanded and the questions of dosage and timing evaluated.

The use of radioiodine and radiophosphorus in suitable patients has been continued as a means of training our own staff and residents. The program envisions no original research on radioiodine and phosphorus but rather is for the purpose of keeping abreast of the tremendous amount of work that is being done elsewhere. Several other projects involving tumor metabolism and tests on newer isotopes are under way. These are frankly exploratory of possible therapeutic usefulness.

2 Types of Patient Studies

In the past, a request has been made for a fairly large number of terminal patients. Much valuable data have been obtained at autopsy. Up to the present, there have been 30 deaths and 30 autopsies. In all cases except one, isotope distribution studies of the tissues have been coordinated with histological studies and autoradiograms. In one case, the autopsy was

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carried out as a decontamination procedure to allow release of the body, the radiation level being too high to allow a detailed autopsy study.

The continued cooperation of consultants in referring patients is noted with appreciation. The patients referred generally have been carefully selected and suitable for studies planned. During the past year, the following types of patients have been requested:

(1) Metastatic carcinoma of the prostate with bone metastases of osteogenic type in whom there is no further effect to be obtained by orchiectomy and hormone therapy.

(2) Primary sarcoma of bone with metastases.

(3) Any type of primary or metastatic neoplasm in which bone involvement was present and the main cause of symptoms. Patients should be in reasonably good general condition.

(4) Pleural metastases from any type of neoplasm in which recurrent pleural effusion is the main problem, preferably without massive intrapulmonary lesions.

(5) Carcinomatosis of the abdomen without obstruction of the urinary or gastro-intestinal tract, in which ascites is the main cause of symptoms.

(6) Carcinoma of the thyroid not amenable to surgical therapy.

(7) Active Hodgkin's disease previously treated; patients for whom there is no satisfactory treatment but who are not terminal.

(8) Multiple myeloma.

(9) Chronic myelocytic leukemia.

(10) Polycythemia vera.

In Table 1 is listed the types of patients by diagnosis accepted and treated within the Medical Division. The largest portion of patients, those with bone sarcomas, myeloma, breast and prostate carcinomas, and Hodgkin's have been studied with gallium. In the next largest portion, pelvic, abdominal, and lung tumors, the main therapy was radiogold. The next largest

group was for the use of iodine and phosphorus. In many cases, especially those involving tracer studies only, more than one isotope has been used in a patient. Twenty-two patients have received therapeutic doses of Gallium^{72}.

Osteogenic Sarcoma	10
Osteochondro Sarcoma	2
Ewings Sarcoma	1
Chondro Sarcoma	1
Reticulum Cell Sarcoma	1
Giant Cell Sarcoma	1
Multiple Myeloma	10
Carcinoma of Breast	3
Carcinoma of Prostate	5
Carcinoma of the Thyroid	9
Teratoma	1
Carcinoma of the Ovary	8
Carcinoma of the Bladder	2
Carcinoma of the Lung	3
Lympho Sarcoma	6
Chronic Myelogenous Leukemia	4
Chronic Lymphotic Leukemia	3
Hodgkins	2
Polycythemia	3
Pancytopenia	1
Melano-Blastoma-Sarcoma	2
Carcinoma of the Liver	1
Carcinoma of the Kidney	1
Carcinoma of the Stomach	1
Carcinoma of the Colon	1
Hyperthyroidism	1
Pheochromocytoma with HCV	1

TABLE 1. TYPES OF PATIENTS TREATED LISTED BY DIAGNOSIS

Twenty-nine additional patients received tracer doses of gallium. Of the sixteen patients who received therapeutic doses of radiogold, eight had peritoneal metastases; five, pleural metastases; one, a bladder tumor, and two were treated with intravenous radiogold. Nine patients have been treated therapeutically with radioiodine and four additional patients had tracer doses. Six of the therapeutic studies have been on carcinoma of the thyroid, two on melanosarcoma and one on a non-maglignant hyperthyroidism.

Eight patients have been given therapeutic doses of radiophosphorus. Four were given tracer amounts of radiosulfur; in one case radiosulfate was used, in two pure radiomethionine, and one case was given sulfur-labeled yeast protein. One patient has been studied with Cobalt$^{56-57}$-labeled Vitamin B_{12}.

3. Hospitalization Statistics

A total of eighty-three patients have been treated in the Hospital. There have been a total of 4,623 patient days. In Table 2, the patient days are listed by months. The average patient stay comes to about 56 days.

	Patient Days
May 1950	17
June	62
July	128
August	371
September	442
October	381
November	368
December	419
January 1951	593
February	441
March	440
April	446
May	513
TOTAL	4,623

TABLE 2

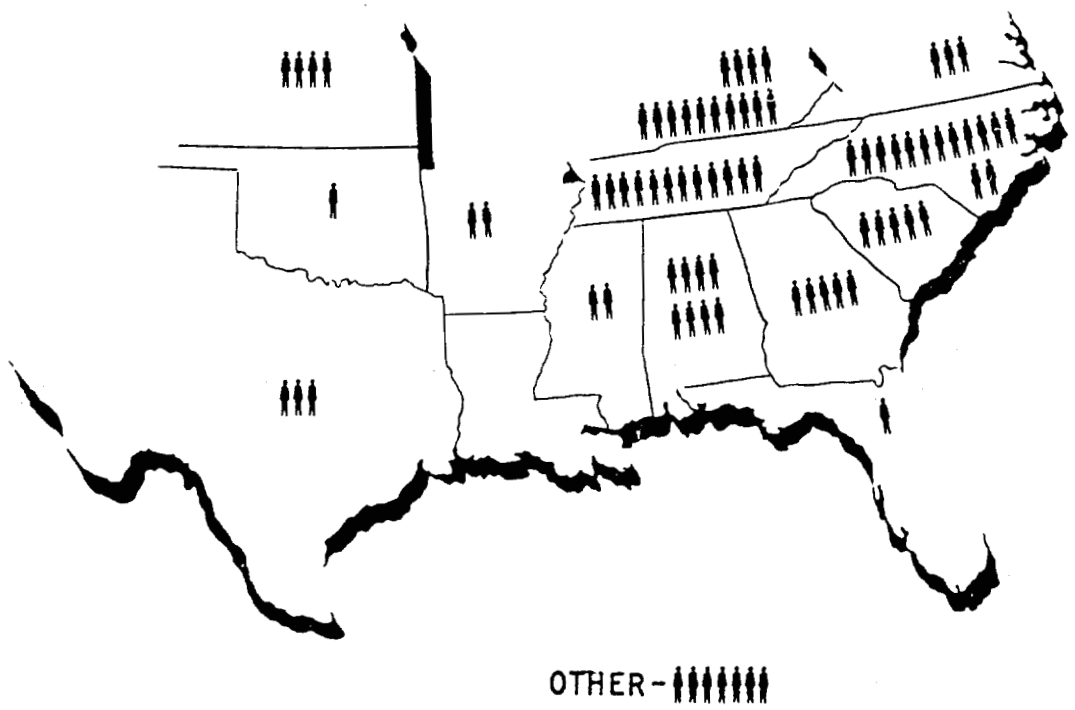
However, this is distorted by the presence of a number of patients who

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spent very long periods of time in the hospital. The usual patient hospitalization is around one month to six weeks.

Although there are 30 beds in the hospital, and hence room for 30 patients, the usual full patient load is closer to 20 patients. This is necessary because beds are arranged in six-bed wards. Five of the rooms, including some two-bed wards, are being used for terminal or very radioactive patients. It is necessary to allow for the separation of male, female, children, very radioactive, and non-radioactive patients. An attempt is being made to keep the patient load over 15 but under 20 and has been accomplished over the past half year. In addition to the usual problems of patient placement and handling, there is the factor of the hazard from radioactivity described in detail later.

Patients have come from most of the Southern states, the largest portion from those states immediately surrounding the Oak Ridge area. The accompanying map shows the origin of the patients so far accepted for treatment. It is



Map Showing Origin of Patients Accepted for Treatment at Medical Division.

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apparent that cost of transportation is an important handicap to some patients who could otherwise be accepted for treatment.

4 Hospital Administration

A large amount of paper work is involved in the administration of a hospital-type program. Most of the forms and procedures are similar to those of any hospital and are not included in this report, but some are peculiar to the Medical Division.

For the benefit of the consultants to the Medical Division admission procedure has been made as simple as possible. The patients are referred by the consultants on the basis of the consultants' knowledge of both the Medical Division program and the suitability of any patient for the therapy being offered. It is not essential that the patient be hospitalized and studied at the participating medical school if the patient's status is already sufficiently established. Each consultant is furnished with a booklet "Information for Patients." (A copy may be obtained on request to the Medical Division.) When it is feasible to do so, and especially in the case of terminal patients, consultants are asked to make it clear to the patient's family that autopsy permission is expected on patients who may die during or after treatment. It is hoped thereby to avoid accepting patients whose families would be opposed to autopsy.

When the patient understands fully the type of program and wishes to be admitted, he is asked to sign an application for admission. The application is signed by the consultant or representative of the participating medical school and mailed to the Institute. In most cases, the admission is relatively urgent and an immediate decision is desired. Consultants have been asked to call either Dr. Gould Andrews or any of the physicians in the Medical Division. In general, patients are accepted in the order in

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which applications are received. In some cases, after telephone conversation with the consultant, the application for admission is signed for the consultant by the Chairman of the Division.

A detailed statement of the cancer research program of the Institute, its general purposes, the relations with patients, the types of studies being done, has been set forth in an article written by Drs. Bruner and Andrews and published in the Southern Surgeon, June 1950.

After newspaper articles appear describing the work of someone connected with the Institute Medical Program or with other organizations using radioactivity, there is usually a large number of letters from individual patients requesting admission. The number of requests has been so large that it was necessary to send out a form letter, in which individual patients were referred to their closest medical school.

Upon arriving in Oak Ridge, the patient and/or his nearest relative is requested to sign a Waiver and Release. The necessity for this Waiver and Release was appreciated upon realization that the medical program involves both the Commission and the Institute in a number of serious legal problems. Also, the problem of malpractice insurance and liability for staff and visiting physicians has been considerably lightened by the use of the Waiver and Release. In event of death of the patient, an autopsy request is signed by the nearest relative.

A number of the forms are being used to maintain radiation records. There are charts for external counting, simple forms to provide a uniform description of both radiation data and radioisotope treatment, and forms for assay of tissue samples. Since there is no prior experience available on what types of forms are best for various procedures, this material is constantly undergoing revision. More experience is necessary before such forms can be recommended for standards for other hospitals. Samples of all of these forms may be obtained from the Medical Division.

5. Organization of the Research Program

The Medical Division research program is not organized around individual problems of research nor is it organized in a vertical pyramid of staff responsibility. The primary philosophy of organization has centered around the individual patient.

Involved in the treatment of one patient are clinical evaluation studies. The clinical staff, nursing staff, biochemist, pathologist, radiologist, and pharmacologist are all concerned, as well as the administrative personnel who have a large amount of work to do in connection with each patient.

On every patient, autoradiographic studies are carried out. Every one of the problems being studied in autoradiography becomes an integral part of the study of the patient.

Metabolism studies are done in both animals and humans. A large part of the animal testing program is actually an integral part of the human treatment. The toxicity studies are for the most part animal work which is done prior to use in patients. Included within the general subject matter of toxicity studies are a number of different attempts to arrive at a biological method of evaluating dosage.

Although there is one health physicist primarily responsible for radiation safety, everyone on the staff is concerned with the exposure problems of patient shielding, routine monitoring, urine collection, storage, the design of protective devices, and their own personal safety. No individual patient could be called a serious radiation hazard, but with as many as 10 to 15 patients under continuous radiation treatment, health physics becomes a serious consideration.

Instrumentation and measurement occupies a large segment of staff time. Most of the instruments that are now commercially available for study with

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radioisotopes are not well adapted to the study of human patients. Much work is necessary in the adaptation and modification of instrumentation techniques to meet the needs of clinical radioisotope usage.

One of the most fruitful developments in the organization of the Medical Division has been the development of a complete radioisotope service. The Medical Division is prepared to initiate discussion on the possible use of a new isotope, to prepare the raw material for pile irradiation, to make the necessary conversion of the irradiated sample for patient use, and then to study its effects after administration. It has integrated within one organization all of the steps required to carry a new isotope from the stage of discussion through the stage of human administration.

IV. THE RESEARCH PROGRAM

1. Gallium

The treatment with gallium of osteoblastic type bone neoplasms, both primary and metastatic, has been one of the major studies of the Medical Division. Although the work was instigated in conversation with personnel from the Naval Medical Research Center, very little data were available concerning gallium. Every phase of the study presented unique problems.

(a) The chemistry of the gallium compounds. In cooperation with the stable isotope chemistry group of Oak Ridge National Laboratory, 15 salts or complexes of gallium were prepared early in the program and after investigation most of them were rejected for either chemical or biological reasons. These compounds are: chloride, carbonate, tartrate, succinate, ascorbate, malate, diethanolamine, phosphate, salicylate, oxalate, benzoate, mandelate, ammonium citrate, lactate, and gluconate. Only the citrate, lactate, and

...nate proved soluble and stable at pH 7.4. The citrate was selected ...se it could be easily and quickly prepared; this is of prime importance ...working with half-curie lots of a short-lived material.

...remote control ion exchange method of preparation was developed and ...been published. Other methods were investigated but the one in present ...a simple remote control addition of reagents of predetermined amounts. ...te synthesis and radioassay requires a little less than two hours.

(b) Stable gallium tissue analyses. A stable gallium chemical analytical ...od for biological tissues has been developed which is satisfactory but ...consuming. Modified from an older procedure it is based on photofluoro- ...of the gallium hydroxyquinoline complex and can detect 2 micrograms of ...metal. The method is essential to any statement of dosage since the concentration of the final solution is commonly 70% of the original salt ...to complex formation. Stable gallium analyses have been carried out on rat, dog, and human tissues. In two patients and some animals it was the only method of assaying the fate of gallium.

(c) Gallium toxicity. The technical difficulty of preparation of gallium samples has been ironed out and it is now possible to assure relatively uniform dosage at many levels of many compounds.

Toxicity studies have been carried out in the rat, dog and in man. Early toxicity studies, using approximately 100 rats, had to be discarded because of the difficulties involved in the chemistry of gallium. With a biologically acceptable citrate complex for a single intravenous injection in approximately 138 rats, 218 milligrams of gallium per kilogram was tolerated. Higher doses caused death by citrate hypertoxicity or hyperchloremia. Following single massive doses, rats showed weight loss, anorexia, and mild diarrhea. Only traces of renal damage were apparent in the sacrificed animals.

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Multiple injection studies have been carried out in 16 rats for the purpose of tissue-enzyme work using Warburg techniques. The latter procedure gave evidence of a difference between radiation and metal toxicity. This work has been expanded and will continue into next year.

In addition, the toxicity and the effects of other compounds going into the final preparation of gallium have been studied. Toxicity of bromothymol blue, bromocreosol purple and citrates alone have been investigated to make sure the toxicity and distribution are specifically that of gallium.

(d) Clinical picture of gallium poisoning. Single and multiple I. V. injections of stable gallium have been carried out on approximately 74 dogs. Following single intravenous injection there develops rapidly a picture of acute toxicity with severe anorexia, bloody diarrhea, weakness, elevated blood urea nitrogen and evidence of severe renal damage. On autopsy, there is a diffuse follicular necrosis in the spleen and lymph nodes, severe liver congestion, and tubular degeneration in the kidneys. The L. D. 50/15 is about 18 mgm Ga---/Kgm. In animals that recovered and were sacrificed, only traces of renal damage were found.

When multiple injection techniques were used in 24 dogs the lethality was accentuated. All dogs died at dosages a fraction of the calculated single dose L. D. 50. Some of the lowest cumlative dosage dogs died without pathology other than albumin in the urine. Stable gallium analyses on the animals showed high accumulation in the bone, liver and spleen.

(e) Distribution of gallium. Approximately 200 rats were used in studies of the distribution of several forms of gallium; gallium chloride, gallium citrate prepared by the addition method, citrate prepared by an ion exchange method, and gallium alizerinate. It is found that the form of preparation makes a very definite difference in metabolism and distribution of the complex. A manuscript is in preparation on this data. Distribution studies

made in 4 pigs and the specific liver distribution and bile excretion gallium lakes have been observed.

(f) Effective dosage studies. In connection with the determination of biologically effective dosage of both stable and radioactive gallium, approximately 100 rats were used in the study of tissue respiration using Warburg techniques. Emphasis is placed on this and other methods of finding suitable biological end point for radiation dosage studies.

(g) Diagnostic potentialities of gallium. An additional program is under way in approximately 84 rabbits studying the metabolism of gallium in relation to bone growth. This is being done in fractures involving the probable localization of gallium in fractured bones. In addition to the usefulness of this problem in studying the rate of bone growth and as a biological end point for dosage studies, there are possible corollary diagnostic applications in studying the rate of healing of fractures and problems of nonunion.

(h) Gallium use in man. In man, test doses and therapeutic doses have been studied in over 50 individuals; the highest dosage given to any person was 88 milligrams of Ga--- per kilogram in divided doses. The usual dosage totaled 30 to 55 milligrams per kilogram in divided doses. Since the radioactive gallium has a low specific activity, 0.2 to 0.4 mc/mg Ga---, the usual single dose of stable gallium is from 2.5 to 6 milligrams per kilo with a total radiation dosage of from 20 to 70 millicuries. The largest single radioactive dose was 92 millicuries and the highest total weight of gallium was 10.4 milligrams per kilogram. Most patients can tolerate 2 to 4 of the ordinary doses. Further dosages give rise to anorexia, nausea, vomiting, and severe mental depression. There is a later development of skin reactions and occasional diarrhea. There is uniformly a very serious bone marrow depression. There is no evidence of renal damage in man except where such

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damage could be expected from the pre-existing disease. Excretion studies have been done routinely on all patients. This data is either published or about to be published.

External counting of gallium as a means of localizing and assaying concentrations in the body has been very unsatisfactory. The methods have not been adequately tested, representing a neglected problem. Biopsy studies have been done on most patients and have accentuated the problem of more accurately determining dosage. Autopsy, clinical studies, and studies of stable gallium distribution long after the radioactivity has decayed are in the process of being published.

(i) Future plans for gallium studies. In general, the whole problem of toxicity of gallium, both the metallic and the radioactive toxicity is an exceedingly difficult one. The high radiation energies are a source of total body "spray" in radiation and the metal is undoubtedly an accumulative poison. It is not possible to get Ga^{72} at a specific activity high enough to minimize the metal toxicity. For this reason the next step in the use of gallium is the development of Ga^{67} source. In addition to providing material of higher specific activity, Ga^{67} is one of three-day half-life in comparison to the 14.8-hour half-life of Ga^{72}. The radiation also is of much lower energy value and consequently reduces the toxicity of the radiation both to the patient and to the Medical Division personnel. With the help of the Oak Ridge National Laboratory cyclotron physical chemistry group, the problem of preparing and developing Ga^{67} is well under way. Preliminary studies of carrier-free gallium^{67} in rats indicate that a significant amount of work must be done before the material can be applied to humans. The available data on Ga^{67} which would allow dosage calculations are known to be incorrect. The decay scheme is being restudied at Oak Ridge National Laboratory on materials purified at the Medical Division. A method of working up highly

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dioactive cyclotron targets and extracting the gallium from zinc has been veloped to a high degree of efficiency using a modified Stang extractor. The problems concerning Ga^{72} are being rounded out and a complete statement will be presented before the Radiological Society Meeting in December in Chicago. In the meantime, the clinical results are such as to warrant continuing study of the metal.

2. Gold

The distribution, localization, and dosimetry of colloidal radiogold has been studied in 40 dogs, 40 rats, and 20 mice. In the dog the colloid was injected intra-arterially to see whether or not localization could be forced. This was tried in the femoral artery with and without occlusion of the femoral vein, in the lumbar aorta with and without tourniquets on the leg, in the renal vein and artery with and without occlusion and dissection of various elements of the portal tree and before and after splenectomy. It was injected intravenously with and without occlusion of the portal and hepatic vein and artery with and without multiple liver biopsies at various periods of time. Gold was injected into the pleural cavity, the peritoneal cavity, the urinary bladder, and a distribution measurement across the placenta was made in one animal. Sufficient data were gathered from this dog study to begin studies of intracavitary and intravenous use of colloidal radiogold in intractable pleural and peritoneal effusions due to neoplasms. Thus usage follows a suggestion by Muller of Switzerland. In man, studies have been carried out on the absorption, excretion, spread of activity, dilution of activity, and the various problems involved in assessing both the effects of therapy and the validity of dosage calculations.

One of the incidental findings of the investigations with radiogold is that radiogold has excellent properties for student work. It is sufficiently

long-lived to allow for slow, meticulous work and yet is sufficiently short-lived to minimize the contamination hazard. It is easy to procure and it can be measured in either very small or very large volumes. An attempt is being made to work out a good student problem for class room use. The clinical results on the use of radiogold are encouraging and it will be pushed as a major clinical study during the next year.

3. Iodine

Since radioactive iodine is readily available and most schools are using radioiodine, no attempt is being made to do original research in thyroid carcinoma with radioactive iodine. However, because the clinical people who are coming to Oak Ridge for training in the use of radioisotopes have a major interest in radioiodine, a number of patients are accepted for iodine therapy. This implies a complete set of standardization and assay procedures. An attempt is being made to stay abreast of the field particularly with reference to dosages, methods, and instrumentation. Thus, an occasional patient is admitted with carcinoma of the thyroid gland, and, rarely, a patient with hyperthyroidism. The instrumentation and methodology are under constant revision.

Recent reports on the use of radioactive iodine in malignant melanoma were responsible for the initation of some clinical investigation along this line. Although it was believed that such a use of radioiodine held little promise of any therapeutic value, a number of patients with malignant melanoma have been accepted and will be accepted in the future in order to determine any possible value in therapy or study of the disease.

4. Phosphorus

The situation with respect to the use of phosphorus in therapy is very similar to that of iodine. Since material is readily available and of long

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life, it is best studied by groups outside of Oak Ridge. Interest primarily in training and keeping up with the field. Most of the P^{32} in the Medical Division is being done in connection with other problems. labeled blood cells along with I^{131}-labeled albumin are used in circulation studies through spleen and other organs. When feasible, the method be used in humans if it can serve a practical purpose in assessing the of one of the regular patients. P^{32} is being used, in addition, in order to study the techniques involved in one-cell autograms in patients with myeloma and lymphoma. This is primarily a study of techniques which, when sufficiently advanced, will be applied to practical problems in patient dosimetry. A specific study of the differential uptake of P^{32} in the nucleoprotein of tumor cells of a lymphosarcoma patient was studied by one of the residents. A report on this procedure has been submitted for publication.

5. Sulphur

Tracer studies on sulfur-labeled yeast, protein, methionine, and sulfate have been made on five patients in a terminal state. The problem is related to specific studies on sulfur uptake in tumors in connection with the large amount of work done elsewhere on sulfur-labeled dyes which are said to selectively deposit radiation in rapidly growing tumor cells. A small amount of work has been done in mouse tumors; however, the problem has been dropped temporarily because of lack of technical help. A report has been accepted for publication on the original biological synthesis method. An additional report is in preparation on the results in humans.

6. Antimony

The distribution of a trivalent organic complex of antimony has been studied in a number of normal rats. There is unusual red cell concentration

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and a high concentration in the liver. The material has been used in five different mouse tumors and rather high concentrations have been found in some. Some of the pentavalent organic complexes are under investigation and it is intended to extend this work to man. The immediate problem however is one of obtaining high specific activity antimony. Metal toxicity will probably prohibit the use of the organic complexes as therapeutic agents in man. During next summer Professor Carl T. Bahner will work full time with the Medical Division and the program will be advanced to the point of knowing whether or not to request special processing to obtain higher specific activity.

7. Medium-Weight Metals

A number of medium weight metals, hafnium, zirconium, indium, et cetera, have shown or theoretically should show interesting localized depositions. Distribution studies have been carried on in approximately 30 rats and some mouse tumors. The problem is one primarily of preparation of biologically acceptable compounds. If sufficient evidence of specific localization is found, an attempt will be made to extend the process to human use. Before this can be done the question of stable toxicity and specific activities available will undoubtedly become a major problem. Before it is reasonable to ask for special processing for high specific activity metals, it is necessary that we have sufficient animal evidence and some tracer human evidence to justify the tremendous expense involved. An interesting localization within the adrenal gland has been discovered in the case of hafnium. Along with Dr. S. Seidlin, a consultant to both the Medical Division and the Isotope Division of the Atomic Energy Commission, a study is in process on the physiological effects of radioactive hafnium in rats. This problem is being jointly carried out at Montefiore Hospital, where a large number of sodium analyses

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...en run, and at the Institute. Most of the work on the medium weight ... has been done by temporary personnel. Therefore, its progress is ...sporadic.

8. Hematoporphyrins

...published article on specific localization in tumors of hematoporphyrins ...d to the suggestion that it be used therapeutically when combined with ...active metal. The localization of hematorporphyrins in various tissues ...tumors of mice was studied by both ultra-violet light and chemical ex-...tion. The work fails to confirm the original published report in that ...concentration was not higher. However, the work must be repeated before ...can be dropped. An interesting observation is that the original statements ...correct in terms of the original measurement. The tumor of treated mice ...does fluoresce to ultra-violet light but there is not more extractable ...matoporphyrin present. This suggests a specific relation between tumor ...hematoporphyrin which ought to be followed up. However, the more immedi-...tely important problem of chemical preparation of Ga^{67} has made it necessary ...to drop the porphyrin work temporarily.

9. Vitamin B_{12} Labeled with Radiocobalt

Through the cooperation of Merck and Company's radiochemists some of the first samples of $Cobalt^{60}$ labeled vitamin B_{12} were obtained. It was intended to study this material in man after doing preliminary animal experiments. However, the material was of such low specific activity that it was transferred to Dr. Comar for use in small animals (baby chicks) and arrangements were made to procure carrier-free cyclotron Co^{56-57}. A ...fficient amount of this material was incorporated into Vitamin B_{12} to be used in one patient. Additional batches of material will be made and

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will be tried out in additional patients. The progress of this program depends completely upon the availability of cyclotron time and the biosynthesis of the labeled B_{12}. The program is a corollary to other studies and is not a part of the therapeutic program.

10. Cobalt 60

It is widely known that the Institute, the M. D. Anderson Hospital, and General Electric X-Ray Corporation are cooperating in the production of a multicurie telecobalt therapy irradiator. The cobalt source has been in the Chalk River reactor for the past year, and it will be removed during the late summer of this year. In the meantime, the design for the device has been revised a number of times. Many engineering and radiation problems have arisen which could not have been predicted on the basis of previous knowledge of the characteristics of Co^{60}. The telecobalt therapy program has been one of the major programs of the Institute and will continue to be long after the device goes into operation early next year. One statement of the work already done has been published; other work is in preparation for publication. The Institute sustained a severe loss in the unexpected death of Dr. Leonard G. Grimmett, physicist at the M. D. Anderson Hospital. Dr. Grimmett had gained world renown in the field of radiotherapy. The cobalt therapy device was built around his ideas and he made a major contribution in putting these ideas into use. He died one month before the shielding head and suspension mechanism was completed.

11. Autoradiography

In connection with the determination of the specific localization and dosimetry to tumor by various isotopes, the field of autoradiography, which is primarily methodology, has become a major effort of the Medical Division.

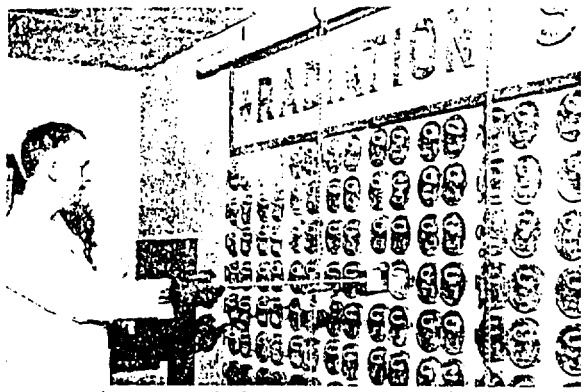
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Use of Radioisotopes In Medical Therapy

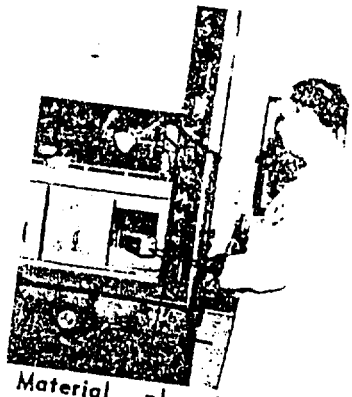
RING MATERIAL FOR INJECTION IN PATIENTS



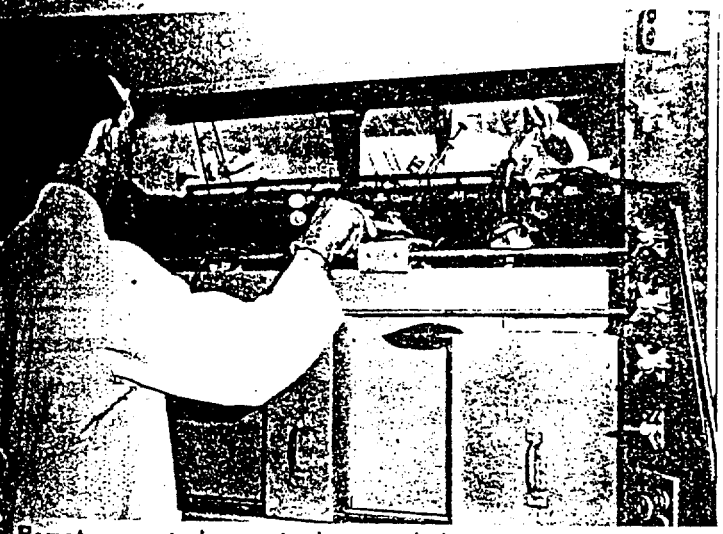
material arrives from National



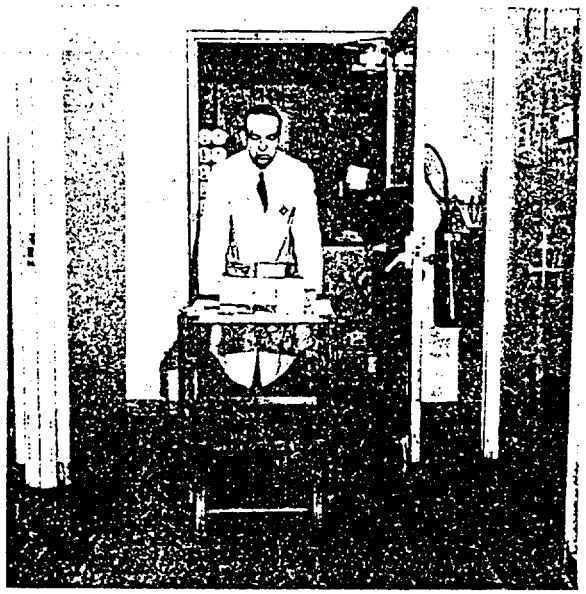
Material removed from storage vault for purifying and diluting.



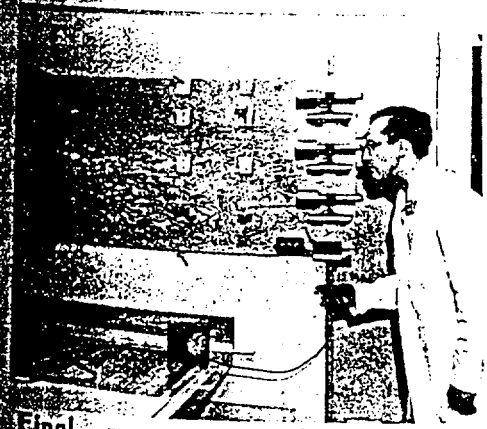
Material placed into isotope manipulator



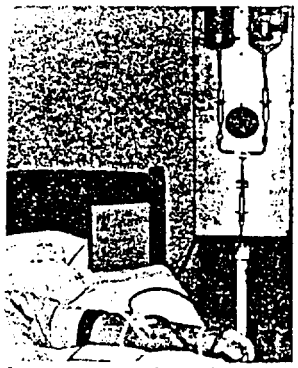
Remote control manipulation behind lead shield



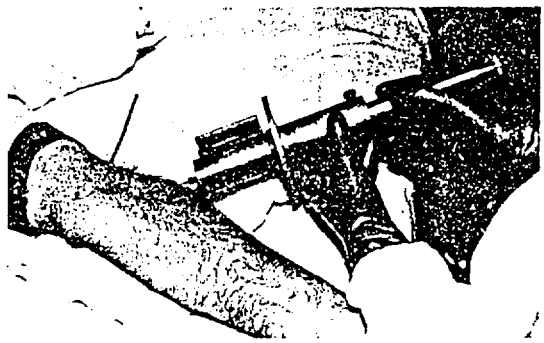
Material wheeled out of preparation room



Final measurement of radioactivity with electroscope

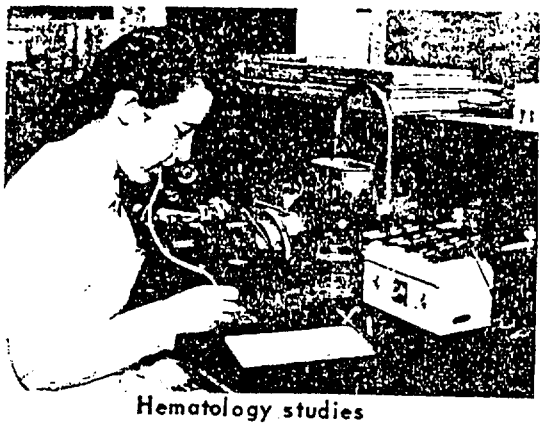


Injecting radiogold with shielded syringe



Apparatus for injecting radiogallium

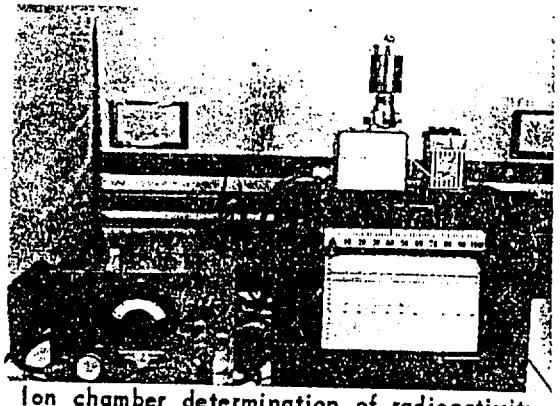
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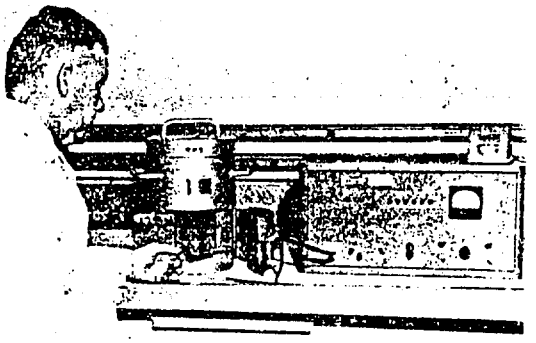
Hematology studies



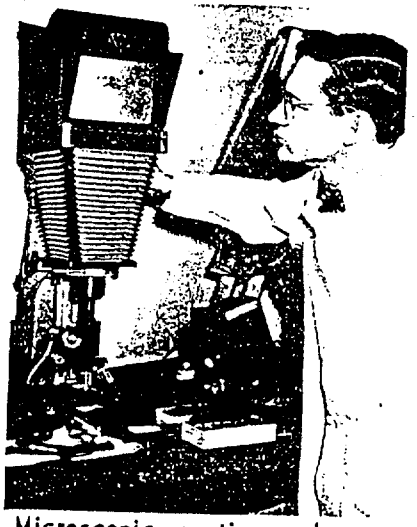
Histology studies



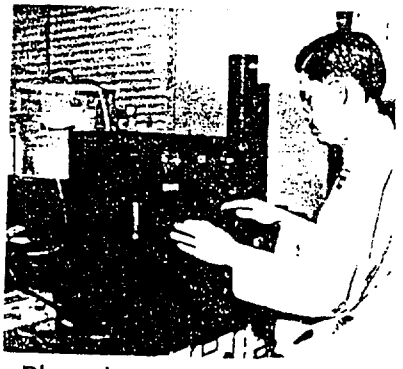
Ion chamber determination of radioactivity in urine



Determination of radioactivity in digested tissues



Microscopic section enlarger for autoradiographic analysis



Photoelectric colorimeter used in clinical blood chemistry studies



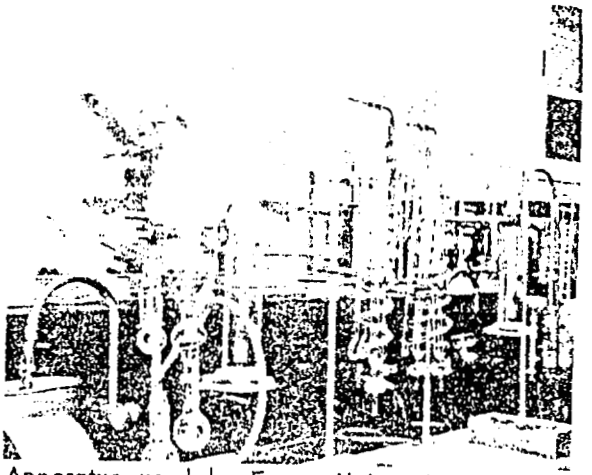
Flame photometer used to analyze blood serum

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RESEARCH



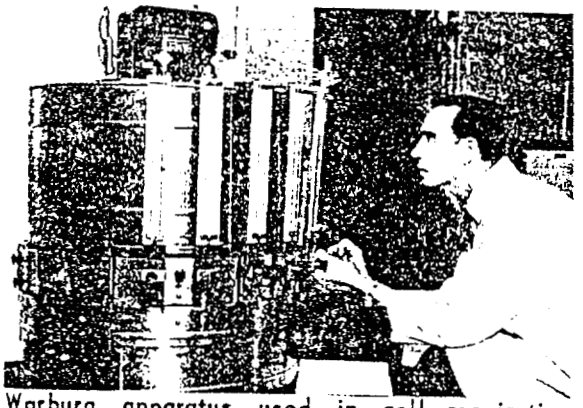
Tissue ashing for gallium analysis



Apparatus used by Emory University scientist in radioactive study of dextran, blood volume expander



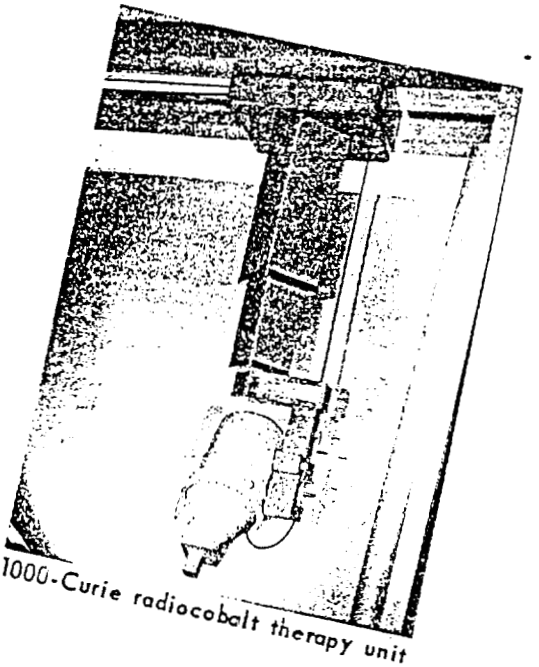
Extensive animal studies are prelude to clinical application



Warburg apparatus used in cell respiration studies



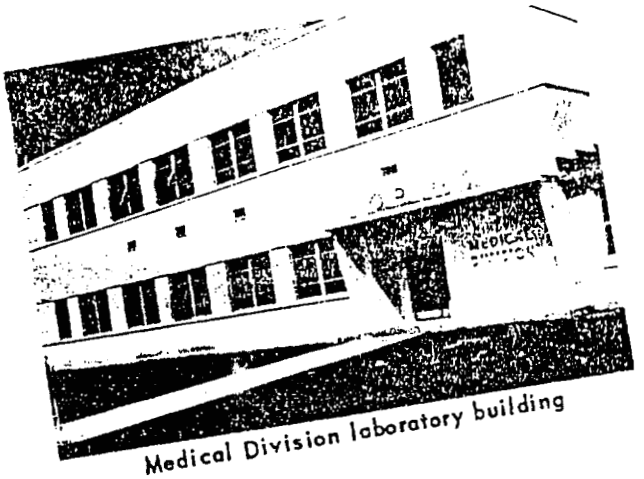
Organ perfusion apparatus used to study bile production by irradiated rat livers



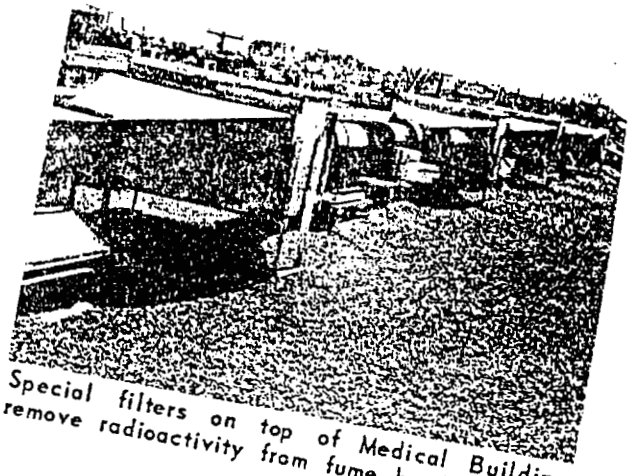
1000-Curie radiocobalt therapy unit

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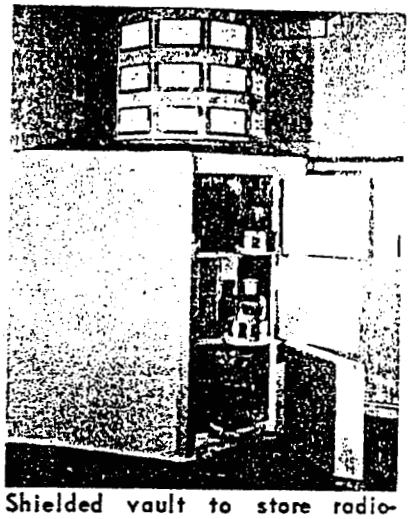
IV. TYPICAL EQUIPMENT



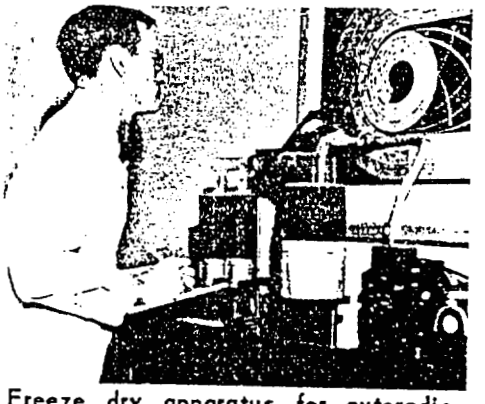
Medical Division laboratory building



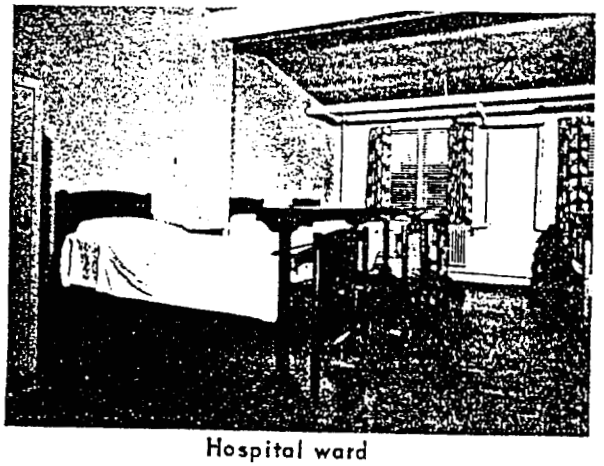
Special filters on top of Medical Building remove radioactivity from fume hood exhausts



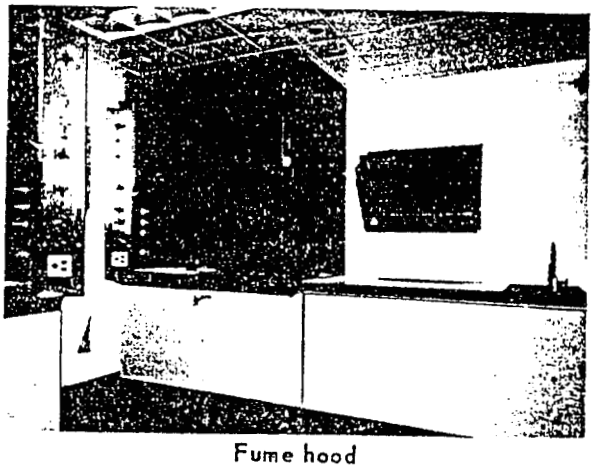
Shielded vault to store radioactive urine specimens



Freeze dry apparatus for autoradiographic studies



Hospital ward



Fume hood

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...tograph technique has been developed and has become a routine ... This method, however, is purely qualitative; work continues on ...tion of gross autograms. The micro-autographic techniques have not ...routine primarily due to lack of help. Interpretation of both ...micro-autoradiograms is in itself a major research study. ...to the autographic problems are specific methods for blood cell ... The problem of radio-colloid distribution in relation to surface ...les of colloids and a method for external autoradiography in humans ...been in the process of development. An article is in preparation on a ...qualitative technique. Another article on the localization of formate ... in leukemia blood cells has been prepared. A third problem on sulfur-... methionine in myeloma cells is being studied. Approximately 50% of ... autoradiography in the Division consists of service investigations for ...members of the staff.

12. Carbon-Labeled Dextran

...In conjunction with the Departments of Biochemistry and Physiology, Emory University Medical School, a problem in assaying the localization, distribution, metabolism and toxicity of dextran was inaugurated in January 1951. It was expected that the problem would be a temporary one involving only a few months of work. However, the past six months have been concerned chiefly with instrumental and methodological procedures, the design of glass cages, absorbing trains, collecting systems for tissues and gases, collection recovery methods for barium carbonate, methods for dry ashing of tissues specifically related to C^{14} determinations, the instrumentation involved in setting up a vibrating reed electrometer, and the regenerating setups for conversion of barium carbonate to CO^2 and transferring the gas to ion chambers. The biological problem and procedures are relatively simple and are not time

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consuming, being mechanical, chemical, and instrumentational in nature. These have been effectively solved during the past six months. It is intended to carry the problem over to human use of various plasma volume expanders.

13 Manganese

Manganese in physiological dosage was studied in 25 rats. No important organ differential was determined with Manganese^{52}. A minor problem being planned (at the convenience of cyclotron time) with Manganese^{54} in guinea pigs and dogs is to check statements that the thyroid takes up Mn. after doses in the toxicologic range. This work is to determine if the amount of carrier-metal changes the distribution pattern. This general question relates to the gallium work since Ga^{72} has excessive carrier metal and Ga^{67} practically none.

14. Sodium

Both sodium and potassium have been used in the Medical Division as investigative tools in human patients. The work will be continued primarily as a training problem for resident physicians. In addition, a three-month study using Sodium^{24} on the water and sodium transport through the frog skin as affected by pituitary solutions was carried out and will become a part of a resident's doctoral thesis.

15. Hematology

In addition to the regular work of the main programs of the Medical Division, there are related studies involving total eosinophil levels in patients undergoing therapy with internally administered isotopes. An additional survey is being done on the blood and bone marrow pictures following both internal and external radiation.

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In connection with other blood work, samples are being collected from irradiated patients for testing the unusual serological reaction at the University of Michigan under the direction of Dr. Reuben Kahn.

In Table 3, the relative programming importance of Medical Division studies is listed. The major portion of time is spent on investigation of gallium,

Gallium	20%
Gold	17%
Iodine	8%
Phosphorus^{32}	5%
Sulfur	2%
Antimony	2%
Medium-Weight Metals	5%
Hematoporphyrins	5%
Vitamin B_{12} Labeled Cobalt	1%
Cobalt^{60}	15%
Autoradiography	10%
Dextran	3%
Manganese	1%
Sodium^{24}	1%
Hematology	5%

TABLE 3. RELATIVE PROGRAMMING IMPORTANCE OF VARIOUS MEDICAL DIVISION ACTIVITIES

gold, cobalt, autoradiography, and iodine. All of these problems directly involve the use of radioisotopes in man.

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V. INSTRUMENTATION, METHODOLOGY, AND PROCEDURES

As stated earlier, one of the biggest problems concerned with the initiation of the Medical Division program arises from the fact that relatively little backlog of experience is available in the use of therapeutic quantities of radioisotopes. Consequently, problems of instrumentation, methodology, and procedures became an intimate part of the research program. Old instruments were adapted and new ones devised to meet clinical problems as they developed. New procedures were established and rendered routine wherever possible.

A discussion of this aspect of the medical program is contained in the following paragraphs.

An ion chamber method of urine assay for gamma emitters was developed in collaboration with the Instrument Branch of Oak Ridge National Laboratory and is now in use. The device is especially useful in measuring hard gamma radiation but also may be used to measure medium soft radiation. It eliminates the necessity for handling radioactive urine samples and reduces the radiation dosage to personnel. For example, the assay time on a sample of gallium has been reduced by a factor of 10.

The Marinelli cup iodine urine assay using a bismuth wall tube has been developed and standardized with NBS standards and is now in use.

A wet cup method of measuring radioactive gold, phosphorus, hafnium and indium has been developed to allow for the routine handling of many samples.

In cooperation with Dr. Farrington Daniels of the University of Wisconsin, a lithium fluoride crystal dosimeter is being studied as a means of determining internal dosage.

A highly collimated counting system has been in use for a year and a half. It utilizes a tungsten head surrounding an ordinary thyrode type G. M.

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attached to a scaler. It was designed by Commander E. R. King, Naval
Officer formerly on duty with the Medical Division and has been
facetiously named King Kong Kollimator because of its massive size. Although
cumbersome and impractical for routine patient usages, it is an excel-
research tool for analyzing the problems of external survey techniques.
is being used at present on phantoms.

An alkaline wet ashing method of assaying tissues for radioiodine with-
loss of the material has been developed.

An attempt is being made to develop a method for measuring tracer amounts
cobalt by plating platinum on ceramic cups shaped to fit a proportional counter.
large volume ion chamber developed by the Special Training Division is being
adapted to handle routine gamma emitting samples without preliminary treatment.
number of scintillation counters have been set up for external counting
procedures.

A number of instrumentation problems excluding counting have been solved
others remain to be solved. A shielded syringe has been developed
primarily for use with radiogold, but is adaptable to other hard beta emitters.
This syringe is being manufactured by the Aloe Scientific Company and is
commercially available. An intravenous infusion apparatus was designed and
built and is also being manufactured by the Aloe organization.

One of the most serious radiation hazards in the Medical Division is that
coming from 24-hour collections of urine from radioactive patients. To
minimize the hazard, a three-tiered rotating table with a capacity of 18
storage bottles within a shield has been developed and is now in use as a
urine storage vault. In connection with the simultaneous measurement of
radiation and volume of highly radioactive urine samples, a design for sample-
taking of urine specimens is being investigated.

The period of most severe radiation exposure in the Medical Division is
that in which radiochemists prepare radioactive samples for patient injection.

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A large radiation shield and pipetting device has been developed to reduce exposure during radiochemical preparation. The shielding is completed and in use, although some work remains to be done on the pipetting apparatus. A shielded Stang extractor has been modified to prepare Gallium^{67}. An artificial organ perfusion system has been built and is now being tested. Its primary purpose is to study problems such as the determination of a biological end point in individual organs, radiation dosage to the liver with various compounds, and problems of the pick-up by the liver and kidney of colloidal compounds.

A shortage of lead for shielding has led to an examination of alberene stone and marble for this purpose. Results indicate that alberene stone may be very good for shielding problems encountered in the medical use of isotopes. In cooperation with Dr. D. C. Bardwell, of Oak Ridge National Laboratory, an intensive study has been in progress on the use of other medium density non-critical materials.

The fume hood problem has been under investigation by the Medical Division for the past two years. Working in close cooperation with the staff of the Medical Division, the E. H. Sheldon and Company organization developed a hood design which has proved most satisfactory for general radiochemical purposes. It is a compromise between expense, practicality, and ideal air-flow performance. During the past year an improved modification of this basic design was placed on the market by the Kewaunee Manufacturing Company.

In conjunction with the instillation of gold into the bladder for superficial malignancies of the bladder wall, a number of compartmented catheters have been designed, constructed and used, but none of the designs so far has proved satisfactory.

An expendable cage to separate urine and feces of rats used in tracer experiments has been built and is in use. A report on it has been published

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...s to correct for physical decay of the most frequently used isotopes ...pared and because of their general usefulness, were published by the ...l Information Service, AEC, as ORO Publication No. 26.

RADIATION PROTECTION AND THE EXPOSURE OF PERSONNEL

...the time of the organization of the Medical Division, there was ...experience available in the large-scale use of radioisotopes. Most ...anticipated problems were based upon exposures encountered in the ...tion and research facilities of the Atomic Energy Commission and were ...totally different order and nature than those of a hospital-type operation. ...many places there was experience using small quantities of radioiodine and ...diophosphorus. The bulk of experience in medical usage was based upon the ...of tracer quantities and sporadic therapeutic doses. Thus, the problems ...olved in the use of a large number of radioisotopes simultaneously in a ...large number of patients were relatively unknown.

One patient receiving even a large dose of radioiodine does not constitute ...hazard, but when many patients are being treated with different isotopes in ...latively large quantities a significant exposure hazard results. Under ...these conditions the question of shielding the patients from the staff and from each other must be considered.

1. Isotopes Used in the Medical Division

During the first full year of operation of the Institute Hospital, 18 different radioisotopes have been employed, totaling almost 25 curies of radioactivity.

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The dosage in individual patients ranged from microcuries to almost a curie. This year's operation has provided a basis for discussion of the contamination and radiation protection problems to be encountered in a small hospital-type operation and has suggested designs for protective measures which appear to have practical usefulness.

2. Possible Exposure Within Patient Areas

Of the total amount of radioactive substances brought into the hospital area only a fraction creates a potential hazard. During transportation, chemical preparation, and storage the activity is well shielded and the problems are mostly those of laboratory design and engineering. It is after the material is injected into a patient that the major problem arises.

It is too early to be dogmatic about whether or not a radioactivity exposu represents a hazard because there are too few data and too many opinions as to how much exposure should be allowed. But as a starting point in setting up regulations for personnel protection, the recommendations of the Chalk River Conference on permissible doses were adopted.*

The working assumption was that all personnel would spend the rest of their lives with some exposure to radioactivity. Therefore, for chronic exposure of the total body, the maximum permissible dose in the critical tissue (bone marrow) should be 0.3 rep roentgens equivalent physical per week. This is considered equivalent to 6.25 milliroentgens per hour or 60 milliroentgens per working day.

If personnel work only in levels of radiation lower than 6.25 milliroentger per hour, there will be no question of either moral or legal aspects of the

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*Unofficial Notes from the Minutes of the Permissible Doses Conference held at Chalk River, Canada, September 1949. This material here quoted has been late amplified and in substance substantiated by the International Commission on Radi logical Protection, London, July 1950. See Nucleonics (No.1), 28-37, January 19

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radiation exposure. Accordingly, the question that remains is practicability of carrying out normal hospital procedures under giving doses no higher than this level and preferably giving the ible exposure.

patient has received a radioactive substance which emits gamma possible to measure the exposure around the patient with reliable, instruments. When measuring a field of unknown radiation it is use an ionization chamber because of its relative wave length inde- However, ionization chambers are less adaptable to untrained personnel inaccuracies introduced with other methods are negligible in routine surveys. The instrument selected for use by the nurses of the 's Medical Division is a portable Geiger-Mueller type monitor by batteries mounted in a plastic container. It weighs six and pounds. This survey meter, called the "Poppycock," has a light flashes with each count, a loud speaker which clicks, and a dial for exposures. By use of a spring switch the device can be set for pecting" for low-level exposure fields or for surveying high level sures. When "prospecting," only the light and the speaker are operating when "surveying," the scale is in the circuit so as to provide a means estimating the level of radiation. Instead of calibrating the scale of meter in milliroentgens, green, yellow, and red colors are painted on to give indication of tolerable, warning, and dangerous levels. When the pointer reads the green area, the nurse has instructions that with most isotopes there are no restrictions on work hours, visitors, and probably no restrictions on sample collections of urine, feces, blood, and linens. When the dial reads in the yellow area, there are no restrictions on work hours and visitors but there are probably some restrictions on sample collection from the patient. When the dial reaches the beginning of the red scale, the dosage

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is at 6.25 milliroentgens per hour. This point reads the only true calibrat on the scale relative to radium. Beyond this point, there are time restricti on working hours. Visitors must be restricted to short visits. All sample collections and waste materials must be monitored by a qualified person. In some cases the nurses themselves are qualified to use standard survey mete to assess the extent of the restrictions.

After the patient is given some radioactive substance, a line can be drawn around the patient at the points where the radiation in the air measures 6.25 milliroentgens per hour; this line is called the hourly maximum permissible isodose line. Immediately after injection of 20 millicuries of Ga^{72} citrate, this isodose line is approximately a circle four meters from the center of the patient. Because Ga^{72} has a very short half life (14.3 hours) and is excreted in the urine rapidly, this isodose line regresses toward the patient rapidly. In two hours the maximum permissible isodose line is three meters from the patient; in sixteen hours the line is at one meter; after two days, it is close to the surface of the body so that there is little hazard to the nurses, aids and orderlies carrying on ordinary hospital routines.

Most of the gamma emission of Ga^{72} is of high energy, or "hard." About 25 percent of the gamma rays are over 2.5 mev; about 50 percent are over 2 mev. Ordinary hospital plaster walls provide almost no shielding; therefore, other persons must be kept away from adjacent hallways and ward rooms. Other patients getting radioactive therapy will probably receive only a negligible fraction of their own dosage from exposure to a gallium patient, but patients not under radioactive therapy must be shielded from active patients.

In another example, a patient received 200 millicuries of radiogold (Au^{198}) intrapleurally. Compared to gallium, Au^{198} emits a much softer gamma ray and fewer rays per disintegration. Hence it is much easier to shield. Ordinary plaster walls have some shielding value but are not adequate with large doses.

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because its half life is longer (2.7 days) the maximum permissible
line regresses toward the patient much more slowly. In the example,
dose line for 6.27 mr/hr was a meter from the patient a week after
injection and did not approximate the body surface until two weeks had
. During this time, according to definition, the area around the
an area of radiation hazard. Time spent close to the patient
of the staff must either be reduced to minimum or the patient must be
. In practice a combination of these two measures is employed.
shielding can be accomplished in many ways: Probably the simplest
build the walls of certain rooms of dense concrete and use such rooms
rivate rooms. Under such conditions the problem is almost non-existent
dosages used so far. A less expensive substitute for this ideal shielding
erect a double layer of four inch marble slabs up to the 6-foot level
critical walls. This was done in the Medical Division Hospital in one
critical area where a physician's office adjoins a private patient's bedroom.
Another simple protective shield is made of a two-inch slab of armor plate
mounted on casters and upholstered. The large shield is six feet long
three feet high; the small one is three feet by three feet.* When
placed L-shaped around the patient's bed the radiation is reduced to
negligible levels. Highly radioactive patients are placed along outside
walls and are kept in bed during the period of greatest radioactivity. With
L-shaped shield added, the potential hazard is reduced to a minimum.

The amount of radiation exposure to an attendant remaining close to the bedside of high dosage patients is considerable. At approximately one meter from the patient during the entire course of intracavitary gold therapy, over

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*The first two shields of this type were constructed on the order of the husband of one of the patients, Mr. H. L. Riley of Rome, Georgia, and presented as a gift to the Medical Division.

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ten roentgens of 400 kilovolt radiation was calculated. Hence, a nurse sitting next to the patient could be expected to absorb one roentgen of total body exposure in three days. The nurse of a patient treated with one hundred millicuries of iodine would receive about one roentgen of exposure in five days and with fifty millicuries of gallium the nurse could be exposed to one roentgen in about two days.

While such exposures may be of no immediate hazard if taken once and never repeated, they are intolerable as a working basis for personnel who make even a short-term career of handling radioactive patients.

3. Personnel Exposure

In the Medical Division of the Oak Ridge Institute of Nuclear Studies, every person wears some form of exposure measurement device. All personnel, including secretaries, visitors to the patients, and janitors, wear the standard film badge. This is considered primarily a legal record of exposure and not a research tool. In addition, those persons exposed to considerable activity, such as nurses, processing technicians, and staff, wear pocket chambers which are read twice weekly by a health physicist, and a continuous record is kept. Selected personnel, those who are in close contact with large sources or may be expected to have the greatest exposure, wear a direct reading pocket dosimeter. The latter are qualified to make their own decisions regarding exposure tolerances. Under special circumstances such as surgical operations, autopsies, preparation of new compounds, and testing new equipment, palm and finger badges, wrist and forehead chambers and other monitoring devices supplement these standard procedures.

A good example of the actual exposures received by various working classes of personnel is shown in Table 4. To construct this table a three-month period was taken, December 1950 through February 1951. During the

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was an average hospital load of 17 patients undergoing some type
therapy. The isotopes brought into the hospital area, except

	No. with Blank Badge*	No. Exposed	Average mr/day Exposure Open Window	Average mr/day Exposure Shielded Window**	Largest Average Exposure in Group-mr/day
	3	10	9.1	9.1	55.7
	1	3	2.0	3.9	10.9
staff	2	9	10.3	11.9	28.5
	0	12	4.9	3.9	10.6
	0	6	4.1	3.7	5.9
	0	2	12.2	11.4	15.9
	0	2	1.8	1.8	3.1
	0	3	0.6	0.6	0.6
nce Men	4	4	1.5	1.3	4.2
rative	1				
Personnel	11	51	6.1	6.1	55.7
Nearby Medical Schools					
ology					
icians	11	5	7.2	4.8	19.0
logists					
ge inside					
on)	0	2	11.6	4.6	7.9
logists					
ge outside					
on)	0	2	112.0	6.5	124.0

the exposure is less than can be measured by photographic densitometry
badge is considered a blank and is not included in the average exposure

film shielded from beta and soft scattered radiation by 1 mm cadmium shield.

BLE 4. EXPOSURE OF SELECTED PERSONNEL MEASURED BY ROUTINE FILM BADGES OVER A THREE MONTH PERIOD (MAXIMUM PERMISSIBLE EXPOSURE BY THIS METHOD IS 60 mr/day)

some long-lived materials already present, were:

3.98 curies of Ga^{72}

2.12 curies of Au^{198}

1.11 curies of I^{131}

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0.04 curies of P^{32}

0.02 curies of Na^{24}

Only the routine film badge data are shown since all personnel wore the film badge. The films measure the total integrated dosage over a set period with readings for hard and soft gamma radiation; in this instance they are returned weekly. The open window reading is an index of the less penetrating radiation. By this method of measurement the maximum permissible dose is considered to be 60 milliroentgens per day for either reading.

The largest exposure was received by a staff chemist who processed the samples of Ga^{72} as they came from the reactor. The second largest exposure was to the chemistry technician helping him. The orderlies who spend most of their time caring for the needs of patients, and technicians who handle the urine, feces, blood, and tissue samples received the largest routine exposures. However, in all cases, these exposures were considerably below maximum permissible levels. In comparison, the personnel of a busy, routine diagnostic x-ray service in a nearby medical school received as much or more radiation than Institute personnel. This level is considered a normal condition in x-ray services and rarely occasions any comment.

A number of special measurements illustrate the hazard in nonroutine procedures. During a two and one-half hour operation to remove the left lung of a patient who had been given a 20 millicurie test dose of Ga^{72} the surgeon and his first assistant each received a total of 400 milliroentgens to their hands according to film badges placed in the palms underneath their rubber gloves, whereas badges under their collars registered 30 milliroentgens. This difference is due in part to the rather energetic beta particles of Ga^{72} which have a maximum penetration of about 18 mm of water. The anesthesist for this operation received total body exposure of 40 milliroentgens. In Table 5 four other operations are reviewed. When most of the isotope is

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to one location as in intra-abdominal therapy with Au^{198}, the hands
rgeon can receive a significant dose. The actual radiation per

	Surgeon			First Assistant			Assistant or Anesthesist		
	Left Hand	Right Hand	Total Body	Left Hand	Right Hand	Total Body	Left Hand	Right Hand	Total Body
otomy allium 72 Exposure	reg	reg	10	reg	reg	10	--	--	10
Source									
otomy Gold 198 our Exposure	155	75	40	35	35	10	50	—	10
rce in Lesser al Space									
rotomy C Gold 198 our Exposure	490	180	80	290	600	80	30	--	10
urce in itoneal Cavity									
lantation of Needles C Radium our Exposure	760	450	90	360	470	90			

5. EXPOSURE TO RADIOACTIVITY DURING SURGICAL OPERATIONS (MILLIROENTGENS TOTAL EXPOSURE TO HANDS AND BODY)

tegration is not as great as with gallium, but the quantity of radio-
ity is disproportionally greater. In the second example in Table 5
old was confined to the lesser omental space; in the third example it
profusely spread over the entire peritoneum. The surgeons here received
what more than the "allowable" hand dosage which is generally taken to be
five times the total body dosage. However, because such operations
not done routinely, the actual risk is minimized. In contrast a far

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greater risk is in a standard implantation of radium needles.

In another series of measurements, the average exposure to the unprotected neck and right forearm of a radiologist during two weeks of routine fluoroscopy was about 84 milliroentgens per day. Two persons holding a baby under a 250 KV therapy machine during three minutes exposure of 200 r each measured 50 milliroentgens on pocket chambers placed under lead aprons. It is generally true that even large amounts of radioisotopes can be handled with greater safety than is now the case in many standard x-ray and radium services.

During the chemical preparation of a radioisotope, exposure of the hands is not ordinarily registered in the routine personnel monitoring devices. For example, during the hour it took to prepare four ampules of Ga^{72} citrate, the chemist received an exposure of 530 milliroentgens on his right hand and 355 milliroentgens on his left hand. If such exposures occur during a routine operation which must be repeated a number of times each week, the equipment must be redesigned to afford better shielding and the chemist must re-educate himself to modified procedures.

A common statement is that the injection of a radioisotope can be done more safely without shielding over the syringe if the operator moves fast. At best, however, the hands are exposed to measurable amounts of radiation. The injection of one millicurie of gallium from an unshielded syringe over 50 seconds gave 13 milliroentgens to the left hand and 15 milliroentgens to the right hand. During the injection of 20 millicuries of radiogold over 60 seconds, using an unshielded syringe, the total exposure was 60 milliroentgens to the left hand and 50 milliroentgens to the right hand. Radioiodine gives about the same exposure as radiogold, and even radiophosphorus gives off bremsstrahlung (soft x-rays) which can help build up hand exposure to supra-tolerable levels. If these so-called rapid procedures are carried out once or twice a week and are the only exposures that the hands receive during the

...there is little or no hazard to using unshielded syringes.

...operation is just one part of other routine exposures the

...issible dose accumulates rapidly and is exceeded quickly.

...intenance of personnel exposure at such low levels has not been

...without considerable time and effort by the entire staff.

...procedures are constantly undergoing revision for the viewpoint

...hat operating conditions should be re-designed before and not

...nnel reach permissible dose levels. The maximum permissible dose

...sure is not considered a safe level; rather the least possible

...is considered the safest exposure. There is probably less radiation

...the Medical Division Hospital than there is in the ordinary x-ray

...

VII. FUTURE PLANS

...major activity for the immediate future concerns the multi-curie radio-

...therapy unit to be tested by the Medical Division and the M. D. Anderson

...al of Houston. A small underground building adjacent to the Medical

...ion building has been completed, and the General Electric Company has

...ctured the shielding and control mechanism for the unit. The cobalt

...ing irradiated in the Chalk River reactor of the Canadian atomic energy

...blishment and is expected to reach full strength around October 1, at

...time it will be shipped to Oak Ridge for loading in the special facilities

... Ridge National Laboratory. It will then be installed in the Medical

...ion structure and exhaustive biological and physical tests of the radi-

...will be made on a variety of animals. Finally, it will be tested on

..., and if it is effective in cancer therapy, a unit will be set up in

... D. Anderson hospital for routine treatment of patients.

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studies will be initiated in the near future concern
neutron sources and the use of neutron irradiation therapy.

A number of steps are planned to improve patient morale. These include the expansion of the patient wards to allow for better separation of patients the development of an occupational therapy and recreative programs.

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Boyd, George A.	Senior Scientist
Bruner, Harry D.	Chief Scientist
Buher, William R.	Laboratory Technician
Byrom, John Peter	Health Physicist
Cantrell, Joe R.	Laboratory Technician
Carden, Blanche	Stenographer
Cargill, Walter H. Jr.	Research Assistant
Carpenter, Elmer A.	Custodian
Cook, Bonnie Louise	Receptionist
Cooper, Betty Ray	Laboratory Technician
Cooper, Betty Marguerite	Senior Scientist
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Dobson, Lewis	Helper
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Urey, Frieda R.	Laboratory Technician
Whitson, Alice H.	Medical Records Librarian
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APPENDIX V

Oak Ridge Hospital Personnel
Assigned to Institute Medical Division

...ary, Supervisor of Nurses
...oona
...orgia
...oberta
...Franklin
...Bobbie
...manita
...ene
...cille
...ela
...Virginia
...len
...Gladys

...nes

...Lucy
...er, Mary
...Jack
...enna
...Marjorie
...James

...ousekeeping

...Luther
...on, Mary

...Chemistry

...ng, E.

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Stevens, L., Nucleoprotein P^{32} in Lymphosarcoma. Submitted for Publication.

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Articles published while on the Medical Division staff but from work done prior to joining:

Brucer 12; Bruner 6; Andrews 2; Kerman 1; Perkinson 2

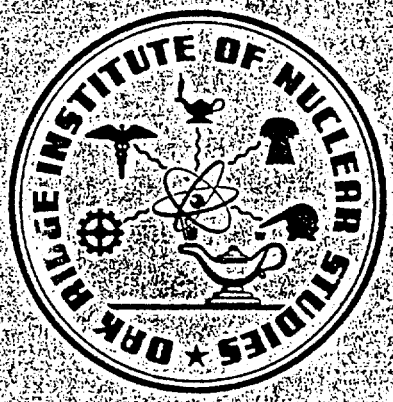
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OAK RIDGE INSTITUTE of NUCLEAR STUDIES

Quarterly Progress Report

July 1 - September 30, 1952



Operating Under Contract AT-40-1-Gen-33
with the
UNITED STATES ATOMIC ENERGY COMMISSION

P. O. Box 117 Oak Ridge, Tennessee

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Not for Re-publication

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INTRODUCTION

This is the first in a series of quarterly reports to be issued by the Oak Ridge Institute of Nuclear Studies. This series is being initiated primarily to provide a periodic report on the Institute's research activities. It will serve as a report both to the Atomic Energy Commission and to the Institute's sponsoring universities.

In the case of the Medical Division, more than the quarterly period is covered in order that research programs underway may be outlined in full. Subsequent reports will be less voluminous, since they will reflect only the quarter's work.

The Medical Division has engaged in considerable research on both internally-administered radioisotopes and in the development of external, or teletherapy, units for the administration of radiation.

In addition to and as a part of its primary objective of investigating the value of radioisotopes in cancer therapy, the Medical Division conducts an extensive training program, largely through the acceptance of residents from cooperating medical schools and the armed forces.

No report is made on the Gallium-72 research which absorbed much of the energies of the Medical Division during its first year, since this project has been terminated. It is discussed fully in a report to the Isotopes Division AEC, under the title: "On the Therapeutic Use of Gallium-72" dated November 15, 1952. The work on Gallium-67 as a therapeutic agent in bone tumor studies is too preliminary to justify a report at this time, but will be incorporated in subsequent reports.

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OAK RIDGE GRADUATE FELLOWSHIP PROGRAM

Through this program, candidates for advanced degrees carry out their thesis research at Oak Ridge National Laboratory or the UT-AEC Agricultural Research Program. A committee representing both the laboratory and the fellow's university supervises his research.

The following Oak Ridge Graduate Fellows are now in Oak Ridge: (6)

Name	Institution	Field	Degree Sought	Beginning Date
Adams, J.M.	Virginia P. Inst.	Biochemistry	Ph. D.	4-16-51
Drucker, B.M.	U. of N.C.	Mathematics	Ph. D.	3-15-51
Gamble, R.L.	U. of Texas	Physics	Ph. D.	8-7-52
Garrett, B.S.	U. of Arkansas	Chemistry	Ph. D.	9-15-52
Meade, T.L.	U. of Florida	An. Nutrition	Ph. D.	6-7-52
Stevens, D.K.	U. of N. C.	Chemistry	Ph. D.	10-1-51

The following Oak Ridge Graduate Fellows have completed their Fellowships during this quarter: (3)

Name	Institution	Field	Degree Sought	Beginning Date	Term. Date
Allen, R.G.	U. of Texas	Physics	Ph. D.	10-2-50	10-1-52
McElroy, D.L.	U. of Ala.	Metallurgy	M. S.	6-1-51	9-14-51
				6-1-52	9-15-52
Rogers, R.W.	U. of Tenn.	Zoology	Ph. D.	9-1-50	8-31-52

The following Oak Ridge Graduate Fellow was called into military service and forced to terminate his Fellowship: (1)

Name	Institution	Field	Degree Sought	Beginning Date	Term. Date
Hall, C. W.,Jr.	U. of Ala.	Metallurgy	M.S.	6-6-52	7-14-52

RESEARCH PARTICIPATION PROGRAM

This program is carried out in order that university faculty members may participate in Oak Ridge research programs for periods of time ranging from three months to one year and, in exceptional cases, somewhat longer.

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The following Research Participants have begun work since the beginning of the present fiscal year: (6)

Name	Institution	Place of Work	Beginning Date
[illegible], T. A.	U. of Georgia	ORNL-Health Physics	7-1-52
[illegible], Edwin G.	U. of Georgia	ORNL-Biology	7-1-52
Eckels, A. R.	N. C. State Col.	ORNL-React. Exp. Engr.	7-1-52
Ganz, Aaron	U. of Tenn. (Med.)	ORINS-Medical	7-1-52
Little, R.C.	U. of Tenn. (Med.)	ORINS-Medical	7-2-52
Walker, C.S.	A.&M. Col. of Tex.	ORNL-Reactor Control	9-8-52

The following Research Participants terminated during this quarter: (67)

Name	Institution	Beginning Date	Term. Date
Anderson, C. E.	Univ. of N. C.	6-5-52	9-2-52
Anderson, F. A.	Univ. of Mississippi	5-29-52	8-22-52
Bailey, P.S.	Univ. of Texas	6-6-52	9-5-52
Barnette, N. H.	Univ. of Arkansas	6-11-52	8-29-52
Barr, Thomas A., Jr.	Univ. of Georgia	7-1-52	9-15-52
Boyd, Gilbert W.	Mich. Col. of Min. & Tech.	6-13-52	9-10-52
Bridgman, Anna J.	Agnes Scott College	6-3-52	9-5-52
Brown, J. H.	Univ. of N. C.	6-3-52	9-12-52
Brumffeld, R. T.	Longwood College	6-4-52	9-12-52
Caswell, R. S.	Univ. of Kentucky	6-2-52	8-22-52
Clothier, R. F.	Alabama Poly. Inst.	6-9-52	8-8-52
Conte, S. D.	Wayne University	6-2-52	8-29-52
Delwiche, E. A.	Cornell University	6-5-52	9-5-52
[illegible]t, J. N.	Univ. of Virginia	6-2-52	9-16-52
[illegible]s, C. H., Jr.	Univ. of Tenn. (Med.)	6-16-52	9-12-52
Fisher, R. A.	Univ. of Texas	6-16-52	9-19-52
Frierson, W. Joe	Agnes Scott College	5-29-52	9-5-52
Fuller, Harold Q.	Missouri School of Mines	6-2-52	8-29-52
Gammill, A. M.	Univ. of Mississippi	5-29-52	8-28-52
Ganz, Aaron	Univ. of Tennessee (Med.)	7-1-52	9-30-52
Goldcamp, T. F.	Alabama Polytechnic Inst.	6-16-52	9-26-52
Goodrich, Max	Louisiana State Univ.	6-2-52	9-3-52
Gully, Arnold J.	Mississippi St. College	6-2-52	8-29-52
Harris, C. F.	Oklahoma A.&M. College	1-31-52	8-29-52
Hearon, John Z.	University of Chicago	4-2-52	7-31-52
Hull, Stacy L.	Univ. of Arkansas	8-30-51	8-29-52
Hunt, Ernest L.	Emory University	6-3-52	9-12-52
Ikenberry, Ernest	Alabama Poly. Institute	6-2-52	8-19-52
Johnson, Rowland E.	Florida State Univ.	6-6-52	9-12-52
Johnston, Perry M.	Univ. of Arkansas	6-12-52	9-12-52
Jones, William H.	Emory University	5-29-52	9-19-52
Keen, Richard C.	Louisiana State Univ.	2-1-52	9-1-52
Keenan, Charles W.	University of Tennessee	6-2-52	8-29-52
Kieffer, William F.	College of Wooster	8-1-51	8-1-52
Knox, Kerro	Univ. of N. C.	6-2-52	8-29-52
Lanterman, Elma J.	North Carolina St. College	6-5-52	9-5-52
LeRoy, Royce H.	A. & M. College of Texas	6-5-52	9-5-52
Lewis, William B.	University of Oklahoma	6-9-52	9-9-52

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Name	Institution	Beginning Date	Term. Date
Little, Robert C.	Univ. of Tenn. (Med.)	7-2-52	9-30-52
Long, Justin T.	Alabama Polytechnic Inst.	6-2-52	8-29-52
Loring, Ralph A.	Univ. of Louisville	2-4-52	8-22-52
Lovelace, Lollie R.	Univ. of South Carolina	9-4-51	9-15-52
Lynn, Joseph T.	N. C. State College	4-7-52	9-5-52
Mahaney, J. P.	Virginia Poly. Inst.	6-5-52	8-22-52
Matthews, David E.	Univ. of Mississippi	5-27-52	9-5-52
Noll, F. H. Waldemar	Berea College	5-28-52	9-19-52
Oxford, Chas. W.	Univ. of Arkansas	6-10-52	8-29-52
Randall, Charles A.,Jr.	Ohio University	6-13-52	9-4-52
Rogosa, G. L.	Florida State University	6-9-52	8-15-52
Rowley, Howard H.	Univ. of Oklahoma	5-29-52	8-29-52
Sartain, C. C.	Univ. of Alabama	6-2-52	9-12-52
Schimmel, Fred A.	Fisk University	5-28-52	9-26-52
Schumann, Fred	Vanderbilt University	6-10-52	9-5-52
Schweyer, H. E.	University of Florida	6-4-52	8-22-52
Sealander,John A.,Jr.	Univ. of Arkansas	6-12-52	9-12-52
Sessions, R. F.	Georgia Inst. of Tech.	6-10-52	9-26-52
Sharrah, Paul C.	Univ. of Arkansas	6-20-52	8-29-52
Swanson, C. A.	Ohio State University	4-14-52	9-16-52
Topp, Allan C.	Georgia Institute of Tech.	6-16-52	9-26-52
Vick, Maurice M.	Louisiana State Univ.	6-2-52	9-5-52
Vingiello, Frank A.	Virginia Poly. Inst.	6-6-52	9-19-52
Waser, Jurg H. E.	Rice Institute	6-13-52	9-8-52
Watson, G. M.	A&M College of Texas	6-4-52	9-5-52
Webb, William H.	U. of Mo. School of Mines	6-2-52	8-29-52
Wilde, W. S.	Tulane Univ. of La.	5-26-52	9-30-52
Williams, H. B.	Univ. of Florida	6-2-52	8-29-52
Wood, John L.	Univ. of Tennessee (Med.)	6-30-52	8-29-52

The following former Research Participants who hold Form S Contracts with the Institute made trips to Oak Ridge during this quarter in order to keep abreast of research developments: (14)

Name	Institution	Department	Date of Trip
Ball, E. A.	N. C. State Col.	Botany	8/18-21/52
Barrentine, B.F.	Mississippi State Col.	An. Husbandry	8/22-23/52
Bonner, O.D.	Univ. of South Carolina	Chemistry	7/13-14/52
Ciereszko, L.S.	Univ. of Oklahoma	Chemistry	9/24-30/52
Davis, D.E.	Alabama Poly. Inst.	Botany	8/21-22/52
Davis, H.W.	Univ. of South Carolina	Chemistry	8/18-19/52
Day, R. A.	Emory University	Chemistry	7/13-14/52
Gregg, J. H.	University of Florida	Biology	9/3-5/52
Hopkins, J. I.	Vanderbilt University	Physics	7/8/52
Howell, E. I.	Mississippi State Col.	Physics	8/25-26/52
Pike, F. P.	North Carolina St. Col.	Chem. Engr.	9/2-3/52
Strobel, H. A.	Duke University	Chemistry	7/18/52
Wheeler, H. E.	Louisiana State Univ.	Botany	8/18-20/52
Young, F. W.	Univ. of Virginia	Chemistry	7/7-8/52

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We are particularly pleased to note that the work of Dr. E. H. Carretson, Research Participant from Lynchburg College, has been recognized by the Laboratory officials as being of very great importance as a direct contribution to a program of vital importance to the Atomic Energy Commission.

SUMMER SYMPOSIA

The Fourth Annual Oak Ridge Summer Symposium on "The Role of Atomic Energy in Agricultural Research" was held in the Center Theatre August 25-30. Three hundred eighty-five people registered and, of these, three hundred fifteen were presumably from outside the Oak Ridge area. Thirty-three speakers participated in the program. Of these, fourteen were local Oak Ridge people connected with the Institute, the UT-AEC Agricultural Research Program, the ORNL, or the AEC.

As is usual, the symposium was presented by the Oak Ridge National Laboratory and the Oak Ridge Institute of Nuclear Studies. This year's sponsor was the University of Tennessee-Atomic Energy Commission Agricultural Research Program.

TRAVELING LECTURE PROGRAM

The Traveling Lecture Program, through which Oak Ridge scientists conduct lectures and lead seminars, is underway for 1952-53. Since the universities do not use many speakers in the summer, the number of requests is small. About 1,000 announcements of the program have been mailed, largely to faculty members of sponsoring universities. In addition, people who have requested them and Research Participants for past year have received announcements.

To date, eleven requests have been received. Of these, four were requests for men from the Oak Ridge National Laboratory. Five speakers have delivered talks and five are scheduled to speak in November.

RESIDENT GRADUATE PROGRAM

This is a service program conducted by the University of Tennessee to provide course work for scientific and technical employees in Oak Ridge.

The following is a summary of enrollment in the Resident Graduate Program for the Summer Quarter, 1952:

A. By courses:

Course	Individuals Registered
Chemistry 451	5
Chemistry 502	1
Chemistry 600	2
Mathematics 461	24
Mathematics 501	1

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Course	Individuals Registered
Mathematics 511	16
Mathematics 543	10
Mathematics 600	1
Mechanical Engineering 501	1
Metallurgy 501	1
Metallurgy 502	1
Metallurgy 503	1
Physics 543	2
Physics 600	2
Total	68

B. By employer:

Employer	Different Employees Registered	Number of Courses Taken
Carbide & Carbon Chem. Co., K-25	15	16
Carbide & Carbon Chem. Co., Y-12	12	14
Oak Ridge National Laboratory, X-10	31	36
General Electric Company	1	1
U. S. Atomic Energy Commission	1	1
Total	60	68

AEC PREDOCTORAL AND POSTDOCTORAL FELLOWSHIP PROGRAMS

The following chart is designed to show the number of active Predoctoral and Postdoctoral Fellows during the first quarter of the 1952-53 fiscal year and the number of terminations occuring during that period.

Life Science

	July	August	September	Terminations
Predoctoral 1st Renewal	58	58	44	14
Predoctoral 2nd Renewal	11	11	10	2
Postdoctoral	17	16	10	7
Postdoctoral Medical	5	5	1	4

Physical Science

Predoctoral 1st Renewal	139	134	113	27
Predoctoral 2nd Renewal	30	25	20	17
Postdoctoral	20	20	9	13

AEC RADIOLOGICAL PHYSICS FELLOWSHIP PROGRAM

I. During the summer months of 1952, nineteen 1951-52 Radiological

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Fellows participated in the field training at ORNL and nineteen in the field training at BNL.

Seventeen Fellowships have been granted for the 1952-53 radiological course at Rochester-BNL and twenty-two for Vanderbilt-ORNL.

II. Three 1951-52 AEC Radiological Physics Fellows were given nine-month appointments to Industrial Hygiene Fellowships as follows:

Mr. R. E. Cunningham, former AEC Radiological Fellow at the University of Rochester-BNL, appointed for work at the Harvard School of Public Health under Dr. Philip Drinker.

Mr. J. E. Turner, former AEC Radiological Fellow at Vanderbilt University-ORNL, appointed for work at the Harvard School of Public Health under Dr. Philip Drinker.

Mr. J. L. Donovan, former AEC Radiological Fellow at the University of Rochester-BNL, appointed for work at Pittsburgh School of Public Health under Dr. T. F. Hatch.

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COURSES

The twenty-eighth and twenty-ninth sessions of the Basic Techniques in Radioisotope Procedures course have been completed. There were thirty-two participants in each course. The total number of participants who have attended the basic course is now 963. Altogether, 1083 participants have attended the basic and advanced courses which have been offered.

An advanced course to cover the application of radioisotopes to biochemical research is planned for November 3 - 13, 1952. Applications are being received for this course, and a selection of about forty participants will be made.

Plans have been made to sponsor symposia on "Nuclear Science in Industry" and "Carbon-14 in Research" at the St. Louis AAAS meeting, December 29, 1952. In addition, a luncheon for former participants is planned for the same day.

STAFF ACTIVITIES

CHEMICAL RESEARCH

Determination of Titanium Activity. An investigation of the 70 d. activity produced when titanium is irradiated with thermal neutrons is in progress. Examination of the gamma-ray spectrum of this activity on the scintillation spectrometer, and comparison with the spectrum of iridium, shows nearly all the gamma energies of the two to be the same. Likewise the half-lives are identical within about 5%. However, iridium also has a 19 h. activity, which, on short irradiations, is produced in amounts similar to the 70 d. activity. A sample of titanium oxide (TiO_2), purified by the National Bureau of Standards, also shows an activity of about 20 hours. No report of this has been found in the literature except one early report of sodium activity from titanium metal, but not found upon irradiation of the oxide. The decay curve and/or relative abundance of the impurity is quite different from sodium, suggesting the possibility of another impurity. Examination of the gamma ray spectrum of the short-lived activity is suggested, and the earlier work on the 70 d. spectrum indicates the desirability of improved resolution. This is being planned. Chemical means for the separation and identification of the activity found upon irradiation of TiO_2 samples are being investigated, as well as methods for the removal of the source of the activity prior to irradiation. Different sources of titanium compounds and different compounds will also be investigated to determine whether the impurity is always the same and, in addition, to determine its relative abundance. (R. H. Firminhac and E. Rona)

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Thorium Determination in Ocean Water. It has been reported that the uranium-radium ratio in sea water differs from the theoretical value. The ratio of sea water radium (Ra) to that expected in the uranium-radium equilibrium (Ra_U) is 0.17, i.e., $Ra/Ra_U = 0.17$. This is probably brought about by the precipitation of the thorium isotope, ionium (Th^{230}), from the sea water to the bottom of the ocean. Due to the very low concentration of this isotope in ocean water, special analytical methods have to be employed, such as activation analysis or the counting of alpha-tracks in nuclear emulsions. Prior to the use of either of these methods, the thorium isotopes must be concentrated and purified from large amounts of ocean water. Current investigations concern a sample of 200 kg of sea water which was collected recently off the Look Out Sea Wall, Beaufort, North Carolina, and concentrated at the U.S. Department of Interior, Fish and Wildlife Service, Beaufort, North Carolina.

These studies are to be used in pursuing further the nature of the radiochemistry of the North Atlantic. (E. Rona)

Isotopic Ratio of Thorium-Ionium in Minerals. This project was started at the Argonne National Laboratory at the suggestion of W. M. Manning. The experiments have the purpose of finding ionium sources of maximum isotopic purity and of determining whether trace thorium content of uranium ores can partly or completely originate from the uranium isotope, U^{236}.

The main emphasis at the present time is put on the second of these purposes. Uranium-236 was produced artificially, but its half-life of 2×10^7 y. makes it appear probable that it occurs in nature, though its concentration at the present time must be very low. The old primary minerals which would not contain detectable amounts of U^{236} would still contain Th^{232} which, because of its long half-life, would remain in direct proportion to the original amount of its U^{236} ancestor. Primary minerals of known age have been carefully selected and the ionium-thorium ratio determined, ionium (Th^{230}) being genetically related to uranium. This procedure has the advantage that the same method of separation can be applied for both isotopes, and both determinations are equally affected by any errors arising from chemical operations. The final purification and concentration of the thorium isotopes is carried out by solvent extraction.

The ratio determination of the purified samples was made by bombarding the sample, together with a standard of known Th^{232}/Th^{230} ratio, with slow neutrons in the CEN pile, followed by counting the beta activity of the Th^{233} with a G-M tube and the alpha activity of Th^{230} in a methane-filled ionization chamber connected to a counting circuit. The beta/alpha ratio of the activities of the two samples allowsthe calculation of the thorium-ionium ratio of the samples under consideration. Experiments on a pitchblende from Katanga, Africa, and a carnotite are under way.

The main source of error in these determinations is an insufficient separation of uranium-238. As it has the same slow neutron cross-section as thorium-232, and, after irradiation, the uranium-239 formed has approximately the same half-life (23 min.) as thorium-233 (23.5 min.), the presence of uranium-238 in the

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sample can be a source of considerable error. Uranium-238 contamination can be measured by taking advantage of the fact that uranium-239 emits gamma rays with an energy of 0.92 Mev, whereas thorium-233 has no gamma rays. The use of a scintillation spectrometer obviates any difficulty from uranium-238 contamination, as the determination of gamma rays with a scintillation spectrometer is more sensitive than the fluoroscopic method and fission counts previously used. Thorium-232/ionium samples prepared at Argonne are checked by this method for uranium contamination. (E. Rona)

Study of RaDEF Chemistry on Anion Exchange Columns. A project has been started to study the chemistry of polonium, using ion exchange methods. The problems under investigation are: the charge of the polonium ion in different media, complex ion formation, and ion exchange versus physical adsorption as methods of separation. Preparatory to this problem, methods to separate RaD, RaE and RaF have been investigated. Ion exchange column and electrochemical separations have been attempted.

It has been found that RaD does not form complex anions in hydrochloric acid of any concentration; consequently, it does not exchange on ion exchange resins in acid solutions in the concentration range 0.1 - 6 M HCl. Also, RaE is strongly adsorbed in HCl, 0.1 - 0.5 M; less strongly in the range, 1 - 6 M. Finally, RaF is very strongly adsorbed at all HCl concentrations which have been investigated (0.5 - 6 M).

Further efforts will be directed toward ion exchange study of RaD, RaE and RaF under varying conditions; the calculation of K_D; and an attempt to determine the charge of the complex ion involved in each case. (E. Rona)

INSTRUMENTATION RESEARCH.

Four vacuum-tube electrometers have been constructed. The major objective in their design was to maintain a reasonable price and a simple circuit which could be constructed by workers not expert in the electronic arts. The cost of the parts is about $140, and all components are standard radio parts except the high-megohm resistors, electrometer tube and heliopot. These are readily available, however. The sensitivity of the electrometers is about 10^{-14} amp minimum current, and the drift does not exceed a few millivolts/day. A recorder of 10 mv sensitivity or less can be used. The electrometers compare quite favorably in operation with a vibrating-reed electrometer.

A set of ionization chambers is being completed which will permit the measurement of solids, gases and liquids. Either beta or gamma activities may be determined at sensitivities comparable to end-window G-M counting. The chambers are all interchangeable on one electrometer.

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A simple, high-resistance selector switch for use with electrometers has been designed and incorporated in the electrometers.. Five positions are provided with the resistance of any position at least 10^{15} ohms. A shorting switch of comparable resistance has also been designed which does not give "kicks" when used in the input of electrometers.

A four-pi proportional beta counter has been completed for use in absolute beta counting. A complete report giving construction details and complete operational data will be written upon completion of these projects.

A logarithmic counting rate meter is about 80% complete. The circuit is similar to that published by E. H. Cooke-Yarborough and E. W. Pulsford, It is planned to include a range of five decades. Selection of the number of decades from one to five will be provided, and provision will also be made for the independent selection of the counting rate at which the first decade begins. The counting rates which can be measured will be from one count per second to 10^5 c/s. Provision for recording on a 10 mv. recorder will be made. The input sensitivity is from -50 to + 100 V, adjustable by an accurate discriminator, and provision is made for connection of a preamplifier when it is required. (R. H. Firminhac)

PHYSICAL RESEARCH

Gamma Exposure Studies. Research is continuing concerning the dosage of animals by the gamma exposure device used by the UT-AEC Agricultural Research Program. This work, in cooperation with the UT-AEC program, is a continuation of studies begun under Contract At-40-1-Gen-242-Sub 10, which terminated effective February 1, 1952.

This work has involved chiefly the use of Victoreen thimble chambers in the following sizes: 25-r, 100-r, and 1000-r. The 1000-r chambers are attached to the animals in order to estimate the whole-body irradiation dose that is received during an exposure. These instruments were said by the manufacturer to be energy-independent above 100 kv, but it has been found that this is not the case. The ionization that takes place in the stem is about one-third of the total ionization that is registered when the entire chamber is exposed to cobalt-60 radiation. This was also observed independently at the National Bureau of Standards. An attempt is being made to measure the air dose of the radiation site and to correlate this with the readings of the Cictoreen r-chambers on the animals.

In connection with this work, consultation was held with National Bureau of Standards personnel (F. H. Day and Scott Smith) on the problem. In addition, Dr. Day visited the local site and further discussions were held. Other consultations were held with Commander W. F. Chambers and Commander Jasper Morgan at the Naval Medical Research Institute, with regard to their experience with Cictoreen 1000-r chambers, and, in addition, to plan a visit by Commander Chambers to the UT-AEC facilities.

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Recent work on the problem has involved: The exposure of colorimetric dosimeters to the cobalt-60 radiation field for the UCLA Atomic Energy program; exposure of a 1000-r chamber and a 25-r chamber in the cobalt exposure device at the ORNL Biology Division; measurement of the radiation rate at the UT-AEC exposure field prior to the exposure of dogs; and the design of four chambers for irradiation of tantalum metal in the ORNL reactor. In addition, simultaneous exposure of 0.25-r, 25-r and 100-r chambers to one cobalt-60 source have been made at the exposure site. Other work has included: The comparison of 22 1000-r chambers for variation of response rate with time; the design and construction of a device to locate a cobalt-60 source accurately at a fixed point in space above the exposure site; the exposure of 30 1000-r and 100-r chambers to the beam from the ORINS Teletherapy Unit to determine their relative response in a broad beam; and exposure studies of 100-r and 1000-r chambers on a burro phantom (lucite and water) to compare their readings to the air-dose readings. The work also includes initiation of a program of nightly exposures of burros to the cobalt-60 field using 1000-r dosimeters. (C.S. Simons)

Calibration of Cobalt-60 Teletherapy Unit. Investigation of the calibration of the cobalt-60 teletherapy unit by the Medical Division of ORINS has involved assistance of the Special Training staff in a consulting capacity and in the provision of some of the instruments used. In addition, use has been made of the unit to investigate the response of 30 Victoreen chambers to the particular radiation available from such a source. (C.S. Simons)

LABORATORY DEVELOPMENT

Gas Counting. A modification of the carbon dioxide chamber-filling apparatus used by the ORNL Biology Division has been adapted for use in the course. The design of equipment to allow four groups of participants to perform the operation of filling chambers with radioactive carbon dioxide for measurement on an electrometer is completed, and the required pieces of apparatus have been ordered. This system will be completed for the next basic course. (D.R. Smith)

Solid Counting. A filtration assembly for the preparation and mounting of solid counting samples--particularly barium carbonate--has been developed. This device uses a sintered stainless steel plate as the sample mount, and the design of the assembly is aimed at eliminating as much as possible the various errors of sample preparation which have obtained with other sampling methods. Testing of the apparatus is incomplete, and no report of its merit is possible at present. (D. R. Smith)

LIBRARY RESEARCH

There has been a noticeable lack of organization of technical

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literature in the field of tracer applications of radioisotopes. This has been pointed up by requests from participants for information and assistance from the Special Training Division in this connection. Although the Division's functions do not at present provide for any such service, considerable effort has been expended toward this end. This work has been devoted to research regarding the mechanism of the organization of technical literature in limited fields, the development of procedures and equipment for this work, and the actual collection and organization of literature in certain instances. Progress to date on this project involves the following developments:

An edge-punched "Keysort" card has been designed for the efficient indexing of the literature. The card which has been worked out is sufficiently versatile to be useful in any field of tracer application. The card and the system used largely eliminate the disadvantage of "extra cards" dropping during the sorting operation, and also are adaptable to very extensive subject indexing of highly specific subjects.

A file involving the punched cards has been worked out for the field of autoradiography. At present, over five hundred references have been collected as reprints and indexed by punched cards and an author index card file. This collection is being completed as rapidly as time will permit. It is intended that the organization of this literature will be kept up-to-date, providing the Special Training Division with a very comprehensive and detailed center of autoradiographic literature. In the short time since the development of this system, it has been used to advantage by several people on the ORINS staff, and these cases have been found to reduce greatly the time and effort formerly required to search the literature for particular subjects in the field of autoradiography.

To test further the desirability of providing information and documentation by Special Training Division, a system is being developed to cover the tracer applications of isotopes in industry. The mechanics of this system will parallel the autoradiography system described above. It is intended that prepared bibliographies in the various general fields of industrial application will be ready for the participants in the Advanced Industrial course planned for 1953. The response of these people to such an innovation can be used as a basis for the evaluation of this type of service.

In addition to the specific applications of punched cards mentioned, there has been repeated occasion to advise ORINS staff members and other local scientists regarding punched card uses and application. (D.R. Smith)

OTHER STAFF ACTIVITIES

An exhibit of counting instruments was designed and set up at the Museum of Atomic Energy for use during the Fourth Annual Oak Ridge Summer Symposium. The instruments were demonstrated and

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consultation was given to the visitors to the exhibit.
(C. S. Simons and J. T. Lynn)

PUBLICATIONS AND LECTURES

R. T. Overman, "Basic Facts about Isotopes," lecture presented at the Fourth Annual Oak Ridge Summer Symposium, August 25, 1952.

C. S. Simons, "Instrumentation for an Agricultural Radioisotope Laboratory," lecture presented at the Fourth Annual Oak Ridge Summer Symposium, August 25, 1952.

D. R. Smith, "Carbon-14 Sample Preparation and Counting Techniques (Solid Counting)," lecture presented at the Fourth Annual Oak Ridge Summer Symposium, August 27, 1952.

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TELETHERAPY UNIT

The Institute Medical Division has devoted much of its energies to the development of external, or teletherapy units. In cooperation with the M.D. Anderson Hospital of the University of Texas and the General Electric Company, a teletherapy cobalt unit was designed and constructed and is now undergoing tests in the Medical Division prior to being sent to the M.D. Anderson Hospital for therapeutic uses. A report on this unit is set out below.

The other line of development has been the organization of the Teletherapy Evaluation Board, comprised of medical school representatives, which is to supervise the design, construction and testing of a kilocurie unit utilizing cesium, europium or cobalt. The present plan is for the Institute to build a prototype unit where preliminary testing will be carried out. Later, several of the cooperating medical schools will obtain units and a thorough testing program will be carried out under the supervision of the board.

COBALT-60 PROGRAM

The housing for the 1000-curie telecobalt source was completed by the General Electric Company and shipped to Oak Ridge in the fall of 1951, although irradiation of the source at Chalk River was not complete. A 180-curie source irradiated at Oak Ridge National Laboratory and allocated to Max Cutler, M.D., Chicago Tumor Institute, was obtained for the preliminary testing program.

The testing program to date concerns the following:

a. Revisions to reduce leakage radiations.
b. Design of treatment cones.
c. Loading the Chalk River source.
d. Measurement of effective curie strength of source.

Revisions to Reduce Leakage Radiation. With the 180-curie source in the "off" position, a survey of the unit was made to determine the mr/hr at points on the surface. The leakage radiation was found to be much larger than was expected. The radiation intensity was also found to be non-uniform around the circumference of the unit. The points of highest intensity were those opposite the attachments for accepting the screws, the "ears," on each side of the source box. This is mainly due to the replacement of the heavimet cut from the wheel by the steel ears of the source box. The container for the 1,000-curie source has been re-constructed with tantalum ears.

Measurements show the absorption of the leakage radiation in lead to be about the same as that of primary cobalt gamma-rays. Two lead shields

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weighing 120 pounds each have been cast. These will be attached to opposite sides of the unit when the 1,000 curie source is loaded. The curvature of the lead was calculated to reduce the radiation to 6.25 mr/hr at any point on the surface other than those opposite the four steel bolts holding the heavimet discs together. This will give the unit a somewhat spherical appearance with a diameter of 18 inches.

Design of Treatment Cones. Much work was spent in finding the optimum materials with which to construct the treatment cones. Other than obtaining a well defined beam, the chief concern was the emission of secondary electrons from the cone. The reduction of these electrons was studied by means of electron build-up measurements. A shallow ionization chamber was used.

Measurements were made at various distances from the end of the cone using 5 cm and 10 cm diameter experimental cones under the following conditions:

(1) All lead cone,
(2) Lead cone with brass inner lining,
(3) Lead cone with lucite inner lining,
(4) Lead cone with lucite over opening,
(5) Lead cone with brass over opening,
(6) Lead cone with pyrex over opening.

Build-up curves were measured at 3.5, 8.5, 13.5, 23.5 and 33.5 centimeters respectively, from the end of the cone.

It was found that using a brass lining and a 0.010" brass shim over the opening gave the best results. Although the effect of the brass decreases with increasing cone to skin distance, the brass was found to show some improvement at all distances.

Erythema studies with rabbits using a 2 cm diameter cone in contact with the skin showed less burning when the cone had a brass lining. No experiments were made using the brass shim because of the long time required to obtain an erythema dose from such a weak source.

Loading the Chalk River Source. The strong source arrived in Oak Ridge near the middle of July and was loaded into the unit on August 1, 1952. Although the temporary source was loaded under water, the strong source was loaded in a dry cell at the Physics of Solid States Building at Oak Ridge National Laboratory. The loading procedure was developed and handled by the ORNL Reactor Division personnel.

Measurement of Effective Curie Strength of Source. After the unit containing the Chalk River source was installed in the cobalt room of the Medical Division, measurements were made to determine the effective curie strength of the source. Using the broadest beam possible, a calibrated Victoreen condenser-type thimble chamber was placed 60 cm above the floor and 50 cm from the source. Using the measured roengtens per minute delivered at this distance in air, the effective strength of the source was calculated from R. D. Evans': value 13.5 r/hr at 1 cm

from a 1 millicurie cobalt-60 source. The calculated value was 851 effective curies on Sept. 16, 1952. The dose rate at that time was 76.6 r/min at 50 cm. This includes about 5 per cent scattering from the cone for which no corrections were made.

INTERNALLY ADMINISTERED RADIATION

Metabolism and Distribution of Colloidal Gold - 198

INTRODUCTION

In the course of a study of the use of colloidal gold-198 in the treatment of ascites and pleural effusions, data have been collected on the distribution and excretion of this isotope. This form of treatment, suggested by J. Muller[1], has proved of some value in symptomatic therapy of patients who have massive fluid collections resulting from metastatic neoplasms involving serous cavities. Clinical results of therapy in our series of cases have been previously reported[2]. The purpose of the present report is to present information on the fate of the injected material and to record some of its general effects.

METHODS

The material used in these studies was a preparation* of colloidal gold-198 containing a total amount of gold usually ranging from 3 to 9 mgm per ml. The radioactivity varied from 10 to 25 mc. per ml. except in a very few cases in which preparations of lower activity were used. Single doses varied from 10 to 235 mc. Details of dosage and method of administration have been reported[2]. The isotope was usually injected through a polyethylene tube inserted into the body cavity. In several patients, two polyethylene tubes, some distance apart, were inserted, one for administration of the gold and one for withdrawal of fluid for determination of radioactivity. (See Fig. 1.) It was believed that fluid drawn through the tube of administration should not be used for assay because it might have artificially high values as a result of poor mixing in the cavity and contamination at the time of withdrawal. Daily complete 24-hour urine specimens and frequent blood samples were collected and assayed for radioactivity. Stool specimens were not assayed after extremely low levels of activity were found in those from the first two patients studied. Biopsy and autopsy specimens were obtained for histologic study, radioassay and autoradiographic exposures. All radioassays were performed by liquid techniques. Solid tissues were dissolved in concentrated nitric acid in preparation for assay while urine and plasma were untreated or were simply diluted with water. In all cases, a 10 ml. specimen was placed in a standard small glass

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* Supplied by Abbott Laboratories

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Petri dish and assayed under a calibrated end-window Geiger tube. All values were corrected for radioactive decay to the time of administration of the isotope. The autoradiograms shown in Figures 4, 9, and 10 were prepared from gross tissue. The soft tissues were frozen solid in a deep freeze, sliced, and exposed on No-Screen film for varying lengths of time. The exposure depended on the degree of radioactivity. The bone autoradiograms were prepared by the method of Lotz, Gallimore and Boyd.[3]

FATE OF THE ISOTOPE IN THE CAVITY

After injection of the colloidal radiogold, the patients were asked to move about at frequent intervals during the first few hours. Our experience suggests that complete mixing of the gold with the fluid in the cavity usually occurs within the first few hours. This was shown in surveys of radiation levels at the surface of the body, made by means of a collimated Geiger tube. Additional evidence of this even distribution in the cavity is found in the radioactivity levels of fluid drawn from the cavity at sites distant from the point of injection. It is found that the fluid at these sites very rapidly reaches a maximum radioactivity.

In several patients rather extensive records were made of the radioactivity levels of the fluid in the cavities for several days after the radiogold injection and Figures 2 and 3 show these data. The fall in concentration of radioactivity, after correction for decay has been made, must be due to dilution of the gold by further fluid production or removal of the gold from the fluid, or both. It is known that active effusion of fluid may continue for some time after the gold is given, even in patients who respond favorably to the treatment, but it is not possible that there was sufficient dilution of the gold in the cavities to explain the major part of the fall in concentration of radioactivity, since this would have required a much greater increase in volume than ever occurred. Studies of blood and urine levels of radioactivity in the period immediately following administration show that there is little absorption or excretion of the gold colloid, and external counting assays over the liver indicate that there is not a prominent localization in this organ. Tissue assays indicate that a large portion of the radiogold becomes fixed in a superficial position on the serous surfaces. Autoradiograms confirm this distribution of the isotope. (See Fig. 4.) The exact mechanism of this deposition is not known but it is believed to be a property of the colloid in relation to the surface. A similar tendency of the colloid to become attached to surfaces is seen in vitro. Another mechanism for uniform dispersion in the concentration of gold particles from their fluid is phagocytosis by macrophages on the walls of the cavity or free in the fluid.

BLOOD RADIOACTIVITY

Venous blood was obtained daily after treatment, heparinized, and, after centrifugation, red cell and plasma fractions were assayed for radioactivity. The plasma showed levels of activity considerably greater than those of the red cells. Since the red cell samples were not washed,

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the activity recorded for them may have been all or in part that of the included plasma.

Plasma radioactivity levels were low in relation to the total dose of the isotope. On the basis of estimated total plasma volumes for the patients, it is calculated that the amount present in the blood at one time is generally less than one per cent of the dose given.

A variable pattern of plasma levels of activity was seen after both intrapleural and intraperitoneal radiogold administration, but for each individual patient, the changes in blood activity levels from day to day were relatively slight. (See Figures 5 and 6.) The patients given isotope intrapleurally appeared to have a more gradual and uniform rise in plasma radioactivity than those treated intraperitoneally.

The pattern of the rise in radioactivity in the blood does not appear to bear a direct time relationship to the fall in concentration in the fluid of the cavity, since the latter occurs much more rapidly. The activity in the blood is thought to be related to delayed mobilization of the colloidal material after it has been deposited on the walls of the cavity. It was not possible to correlate the plasma levels with degree of fibrosis of the serous surfaces. One patient, C. F., had relatively high blood radioactivity levels after only 14 mc of radiogold. This patient had a chylous effusion due to neoplasm invading the thoracic duct, and it is possible that much of the radiogold which reached the blood stream did so by entering this lymph channel directly from the pleural space.

No studies have been done to determine whether the relatively small quantity of radiogold which reaches the blood stream is in colloidal form, or whether it may represent a small fraction of the gold which is ionized at the time of administration, or which becomes ionized in the body. However, the distribution in liver, spleen, bone marrow, and other organs is similar to that seen after intravenous injection of a known colloidal preparation. This suggests that the gold which enters the blood stream is in colloidal form.

URINARY EXCRETION

A small, but highly variable, portion of the total dose given is excreted in the urine. Figures 7 and 8 indicate the daily excretion levels for the two groups (intrapleural and intraperitoneal). The excretion curves differ decidedly from those of the blood levels in that the highest excretion occurs in the first 24 hours, while blood activity is low. After this initial period there is a tendency for the amount excreted in the urine to be proportional to the blood levels in individual patients. It is suggested that the early relatively high urinary concentration may be explained by the presence of a small amount of ionized gold in the preparation given, this fraction being readily absorbed and readily excreted, while the later values may represent the colloidal material which is both slowly absorbed and poorly excreted.

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TISSUE ASSAYS

In studying the tissue distribution of isotopes injected into body cavities, we have encountered one particular difficulty: The presence of the isotope in the free fluid of the body cavity is likely to lead to smearing and contamination of tissues removed at operation or autopsy so that assay of these tissues for radioactivity may be misleading. In an effort to avoid this error at the time of autopsy, the cavity containing the isotope is not entered until all other available tissues have been obtained for radioassay. In selecting specimens from the treated cavity for radioassay, when an area not including the serous surface is to be assayed, the free fluid is first wiped off and the contaminated exterior is then carefully cut off with the use of successive clean knives. It has been found that once the gold is deposited on the lining of the cavity it is not easily dislodged, so that the main source of contamination is the relatively small amount of the isotope free in the fluid of the cavity.

In assaying the serous surfaces of the treated cavities for radioactivity, we have generally cut a thin layer of tissue for assay and determined the radioactivity per unit weight. It now appears that this is a rather unsatisfactory procedure since most of the colloidal gold is in an extremely superficial layer and specimens usually include some deeper tissues which contain very little of the isotope. Thus, the thickness of the specimens may influence the apparent concentration of gold if calculations are made on the basis of weight. It appears that a much more significant value under these circumstances is the activity per unit of surface area, and we are now attempting to obtain this information.

SURGICAL DATA

On several occasions following the administration of intracavitary radiogold, operations were done which yielded tissue specimens for study. These cases and the radioactivity levels of the tissues are summarized below:

- 010034 - The patient was a 37-year-old woman who had extensive intra-abdominal metastases of a papillary adenocarcinoma, probably of ovarian origin. She had a localized collection of fluid in the lesser omental cavity, which had been temporarily relieved by previous surgery. On October 15, 1950, 100 mc of colloidal Au^{198} were injected by means of a long needle inserted into what was believed to be the lesser omental cavity.

One week after the injection of the gold, another laparotomy was done, and the following are fluid and tissue radioassay values.

Specimen	µc/gm
Peritoneum from lesser omental cavity	115.16
Peritoneum from greater omental cavity	0.05

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Specimen		µc/gm
Tumor from mesocolon		1.71
Fluid from lesser omental cavity		0.34
Fluid from greater omental cavity		0.05
Fluid from cystic spaces in neoplasm	(sample a	0.19
	(sample b	0.11

- 110123 - The patient was a 46-year-old male who had been subjected to a thoracotomy after the discovery of a pleural effusion and an abdominal mass. Tissue obtained at this operation had revealed an unusual malignant lesion, probably a mesothelioma. When the patient was in almost terminal condition a laparotomy was done 9 days after 181 mc Au^{198} had been given intraperitoneally. This second operation was performed in an attempt to relieve distention believed due to loculated fluid. Several biopsies were obtained.

Specimen		µc/gm
Tumor from two different areas	(sample a	0.28
	(sample b	0.50
Parietal peritoneum		1.18
Abdominal fluid		0.24
Skin		0.04
Plasma		0.04

- 110051 - This 48-year-old white woman had extensive intra-abdominal metastases from a pseudomucin forming carcinoma of the ovary. A laparotomy was done 3 days after intraperitoneal administration of 48.2 mc of colloidal Au^{198}.

Specimen		µc/gm
Thin layer of normal peritoneum		8.72
Fat from just beneath peritoneum		0.02
Peritoneum with tumor		0.48
Tumor (a)	Superficial gelatinous nodules	115.12
(b)	Cystic superficial nodules	3.83
(c)	Solid, more than 1 cm from surface	0.00

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	(d) Other tumor samples	0.07, 0.42, 0.73, 5.63
Abdominal fluid		2.08
Liver without capsule		0.82
Muscle from abdominal wall		0.07

- 110078 - This 53-year-old white woman had a carcinoma of the uterus with multiple intra-abdominal metastases. On May 24, 1951, she was given 232 mc of colloidal Au^{198} intraperitoneally. On June 19, 1951, 26 days later, a laparotomy was necessary because of obstruction of the colon.

The peritoneum, where it was not involved with tumor, showed pronounced variation in color. The surface in the upper abdomen looked normal, while that in the pelvis and around the bladder had a distinct bluish-purple pigmentation, presumably due to the gold.

Specimen		µc/gm
Normal peritoneum		22.29
Pigmented peritoneum		3271.42
Tumor	(a) Nodule free in abdominal cavity	764.29
	(b) Mass in omentum	144.29
	(c) Mass between two loops of small bowel	7.93

Parietal peritoneum with microscopic area of tumor	6.51
Plasma	0.13

- 010032 - This patient was a 69-year-old woman who had a pseudomucin forming carcinoma of the ovary with extensive intra-abdominal metastases. During the three months preceding operation, the patient had received 7 intraperitoneal injections of colloidal radiogold^{198}, varying from 10 to 110 mc. The last dose, 3 days before operation, was of 52 mc. The operation was done to evaluate effects of treatment.

Specimen		μc/gm
Tumor	(a) Cystic areas in omentum	1.71
	(b) Nodule in omentum	6.13
	(c) Nodule on surface of bowel	24.22
	(d) Deep cystic area	0.01
	(e) Deep solid area	0.05
Peritoneum with pseudomyxomatous tissue	(sample a	0.28
	(sample b	31.63
Omentum		0.21
Adhesions around tumor		0.56
Gelatinous fluid		3.24
Fluid from within cysts		0.00
Skin		0.00

The radioactivity values of the surgical specimens show wide variations in concentration of the isotope, which cannot be explained by the nature of the tissue assayed. Most of these variations are due to the fact that the isotope is deposited on the surface of the specimens and the amount of surface varies greatly in relation to the weight of the sample. In one patient ( ), there was an extreme difference in the radioactivity of two specimens of peritoneum without tumor. The specimen having a high activity was pigmented; the one having a low activity was not. There was obviously a very uneven deposition of the isotope on the surface in this case.

The radioassays from surgical material confirm the fact that the radioactivity of the fluid becomes less than that of the serosal surfaces. They also serve to emphasize the almost complete failure

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of the isotope to penetrate significantly beneath the surface.

AUTOPSY STUDIES

Data are available on radioactivity of tissues obtained at autopsy from 9 patients, who died at intervals of from 1 to 16 days following injection of gold.

Table No. 1 indicates the radioactivity levels per gram of a representative group of tissues. The values for the walls of the treated cavities show great fluctuations, which may be explained partly on the basis of the variations in the thickness of the samples taken for assay. In most instances the cavity walls had an activity per gram considerably higher than that of the fluid within the cavity. One patient ( ) had relatively low activity in the specimen from the cavity wall as compared with liver and spleen. These findings are believed to be explained by unusual degree of absorption into the blood stream of the colloidal material in this case.

Table No. 2 shows the total per cent of the injected radioactivity which could be recovered in the livers and spleens of patients autopsied at varying intervals after treatment. These values were obtained by multiplying the activity per gram of samples of these organs by the total organ weights.

In a few instances, where more than one treatment had been given, the calculated residual activity in the body from earlier injections was added to the amount of the latest dose as a basis for percentage calculations. In no case was this residual activity large in relation to the last dose. One patient ( ) was excluded from the chart because of unsatisfactory assays of liver and spleen activity. In this case the calculated recovery is greater than the initial dose given. In other cases where multiple samples of liver were assayed there was close agreement in isotope concentrations.

On the basis of limited data, it appears that lymph nodes adjacent to the cavity of injection have relatively high concentrations of radioactivity, while those distant from this site have much lower values. A more complete study of this aspect of the distribution would be of value.

EFFECTS OF RADIATION FROM COLLOIDAL Au^{198}

The locally effective radiation is almost entirely the result of the β emission of the isotope. This radiation is largely dissipated in the first millimeter of the surface of the cavity lining. Assuming that the isotope is concentrated in a thin film at the surface, Chamberlain[4] has calculated that the β dosage at the surface is approximately 900 equivilent roentgens for each 1 mc spread over 1000 square centimeters.. If 100 mc were injected intraperitoneally in an average adult with a peritoneal surface of 30,000 square centimeters, the average surface dose would be about 3000 equivalent roentgens, assuming, of course, all of it deposited on the surface.

The γ emissions are of such energy that a significant part of their ionization occurs outside the body, and within the body their effect is

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quite diffuse. The gamma emission from the gold probably has little to do with the effect upon fluid formation but contributes significantly to the total body radiation effect.

Since a large portion of the radiogold which reaches the blood stream is removed by the liver, it was of interest to study liver function tests in relation to the gold injections. In eight patients thymol turbidity and cephalin-cholesterol flocculation tests were performed upon the serum before and at varying intervals after treatment. Half of this group had abnormalities by these tests before the radiogold was given. Following treatment, there were some fluctuations but no distinct effect which appeared related to the radioisotope treatment.

Hematologic studies showed a variable early mild leukocytosis and distinct eosinopenia, particularly in those patients who had evidence of local inflammatory reaction after injection. Individuals who received large doses of the radiogold showed, in addition, a more uniform sequence of changes characteristic of mild radiation damage to the bone marrow. These effects included a prompt lymphopenia with a later mild depression of granulocytes and thrombocytes. A delayed monocytosis was prominent in some cases. Patients given multiple intracavitary injections of the isotope, with a large total dose, developed a moderately severe leukopenia which persisted for months. Effects upon red cell values were difficult to interpret because of multiple factors contributing to anemia.

DISCUSSION

Since relatively little is known about the factors causing fluid accumulation in patients with neoplasms, it is difficult to understand the therapeutic action of colloidal gold^{198} in these situations.. Whatever the mode of operation, it is obvious that the balance between fluid formation and fluid removal must be altered. Most patients with carcinoma do not have effusions in the absence of lesions involving the serous surfaces of body cavities. Hodgkin's disease, on the other hand, sometimes produces pleural fluid collections which appear to result form lymphatic blockage without direct invasion of the pleura.

Several possible mechanisms for the action of the radioisotope in controlling fluid collection have been suggested:

1. The radiogold may produce superficial radiation damage and resultant fibrosis of the tumor surface projecting into the cavity. The formation in our studies seems compatible with this theory. However, there is no evidence of selective deposition of the isotope on the surfaces of the neoplasms, and morphologic evidences of radiation effects upon the tumors have been rather slight.

2. The radiogold carried to lymph nodes in the region of the cavities may control neoplasm there and relieve lymphatic obstruction. This seems unlikely in view of the relatively small amount of gold which reaches the lymph nodes and the absence of radiation effect upon neoplasm in these nodes. It seem probable that if this mechanism has any importance it is chiefly in patients with Hodgkin's disease and lymphoma.

3. An inflammatory response resulting in obliteration of the serous

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cavity might account for the cessation of fluid collection. Our experience indicates that a mild inflammatory response does sometimes occur, but autopsy studies fail to show extensive fibrous adhesions obliterating the cavities.

4. Some unknown mechanism of action, possibly upon surfaces not involved with tumor, may be important.

Animal work by Goldie, et al.,[5] has indicated that intraperitoneal injections of colloidal gold^{198} have a profound effect upon tumor cells inoculated into the body cavity and that treatment will greatly prolong the life of the animals. This seems to substantiate a true radiotherapeutic effect upon malignant tissue. However, in this situatuon the free malignant cells are dispersed in a manner which makes them highly vulnerable to the short range β particles. The disappearance of free tumor cells from fluids which we have noted after treatment of certain human patients appears to be a complete effect. Fixed masses of tumor in the walls of the cavity are usually too thick to be affected, except on their most superficial areas, but this may be sufficient to decrease fluid exudation.

SUMMARY

1. Information has been presented which shows the fate and distribution of colloidal gold^{198} injected into serous cavities. This data was obtained from a group of thirty patients treated with this isotope for effusions caused by malignant neoplasm.

2. The majority of the colloidal radiogold injected into the body cavities is rather rapidly removed from the free fluid and is fixed on or near the surface of the lining of the cavity, partly within phagocytes and partly adsorbed on surfaces. Although the colloidal material generally mixes well with the fluid in the body cavity, its deposition on the walls is uneven. No special affinity for local tumor implants has been demonstrated.

3. The gold^{198} does not penetrate significantly into the neoplastic or normal tissues adjoining the cavity. The superficial location of most of the colloid on the walls of the cavity and the short range of its beta emission prohibit effective radiation beyond a depth of 2 or 3 millimeters.

4. A small but appreciable quantity of the isotope slowly finds its way, probably through lymphatic channels, into the blood stream, from which it is largely removed by the liver, spleen and bone marrow. A small amount is excreted chiefly in the urine and measurable quantities are found in many organs.

5. The penetrating gamma emission from the treated cavity combined with the local radiation in distant organs from the blood-borne and lymph-borne fractions result in significant total body radiation. Indications of this are seen chiefly in the blood and bone marrow changes during a period of a few weeks following injection of the isotope.

6. Although the metabolism and distribution of this isotope have been studied in some detail, its exact mechanism of action is not as yet known.

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Figure 1. Photograph of patient during injection of colloidal gold^{198} into the pleural cavity. The additional polyethylene tube is for withdrawal of samples of pleural fluid after treatment.

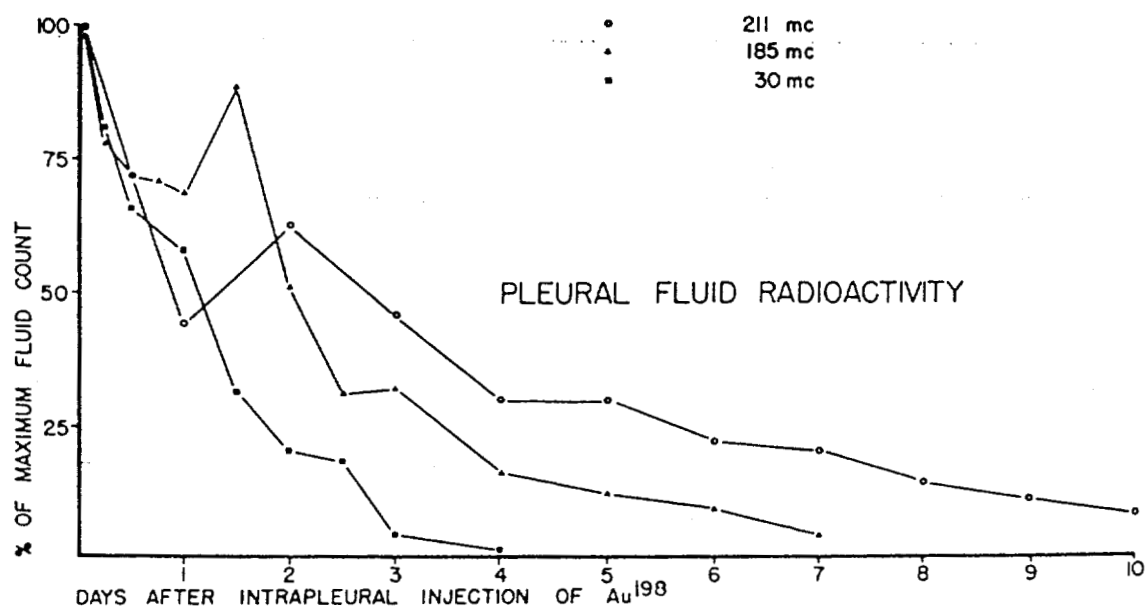


Figure 2. Radioactivity of pleural fluid following intrapleural injection of colloidal gold^{198}. All values are corrected for radioactive decay.

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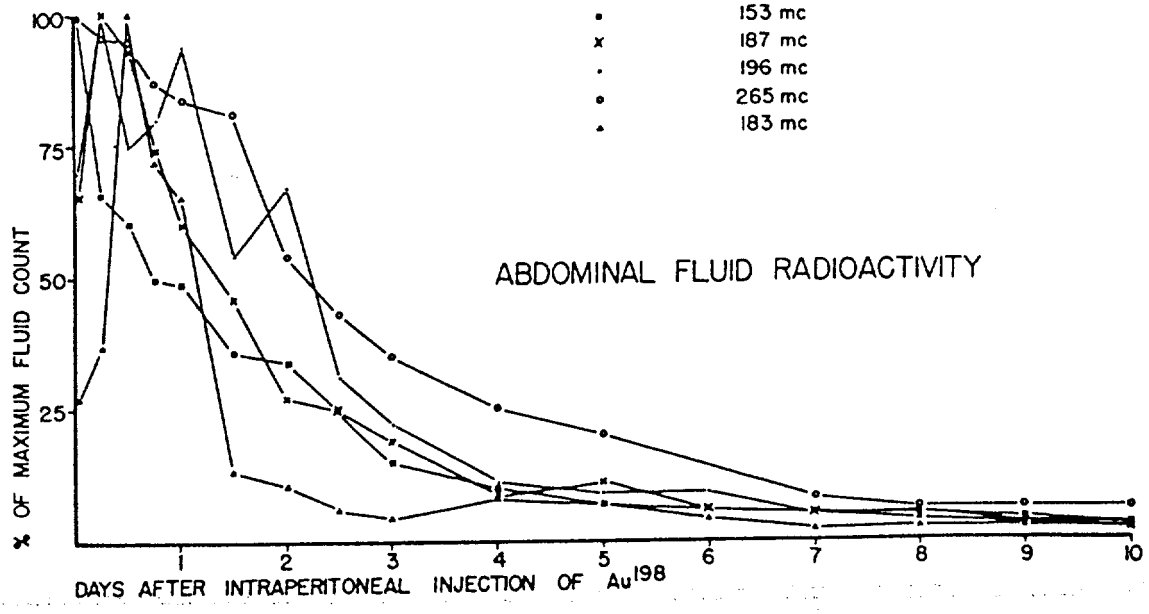


Figure 3. Radioactivity of ascitic fluid following intraperitoneal injection of colloidal gold^{198}. All values are corrected for radioactive decay.

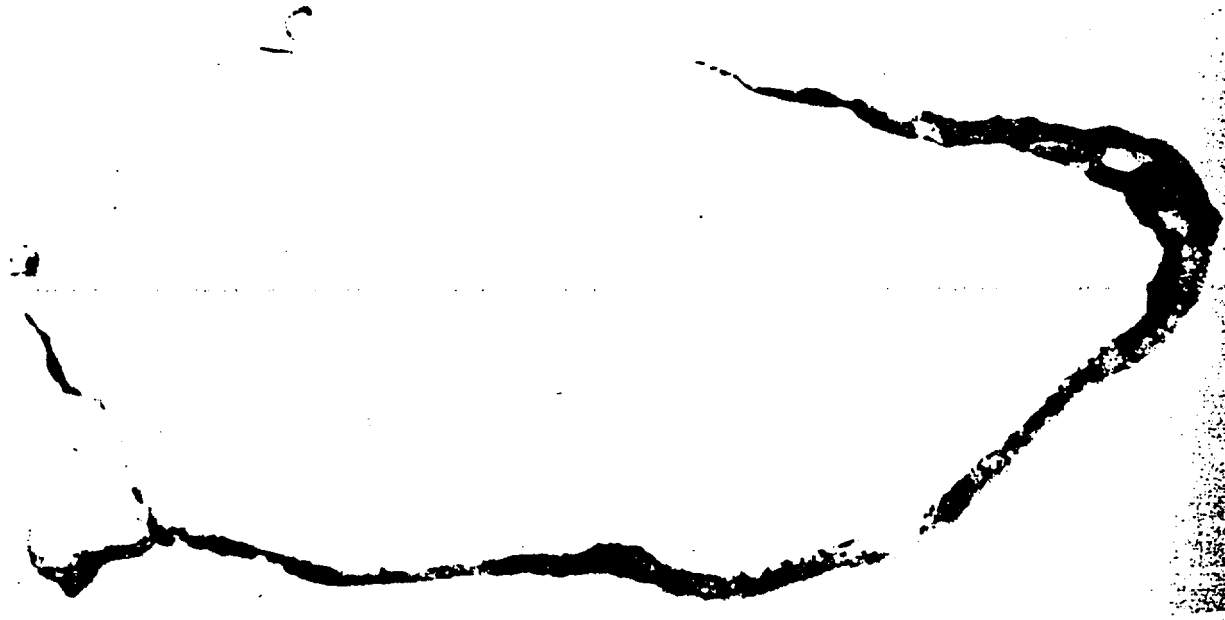


Figure 4. Gross autoradiogram of lung of patient who received 78.4 mc of colloidal gold^{198} intrapleurally 16 days before death. The width of the area of blackening is partly explained by the fact that the pleural surface was not perpendicular to the film, but was folded and partially flattened against the film. The actual penetration into the tissue was thus less than it appears on the autoradiogram.

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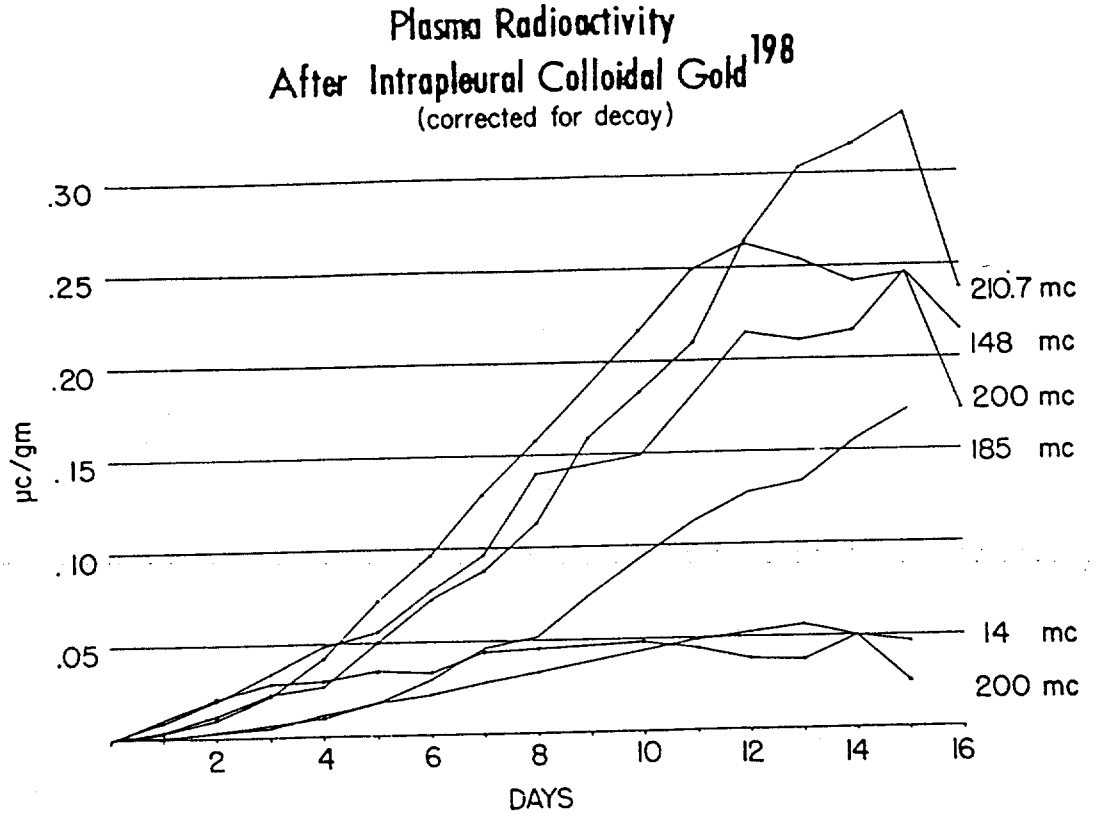


Figure 5. Radioactivity of plasma following intrapleural injection of gold[198] in six patients.

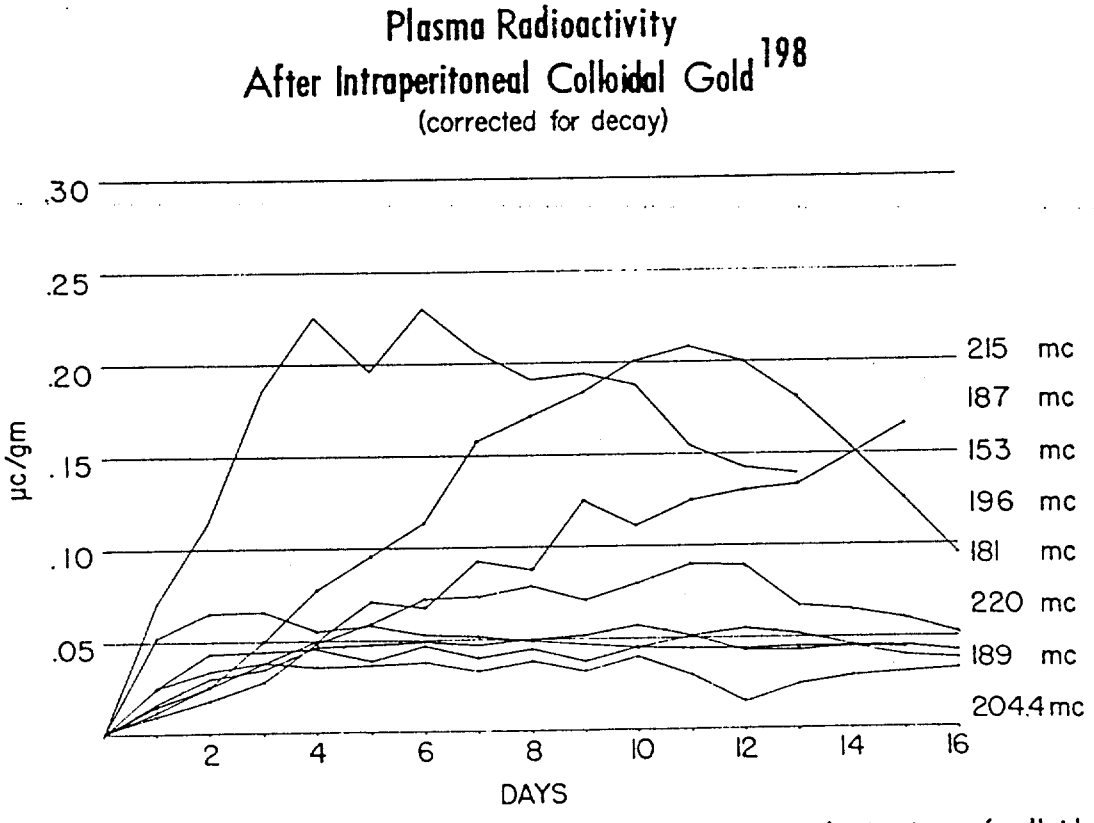


Figure 6. Plasma radioactivity in eight patients after intraperitoneal injections of colloidal gold[198].

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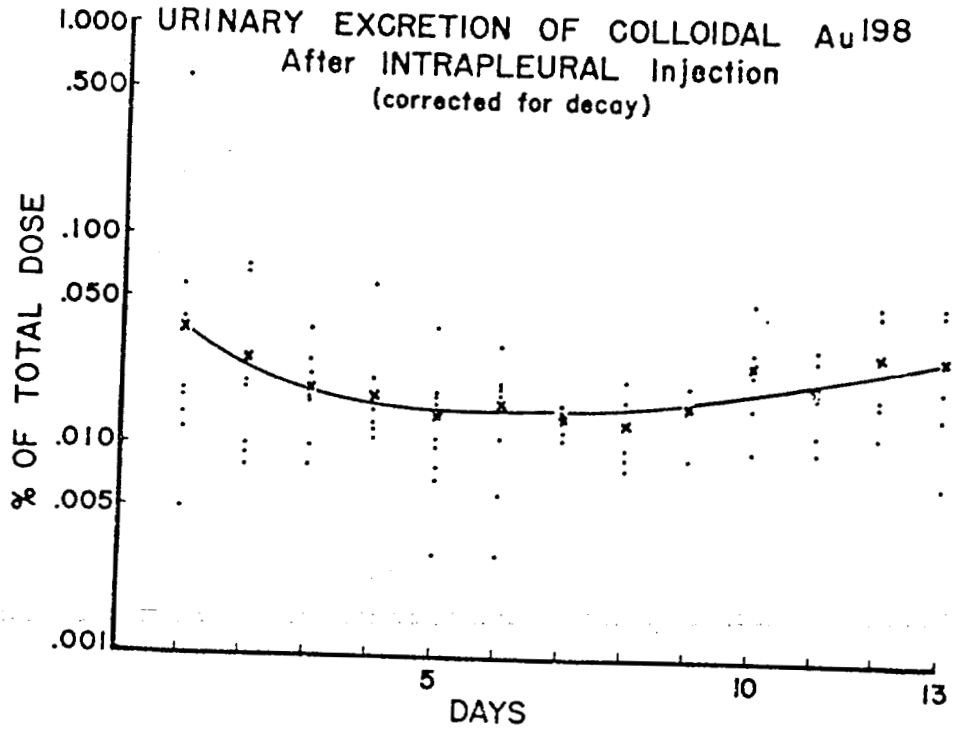


Figure 7. Urinary excretion of radioactive gold after intrapleural injection. Each dot represents the total 4 hour excretion for one patient, charted on a semilog scale. The line represents the approximate mean excretion.

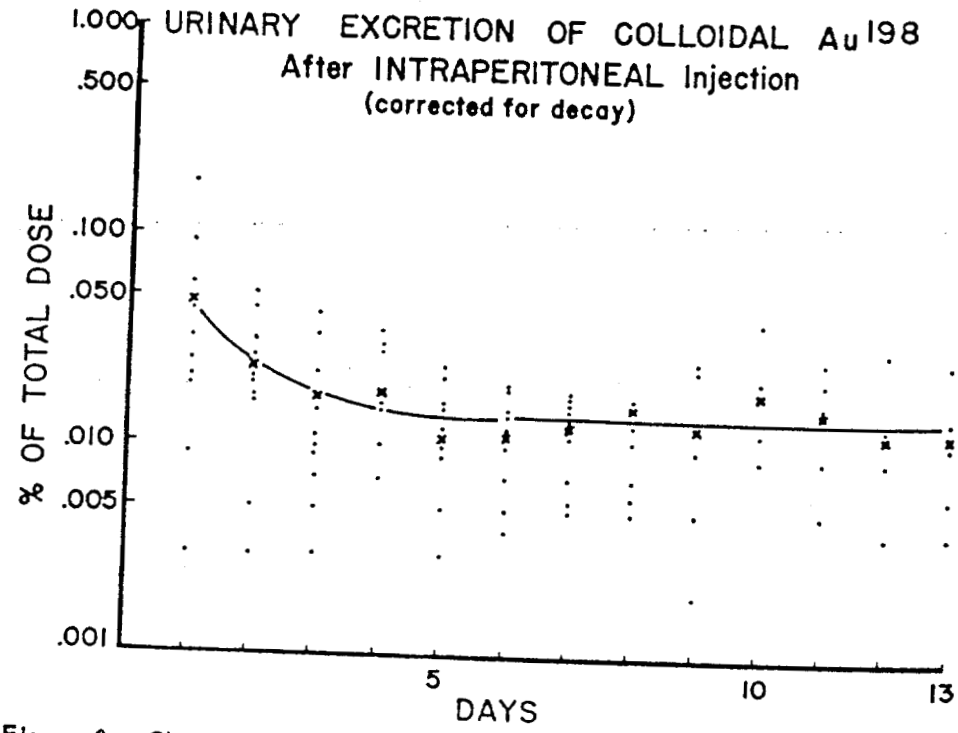


Figure 8. Chart similar to Figure 7, showing the excretion following intraperitoneal injection.

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Figure 9. Gross autoradiogram of spleen of patient who died 14 days after 187 mc. of colloidal gold^{198} were given intraperitoneally. This shows the superficially deposited isotope on the surface of the organ, as well as the diffusely spread blood-borune radiogold through parenchyma.

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Figure 10. Gross autogram of upper end of femur from patient who died 11 days after 33 mc of colloidal gold^{198} were given intrapleurally. The isotope is seen to be deposited in the areas of active marrow.

TABLE NO. 1

RADIOACTIVITY PER GRAM OF TISSUES OBTAINED AT AUTOPSY AFTER INTRACAVITARY GOLD^{198} TREATMENT

All Counts are Corrected to Time of Last Dose

Patient Hospital No	210203	110077	110084	210148	110132	110082	110123	110052	110070
Amount of last dose	78.4 mc	19 mc	23 mc	3 mc	187 mc	156.5 mc	34 mc	11 mc	10 mc
Residual in body from previous doses at time of last dose	0	1.38	0	0	0	0	0	2.33	1.39
Route of administration	L. Pleural	L Pleural	R. Pleural	R. Pleural	Peritoneal	Peritoneal	Peritoneal	Peritoneal	Peritoneal
Time from last dose to death	16 days	3 days	11 days	5 days	14 days	1 day	12 days	5 days	6 days
Fluid from cavity	.25 μc/gm	9.79 μc/gm	0.01 μc/gm	.32 μc/gm	1.04 μc/gm	20.0 μc/gm		6.11 μc/gm	19.21 μc/gm
Serous lining of treated cavity	463.21	2.79	*0.13	9.29	10.07	49.14	17.93	18.82	145.71
Liver	.95	0.02	2.21	BKG	17.0	**4.1	/18.0	0.72	0.30
Spleen	.52	0.02	1.07	.16	59.57	0.04	/13.57	3.76	0.10
Bone Marrow		0.01	0.11		6.6	0.07		1.01	0.01
Thyroid	BKG	0.01	BKG	BKG		0.01	0.01	0.01	
Adrenal	BKG	BKG	0.03	BKG	1.39			0.41	0.14
Lung	.06	BKG		.04		0.04		0.04	0.01
Plasma	.06		BKG		0.15	0.01		0.01	0.01
Bladder	BKG	BKG		BKG				0.02	0.03
Lymph node near treated cavity		BKG		.05		0.05		9.30	0.01
Lymph node -- distant	BKG		0.17	0.01					
Kidney	.17	0.01	0.04	.01	0.74	0.01		0.08	0.03
Pancreas	BKG	BKG		BKG		0.02		0.18	
Bile	BKG			BKG				0.01	BKG

* Extensive tumor may have prevented free spread in cavity.

/ These values are believed not representative of the average of liver and spleen, since when multiplied by the weights of the organs the calculated recovery is greater than the administered dose.

** Value believed erroneous because of contamination.

BKG Backgrou

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TABLE NO. 2

AUTOPSY DISTRIBUTION OF COLLOIDAL Au^{198}

AFTER INTRACAVITARY INJECTION

Patient	Time After Last Dose	Cavity of Injection	Per Cent in Liver	Per Cent in Spleen
	1 Day	Peritoneal	*3.88	0.002
	3 Days	Pleural	0.10	0.01
	4 Days	Pleural	B.G.	0.0003
	5 Days	Pleural	1.12	0.38
	5 Days	Peritoneal	5.26	4.21
	6 Days	Peritoneal	3.02	0.09
	11 Days	Pleural	15.39	0.83
	14 Days	Peritoneal	11.27	3.19
	16 Days	Pleural	2.39	0.15

* Probable false high value due to smearing.

Value believed ...neous because of contamination.
...ful ... KG Background

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INTRODUCTION

One of the distressing complications of carcinomatosis is the involvement of serosal surfaces, either pleural or peritoneal, with the resultant accumulation of large amounts of fluid in these spaces. Frequently, this fluid accumulates rapidly and produces discomfort or impaired function of the structures which it compresses. Among those agents suggested for treatment of these serosal surfaces is radioactive colloidal gold, Au^{198}, since this has both a suitable half-life and suitable radiation characteristics.4 It possesses relatively low energy beta particles (0.8 Mev.) which have a short range (Max. 8 mm. in tissue or water). It has also a low energy gamma ray (0.44 Mev.). The half-life, 2.7 days, is suitable for therapeutic use.

During the past two years, we have made clinical and autopsy studies on a series of patients who have been treated with intracavitary radioactive colloidal gold in an attempt to control effusions occuring as a complication of carcinoma. Approximately 30 patients have been treated up to the present time and this report is based on autopsy studies in 12 cases.

MATERIALS AND METHODS

Nine of the autopsied patients were female and three were male, ranging in age from 26 to 76 years. All the patients were afflicted with a malignant neoplasm. (Table 1) They were incapacitated with distressing symptoms due to the formation of intraperitoneal or intrapleural fluid or both. All were in an advanced stage of their disease, incurable by surgical or radiotherapeutic procedures. The main objective of treatment was an attempt to inhibit the formation of the fluid.

Extensive clinical examinations were made during the course of the patients' illness: assays of the excretion of Au^{198}, measurement of the radiations from the body surface, various hematologic studies including bone marrow examinations and blood chemical determinations and function tests. The rate of formation of the intracavitary fluid was measured and assays of the concentration of the isotope in the fluid at varying intervals following the administration were performed.

Doses of Au^{198} varied widely, the largest single dose being 187 mc. (Table 1) The isotope was administered as the colloid, and was injected directly into the cavity to be treated. The largest amount given to any one patient was a total of 660 mc. over a 10-month period. In all cases where death appeared imminent after the previously administered radiogold had largely decayed, a small additional dose of Au^{198} was given in expectation of post mortem studies in order to measure the concentration and distribution of the isotope in various tissues.

At autopsy, tissues were taken for routine histologic sections, and samples of various organs and tissues were collected for radioassay.

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Gross autoradiographs were made from various organs. The clinical findings in 25 cases which have been treated have been reported.2 Metabolic, distribution and autoradiographic studies will be reported elsewhere.1

Tissues were routinely prepared by formalin fixation and alcohol dehydration, and were imbedded in paraffin. Routine hematoxylin and eosin stains were employed. Sections of the serosal surfaces treated with Au^{198} were stained with phospho-tungstic acid hematoxylin. Micro-incineration of some of the sections of cavity wall also was performed.

CASE REPORTS

Case No. 010033: This 44-year-old white married male was admitted to the hospital on November 6, 1950. In February, 1949, the patient had had a cervical lymph node biopsy. The node had been present for 2 years but recently had grown rapidly. A diagnosis of giant follicular lymphoma was made. X-ray therapy was given and the patient remained well until May, 1950, when multiple areas of lymph node involvement developed. He was given additional x-ray therapy and nitrogen mustard. In August, 1950, a left pleural effusion developed requiring multiple thoracenteses. Injections of colloidal radiogold were given as follows into the left pleural space.

November 15, 1950	43.8 mc.
November 22, 1950	48.7 mc.
November 29, 1950	47.8 mc.
December 7, 1950	39.6 mc.
December 13, 1950	48.6 mc.

Two additional doses of Au^{198} were given intravenously.

January 17, 1951	19.2 mc.
March 8, 1951	2.3 mc.

The patient continued to require paracenteses.. He became weaker and died March 8, 1951.

Post mortem examination revealed a lymphosarcoma involving the spleen, lymph nodes, pleura, epicardium, pancreas, kidneys, and bone marrow. There was a large hemothorax (1400 cc.) in the left pleural space and hydrothorax (300 cc.) in the right pleural space. The left pleura was moderately thickened and showed pigmentation thought to be gold.

Histologic examination showed a lymphocytic sarcoma. A moderately thickened parietal pleura was demonstrated. There was organized exudate covering the pleura of the left lower lobe.

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Case No. 110077: This 51-year-old female was admitted to the hospital May 2, 1951. She had developed a cough and shortness of breath in January, 1951, and in early April a left pleural effusion was discovered. On April 25, 1951, a thoracotomy was done at which time an inoperable squamous cell carcinoma was found involving lung and pleura. Bloody pleural fluid recurred after operation and was aspirated repeatedly.

Injections of colloidal gold^{198} were made into the left pleural space as follows:

May 17, 1951	155 mc.
June 14, 1951	148 mc.

After the first two doses of gold, the patient was discharged, temporarily improved, and thoracenteses were discontinued. She was readmitted on August 29, 1951 and the following injections were made into left pleural space:

September 12, 1951	22 mc.
September 24, 1951	17.25 mc.
October 4, 1951	19 mc.

She died on October 7, 1951.

Post mortem examination revealed a carcinomatous process involving the left lung, left visceral and parietal pleura. This was a firm, fibrous tumor, showing severe fibrous thickening of the pleura. The left lung was completely collapsed. Metastases to the hilar, peritoneal, periaortic and left axillary lymph nodes were present. The surface of the pleura on the left was mottled, gray and hemorrhagic, with fibrinous tags attached to the surface. Small nodular metastases to the right lung and right pleura were also found.

Histologic studies showed an undifferentiated carcinoma, with areas of definite squamous cell type, characteristic of carcinoma arising in the lung. The pleura on the involved side showed three zones. Nearest the surface was a zone of fibrin deposition and rather acellular fibrous tissue; beneath this there was a zone in which ghost-like remnants of tumor were observed within fibrous tissue; and then finally there was a layer of fibrous tissue which contained nests of viable tumor cells. The sections of the lung showed a zone of fibrosis and necrosis of the tissue adjacent to the pleural space. In addition, there were ghost-like remnants of necrotic tumor. In contrast, the section of diaphragm demonstrated tumor throughout the width of this structure. This was accompanied by a rather marked desmoplastic response and tumor was seen on the surface of both the pleural and peritoneal sides of the section. It did not show the necrosis observed in the surfaces of the lung and parietal pleura of the chest wall.

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Case . ., No. 110084: This 43-year-old man was admitted on June 11, 1951. He had been troubled by vague abdominal symptoms for 7 months, and with abdominal swelling and shortness of breath for 3 months. Two and one-half months before admission, a laparotomy revealed an extensive retroperitoneal tumor of undifferentiated type, with chylous effusion in the abdomen and in both pleural spaces. On admission there were findings of abdominal and pleural effusion; no distinct masses were palpable. Injections of colloidal gold^{198} were made as follows:

June 21, 1951	161.9 mc right pleura
June 28, 1951	122 mc peritoneum
August 2, 1951	14 mc. right pleura
August 21, 1951	94.5 mc. right pleura
September 10, 1951	15.7 mc. right pleura
October 4, 1951	23.mc. right pleura

The patient continued to require paracenteses. An abdominal mass became apparent, and increased in size. He died on October 15, 1951.

Post mortem examination showed an undifferentiated adenocarcinoma apparently originating in the pancreas, and producing a large retroperitoneal mass, as well as a large tumor of the upper abdomen. There were metastases to the abdominal lymph nodes, lumber vertebrae, pleura, and right inguinal node. The peritoneal space contained 4000 cc. of fluid, and in the lower portion of the abdominal cavity, a dark mottled gray staining of the surface was observed. There were 1500 cc. of chylous fluid in the right pleural space and a dark discoloration presumed to be due to the injections of radioactive gold was present on the surface.

Histologic examination showed an undifferentiated adenocarcinoma composed of fairly uniform small cells growing in closely packed sheets and single columns. The pleural surfaces of the right side showed fibrous thickening with deposition of fibrin on the surface and organization of this fibrin. A rather dense fibrous thickening of the serosal surface of the ileum was noted and the omentum also showed fibrous tissue thickening. Phagocytosed gold pigment was demonstrated near the peritoneal surface.

Case . , No. 010032: This 69-year-old white widow was admitted to the hospital on November 5, 1950. She had been in chronic ill health for several years with gastrointestinal complaints. She had recently been treated for active pulmonary tuberculosis. Swelling of her abdomen began in the summer of 1949. In September, 1949, a laparotomy disclosed a pseudomucin forming cystic lesion of the right ovary. The abdomen contained a considerable amount of gelatinous material which could not be completely removed. The patient was treated over a prolonged period at Oak Ridge but was not hospitalized continuously. Two laparotomies were performed. Intraperitoneal radioactive colloidal

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gold was given as follows:

November 15, 1950	10 mc.
November 22, 1950	30 mc.
December 7, 1950	100 mc.
December 13, 1950	85 mc.
January 11, 1951	96 mc.
February 8, 1951	22 mc.
February 24, 1951	52 mc.
March 12, 1951	50 mc.
September 7, 1951	215 mc.

The patient became gradually worse, with intractable vomiting, and died December 2, 1951.

Post mortem examination showed extensive pseudomyxoma peritonei with fluid measuring 5500 cc. This arose from a confluent mass of a pseudomucinous tumor in the pelvis. Associated with this was a diffuse thickening of the visceral and parietal peritoneum, and a deep bluish-gray discoloration. In places, the pigment was arranged in reticulated linear patterns, suggesting deposition along lymphatics. In addition, a moderately severe biliary cirrhosis was present.

Microscopic study showed a fibrous tissue reaction on the peritoneal surfaces. Aggregates of black gold pigment were found within this fibrous tissue. In addition, there was a fibrinous exudate and numerous polymorphnuclear leukocytes. Often this was co-existent with the pseudomucinous material. Some of the sections of the abdominal wall showed fairly distinctive changes: There was a layer of fibrinous and purulent exudate, beneath this a layer of fibrous tissue containing phagocytes which were laden with gold pigment, and then a layer of skeletal muscle. The muscle fibers nearest the peritoneal surface showed degenerative changes characterized by replacement by fibrous tissue and by the presence of large, bizarre fibers containing hyperchromatic giant nuclei, characteristic of degenerating skeletal muscle.

Case [illegible]., No. 110070: This 47-year-old woman was admitted to the hospital on April 17, 1951. The patient entered the hospital with symptoms of bowel obstruction present for two weeks. The illness began about 3 years previously when tumor nodules on the abdominal wall appeared. In October, 1948, a panhysterectomy was performed for ovarian carcinoma with metastases. Subsequently high voltage x-ray therapy had been given. Ascitic fluid began to form about 1 month prior to admission. A laparotomy was performed on April 25, 1951, to relieve intestinal obstruction. Pleural effusion appeared and continued. The following injections of Au^{198} were

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given intraperitoneally.

April 20, 1951	1.4 mc.
May 3, 1951	8.1 mc.
May 31, 1951	6.5 mc.
June 7, 1951	10.7 mc.
June 13, 1951	1.4 mc.
June 22, 1951	8.1 mc.
June 29, 1951	10 mc.

The patient became worse and died on July 5, 1951.

Post mortem examination revealed a large mass of adenocarcinoma involving the liver, with multiple metastases to the peritoneal surfaces which matted together the loops of intestine. There were mottled patchy black staining zones on the peritoneal surfaces. There were also metastases to the pleura, lungs, hilar lymph nodes and the supraclavicular lymph nodes. Pleural effusion of 1500 cc was found in the right chest with atelectasis of the right lung. Histologic sections showed a rather anaplastic adenocarcinoma which was attempting to form acini in places. The section of abdominal wall showed deposition of fibrin on the peritoneal surface and a considerable amount of black pigment which was thought to be gold. The underlying tissue showed fibrous tissue proliferation and contained hemosiderin scattered here and there. No alteration in the characteristics of the tumor which could be attributed to the gold therapy was observed.

Case ., No. 110123: This 46-year-old man was admitted to the hospital on October 4, 1951. In July, 1950, he had developed shortness of breath on exertion, but it was not until 6 months later that he was found to have a pleural effusion on the right side. Multiple thoracenteses were performed, and on August 14, 1951, a thoracotomy was done. At this operation, the lung was found to be surrounded by a thick nonresectable layer of tumor. A biopsy was done which suggested a diagnosis of mesothelioma. Three weeks later the patient developed ascites, and an abdominal mass was discovered. On admission, the left side of the chest was dull and moved a little on respiration. There were ascites and a large left lower quadrant abdominal mass. Two intraperitoneal injections of radioactive colloidal gold were made.

October 11, 1951	170 mc.
November 8, 1951	34 mc.

The patient's general condition became gradually worse and he died on November 20, 1951.

At autopsy, a diffuse fibrosing tumor was found involving the right

and left pleurae, [illegible] visceral and parietal peritoneum, mesentery, retroperitoneal space, lungs, hilar lymph nodes, [illegible] nodule in the kidney. A very thorough search for a primary carcinoma was made and no lesion was found. The peculiar histologic character of the lesion, as well as its distribution, has led us to regard this as a possible mesothelioma or as undifferentiated carcinoma of unknown origin. Two loculated areas were encountered in the abdominal space and were thought to be the sites of the injections of gold. The most recent one was in the upper abdominal area and was encapsulated by loops of intestine and tumor. The wall of this area was blackish-purple in color and contained a fibrinous, dark-red hemorrhagic exudate and clot. In the lower abdomen, the other focal area of blackish pigmentation somewhat stippled in appearance was encountered. This involved the parietal peritoneal surface of the right lower abdomen. There was an adjoining loculated area surrounded by loops of intestine tumor, which had a mottled gray pigmented lining.

Histologic examination of tissues from the wall of the two loculated cavities showed a deposition of fibrin and, adjacent to this an organization of this fibrin with alternating zones of deposited fibrin and fibrous connective tissue. Intermingled with the fibrin were numerous clumps of black pigment granules presumed to be gold. These were clumped sometimes within macrophages. The tumor cells adjacent to this deposit of gold, in contrast to the tumor in all other areas, showed pleomorphism with giant forms and with vacuoles in the cytoplasm and nuclei. Other cells showed pyknotic changes. There was an area of acute ulceration of the intestine, in a loop forming part of this wall.

Case [illegible], No. 110107: This 67-year-old white woman was admitted to the hospital on August 14, 1951. In 1947, a left simple mastectomy was done as a palliative procedure for carcinoma of the breast. In February, 1951, she developed a left pleural effusion. This recurred and required multiple thoracenteses. A single injection of gold^{198} was made into the left pleural space.

August 30, 1951 210.7 mc.

The patient showed evidence of continued tumor growth in the mediastinum and died on November 14, 1951.

At post mortem examination, metastases were found in the right and left lung, pleurae, pericardium, hilar lymph nodes, diaphragm, peritoneum, skin of chest, liver, vertebrae and ilium. Pleural effusion, 1000 cc., was found in the right pleura and 500 cc. in the left. The lung was completely atelectatic and surrounded by a fibrous thickened pleura. Both the visceral and parietal surfaces showed mottled grayish-black pigmentation as well as several sessile nodulations on the parietal pleura. Implants of metastatic carcinoma were found in the right pleural space. There were focal areas of firm, fibrous tumor on the anterior surface of the right lung, as well as scattered nodules of metastatic tumor in the parenchyma. The contrast in the color and degree of fibrosis of the right and left pleura was remarkable. Histologic examination of the visceral and parietal surfaces of the pleura on

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the left showed a distinct zone of fibrous thickening. It is of interest that the widest zone of fibrosis was in the leaf of the left diaphragm. A narrower band of fibrous tissue was present also on the right leaf of the diaphragm. There was interstitial fibrosis of the superficial portions of the left lung.

Case . ., No. 210148: This 42-year-old white woman was admitted to the hospital on February 12, 1952. A left radical mastectomy had been performed in 1948. Testosterone had been administered during 1949. In 1951, she began to have pain and swelling in the clavicular and cervical region. A left pleural effusion appeared in December, 1951, and increased in severity causing marked dyspnea. While the patient was in the hospital, numerous paracenteses were necessary. Au^{198} was given into the right pleural space as follows:

March 23, 1952	80 mc.
April 30, 1952	3 mc.

She became irrational, weakened and died on May 5, 1952.

At post mortem examination, there were metastases to the left and right pleurae, pericardium, para-aortic, right axillary, celiac lymph nodes, mediastinum, liver, right adrenal, bones, subcutaneous tissue and cul-de-sac. There was obliteration of the left pleural space. The right pleural surface showed blue-gray mottling but no generalized fibrosis. Histologically, alteration of tumor by irradiation could not be demonstrated, nor was there any remarkable thickening of the pleural surfaces.

Case . ., No. 110052: This 76-year-old white widow was admitted to the hospital on January 10, 1951. In April, 1950, a partial gastrectomy for carcinoma of the stomach had been performed. She was quite well following this surgery until December, 1950, when she developed swelling of the abdomen, anorexia, and intermittent vomiting. Following an abdominal paracentesis early in January, 1951, she was temporarily slightly improved, but rapidly became worse with severe vomiting.

On admission, the patient appeared chronically ill, dehydrated, and semi-comatose. The abdomen was greatly distended with fluid; no masses could be made out. There was a severe degree of prolapse of the uterus. Two intraperitoneal injections of colloidal radiogold were given.

January 11, 1951	86 mc.
January 25, 1951	11 mc.

The patient required intravenous fluids, became gradually weaker, and expired on January 30, 1951.

At autopsy a widespread abdominal carcinomatosis with multiple serosal nodules over intestine was found. Histologic study showed a

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signet-ring mucin producing carcinoma. There was some fibrin deposited on the peritoneal surfaces with organization in some areas. Pigment, often clumped in phagocytes, was found in the fibrin. Para-aortic lymph nodes showed rather marked atrophy with increased plasma cells and phagocytosed pigment.

Case No. 110132: This 42-year-old white housewife was admitted to the hospital on December 4, 1951. Early in 1951, the patient noted the insidious onset of morning nausea, abdominal distention and a sense of fullness after eating even small amounts. In July, 1951, she noted a generalized swelling of the abdomen, which became progressively more prominent. On October 5, 1951, a laparotomy was done and bilateral ovarian tumors of Krukenberg type were found. Ascitic fluid became an increasing problem and paracenteses were required. On admission, the patient was chronically ill, with ascites and a poorly outlined mass in the left lower quadrant. A single intraperitoneal injection of colloid Au^{198} was given.

December 13, 1951 187 mc.

The patient expired December 27, 1951.

Post mortem examination showed a diffuse sclerosing carcinoma of the stomach. There was no massive tumor, either in the stomach or in any of the sites of metastases. Rather, the tumor was manifested as zones of fibrous thickening. There were metastases of the lungs, esophagus and celiac lymph nodes; multiple points of partial intestinal obstruction were associated with metastases in the omentum, mesentery and peritoneum. There was a recent pulmonary embolus with infraction of the right lower lobe of the lung, and surgical absence of the ovaries. The pelvic peritoneal surface, in addition to mosaic-like areas of fibrous thickening, showed patchy deposition of black pigment which was regarded as gold. In addition, the structures of the pelvis had a mottled, hemorrhagic, friable appearance. Microscopic examination showed an anaplastic signet-ring carcinoma, which produced a marked desmoplastic response in many of its sites of metastases. Because this was a general feature of the tumor, the fibrosis of the peritoneum could not be attributed to the effect of the injected Au^{198}. Clumps of black pigment were seen on the peritoneal surfaces in a number of sections. Many sections showed deposition of fibrin, zones of hemorrhage and necrosis. No actual changes in the tumor cells which could be attributed to the effects of radiation were seen.

Case No. 110066: The patient, a 26-year-old single woman, was admitted April 6, 1951. In August, 1950, she had noted a small lump in the right axilla. This was promptly biopsied and a diagnosis of probable lymphosarcoma was made. She was given x-ray therapy. In January, 1951, she developed a right pleural effusion, and repeated thoracenteses were done. On admission, the physical findings were those of a right pleural effusion. There was edema of the right chest wall. A single injection of colloidal $gold^{198}$ was made into the right pleural space.

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April 24, 1951 6 mc.

The patient became so rapidly worse that it was considered useless to give a larger amount of radioactive gold, and she died four days later.

Post mortem examination revealed a large tumor which involved the mediastinum and the right pleural space. There were metastases to the lung, diaphragm, retroperitoneal space, axillary lymph nodes, scalp, and peritoneum. There was compression of the great vessels by the tumor with a resulting passive congestion of the liver. The surface of the right pleural space had a deep purplish-red color and contained blood clot. The color change was thought to be due in part to the gold which had been recently administered. Histologic examination showed a pleomorphic sarcoma, which in places resembled reticulum-cell sarcoma but elswehere was more like a rhabodo-myosarcoma, fibrosarcoma and myxoma. Because of the varied appearance, this was labelled as a malignant mesenchymoma. No effects which could be attributed to the Au^{198} were observed in this case.

Case . No. 110082: This 45-year-old single woman was admitted on May 22, 1951. About 3 months before admission, she began to have anorexia and constipation. About 2 months after the onset, enlargement of the abdomen was detected and on April 29, 1951, there was a sudden onset of severe abdominal pain. A laparotomy, 4 days later, revealed bloody ascitic fluid and multiple large cysts filling most of the lower abdomen. A biopsy was done, and this showed adenocarcinoma of unknown origin. On admission, the patient's abdomen was greatly distended, the lower half containing a large poorly outlined mass. One dose of radioactive colloidal gold was given intraperitoneally.

May 31, 1951 160 mc.

The patient died June 1, 1951.

Post mortem examination was done in limited fashion instead of following the usual routine because of the extremely high level of radioactivity (500 Milliroentgens/hour at the surface of the abdomen). An almost solid mass of tumor was found extending from the bottom of the pelvis over the entire right side of the abdomen up to and covering the diaphragm. All of the intra-abdominal organs were enmeshed in tumor and there was an area of obstruction in the mid-portion of the small intestine due to the neoplastic process. On the left side of the abdomen, there were multiple nodules and dense sheets on the surfaces of the peritoneum. The abdominal wall was ecchymotic, particularly on the right side. Histologic sections showed an undifferentiated adenocarcinoma, which was growing in closely-packed sheets of cells with small islands of gland formation. Effects attributable to the Au^{198} were not seen.

OBSERVATIONS AND DISCUSSION

This series of observations is on a small, varied group of patients. There has been a wide range in types of tumor, dosages of Au^{198}, and

intervals between treatment and death. There was no obvious pattern of response to the isotope found in every patient, and interpretation of the findings was difficult due to the many factors other than treatment with Au^{198}. For these reasons it does not seem possible to give any definitive description of general pattern of events following intracavitary administration of colloidal Au^{198}. However, in view of the increasing use of this form of treatment, the specific information collected on this group of patients will be useful.

The walls of the treated cavities do have a fairly typical gross appearance. Colloidal gold stained some of the surfaces a dark bluish-purple color. In certain cases examined at long intervals after treatment, the gold apparently had been collected, possibly within lymphatics, and a coarse reticulated pattern was seen on the serosal surface (Fig. 1). Here, the color was black or gray, rather than bluish-purple. In isolated instances, zones of hemorrhage and necrosis were seen on these treated surfaces. The gross changes also included a thickening of the pleural or peritoneal surfaces which varied widely in degree. No definite correlation of the fibrosis with the length of therapy or the dose was found. Obliteration of the spaces was not a characteristic feature but partial obliteration was occasionally seen.

Several complicating factors make interpretation of this fibrous thickening difficult. Some of the tumors were associated with a pronounced desmoplastic response which was not limited to serosal surfaces. In all cases, the cavities were insulted not only by the instillation of the radioactive colloidal gold but by repeated paracenteses. We recognize that the mechanism for the production of the effusions is variable and poorly understood. In some instances, it may be due to obstruction of lymphatics, while in other instances, it may be due to venous obstruction. Serosal implants on the surface probably play an important part associated with either of these obstructive factors. Following Au^{198} treatment, the histologic change is somewhat characteristic, consisting of a zone of fibrous thickening of the pleura or peritoneum usually with a layer of fibrin on the surface. (Fig. 4) The fibrosis varies markedly in severity. (Figs. 2, 3) The fibrin in many sections is being organized and is enmeshed with fibrous tissue. (Fig. 5) In some of the cases, tumor can be seen very near or on the treated surface. One could not determine with certainty whether this growth of tumor had occurred in spite of the radiation, or had developed after the decay of the radioactive colloidal gold.

Colloidal Au^{198}, when injected, has been estimated to be in particle sizes on the order of 100 to 200 millimicrons. Only a fraction of this material remains in colloidal suspension within the fluid-filled cavity. A larger portion is adsorbed on the surfaces of the cavity where some of it is phagocytosed. This concentration of the radioactive material on or near the surfaces of the cavity has been demonstrated also by radioassay of tissues and autoradiographic studies. The original colloidal particles coalesce to form granules up to approximately 2 microns in diameter. Numerous clumps of these are seen at various levels near the surface. Sometimes these granules are extracellular, emeshed in fibrin on the surface; more often they are clumped in phagocytes which are enmeshed in the fibrin. (Fig. 6) In other instances, the phagocytes are deeper in the wall of the cavity and are lying in fibrous tissue. (Figs. 7,8) Occasionally, no pigment or phagocytes are seen or

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are in the walls of the treated cavity. In routine sections of treated pleural cavities, it is difficult to distinguish between phagocytes with carbon pigment and those containing gold. Micro-incineration has been used successfully to distinguish these particles.

The life history of the phagocytes which first pick up the Au^{198} is not known. It is possible that these phagocytes are destroyed by radiation, and that the released particles are again phagocytosed. However, the presence in most cases of large numbers of seemingly viable phagocytes, filled with granules, leads us to believe that these cells are quite radio-resistant. Such viable phagocytes are also found laden with gold pigment in cell blocks of paracentesis fluids. The repeated paracenteses before and following instillation of gold have been studied and detailed reports of these observations will appear elsewhere.5

Our observations on the lymph nodes adjacent to the treated cavity were not as complete as would be desired. Some of the lymph nodes showed a rather atrophic appearance with fat replacement and loss of the germinal follicles. This was accompanied by increased plasma cells. In several nodes, phagocytes with black pigment, presumed to be gold, were found in the sinusoids. In the case of a patient (P. T., 110132) who died two weeks after 187 mc. was given intraperitoneally, sections of the celiac nodes showed metastatic tumor. Clumps of black pigment within phagocytes were seen in several local areas and scattered diffusely in this node. No effects of radiation could be seen in the tumor. In other patients, there were lymph nodes massively replaced by tumor, not showing any radiation effect.

Also of interest among effects of the radiation are those on adjacent normal tissues, and on distant tissues. The radiation effect in the immediate area of the treated cavity is chiefly due to the short-range beta particles from the isotope. In the rest of the body, the radiation effect is that of the gamma emission from the gold in the cavity. But in certain tissues this is augmented by the beta emission of small amounts of gold, transported chiefly to reticuloendothelial organs by the blood stream. In general, it can be said that there are no demonstrable gross adverse effects produced on neighboring organs by the radioactive colloidal gold. Radiation ulcers in the intestines were not found except in one case (O 110123). The lungs in the cases where intrapleural Au^{198} was given were not damaged to any noteworthy degree. In the doses employed, total body irradiation damage as reflected in bone marrow was not prominent. (Fig. 9) Hematopoiesis for the most part was unaltered. However, moderate degrees of bone marrow depression were recorded in some patients subsequent to treatment. In most instances, recovery of the bone marrow had occurred before death. No characteristic changes which could be ascribed to this therapy were observed in either the spleen or the liver. The liver findings are not surprising since, experimentally, liver damage due to radioactive gold is found only when high concentrations are produced by the intravenous route of administration.3

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SUMMARY

1. Twelve patients with advanced malignancy, who were treated with colloidal Au^{198} for relief of effusion, were studied at autopsy and the findings are reported.

2. The colloidal Au^{198} is adsorbed on the cavity surfaces where it precipitates in the form of relatively large aggregates and is phagocytosed.

3. Frequently, fibrous thickening of the pleura or peritoneum is found, usually without extensive adhesion.

4. Radiation damage to the tumor was not prominent and was limited to very superficial zones.

5. Morphologic evidence of whole body radiation was minimal.

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Figure 1



Figure 2

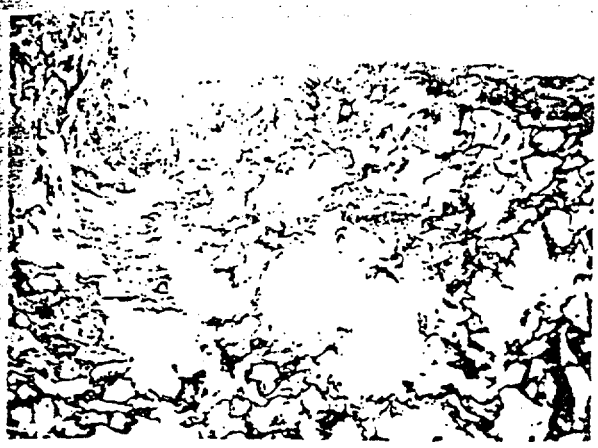


Figure 3



Figure 5



Figure 4

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Figure 6.



Figure 7.



Figure 8

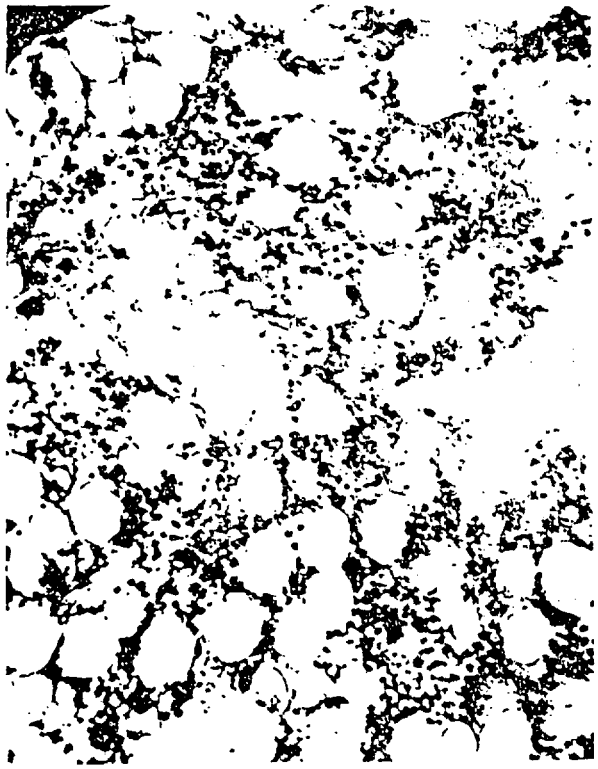


Figure 9

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FIGURES

Fig. 1. Gross photograph of parietal peritoneum, patient (010032), showing coarse reticulated pattern. 660 mc. Au^{198} over 10 month period, with the last dose 3 months before death.

Fig. 2. Left parietal pleura, patient (110107). 211 mc. given intrapleurally $2\frac{1}{2}$ months before death. There is fibrosis of the pleura with a thin layer of fibrin on the surface. PTAH stain x 30.

Fig. 3. Right lower lobe lung, patient (210148). 80 mc. Au^{198} 43 days before death. There is minimal fibrous thickening of the pleural surface. x 30.

Fig. 4. Ileum, patient (010032). 660 mc. Au^{198} over a 13 month period. Fibrous thickening of peritoneum. Note fibrin strands near surface. PTAH stain x 30.

Fig. 5. Parietal pleura, patient (010033). 217 mc. Au^{198} intrapleurally over 3 3/4 month period before death. Surface deposition of fibrin which is being replaced by fibrous tissue. PTAH stain x 30.

Fig. 6. Patient (110123). 201 mc. Au^{198} intraperitoneally 4 weeks before death. Phagocytes which contain gold particles are enmeshed in fibrin in walls of the cavity. x 972.

Fig. 7. Patient (110132) given 187 mc. Au^{198} intraperitoneally 2 weeks before death. Phagocytes with fold particles are lying in fibrous tissue. x 972.

Fig. 8. Patient (110084), given 122 mc. intraperitoneally $3\frac{1}{2}$ months before death. Phagocytes containing gold pigment are still present in fibrous tissue wall of the cavity. x 972.

Fig. 9. Bone marrow of patient (110132). Death 14 days after 187 mc. Au^{198} was given intraperitoneally. There is no evidence of pronounced radiation damage. x 150.

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TABLE 1

DIAGNOSIS AND Au^{198} TREATMENT

Acct. No.	Age Sex	Diagnosis	Treatment
010033	44 F	Lymphocytic Sarcoma	228.5 mc. total intrapleurally. Weekly injection 3 3/4 mo. before death.
110077	61 F	Squamous carcinoma (probable primary left lung)	303 mc. toatl. 155 mc. 4 mo. and 148 mc. 3 mo. before death.
110084	42 M	Adenocarcinoma pancreas	431 mc. total. 122 mc. intraperitoneally in single injection; 309 mc. intrapleurally in 5 injections $3\frac{1}{2}$, 4 mo. before death.
010032	69 F	Pseudomucinous cystadenocarcinoma ovary	659 m. intraperitoneally over 10 mo. period, death in 13 months.
110070	47 F	Adenocarcinoma ovary	46.2 mc. total intraperitoneally in 7 small doses over 2 months prior to death.
110123	46 M	Mesothelioma (?) pleura, peritoneum	210 mc. intraperitoneally in 2 injections. Death in 6 weeks.
110107	57 F	Adenocarcinoma breast	210.7 mc. intrapleurally $2\frac{1}{2}$ months before death
210148	42 F	Adenocarcinoma breast	80 mc. intraperitoneally 43 days and 3 mc. 6 days before death.
110052	76 F	Adenocarcinoma stomach	97 mc. total intraperitoneally in 2 injections 19 days before death.
110132	43 F	Adenocarcinoma stomach	187 mc. single injection intraperitoneally 2 wks. before death.
110066	26 F	Malignant mesenchymoma	6 mc. single dose 4 days before death.
110082	45 F	Abdominal carcinomatosis, primary ovary (?)	154 mc. intraperitoneally 1 day before death.

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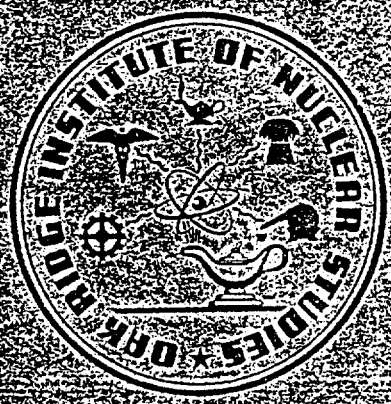
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OAK RIDGE INSTITUTE of NUCLEAR STUDIES

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Operating Under Contract AT-40-1-Gen-33
with the
UNITED STATES ATOMIC ENERGY COMMISSION

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MEDICAL DIVISION

The three papers following serve as a partial index to the work of the Medical Division during the quarter. The first, "Cellular Changes in Effusions Following Intracavitary Administration of Colloidal Au^{198} in Humans," is the work of Vernie A. Stembridge*, M. D., Ralph M. Kniseley, M. D., and Gould A. Andrews, M. D., all of the Medical Division. The second paper, "A Note on Shaped Sources for Teletherapy Units," was prepared by Marshall Brucer, M. D., and William G. Pollard of the Institute; Harry Leiter, Franklin Institute, Philadelphia; and Herbert Scarf, Department of Mathematics, Princeton University, New Jersey. The final paper, "Preparation of Dosages of I^{131} for Oral Administration," was written by James Eldridge of the Medical Division, in response to requests for the procedure followed by the Division in this preparation.

(A fourth paper, "Teletherapy Design Problems," has been prepared by Dr. Brucer and will be published in the near future by the Radiological Society of North America.)

*On leave from the University of Texas, Medical Branch, Galveston, Texas; work done under Resident Physician Contract, Oak Ridge Insitute of Nuclear Studies.

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CELLULAR CHANGES IN EFFUSIONS FOLLOWING INTRACAVITARY ADMINISTRATION OF COLLOIDAL Au^{198} IN HUMANS

The effusions of serous cavities accompanying carcinomatosis have been treated recently with instillations of radioactive colloidal gold (Au^{198}). There is interest in the mechanism of action of this radioactive colloid, and in the fate of the colloid following its injection.

At the time of injection, the Au^{198} is a colloid having a submicroscopic particle size, estimated by different workers in ranges from .002 to .003 microns to .1 to .2 microns[1]. However, following its administration, it has been detected in particles and aggregates in the range of 1 to 5 microns in size. These are easily observed under a microscope, and have been seen by various workers. Sherman, et. al.[2], described gold particles which were phagocytosed by large mononuclear leukocytes, segmented neutrophils, and giant cells in patients who had been given parametrial injections of Au^{198}. Similarly, patients given intracavitary injections of Au^{198}, and subsequently studied at autopsy, were found to have aggregates of black pigment on or near the surfaces of treated cavities[3]. Particles were present both free and within phagocytes. Goldie and Hahn have also observed phagocytosis of gold particles after intraperitoneal injection of colloidal radiogold into mice[4].

Factors causing the fluid accumulation in carcinomatosis are poorly understood and therapeutic action of $gold^{198}$ in serous cavities is not well explained. Experimental work has demonstrated the effective treatment of free S-37 carcinomas in mice, but in treatment of more solid masses of tumor in humans, alteration of tumor by colloidal Au^{198} is not expected, nor has it been demonstrated except on superficial portions of the treated surfaces[5].

MATERIALS AND METHODS

This study is based on thirty patients who were treated with single or multiple instillations of radioactive colloidal Au^{198}. There were twenty-three females and seven males, and all had malignant tumors which were associated with persistent accumulations of ascitic or pleural fluid. The doses varied widely, since at the outset of the series multiple small doses of Au^{198} were given, while later the general plan was to give single large doses. Some of the patients received a series of rather large doses and several were treated both in the pleural and peritoneal cavities. The largest single dose was 232 mc.

The $gold^{198}$ used was a sterile colloidal solution* containing at the time of injection usually 10 to 25 millicuries per milliliter of radioactivity. The amount of stable gold present was generally in the range of 3 to 9 milligrams per milliliter.

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*Supplied by Abbott Laboratories, North Chicago, Illinois

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nteses for relief of symptoms were performed before and sometimes
illation of the Au^{198}. In addition, in certain instances, samples
ere taken following the instillation of the colloidal gold, princi-
termine the radioactivity. A total of 207 fluids were examined,
of samples from a single patient varying from one to twenty-three,
rals after treatment ranging from one day to six months. Cell
otein content, specific gravity, and volume were recorded in most
liquots of fluids were fixed in formalin and cell blocks were pre-
centrifuged sediments. These were stained with hematoxylin and
were examined for total cellularity, malignant cells, and pig-
rophages.

technique was adopted as a simple and practical method of obtain-
tion about the cell content of the fluids. More complete infor-
articularly concerning the presence of malignant cells, would un-
have been obtained if more elaborate methods of cytologic diag-
been used.

bles I and II indicate the presence or absence of malignant cells
-containing phagocytes, respectively, following therapy. In each
the findings in subsequent paracenteses are tabulated according to
interval after a single dose or the last dose of a series. A
consisted of two or more doses given in a relatively short period
e. In cases where two or more doses were given with long intervals
m, each was considered separately.

alignant Cells: In fourteen of the thirty cases, malignant cells
ound in the fluids following injection of the colloidal radiogold.
I shows the dose and site of the injected Au^{198}, and the intervals
ys between the injection and the aspiration of fluids. It is noted
umor cells were seen at a rather wide range of intervals (see Figure
This suggests that the radioactive gold does not rid the serosal
ces of tumor even though clinical relief of fluid formation may be
ned.

Inflammatory Cells: In evaluating the cellular exudation following
inistration of colloidal radiogold, we have studied the presence of
gocytes containing black pigment granules and the presence also of a
iety of other inflammatory cells. It might be expected that the trau-
ic effect of the beta radiation on the peritoneal or pleural surface
uld excite an inflammatory reaction. This has been seen in a number of
fluids. Thirteen patients showed the presence of numberous poly-
phonuclear leukocytes following the injection. However, five of these
tients had similar findings in the fluid before therapy. When leukocyte
unts were available they were over 2000/cm^3 and the blocks were obviously
llular. In only one case was the inflammatory response after treatment
lieved due to pyogenic infection of the cavity. No clear pattern of
action existed. The cellular response varied widely from patient to
tient, and some individuals had remarkably few cells in the effusion
ter large doses. This is well demonstrated in Case No. 29, L.R., where
20 mc were given into the left pleura. Following treatment, the histologic
udies of the fluid showed few cells, and leukocyte counts ranged from 15
1750/cm^3.

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The general pattern of phagocytic activity shows an early appearance of gold-bearing macrophages in the fluid, the earliest positive sample having been obtained one day following the injection of the Au^{198}. These pigment-bearing phagocytes are seen rather consistently in the fluids but gradually decrease in number with the passage of time. Table II shows the time intervals following treatment when pigmented phagocytes were encountered in the effusion. In general, the fluids removed up to four or five weeks following therapy contained these cells, while most fluids after five weeks did not contain them. In cases where a series of fluids were available for study, the number of phagocytes gradually decreased during the month following injection of the Au^{198}.

DISCUSSION

There are several possible explanations for the fact that the radioactive gold therapy does not consistently rid the serosal surfaces of tumor, even though retardation of fluid formation may be obtained. First, even though surfaces of pre-existing neoplasm may have been effectively irradiated, continued growth of implants beneath the surface will result in an invasion of the surface and will add a fresh source of exfoliating cells. The effective depth of radiation of the Au^{198} is only a millimeter or so, and it has been demonstrated that the colloidal Au^{198} does not penetrate solid areas of neoplasm sufficiently to produce effective radiation of deeper tissues following the intracavitary injection(5). A second possible explanation for the persistence of malignant cells is the fact that serosal surface distribution of the colloidal gold is uneven. An effort is made after injection of the gold to insure adequate mixing by shifting the patient about in various positions; but tissue radioassays at autopsy and surgical explorations show rather wide variations in concentration of radioactivity(5). Another factor of importance in some cases is the presence of pockets of fluid which are partially walled off by fibrous or neoplastic adhesions. These pockets may not be reached by the gold instilled into the larger serosal cavity.

In untreated patients with effusions caused by neoplasms, the finding of malignant cells is rather unpredictable. Therefore, in cases where negative samples are obtained following treatment, we are hesitant to conclude that the therapy has caused the disappearance of malignant cells from the fluid. Some of these negative results appear to be simply chance variations in patients having fluids which were not consistently positive even before treatment. In addition, the samples studied following treatment were often smaller in volume. It is of interest that malignant cells persist in a significant number of the cases, and that clinical relief from rapid fluid accumulation was afforded some of these patients.

The small particles of gold which are found in aggregates within phagocytes are rather variable in size, but are estimated in the range from 1 to 2 microns. Polymorphonuclear leukocytes apparently fail to phagocytose the Au^{198}, or disintegrate rapidly after the injection of the material, since only in rare instances are aggregates of pigment found in neutrophilic leukocytes. Goldie and Hahn(4) found in mice that macrophages were quite resistant to destruction by Au^{198} and, in contrast, polymorphonuclear leukocytes were highly sensitive. In twenty-four to forty-eight hours after injection, dot-like gold particles were found in

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ocytes. They also noted that radioactive gold tended to aggregate one or two large particles of irregular outline in the phagocytes, while in control animals given stable gold colloid, particles tended to be smaller, more numerous and dispersed. Our data from human cases of effusions do not show this tendency of the aggregates of Au^{198} to coalesce to the extent of forming only one or two large particles. Figure 2 shows the appearance of these phagocytes in one case at varying intervals following the injection.

One of the chief problems still unsolved is the reason for the aggregation of the colloidal material into particles so large that they are readily visible under the microscope. Perhaps this is accomplished by the clumping of multiple smaller particles within the cytoplasm of phagocytic cells. Even though the large particles are extracellular in the walls of the treated cavities, it is possible that they previously originated within phagocytic cells which have subsequently disintegrated. On the other hand it seems to us more likely that these larger particles are formed as a result of the presence of protein or some other substance in the cavity.

SUMMARY

1. Pleural and ascitic fluids associated with malignant neoplasms have been studied in an effort to clarify the mechanisms involved in intracavitary radiogold therapy. Following treatment, malignant cells persist in a significant proportion of cases.

2. The inflammatory cellular response to the injection of the radioactive gold is quite variable.

3. Phagocytes containing gold pigment are found with regularity at various intervals following therapy, being seen as early as one day and usually present during the first four to five weeks after treatment. Subsequently, they are infrequently found.

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TABLE NO. 1

MALIGNANT CELLS FOUND IN EFFUSIONS FOLLOWING THERAPY WITH Au^{198}

No.	Patient	Primary Site of Neoplasm	Dose and Site	Malignant Cells Before Rx	Interval in Days*										
					1-5	6-10	11-15	16-20	21-25	26-30	31-40	41-50	51-60	61-100	101-200
1	L.C.	Breast	55 mc in 2 doses rt. pl. 40 mc rt. pl.	++ +	o	+ o									
2	J.McG.	Uterus	232 mc pe.	+o		#			?		o	oo			
3	B.B.	Ovary	9.5 mc in 2 doses pe.							+					
4	S.W.	Lung	155 mc lt. pl. 148 mc lt. pl.	+ +		+	+	++		o				to	o
5	C.F.	Pancreas	162 mc rt. pl. 122 mc pe.	o			o	o			to #	oo	oo		
6	G.H.	Breast	210 mc lt. pl.	o									+	o	
7	I.W.	Ovary	205 mc pe.	+		+									
8	E.K.	Ovary	200 mc lt. pl.	++o++	+		++	o	ooo	+		+			
9	P.N.	Not known	185 mc rt. pl.	?	o			?			+				
10	E.F.	Ovary	170 mc pe.	#		o	+								
11	J.C.	Ovary	196 mc pe.				+				o				
12	C.R.	Lung	166 mc lt. pl.	oo			+								
13	M.D.	Lung	78 mc rt. pl.	+			+								
14	P.B.	Lung	74 mc rt. pl.	+		o		o							
15	H.R.	Ovary	101 mc pe.	+		+		o	o	o	o				
16	M.B.	Not known	144 mc pe.	++o		o									
17	O.S.	Breast	80 mc rt. pl.	+ooo++oo++++o			o	o	o	o		o			
18	M.G.	Ovary	105 mc pe.	+o		o									
19	I.B.	Breast	78 mc lt. pl.	+			o								
20	E.K.	Ovary	100 mc pe.	oo+		o	o								
21	R.H.	Breast	107 mc pe.	+								o	o		

pl. Pleura

pe. Peritoneum

* Interval in days from dose or last dose in a series

\+ Positive

o Negative

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TABLE NO. II

PHAGOCYTES CONTAINING AU PIGMENT IN EFFUSIONS FOLLOWING THERAPY

No.	Patient	Dose and Site	Interval in Days** 1-5	6-10	11-15	16-20	21-30	31-40	41-50	51-60	61-80	81-100	101-200
1	L.C.	30 mc rt. pl. 25 mc, 39 mc rt. pl.	+	+									
2	J.McG.	232 mc pe.			+	+	+	+	o	o			
3	B.B.	46 mc in 7 doses pe. over 2 month period*	o										
4	S.W.	155 mc lt. pl. 148 mc lt. pl. 22 mc, 17 mc lt. pl.	+	+	+	++	o						
5	C.F.	162 mc rt. pl. 122 mc pe. 14 mc rt. pl. 95 mc rt. pl. 16 mc rt. pl. 23 mc rt. pl.	+	+ o o	+ +	+	o		o		+ oo	oo o	
6	G.H.	211 mc lt. pl.		o									
7	I.W.	205 mc pe.											
8	E.K.	200 mc lt. pl.											
9	P.N.	185 mc rt. pl.	o +		oo	o +	+o+o+	+++o +	oo				
10	E.F.	169 mc pe.		+	+			+					
11	J.C.	196 mc pe.			+								
12	C.R.	166 mc lt. pl.							o				
13	M.D.	78 mc rt. pl.			+								
14	P.B.	74 mc rt. pl.		+	+								o
15	H.R.	101 mc pe. 49 mc rt. pl.		+		+	oo +o						
16	M.B.	144 mc pe.		+									
17	O.S.	80 mc rt. pl. 3 mc rt. pl.	+		+	+	++						
18	M.G.	105 mc pe. 54 mc lt. pl.		+	oo								
19	I.B.	78 mc lt. pl.			+								
20	E.K.	100 mc pe.		+	+								
21	R.H.	107 mc pe.											
22	B.F.	6 mc rt. pl.	+						+				o
23	E.R.	60 mc, 100 mc, 100 mc pe.				+		+					
24	G.C.	44 mc, 49 mc lt. pl. 48 mc lt. pl. 40 mc lt. pl.		+ +									
25	A.M.	342 mc in 6 doses pe. 52 mc pe. 50 mc pe.	o	•		o +			+		ooo		
26	C.C.	189 mc pe.											ooo
27	J.H.	185 mc rt. pl.				+							
28	M.Z.	70 mc lt. pl.			+			o	o	oo			
29	L.R.	200 mc lt. pl.		+									
					o	o	oo	o+o					

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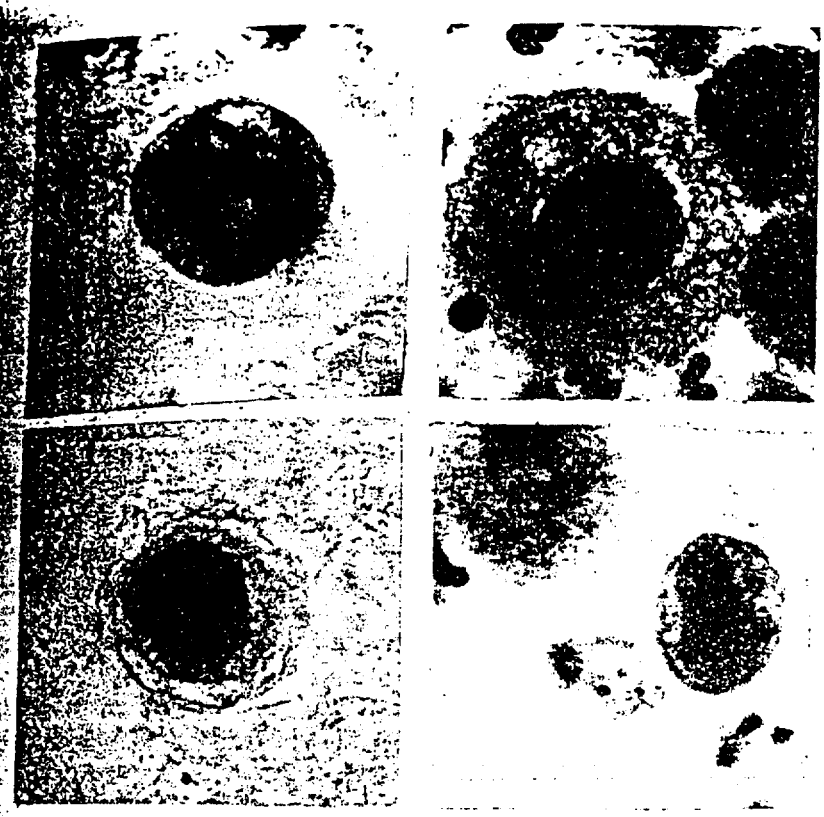


FIGURE 1. MALIGNANT CELLS PERSISTING IN PLEURAL fluid after injection of 155 mc of colloidal Au^{198}. Magnification X 1164. A. Six-day interval. B. Twelve-day interval. C. Eighteen-day interval. D. Twenty-one day interval.

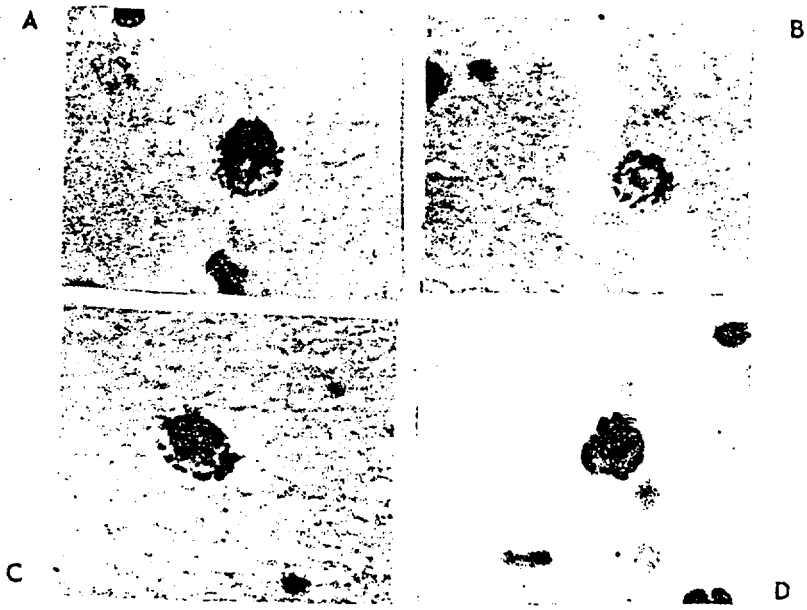


FIGURE 2. PHAGOCYTES CONTAINING BLACK AGGREgates of gold at varying intervals following injection into pleural space. Magnification X 1164. A. Six days. B. Twelve days. C. Eighteen days. D. Twenty-one days.

1033321

A NOTE ON SHAPED SOURCES FOR TELETHERAPY UNITS

One of the limiting factors in designing teletherapy units with radioactive isotope sources is the attainable volume specific activity. The mass specific activity of europium$^{152-154}$ and cobalt^{60} is limited by reactor time and flux. The maximum obtainable mass specific activity of Cs^{137} in the form of the sulfate is about 23 curies/gram. By compression Cs^{137} in this chemical form can be brought to a volume specific activity of about 95 curies/cc. Europium$^{152-154}$ and cobalt^{60} can be pushed much higher but self absorption markedly reduces their efficiency.

It has been suggested to us repeatedly that the efficiency of the sources could be greatly improved by distorting their shape to give a greater surface area per unit volume. We have concluded that this is impossible for the reasons presented in the following discussion.

1. THE BASIC DESIGN:

Assuming that a unisource unit only is being discussed, the basic features of the design of any unit will be a source of activity enclosed within a shield with some mechanism for turning the beam on and off as illustrated in Fig. 1. There must also be some form of collimating cone. Diaphragms or beam limiting devices would necessarily be added somewhere in the collimating cone.

2. THE CROSS SECTION OF THE PRESENTING FACE

If a beam with fixed cross section is desired, then the presenting shape of the face of the source should be that of the desired beam. If more than one beam cross section is to be used, as is true in most cases, the cross section of the source should be that best fitting all shapes. Since penumbra is one of the limiting factors of source diameter, the shape giving the greatest area for the least diameter would also give the greatest volume for the least penumbra. This is found in a circular cross section which fits the demand for any configuration of beam limiting device. Therefore, it has been accepted that a circular cross section is most efficient for any unisource unit.

3. THE POSSIBLE SHAPES OF THE PRESENTING FACE

The simplest circular cross section source would be a right cylinder. The question has been raised concerning the use of shaped sources. For example, a cone with its apex in the presenting face has a greater presenting surface area and might, therefore, impose less self absorption in its depth and, hence, yield a greater intensity of useful radiation. If the apex of a cone or other shaped source is fixed at a height equal to the radius of the cross section, i. e. 1.5 cm, then the area of a circle would be 2.25π, a right cone would be 3.21π, a paraboloid 3.75π, a hemisphere 4.50π. This progression would continue as the hemispheroid became more prolate until it approached the shape of a right cylinder moved 1.5 cm down the collimating cone. The surface area of the face of a hemisphere is twice that of a flat circle. It can be used as the type example.

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holds true to a greater or lesser extent for any other shape.

HEMISPHERICAL CUP VERSUS THE RIGHT CYLINDER

hemisphere were used, then the diameter of the source would fix volume. However, by taking a hemispherical surface and extending height to match the shape of a right cylinder, the volume is Therefore, the hemispherical cup, as shown in Fig. 2, should figure to compare with a right cylinder. A large number of parameters affected when the shape of the source face is changed, i. e., certain distance, the radiation intensity over the field, the the volume of material in the source, self absorption factors, number of simplifying factors must be introduced before the problem analyzed.

order to keep a reasonably flat radiation field at the source-skin assume that the SSD is between 50 to 100 cm and only about a 5% variation over the cross section is desirable. Assuming that only parallel primary photons are measured, then the greatest possible tion in SSD allowable is calculatable from the inverse square law. variation between points A and B in Fig. 2, there is about a 6% tion in the inverse square factor at 100 cm and about 13% at 50 cm. cm variation between points A and B this factor will more than Hence, we can fix a maximum source diameter at about 3 cm. The ment will hold true for any diameter but can more easily be calculated fixed diameter. If we accept a radius of 1.5 cm (points A-B) and source depth (points B-C) of 1.5 cm, then the volume of the hemispherical the same as that of a right cylinder of radius = height = 1.5 cm.

Since the source-skin distance is long in comparison with the distance between A and B (the depth of the source), no matter what the shape of the presenting face it is effectively a circle and the effective presenting is πr^2. (This argument breaks down at very short distances.)

The volume of the source is always identical in any shape of cup is equal to or greater than h and this volume is equal to that of right cylinder. If the volume is going to be very much less than $\pi r^2 h$, then shaping of sources will allow for a decreased self absorption a more efficient usage of the source material. Table I shows that such volumes are useless for teletherapy units. The problem of teletherapy any reasonable diameter will demand over 10 rmm at SSD and such sources to bound to have h > r with the expected specific activity of Cs^{137}. It is shown later that this argument does not break down even with Co^{60} or ^{152,154} where specific activities over 100 curies/gram could be produced.

If the volume of a hemispherical cup and a right cylinder source are about equal, then the attenuation due to distance and self absorption are the same from point X in Fig. 2. Since the most forward point defines the limits of the closing device on a machine, a right cylinder source comparable to the hemispherical cup could be placed at A-B. This means that radiation from point Y has significant attenuation both from self-absorption and distance in a hemispherical cup. All of the radiation from the most effective portion of the forward edge of a right cylinder at point Z is lost in a hemispherical cup or any other shaped source.

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If the source volume is small enough and there is no preferred direction of radiation, then a sphere would be the best shape, since the volume to total integral linear dimension ratio is optimum. Table I gives a definition for "small enough" for each diameter from 1 cm to 5 cm. To illustrate the interpretation of the table, if a 3 cm diameter presenting face is allowed, then it is possible to use a sphere with about 14 cm^3 volume. This would contain a maximum of 1089 curies of Cs^{137}. A right cylinder of the same diameter would be 2 cm high. There would actually be 2% less self absorption from the cylinder than from the sphere when the radiation has a preferred direction and is collimated.

Table I

The Volume at Which Sphere and Right Cylinder Are Equal With Fixed Presenting Face Diameter.

Diameter of Source cm.	Volume of a Sphere cm^3	Height of a Right Cylinder Which Would Give Equal Volume	Number of Curies in Source When Volume of Cylinder Equals Sphere	% of Intensity Reduced by Self Absorption For Given Diameter of	
				Cylinder	Sphere
1	0.52	0.66	40	7%	8%
2	4.19	1.33	322	14%	15%
3	14.14	2.00	1089	20%	22%
4	33.51	2.67	2580	26%	28%
5	65.45	3.33	5040	30%	32%

Since the same self absorption function holds for ellipsoids, to increase the volume by stretching the sphere in an axis perpendicular to the presenting face without changing the diameter of the presenting face does nothing more than approach the efficiency of a right cylinder. If a parabola or a right cone were stretched so that its apex came closer to the skin there will be an obvious increase in intensity, especially where the stretching has reached a point where h is much less than r with any fixed volume. However, at this point there is no longer a collimated beam if SSD is kept at or below 100 cm. Therefore, it seems obvious that the right cylinder with the base as a presenting face is the most efficient source shape for a teletherapy unit.

5. GENERAL SOLUTION

A more general solution can be derived mathematically for a source of any given shape. We consider first a source such as that shown in Fig. 3. The source is taken to have a fixed given volume V and to consist of material of specific activity a expressed in curies per cc. The total radiation emitted from the source per second is denoted by S and is given by

$$S = k a V$$

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a constant, characteristic of the radioisotope of which the made. S could be expressed in terms of photons emitted by the second, or it could be expressed in roentgens per second.

the source have a radius R and the collimating tube have a cross section of this same radius and length L, as shown in Fig. 3. point source placed at the origin O of source strength S would a solid angle at the collimator portal of

$$\Omega = \frac{\pi R^2}{L^2}$$

radiation I leaving the collimator portal will be

$$I = S \frac{\Omega}{4\pi} = S \left(\frac{R}{2L}\right)^2 \qquad (1)$$

For an extended source of any given shape the portion of the total tion emitted from the source which passes through the collimator will differ from that for a point source by a factor f which de- on the size and shape of the source and the collimator distance L, that for this source

$$I = S \left(\frac{R}{2L}\right)^2 f \qquad (2)$$

It is our purpose to evaluate the factor f for sources which all the same volume V and total activity S but are made in various pes. It will be convenient to compare the value of f for each shape the comparable value f_o for a disc shaped source of radius R and ness b which is taken as a standard. The volume of the standard ce is

$$V = \pi R^2 b$$

all other shaped sources will be adjusted to have this volume.

All sources here considered are taken to have axial symmetry about the axis of the collimator. We introduce polar coordinates ρ, φ, z and let the surface of the source be defined by $\rho = r = r(z)$ where r is function of z. The point on the source nearest the collimator portal taken at the origin of coordinates, O. The volume of that part of the ource lying below a given plane z is given by

$$\tau = \tau(z) = \int_0^z dz \int_0^r 2\pi \rho \, d\rho = \pi \int_0^z r^2 \, dz \qquad (3)$$

The total volume of the source is then

$$V = \tau(B) = \pi R^2 b \qquad (4)$$

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It is convenient to introduce the dimensionless quantities x, y, β and τ as follows

$$r = xR, \quad z = yb, \quad B = \beta b, \quad \tau = \nu V$$

$$\text{or } \tau(z) = \pi R^2 b \nu(y)$$

We find then

$$\nu(y) = \int_0^y x^2 \, dy$$

$$\nu(\beta) = 1$$

The volume element $d\tau$ has a radiation strength $(S/V)\,d\tau$ and subtends the solid angle at the collimator portal

$$\Omega = \frac{\pi R^2 \cos\theta}{(L+z)^2 + \rho^2} = \frac{\pi R^2 (L+z)}{\left[(L+z)^2 + \rho^2\right]^{3/2}}$$

Thus the radiation admitted through the collimator portal is

$$I = \frac{S}{V} \int \frac{\Omega}{4\pi} \, d\tau$$

and the factor f is given by

$$f = \frac{L^2}{\pi R^2 V} \int \Omega \, d\tau \qquad (7)$$

Introducing the expression for Ω this becomes

$$f = \frac{L^2}{V} \int_0^B (L+z)\,dz \int_0^r \frac{2\pi \rho \, d\rho}{\left[(L+z)^2 + \rho^2\right]^{3/2}}$$

$$= \frac{2\pi L^2}{V} \int_0^B \left[1 - \frac{1}{\sqrt{1+\left(\frac{r}{L+z}\right)^2}}\right] dz$$

Expanding the integral and neglecting terms in $(z/L)^2$ this becomes

103332b

$$f = \frac{\pi}{V} \int_0^B r^2 \left(1 - 2\frac{z}{L}\right) dz$$

...rring to variables x, y, and v by Eq. (5) and using Eq. (6),
...comes

$$f = 1 - (2b/L) \int_0^B x^2 y\, dy$$

...integrating by parts

$$f = 1 - (2b/L)\left[B - \int_0^B v(y)\, dy\right]$$

...For a disk $B = 1$ and $v(y) = y$. Thus

$$f_0 = 1 - b/L \qquad (8)$$

...mily of source shapes of a given type may be obtained by choosing

$$x = (y/B)^n \qquad (9)$$

...which $n = 0$ = a right cylinder or disk
$n = 1/2$ = a paraboloid
$n = 1$ = cone

...For such sources

$$v(y) = \int_0^y x^2\, dy = y^{2n+1} \Big/ (2n+1) B^{2n}$$

...nd the condition of Eq. (6) gives

$$B = 2n + 1$$

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so that $\beta = 2$ for the paraboloid and $\beta = 3$ for a cone.

For such sources we find

$$\int_0^{\beta} \tau(y)\, dy = \frac{2n+1}{2n+2}$$

so that

$$f = 1 - \frac{(2n+1)^2}{n+1} \cdot \frac{b}{L} \qquad (10)$$

and is thus smaller for all sources (all $n > 0$) than its value for a disk. Thus the disk gives the best shape.

In all of the preceding calculations, the radiation from each volume element $d\tau$ in the source is regarded as contributing its full intensity to the radiation leaving the collimator portal. This means that the source material is regarded as being completely transparent to the radiation and thus, self-absorption has been neglected. If, however, self-absorption is important, as it usually is, deep lying portions of the source, such as those in the neighborhood of $z = \beta$, $\rho = 0$ in Fig. 3, will contribute very little to the portal radiation because of severe attenuation in passing through the intervening source material.

In order to take self-absorption properly into account, the radiation strength $(S/V)\, d\tau$ of each volume element should be multiplied by an attenuation factor

$$e^{-\mu [y - y(r)]} \qquad (11)$$

where $y(r)$ is the inverse of the function $r(y)$. This, however, not only involves extensive mathematical complexity but does not lead to particularly useful results. The reason is that, since with self-absorption deep-lying portions of the source are largely wasted, it is much better to remove them and redistribute the source material so that none of it lies deeper than a preassigned axial distance from the front surface of the source. This can be done by simply translating the surface $r = r(z)$ in Fig. 3 a distance b along z to produce an "interior" source surface

$$r = r_i(z) = r(z - b) \qquad (12)$$

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Fig. 4. This makes the z-dimensions of the source at each ... the same and provides all annular sections with the same average ... factor (11). Thus, the attenuation can be incorporated in the ... length S and the calculation carried out without explicit use of ... orption factor.

... source now divides itself into three regions

(1) $0 \leq z < b$, ρ varies from 0 to r
(2) $b \leq z < B$, ρ varies from r_i to r
(3) $B \leq z < B+b$, ρ varies from r_i to R

... convenient to retain the function $\tau(z)$ as defined by Eq. (3). ... of τ for $z = B$ is now, however, no longer equal to the volume ... source, so that Eq. (4) no longer holds. In order to find the ... the source, we have contributions from each of the above three ... follows

$$V = \int_0^b dz \int_0^r 2\pi\rho\, d\rho + \int_b^B dz \int_{r_i}^r 2\pi\rho\, d\rho + \int_B^{B+b} dz \int_{r_i}^R 2\pi\rho\, d\rho$$

$$= \pi \int_0^B r^2 dz - \pi \int_b^{B+b} r_i^2\, dz + \pi R^2 \int_B^{B+b} dz$$

$$= \pi R^2 b$$

... we have used Eq. (12) and a change of coordinates to $z = u+b$ in the ... integral to show that the second integral reduces to the first so ... their difference vanishes. Thus the volume of any source of this ... and character is the same as that of a disk of the same axial thick-

... if we now evaluate Eq. (7) for the three regions above we find

$$= \frac{2\pi L^2}{V} \left\{ \int_0^b \left[1 - \frac{1}{\sqrt{1+\left(\frac{r}{L+z}\right)^2}} \right] dz + \int_b^B \left[\frac{1}{\sqrt{1+\left(\frac{r_i}{L+z}\right)^2}} - \frac{1}{\sqrt{1+\left(\frac{r}{L+z}\right)^2}} \right] dz \right.$$

$$\left. + \int_B^{B+b} \left[\frac{1}{\sqrt{1+\left(\frac{r_i}{L+z}\right)^2}} - \frac{1}{\sqrt{1+\left(\frac{R}{L+z}\right)^2}} \right] dz \right.$$

... panding the integrals as before and neglecting all terms in $1/L^2$, we ... thin

$$= \frac{\pi}{V} \left\{ \int_0^B r^2 \left(1 - 2\frac{z}{L}\right) dz - \int_b^{B+b} r_i^2 \left(1 - 2\frac{z}{L}\right) dz + \int_B^{B+b} R^2 \left(1 - 2\frac{z}{L}\right) dz \right.$$

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Again using Eq. (12) and the transformation $\mu = Z - b$ in the second integral this becomes:

$$f = \frac{\pi}{V}\left\{2\frac{b}{L}\int_0^B r^2 d\mu + R^2\left(b - \frac{2Bb + b^2}{L}\right)\right\}$$

Finally, using Eq. (5) and $V = \pi R^2 b$, we obtain

$$f = 1 - \left\{1 + 2\left[\beta - v(\beta)\right]\right\}\frac{b}{L} \qquad (13)$$

This equation is entirely general and holds for any shape source whatever which satisfies the conditions specified in Fig. 4. For the particular family of sources specified by Eq. (9) we have

$$v(\beta) = \beta/(2n+1)$$

so that

$$f = 1 - \left(1 + \frac{4n\beta}{2n+1}\right)\frac{b}{L} \qquad (14)$$

Again it can be seen that the largest factor f is obtained for any given b/L with a disk for which $n = 0$ and Eq. (14) reduces to Eq. (8).

Thus, under either of the conditions considered here, the disk shaped source gives maximum radiation at the collimator portal. For such a source the amount of radiation leaving the portal is given by combining Eqs. (2) and (8) as

$$I = S\left(R/2L\right)^2\left(1 - b/L\right).$$

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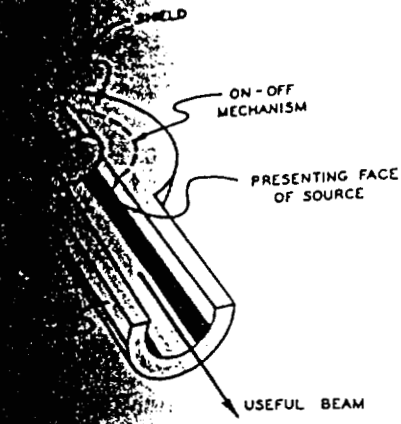


FIG. 1
...DESIGN OF ANY UNISOURCE ...RAPY UNIT

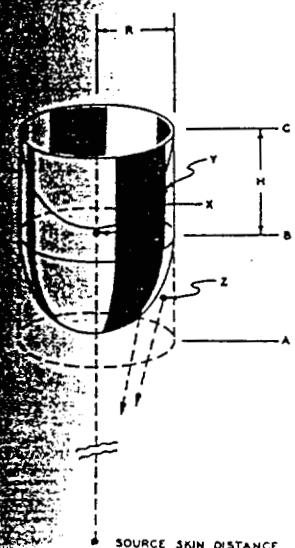
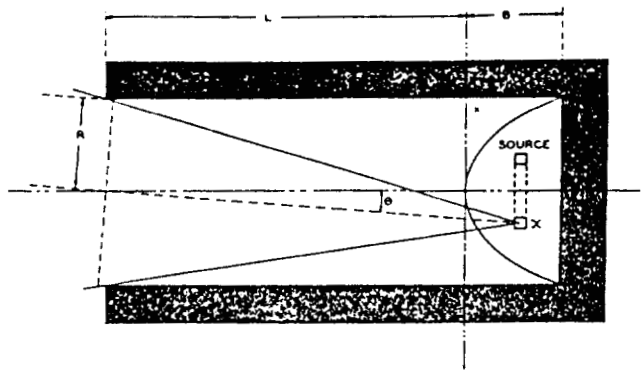


FIG. 2
...HEMISPHERICAL CUP SHAPED SOURCE ...WITH A DISK SOURCE OF EQUAL VOLUME



EFFECT OF SOURCE SHAPE ON INTENSITY

FIG. 3

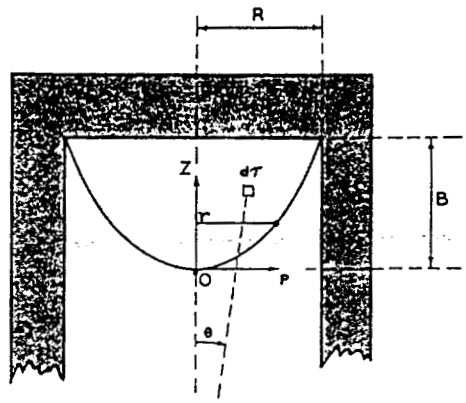


FIG. 4

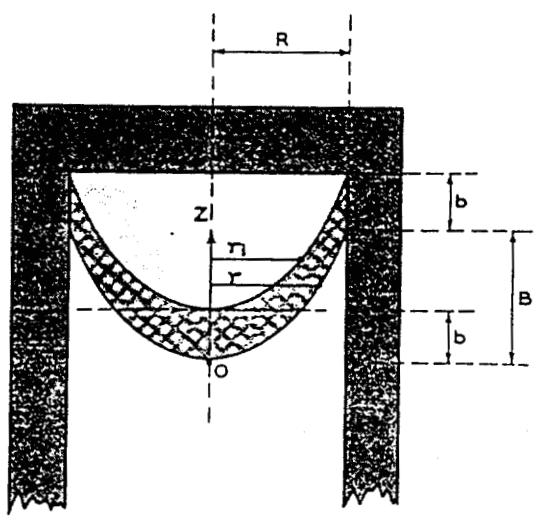


FIG. 5

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The shipments of I^{131} as received from Oak Ridge National Laboratory are contained in a cardboard box. Within this box there is a sealed metal can containing a lead shield which surrounds a one-half ounce screw-cap bottle containing the radioiodine. Included in the cardboard box is a packing slip which gives the radioassay and other pertinent data concerning the composition of the solution. For purposes of safety, health physics survey readings concerning the radiation coming from the container and the unshielded bottle are included on the packing slip.

1. When the shipping container is opened, record is made of the data on the packing slip, and a serial number is assigned to each shipment. After the data is recorded from the packing slip, the slip is placed in a permanent file.

2. The metal can is then opened - using a can opener - and the lead shield containing the I^{131} bottle is removed and checked for external contamination.

3. If no contamination is found, the shield is carried to the instrument room where an assay of the solution is made using a Lauritsen electroscope, which is standardized with a National Bureau of Standards radium needle. This method of assay is periodically checked against an N. B. S. iodine sample.

After assaying the solution, one of two methods is used in preparing the doses.

4-A. For doses of 5 mc or less, a convenient volume of I^{131} solution containing slightly more than the desired dose is pipetted into a 25 ml volumetric flask containing 10 γ of stable iodine as NaI. From this dilution, the appropriate volume containing the exact dose is pipetted into a waxed paper cup. The patient then drinks the solution from the paper cup. The cup is rinsed twice with H_2O and the patient drinks the washings.

An aliquot of the dilution containing approximately 100 μc is placed in a 2 oz. bottle containing 25 ml of water. This dilution is used as a standard for the scintillation counter which is used in thyroid uptake studies.

4-B. For doses of 5 mc or larger, the bottle containing the I^{131} is assayed, and the volume necessary to give the required dose is pipetted by remote control into a paper cup containing 10 γ stable iodine as NaI. A graduated pipette is used for this work. Pipetting by remote control is not sufficiently accurate for most purposes, so the pipette is rinsed thoroughly and the rinsings are added to the cup. The bottle is reassayed and the exact dose is calculated from the two assays by subtraction and correction for decay.

patient drinks the I-- from the cup in the same manner as in
er doses; the cup is rinsed twice, and the rinsings are also
the patient.

liquot containing approximately 100 μc is removed from the
bottle by means of a micro-pipette and is placed in a 2 oz.
a standard for thyroid uptake studies.

llowing is an example of the calculations used in preparing
doses of less than five millicuries.

Batch # I-70 Received 2/22/52
mc I^{131} in 0.6 ml $NaHSO_3$ Solution pH 11.0
Carrier Added. 17.62 ± 10% mc/ml at 0800 2/22/52
assay: 17.15 mc/ml at 1400 2/22/52 (24 hour clock used)

February 25, 1952, three doses were to be prepared: Two doses of
ch and one dose of 0.3 mc. At 1000 on this day the solution would

17.15 x 0.7823 = 13.4 mc/ml

7823 is the value of $e^{-\lambda t}$ for the period of 2 days and 20 hours.

In order to have the desired 2.3 mc plus an excess, a convenient
e of solution to measure would be 0.2 ml. Therefore a 200 γ
tte was used to place the solution into a 25 ml volumetric flask
ining 10 γ of stable iodine as NaI in approximately 24 ml of water.
pipette was washed five times by pulling the liquid from the flask up
down in the pipette by means of the micro-pipettor. The solution was
ted to 25 ml with water and shaken thoroughly. The solution contained
mc in 25 ml or 0.107 mc/ml.

In order to get one mc, it was necessary to use 1/0.107 or 9.3 ml.
9.3 ml of solution was then pipetted into a waxed paper cup using a
l serological pipette.

In order that all the calculations could be conveniently carried out,
values were written:

$$\text{dose} = 17.15 \times 0.2 \times \frac{9.3}{25} \times 0.7823 = 1.0 \text{ mc}$$

re 17.15 is the number of mc/ml at time of assay; 0.2 is the volume of
olution placed in the 25 ml volumetric flask; 9.3/25 is the fraction of
e solution placed in the waxed cup; and 0.7823 is the value of $e^{-\lambda t}$ to
rrect for decay of 2 days and 20 hours.

In order to get the 0.3 mc, it was necessary to use $\frac{0.3}{0.107}$ or 2.8 ml.

The 2.8 ml of solution was placed in another waxed cup using the
e pipette:

$$\text{dose} = 17.15 \times 0.2 \times \frac{2.8}{25} \times 0.7823 = 0.3 \text{ mc}$$

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For the scintillation counter standard, 1.0 ml of this dilution was diluted to 25 ml and placed in a 2 oz. bottle.

As an illustration of a dose larger than 5 mc we will take the following example:

ORINS assay: 130 mc I^{131} in 8.4 ml or 15.5 mc/ml as of 0900 6-11-52

The desired dose was approximately 75 mc. Therefore: $\frac{75}{15.5}$ or 4.8 ml were required.

A 5 ml serological pipette was used to measure the solution into a waxed paper cup containing 10 γ stable iodine as NaI. The pipette was rinsed and the rinsings placed into the cup containing the dose.

The bottle was reassayed at 1000, 6-11-52 and found to contain 57.3 mc.

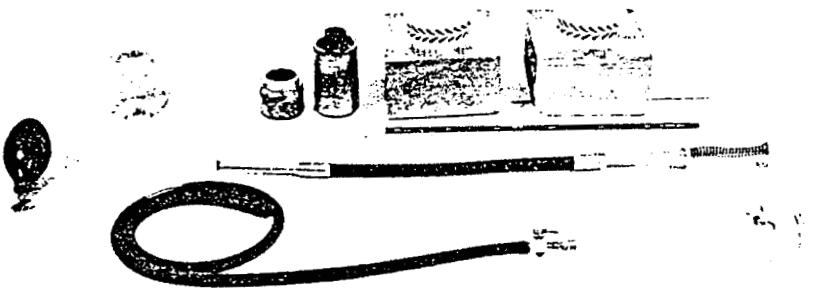
$\therefore$ dose = 130 - 57.3 = 72.7 mc.

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THE FOLLOWING PHOTOGRAPHS SHOW THE EQUIPMENT USED in preparing the doses of radioiodine:



THE MINIMUM EQUIPMENT NECESSARY FOR PREPARING tracer doses of radioiodine. From left to right, the equipment in the foreground is: solution of stable sodium iodide (10 γ I^- per ml), 1 ml pipette, 25 ml volumetric flask and stopper, micro-pipette and micro-pipettor, 10 ml serological pipette, pipetting bulb. Also shown are the radioiodine in its shielded bottle, paper cups for the dose and rinse water, and a plastic wash bottle.



THE MINIMUM EQUIPMENT NECESSARY FOR PREPARING THERAPEUTIC doses of radioiodine. (lead shield and mirror are not shown). From left to right, the equipment in the background is: pipetting bulb, 1 ml pipette, solution of stable sodium iodide (10 γ I^- per ml), radioiodine in its shielded bottle, and paper cups for the dose and rinse water. The "mechanical finger" is used to hold the serological pipette behind a lead shield, and the syringe and rubber tubing is attached to the pipette in order to draw up the required volume of radioiodine.

ORO-97

OAK RIDGE INSTITUTE of NUCLEAR STUDIES

Quarterly Progress Report

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P. O. Box 117 Oak Ridge, Tennessee

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UNIVERSITY RELATIONS DIVISION

OAK RIDGE GRADUATE PROGRAM

The following Oak Ridge Graduate Fellows who are candidates for the Ph.D. degree are now in Oak Ridge: (9)

Name	Institution	Place of Work	Beginning Date
Adams, James M.	Va. P. Inst.	ORNL--Biology	4-16-51
Blackstock, A. W.	N. C. St. Col.	ORNL--Health Physics	1-29-53
Drucker, B. M.	U. of N. C.	ORNL--Mathematics	3-15-51
Gamble, Roger L.	U. of Texas	ORNL--Physics	8-7-52
Garrett, Bowman S.	U. of Arkansas	ORNL--Chemistry	9-15-52
Meade, Thomas L.	U. of Florida	UT-AEC Ag. Res. Prog.	6-9-52
Murray, Richard B.	U. of Tenn.	ORNL--Physics	12-19-52
Stevens, Donald K.	U. of N. C.	ORNL--Metallurgy	10-1-51
Trail, Carroll C.	A. & M. College of Texas	ORNL-Physics	10-6-52

The following Oak Ridge Graduate Committee members visited the Laboratory during this quarter: (3)

Name	Institution	Field	Fellow	Date
Edwards, R. R.	U. of Arkansas	Chemistry	B. S. Garrett	1/27-29/53
Underwood, Newton	N. C. St. Col.	Physics	A. W. Blackstock	3/10-14/53
Weekes, D. F.	A. & M. Col. of Texas	Physics	C. C. Trail	3/28-4/1/53

OAK RIDGE RESEARCH PARTICIPATION PROGRAM

The following former Research Participants who hold Form S contracts with the Institute made trips to Oak Ridge during this quarter in order to keep abreast of research developments: (15)

Name	Institution	Department	Date of Visit
Bailey, Philip S.	U. of Texas	Chemistry	2/22-24/53
Baxter, John F., Jr.	U. of Florida	Chemistry	2/26-3/1/53
Ciereszko, Leon S.	U. of Oklahoma	Chemistry	1/24-27/53
Day, Reuben A., Jr.	Emory University	Chemistry	2/22-23/53
Dent, James N.	U. of Virginia	Biology	1/29-2/1/53
Goodrich, Max	La. St. Univ.	Physics	1/7-11/53
Hopkins, John I.	Vanderbilt Univ.	Physics	3/12-14/53
Hunt, Ernest L.	Emory University	Biology	1/29-31/53
Jones, William H.	Emory University	Chemistry	2/5-7/53
Knox, Kerro	U. of N. C.	Chemistry	1/22-23/53
LeRoy, Royce H.	A.&M. Col. of Texas	Chemistry	2/1-4/53
Lovelace, Roberta	U. of S. C.	Biology	1/1-5/53

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Name	Institution	Department	Date of Visit
Noll, Waldemar	Berea College	Physics	1/11-13/53
Pike, Frederick P.	N. C. St. Col.	Chem. Engr.	3/2-6/53
Young, F. W., Jr.	U. of Virginia	Chemistry	3/22-25/53

The following Research Participants are now in Oak Ridge: (2)

Name	Institution	Place of Work	Beginning Date
Richardson, J. E.	U. of Texas	ORINS-Medical	8-1-51
Walker, C. S.	A.&M. Col. of Texas	ORNL-Reactor Controls	9-8-52

The following Research Participant terminated during this quarter: (1)

Name	Institution	Place of Work	Beginning Date	Termination Date
Whitney, J. B., Jr.	Clemson Agr. Col.	UT-AEC Agr. Res. Program	2-4-52	2-3-53

OAK RIDGE TRAVELING LECTURE PROGRAM

Lectures scheduled	168
Lectures declined or canceled	70
Lectures to be arranged	59
Total requests received	297

OAK RIDGE RESIDENT GRADUATE PROGRAM

The following is a summary of enrollment by employer in the Resident Graduate Program for the winter quarter, 1953: (January 5 - March 20, 1953)

Employer	Different Employees Registered	Number of Courses Taken
Carbide and Carbon Chemicals Company, K-25	51	59
Carbide and Carbon Chemicals Company, Y-12	52	61
Carbide and Carbon Chemicals Company, X-10	68	85
Cerebral Palsy Center	1	1
U. S. Atomic Energy Commission	6	6
Oak Ridge Institute of Nuclear Studies	4	5
UT-AEC Agricultural Research Program	1	1
Total	183	218

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The following courses were offered in Oak Ridge during the winter quarter:

Chemical Engineering 565	Liquid-Liquid Extraction
Chemistry 512c	Advanced Organic Chemistry
Chemistry 523	Special Analytical Techniques
Chemistry 542	Advanced Physical Chemistry
Mathematics 452	Introduction to Analysis
Mathematics 522	Theory of Functions of a Real Variable
Mathematics 562	Mathematical Methods in Physics
Mathematics 699b	Seminar--Geometry
Metallurgy 592	Metallurgical Thermodynamics
Physics 412	Atomic and Molecular Structure
Physics 452	Atomic Physics Laboratory
Physics 542	Electromagnetic Theory
Physics 531	Advanced Dynamics

GENERAL

The University Relations Committee of the Council met in the conference room of the Medical Division on March 24, 1953. Members attending were: W.W. Grigorieff, Chairman; C. K. Beck; H. W. Davis; Roland B. Eutsler; P. K. McCarter; R. T. Nieset; and C. D. Van Cleave. Also attending this meeting in an ex officio capacity were: George H. Boyd; Marshall Brucer, M. D.; Marion T. Clark; William Dryden; William G. Pollard; and Russell S. Poor. This committee reviewed the progress of the University Relations Division and discussed plans for future activities.

AEC PREDOCTORAL AND POSTDOCTORAL FELLOWSHIP PROGRAMS

The following chart is designed to show the number of active AEC Predoctoral and Postdoctoral Fellows during the third quarter of the 1952-53 fiscal year and the number of terminations occuring during that period:

Life Science

	January	February	March	Terminations Within Quarter
Predoctoral	45	43	42	3
Postdoctoral	8	8	8	0
Postdoctoral medical	1	1	1	0

Physical Science

Predoctoral	107	99	94	18
Postdoctoral	6	6	6	0

Monthly figures are subject to slight adjustment, pending receipt of the exact termination data on some individual cases. Fellows holding active appointments for fifteen or more days within a given month are reported here as having an active fellowship during that month even though they may also have terminated in that month.

AEC RADIOLOGICAL PHYSICS FELLOWSHIP PROGRAM

Active Radiological Physics Fellows:

	First Appointees	Renewals
Vanderbilt	21	9*
Rochester**	16***	6

1953-54 Radiological Physics Fellowship Program:

The following 128 applications were received for the 1953-54 AEC Radiological Physics Fellowship Program:

Vanderbilt University	53
University of Rochester	51
University of Washington	24
Total	128

The Radiological Physics Fellowship Committee met March 13, 1953. Present were: Elda E. Anderson, ORNL; John I. Hopkins, Vanderbilt University; John Manley, University of Washington; M. L. Michelson, Hanford Works; R. A. Patterson, BNL; H. M. Roth, AEC; and J. N. Stannard, University of Rochester. M. T. Clark and R. S. Poor were present in an ex officio capacity. After general discussion, applications were reviewed by each group.

The following 55 appointments were made:

	Appointees	Alternates
Vanderbilt University	25	6
University of Rochester	23	5
University of Washington	7	0

In addition to these appointments, one award was made for 3 summer months for work at Brookhaven National Laboratory with the 1952-53 Fellows.

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* At the beginning of the quarter, 8 Fellows were working toward their master's degrees at Vanderbilt. One Fellow did work toward his master's degree at the Oak Ridge National Laboratory. To date, 4 of these 9 Fellows have completed their theses, 3 have completed compilation of data, and 2 did not complete their work under their renewal term which expired March 14, 1953.

** The renewal term for the Rochester Fellows continues through April 30, 1953.

*** At the beginning of the quarter there were 15 first appointees. One Fellow did not enter the program until March 25, 1953, due to a delay in security clearance.

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AEC INDUSTRIAL HYGIENE FELLOWSHIP PROGRAM

The following 3 Radiological Physics Fellows of the class of 1952-53 who were granted extensions to pursue studies in industrial hygiene are enrolled as follows and are making satisfactory progress:

Richard E. Cunningham	Harvard University School of Public Health
John L. Donovan	University of Pittsburgh School of Public Health
James E. Turner	Harvard University School of Public Health

1953-54 Industrial Hygiene Fellowship Program:

Thirty applications were received for the 1953-54 AEC Industrial Hygiene Fellowship Program.

The Industrial Hygiene Fellowship Committee met on March 20, 1953. Members present were: H. F. Schulte, Los Alamos; Theodore F. Hatch, University of Pittsburgh; N. V. Hendricks, Esso Laboratories; and Leslie Silverman, Harvard University. Merrill Eisenbud, NYOO, USAEC, was absent from the meeting. Present in an ex officio capacity were: H. J. McAlduff, Jr., ORO, AEC; Charles L. Dunham, Chief, Medical Branch, AEC, Washington, D. C.; and M. T. Clark, ORINS.

After discussion of matters of policy, applications were reviewed. Seven Fellows were selected contingent upon the satisfactory outcome of personal interviews with a committee member or some designated representative. Six of these Fellows proved satisfactory on interview and were given appointments.

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EXHIBITS DIVISION

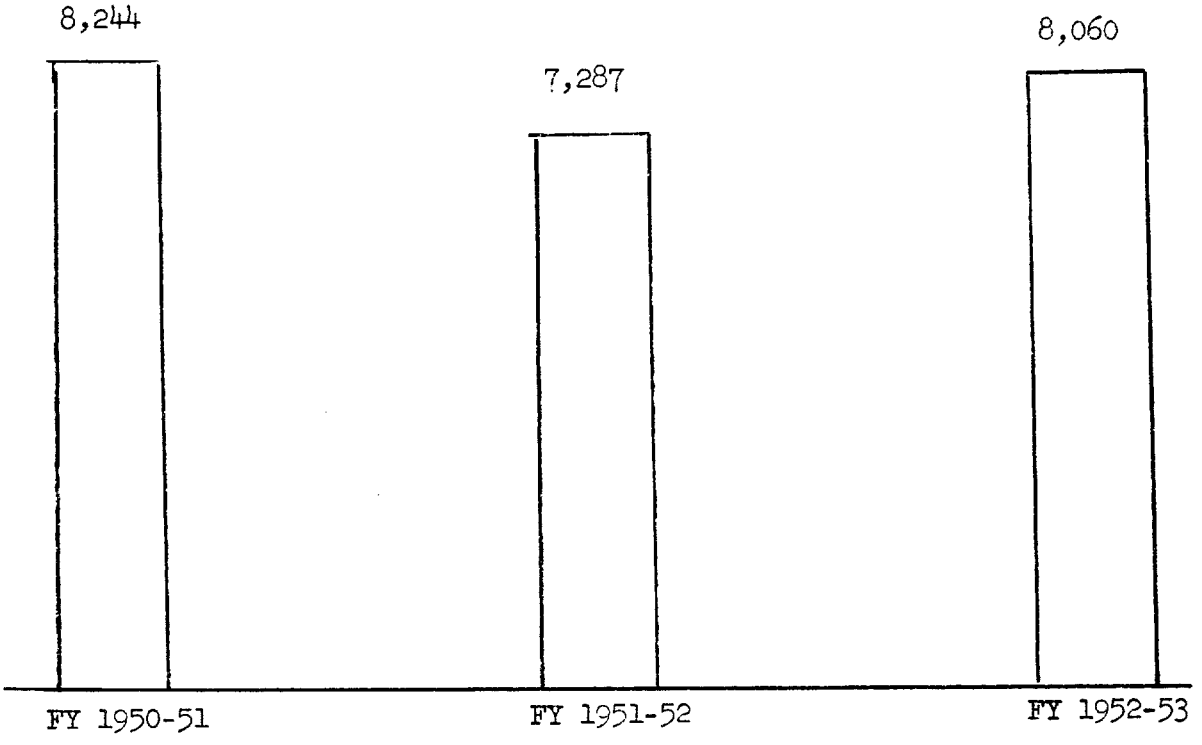
MUSEUM ATTENDANCE

NUMBER OF VISITORS DURING THIRD QUARTER:

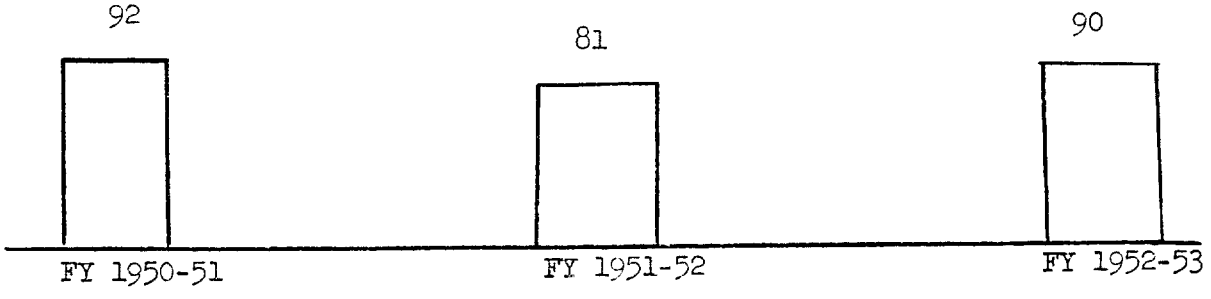
Total. 8,060
Daily Average. 90

COMPARISONS WITH PREVIOUS THIRD QUARTERS:

Total for the Quarter



Daily Average for the Quarter



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MUSEUM ATTENDANCE BREAKDOWN:

Item	Jan.	Feb.	Mar.	Totals
Regular ticket admissions	1,383	1,919	2,592	5,894
Annual ticket admissions	1	2	4	7
Children under 12 years	225	304	547	1,076
Other admissions (Free)	130	140	649	919
School groups (number of groups)	5	7	24	36
Special groups (number of groups)	1	2	7	10
Receptions (number of people)	79	35	50	164
TOTAL ATTENDANCE	1,818	2,400	3,842	8,060
AVERAGE DAILY ATTENDANCE	59	86	124	90

BREAKDOWN COMPARED WITH OTHER THIRD QUARTERS:

Item	FY 1950-51	FY 1951-52	FY 1952-53
Regular ticket admissions	6,962	5,713	5,894
Annual ticket admissions	21	29	7
Children under 12 years	1,073	894	1,076
Other admissions (Free)	7	591	919
School groups (number of groups)	24	27	36
Special groups (number of groups)	6	12	10
Receptions (number of people)	181	60	164
TOTAL ATTENDANCE	8,244	7,287	8,060

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CIRCULATING EXHIBITS PROGRAM ATTENDANCE (NUEA)

SPONSOR WITHIN STATE	PLACE	DAYS	ATTENDANCE
University of Texas	San Antonio, Texas	4	8,000
University of Texas	Waco, Texas	3	9,461
University of Texas	Corpus Christi, Texas	3	25,750
University of Texas	Houston, Texas	4	18,806
University of Texas	Beaumont, Texas	3	7,300
Louisiana State Univ.	Lake Charles, La.	3	2,700
Louisiana State Univ.	Shreveport, La.	4	10,252

PHYSICAL PLANT

New chairs and seats are now in the lobby, agriculture room, and lounge. Later, some of these will be placed in the reading room, which is currently being remodeled. Remodeling of rest rooms is complete, including the addition of a women's lounge. The outside of the museum building has been repainted and a flagpole has been erected near the main entrance.

NEW EXHIBITS, ETC.

During the quarter, the exhibit shop has produced the following new exhibits for the Number 2 Traveling Exhibit which will be inaugurated on May 1 with showings in Chillicothe and Portsmouth, Ohio:

(1) Basic - a series of 4 panels introducing the atom and presenting some of the fundamental facts related to atomic energy.

(2) Gaseous Diffusion - an analogy of the separation of uranium isotopes by gaseous diffusion based on moving patterns of lights.

(3) Medical Exhibit - summary of uses of radioisotopes in medicine.

(4) Van de Graaff - background panels and mountings for Van de Graaff electrostatic generator.

(5) Mineral Exhibit - exhibit including revolving wheel with mounted specimens of radioactive ores, showcase containing ore samples, world map showing deposits, and fluorescent specimens.

(6) Isotope Story - summary of information about isotopes, including what they are, how they are produced, and how they are used.

(7) Plutonium Production - simple explanation of how uranium 238 is converted by stages to plutonium 239.

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SPECIAL VISITORS

Among the visitors to the Museum during the quarter were:

Foreign editors from Manila, Hong Kong, New Delhi
Newspaper correspondents from NATO countries
Students from Army Chemical School, Ft. McClellan, Alabama
Members of Virginia Travel Council
Turkish technical visitors (TVA group)
Industrial relations study group, West Berlin, Germany
Members of Tennessee Orthopedic Association
Members of Oak Ridge Chapter of American Association of University Women
Official visitors introduced by local AEC offices
One government official from Bangkok

The following school groups have visited the Museum during the past quarter:

Jan. 8	Rutledge High School, Rutledge, Tennessee
Jan. 15	Rhea Central High School, Dayton, Tennessee
Jan. 15	Boones Creek High School, Jonesboro, Tennessee
Jan. 23	Trumansburg Central School, Trumansburg, New York
Jan. 24	Middle Tenn. State College, Murfreesboro, Tennessee
Feb. 9	Virginia Polytechnic Institute, Blacksburg, Virginia
Feb. 10	Spring City School, Spring City, Tennessee
Feb. 14	Carson Newman College, Jefferson City, Tennessee
Feb. 25	Arminda School, Arminda, Tennessee
Feb. 26	Indian Springs School, Helena, Alabama
Feb. 26	Willowbrook School, Oak Ridge, Tennessee
Feb. 26	Western Carolina Teachers College, Cullowhee, North Carolina
Mar. 2	Rhea Central High School, Dayton, Tennessee
Mar. 3	North City School, Athens, Tennessee
Mar. 4	Sevier County High School, Sevierville, Tennessee
Mar. 4	Everett High School, Maryville, Tennessee
Mar. 5	Indian Springs High School, Helena, Alabama
Mar. 12	Crossville High School, Crossville, Tennessee
Mar. 13	Oak Ridge High School, Oak Ridge, Tennessee
Mar. 13	Oak Ridge High School, Oak Ridge, Tennessee
Mar. 13	St. Andrews School, Sewanee, Tennessee
Mar. 13	Jefferson High School, Jefferson City, Tennessee
Mar. 18	Scarboro School, Oak Ridge, Tennessee
Mar. 19	Highland View School, Oak Ridge, Tennessee
Mar. 19	Linden Elementary School, Oak Ridge, Tennessee
Mar. 19	Young America High School, Metcalf, Illinois
Mar. 21	Western Reserve Academy, Hudson, Ohio
Mar. 21	St. James High School, Greeneville, Tennessee
Mar. 21	Central High School, Wartburg, Tennessee
Mar. 23	Willowbrook School, Oak Ridge, Tennessee
Mar. 24	Willowbrook School, Oak Ridge, Tennessee
Mar. 24	Elm Grove School, Oak Ridge, Tennessee
Mar. 24	Linden School, Oak Ridge, Tennessee
Mar. 26	Fulton High School, Knoxville, Tennessee
Mar. 27	Tempton Hill School, Cleveland, Tennessee
Mar. 27	King College, Bristol, Tennessee

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SPECIAL TRAINING DIVISION

Three basic radioisotope techniques courses were conducted by the Special Training Division during the quarter.

The 30th course began January 5 and was concluded January 30. It was attended by participants from 17 states and the District of Columbia.

The 31st course was held February 3-February 27. The 32 enrollees represented 16 different states, the District of Columbia, Egypt, Canada, Peru, Israel, Switzerland, Cuba, Italy, and Norway.

Attending the 32nd course (March 2-27) were 32 participants from 13 states, the District of Columbia, Puerto Rico, and Argentina, including 12 members of the armed forces, who came to Oak Ridge from Reed College, Portland, Oregon, for special training.

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MEDICAL DIVISION

Subcommittee No. 1 of the Teletherapy Evaluation Board (Source Evaluation and Shield Design) met on March 29. It was recommended, in summarizing the desirability and availability of isotopes for teletherapy sources, that proposed university contracts with the Commission specify Co^{60}, $Eu^{152-154}$, or Cs^{137}, whichever is available; and that the executive committee should decide immediately on submission of applications for sources. Of the isotopes specified, Co^{60}, at 240 curies/cc, should be available to a few persons in the coming year; $Eu^{152-154}$ production is pending further studies; and Cs^{137} eventually will be available in very large quantities. Limiting factors and functional requirements of the experimental prototype unit were discussed and the need for maximum motion and utilization was questioned. However, since the unit is experimental, maximum flexibility is a requirement, with preliminary studies indicating which operational characteristics may be omitted, and major engineering cost should be absorbed in the prototype design. Insistance on a head to permit field loading of a Co^{60} unit prompted the committee to request a design to permit loading by medical school personnel. The shutter "on" time for therapy was set at 10 minutes, but experimental studies may require 4-5 hour exposures. Centrifugal, gravity, magnetic clutch, over-drive, and other shutter mechanisms were discarded in favor of a pneumatic mechanism used by W. F. and John Barnes Company in many industrial applications. The pneumatic system was considered desirable for safety features, opening cycle, and simplicity of repair. A variable aperture disphragm, of an iris design opening to 15 inches, was introduced for discussion. It serves the dual function of variable circular aperture and supporting collar for rectangular and irregular portals. The committee discussed materials and fabrication, concluding that thickness requirements were not critical and that a medium Z metal might be used, although this would give a higher transmitted penumbra. The committee also discussed use of the Co^{60} light localizer to delineate the penumbra, table design problems, rest position of the unit, and automatic wedge filter control problems. The need was recognized for micro switches to stop the machine in the event of emergency, and the committee recommended a simple design for this safety feature.

ABSTRACTS

TELETHERAPY DESIGN PROBLEMS

by

Marshall Brucer, M.D., Chairman of the Medical Division, ORINS

About one-third of the Medical Division program is concentrated on the problems of the use of isotopes in external radiation therapy. Machine designs are being studied for neutron, beta, and gamma beam therapy. The current program is emphasizing the construction of two gamma therapy units. One is a large kilocurie source unit designed to produce 30 r/min at 1 meter distance. The other is a lower curiage machine for limited use designed to

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produce 45 r/min at 30 cm distance.

The prototype of the large unit is now under construction. It will consist of a kilocurie source in a lead shield opened by a rotating wheel shutter. The shield will be suspended from a ceiling mount and will allow a complete spherical range of motion with the beam always focused at a single point in space. The control of the patterns of rotation will be through an analogue computer mechanism which will allow for the reproduction of predetermined isodose distributions within tissue.

The essential design features of the small curiage machine are shown in Figure 1 on Page 21. The primary problem is directed toward head and neck therapy; therefore, the fundamental design problem is to remove as much of the mass of the machine as possible away from the planes represented by the shoulders and head, with the neck as the focal point. This machine is now under construction.

Since the problem of teletherapy units is so eminently practical, twenty-two medical schools have joined with the Medical Division of the Institute to investigate, develop, and evaluate radioisotopes for teletherapy. A Teletherapy Evaluation Board composed of one representative from each participating school has been organized. The funds supporting the board are furnished in part by the medical schools and, in part, by the United States Atomic Energy Commission.

The program of the Teletherapy Evaluation Board will explore initially the possibilities of utilizing three isotopes for teletherapy devices: europium-152-154; cesium-137; and cobalt-60. An effort will be made to exploit the inherent physical advantages of each isotope so that a variety of unit designs may be possible.

By far the most important part of the Teletherapy Evaluation Board is to evaluate methods of therapy. The pros and cons of the suitability of the various isotopes and minor differences of design have only a passing importance. The essential feature of the program is the evaluation of the method of using the machine. It is expected that eventually each of the participating medical schools will construct or purchase a machine similar in design to the units now under construction. A large portion of the therapeutic research will be done at the universities as a long-term project.

SKIN DOSE FROM A Co^{60} TELETHERAPY UNIT

by
Jasper E. Richardson, Assistant Physicist, University of Texas M. D. Anderson Hospital for Cancer Research*

Marshall Brucer, M. D., Chairman of the Medical Division, ORINS

Among the advantages of Co^{60} gamma radiation in the treatment of deep seated tumors is the possibility of a lower skin dose. This results from

*Work done under Research Participation Program at ORINS Medical Division (August 1, 1951 -)

the phenomenon of electron build-up in the first few millimeters of tissue for treatment at short cone to skin distances. However, the Co^{60} gamma ray beam is contaminated by electrons from the collimating system and the skin dose becomes appreciable. A study has been made to determine the optimum design of the treatment cone relative to the electron contamination of the gamma ray beam.

Various materials were tried as inner linings of the cone and as electron filters over the end of the cone. It was felt that materials of intermediate atomic number would prove most desirable; other materials were tried in order to determine the importance of the atomic number for this particular use. Typical results of the measurements are shown in Figure 1 on Page 22.

As an inner lining of the treatment cone, a material of intermediate atomic number proved superior to both low and high Z materials. For an electron filter placed over the end of the cone, materials of intermediate atomic number were superior to those of low atomic number. There was little difference between materials of medium and high atomic numbers. The effectiveness of an electron filter was also studied at different distances. Beyond 20 cm cone to skin distance, there was found to be little need for an electron filter even on the largest cone studied.

MODIFICATION OF ELECTRON FILTER TO IMPROVE LIGHT LOCALIZATION OF A COBALT-60 BEAM

by
Jasper E. Richardson, Assistant Physicist, University of Texas M. D. Anderson Hospital for Cancer Research*

Marshall Brucer, M. D., Chairman of the Medical Division, ORINS

When using short cone to skin distances with cobalt-60 teletherapy units, it is advantageous to filter the electron emission with a thin sheet of cadmium over the cone aperture. This filter can be placed to further use in connection with a light localizer to outline the goemetrical penumbra if a narrow opening is left around the periphery. With this arrangement, a band of light delineates the true geometrical beam of gamma rays and a fixed penumbra width as shown in the figure on Page 22.

EFFECT OF CHAMBER VOLTAGE ON ELECTRON BUILD-UP MEASUREMENTS

by
Jasper E. Richardson, Assistant Physicist, University of Texas M. D. Anderson Hospital for Cancer Research*

A parallel plate ionization chamber was used to investigate the effect of reversing the polarity of the chamber voltage in electron build-up measurements. An airless ionization chamber was built in order to localize

*Work done under Research Participation Program at ORINS Medical Division (August 1, 1951 -)

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the observed effect. The dependence of the measured ionization upon the polarity of the chamber voltage was found to be a characteristic of parallel plate type ionization chambers and to be due to the removal by gamma rays of electrons from the neighborhood of the current collector.

OPEN AIR MEASUREMENTS OF A LARGE Co^{60} SOURCE

by

Harold J. McAlduff, Jr., Atomic Energy Commission, Oak Ridge

Marshall Brucer, M. D., Chairman of the Medical Division, ORINS

Herbert D. Kerman, M. D., Chairman, Department of Radiology, University of Louisville

Jasper E. Richardson, Assistant Physicist, University of Texas M. D. Anderson Hospital for Cancer Research

Personnel of the Medical Division, ORINS, and of the Health Physics Division, ORNL, made open air measurements of the 300 curie Co^{60} source for the following purposes: (1) to determine the scatter characteristics of a large source in air with minimum scattering material in the field; (2) to compare dosage rates in open air with those obtained at equivalent distances in the collimated beam when the source had been placed in the therapeutic shield; (3) to determine the apparent curie strength of the sources; (4) to give training and experience to a large group of people in the handling and manipulating of large radioactive sources.

The instruments used were three Lauritsen electroscopes which had been previously calibrated in open air using a radium source. The measurements were made in an open air calibration field. A map of the field is shown in Figure 1, Page 23. Beginning at 25 meters from the source, measurements were made at 25 meter intervals out to 150 meters, with some incidental measurements both at closer and farther distances. Readings were taken at ground level, and using four step-ladders, at heights above the ground of 1.21 meters, 2.4 meters, and 4.6 meters. These readings were taken with the source suspended at 1 meter, 4 meters, and 7 meters above the ground.

A 3-dimensional plot of the radiation intensity over the measured segment of the field is shown in Figure 2, Page 24.

HAFNIUM COMPLEXES FOR BIOLOGICAL INVESTIGATION

by

Etta Macdonald, M. D., Assistant Professor of Bacteriology and Parasitology, University of Texas Medical Branch*

Carl Bahner, Professor of Chemistry, Carson Newman College; Consultant to the ORINS Medical Division

*Work done under Research Participation Program at ORINS Medical Division (May 4, 1951 - August 3, 1951)

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Following earlier work here on the distribution of hafnium administered to rats as a mandelate complex, studies have been made using catechol disulphunate, citrate, and gluconate complexes. Marked differences in the distribution pattern of the four complexes suggest the possibility that the usefulness of radioactive isotopes may be increased by directing the localization in tissues through the use of suitable complexing agents.

EFFECT OF ACTH ON EOSINOPHIL COUNT IN PERIPHERAL BLOOD AND BONE MARROW

by
Samuel W. Root, M. D., Clinician, ORINS

It has been shown repeatedly that the administration of ACTH or of cortisone may produce a decrease in the circulating eosinophils. It has not been shown how this decrease is brought about. If the maturation rate of eosinophils is decreased or their release from the bone marrow is interfered with or they are sequestered in the marrow, it should be possible to show a change in a number of marrow eosinophils following the administration of ACTH or cortisone.. Since the eosinopenia in the peripheral blood occurs very rapidly, one might expect an equally rapid alternation in the cycology of the bone marrow, if this were the primary site of the essential change in the rate of eosinophil formation or removal. The present study was done to compare the immediate effect of ACTH on the marrow with that on peripheral blood.

Twelve patients were selected who had eosinophils in the blood ranging from 3 to 16.7 per cent. ACTH was given by both intramuscular and intravenous routes. Bone marrow aspirations from either the sternum or the iliac crest were done immediately before and 4 hours after the intramuscular ACTH and immediately after the completion of the ACTH infusion in the cases in which it was given intravenously. Peripheral blood specimens were obtained before and at two hour intervals and at the same time as the last bone marrow aspiration. The essential counts of marrow cells were made on films stained with Wright stain and 1,000 cells counted before and after the administration of ACTH. Routine differential counts on 200 peripheral blood cells were done using Wright stained film.

There was an average percentage decrease of 69 per cent of the ecsinophils in the peripheral blood. There was no consistent change in the marrow eosinophils immediately following ACTH. In fact, the total numbers before and after was remarkably constant. Furthermore, there was no significant change in the number of marrow eosinophils in the various stages of development or evidence of degenerating forms. A comparison of the averages of the other marrow cells before and after ACTH likewise revealed little change.

Studies of the blood and bone marrow showed that the immediate eosinopenic response to ACTH was not associated with morphologic evidence of disturbed maturation of the eosinophils. Neither was there evidence of depletion of mature forms by rapid removal nor of destruction of these cells in the marrow.

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PATHOLOGIC CHANGES IN NORMAL HUMAN THYROID TISSUE FOLLOWING LARGE DOSES OF I^{131}

by

Gould A. Andrews, M. D., Chief of Clinical Services, ORINS

Ralph M. Kniseley, M. D., Pathologist, ORINS

R. R. Bigelow, M. D., Oak Ridge Surgeon; Consultant to the ORINS Medical Division

Samuel W. Root, M. D., Clinician, ORINS

Marshall Brucer, M. D., Chairman of the Medical Division, ORINS

The histologic changes which occur in normal thyroid tissue after relatively large doses of I^{131} have been described on the basis of information obtained from ten patients. These patients, with one exception, were admitted to ORINS Medical Division Hospital with carcinoma of the thyroid which could not be treated by surgical methods alone. The single exception was a patient with widespread metastatic malignant melanoma. The I^{131} was given to this patient in order to obtain information concerning the concentration of I^{131} in the lesions of malignant melanoma. The patients with thyroid carcinoma all had some normal remaining thyroid tissue, and in all of them there was an opportunity to study the pathologic effect of large doses of I^{131} in this tissue. The earliest thyroid specimen available for a study was at two days and other examples were seen at three, five, nine, thirteen, sixteen, and forty-two days. The severity of the damage seen at the various intervals was not uniform. There were examples of apparent radio-resistence on one hand, and a range of destructive changes from mild to a severe diffuse hemorrhagic necrosis. The radiation dose to tissue could not be closely correlated with the total dose administered, because of variations in the gland and because of differences in concentration and in retention of the isotope. It was not possible to predict the biologic response on the basis of dosage even when all the factors known to influence tissue radiation dosage were considered. Complete destruction of thyroid by means of a single, safe dose of radioiodine was found to be an uncertain procedure. In some cases, large total doses have failed to cause complete necrosis of the gland.

THE RATE OF DISAPPEARANCE OF IODINATED HUMAN SERUM ALBUMIN FROM THE BLOOD AND PERITONEAL CAVITIES IN PATIENTS WITH ASCITES FROM ABDOMINAL CARCINOMATOSIS

by

Malcolm Tyor, M. D., Clinician, ORINS

The intracavitary administration of colloidal $gold^{198}$ is beneficial to certain patients with serous effusions from carcinomatosis. The use of this form of therapy in such patients has stimulated interest in the broader problem of serous effusions and their mode of formation.

Albumin is the protein fraction which is chiefly present in plasma and

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serous fluids.

In the present study, iodinated human serum albumin was injected intravenously and intraperitoneally into patients with ascites from abdominal carcinomatosis and frequent samples of blood and ascitic fluid were obtained. The rates of disappearance from the injected compartment and appearance in the other were then compared for the five-day period following injection.

Regardless of the site of injection, there was a uniform disappearance from the injected compartment and appearance in the other during the period of observation.

DISTRIBUTION STUDY OF INTRAVENOUS RADIOGOLD IN RAT LIVER AND SPLEEN

by
Ralph M. Kniseley, M. D., Pathologist, ORINS

Adult Wistar male rats weighing 250 to 300 gms were given 500 μc of colloidal radiogold (Au^{198}) intravenously and serial sacrifices were made at 4, 8, and 20 minutes; 1, 12, 24, 72, and 144 hours. Microscopic autoradiograms were made to study the distribution of the gold following the intravenous administration in rats at these times. Focal concentrations were noted in some Küpffer cells and radioactivity was localized for the most part in the peripheral portions of the liver lobules. The distribution in the spleen was heaviest in the red pulp. The adrenal showed cortical concentrations and in the kidney most activity was in the glomeruli.

This focal concentration in the peripheral portions of the lobule does not conform to the areas of degeneration and necrosis which have been reported in rat livers after large amounts of Au^{198}. Therefore, a second group of animals was injected intravenously with a large dose of Au^{198} (20 μc per gram of weight) and animals were sacrificed at 3, 6, 9, 12, and 22 days. Again, the autoradiographic distribution was in the peripheral portions of the lobule, with focal concentrations of radioactivity apparently due to aggregates in Küpffer cells. At 12 days, the activity was more focal in nature but more random in its distribution throughout the lobules. In autoradiograms of the spleens given the larger dose, there was localization again in the red pulp with the heaviest concentrations in the zone immediately adjacent to the white pulp.

It is apparent that at the time when the liver is being delivered the large dose of radiation by the radiogold, the material is localized to the peripheral portions of the lobule; this is of interest since the pathologic changes, which have been described in livers following intravenous gold given to rats, are said to be in the mid-zone and central portions of the liver lobule. Pathogenic factors other than irradiation may be involved, at least in part, in production of the sites of necrosis which have been described. It is possible that the autoradiograms, being virtually two-dimensional studies of the beta emission, do not in fact show the three-dimensional picture of radiation to the liver lobule.

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STUDIES IN PROGRESS

by

Granvil C. Kyker, Principal Scientist, ORINS

1. Intrapleural Colloidal Chromic Phosphate

The localization of an internally administered dose of radioisotope within a particular tissue or area requires the use of a preparation with minimum ability to pass through a cell membrane and become mobilized by the metabolic processes of the body. The wide current interest in the study and use of colloidal gold is an example of this approach.

In order to evaluate another colloid, the distribution of intrapleurally injected chromic phosphate containing phosphorus-32 has been studied radiochemically and autoradiographically both in rats and in dogs. In contrast to colloidal gold, the radioisotope in this colloid is a source for beta radiation only.

The data include observations on approximately 50 rats and 5 dogs. In one series of animals sacrificed at intervals from 1 to 56 days, approximately 95 per cent of the intrapleural dose remained within the chest for one half-life and decreased to slightly less than 90 per cent after a period of 4 half-lives. The liver accounted for approximately one-half of the amount which left the chest cavity. The spleen showed approximately the same specific activity as the liver but because of its size accounts for a much smaller amount of the activity outside the chest. The distribution of activity in other organs and tissues outside the chest was in general quite low. In a second series of animals which received injections from a different batch of colloidal chromic phosphate (Abbott Laboratories), the pattern of distribution inside and outside the chest was qualitatively similar but quantitatively different. In the latter series, approximately 80 per cent of the injected dose remained in the chest. Percentagewise, the distribution agreed with that of the first series of animals.

The data by radiochemical assay indicate that most of the colloidal chromic phosphate is deposited on various pleural surfaces during the first day. The relative deposition on various surfaces within the chest does appear to change during the first half-life period. The mediastinal tissues accumulate the most activity. Autoradiographic studies confirm the radiochemical results and show that the activity is deposited on surfaces and that the deposition is uneven and irregular. (Manuscript in preparation.)

2. Beta Counting in Liquid Samples

The beta counting of liquid samples of radioisotopes affords much convenience in equipment and a great saving of time as compared to the various techniques (precipitation, filtration, electrodeposition) for preparing and mounting solid samples. The simple expedient of disolving a sample of tissue in concentrated nitric acid, boiling for brief period, diluting to an appropriate specific activity, and counting an aliquot, has found considerable usage in studies which present numerous samples.

The acid solution of tissue, frequently called the "digest," contains much undigested organic material of unknown nature. The tissue lipoids are

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only partially destroyed and, although these may be rather homogenously dispersed when the "digest" is first prepared, the dispersed particles tend to coalesce and to form a surface layer as a result of standing or dilution. This problem has been recognized by others and various attempts to overcome the difficulty have received attention. Also, the "digest" of a tissue sample contains an unknown amount and type of intermediate hydrolytic products of proteins which may or may not form complexes or precipitates that affect the homogeneity of the preparation. Since procedures for liquid counting generally employ a sample which exceeds the range of the beta particles, the observed result is a function of the specific activity of the sample. The dilution of the acid "digest" to different volumes yields samples which vary in their specific gravity. This difference among samples has not always been taken into account.

The stability of liquid samples of various radioisotopes has been under investigation in this laboratory with respect to a number of influencing factors. Hafnium-181 has received more attention than any other among those studied. Others include calcium-45, yttrium-91, gallium-67, gallium-72, gold-198, and lutecium-177. When instability in a sample appears, an apparent increase in the activity of the sample is the most frequent observation. As high as 300 per cent apparent increase has been observed under some of the conditions. The extent and rate of change in apparent activity is influenced by: (1) the nature of the acid (nitric, hydorchloric, sulfuric); (2) the concentration of the acid (8 molar to 0.005 molar); (3) the nature of the isotope; (4) the concentration of the isotope; (5) the nature of the tissue; (6) concentration of the tissue digest; (7) complexing agents; (8) surface active agents; and (9) the type of counting dish.

Although an interpretation cannot be offered at present to account for the wide scope of factors which influence the stability of the counting sample, the observations do accentuate the importance of strict attention to every detail in procedures for the beta counting of liquid samples. Where a choice exists, gamma counting should be considered. (Work is in progress on the preparation of a report of these studies.)

3. Preparation of Tissue Samples

The frequently used method of "digestion" of tissues with concentrated nitric acid yields liquid samples which are completely satisfactory for radiochemical assay in the case of all radioactive isotopes. In certain laboratories, a complete wet-ashing of tissue samples with perchloric acid is used. The latter yields "digests" which are free of organic material, but is appraised in this laboratory to be a potentially explosive hazard for routine technical use.

A method for the digestion of tissues which consists of preliminary treatment with copper and nitric acid followed by heating with sulfuric acid, which removes the nitric acid and completes the oxidation of organic matter, offers certain advantages. The use of this procedure is limited to isotopes which are non-volatile at the temperature of boiling sulfuric acid. The procedure has been tested on numerous samples of different tissues and is satisfactory in general except for skeletal tissue in which case an insoluble precipitate of calcium sulfate may introduce an error by adsorption of the radioisotope on the surface of the solid phase. A specimen of tissue requires from 1 to 1½ hours for complete digestion and little attention is

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necessary during this time. Other considerations to the preparations of tissue samples for radiochemical assay have resulted in the use of: (1) special weighing dishes for the tissue specimens; (2) special heaters for the routine digestion of multiple samples; and (3) dilution of samples to the same specific gravity prior to counting.

4. Studies with Lutecium-177

An appraisal by Brucer (Merck Report, Page 9, January, 1952) of the Therapeutic Potentialities of the Radioisotopes projects a list of 25 which are suitable for internal use and which can be produced by thermal neutron reactions. Gold-198, which has received widespread medical attention, stands at the top of the list which is arranged according to activation index. Out of the remaining 24, there appear 8 nuclides belonging to the lanthanide series of rare earth elements. Lutecium-177 and holmium-166 stand next to gold-198, and 5 others, or a total of 7 out of the 8 rare earths, appear in the first half of the list. This focuses sharp attention on the rare earth elements for an investigation of their therapeutic value.

A study of lutecium-177 is in progress. Lutecium occurs as a mixture of lutecium-175 (97.4%) and lutecium-176 (2.6%). Although less than one in 40 atoms of those naturally occurring is lutecium-176, the neutron cross section is approximately 135 times that of lutecium-175. Thus, the yield of lutecium-177 by reaction with thermal neutrons is more than $3\frac{1}{2}$ times that of radioactive lutecium-176. The half-life of lutecium-177 (6.8 days) is approximately 45 times that of lutecium-176, so that the latter decays out of the irradiated sample without much loss of the former. The activity due to the lutecium-177 is approximately 2.4, 3.6, and 4.2 millicuries per milligram after 1, 2, and 3 weeks, respectively, of irradiation in the Oak Ridge reactor. The specific activity is somewhat less than that of gold-198 produced under similar conditions. Like gold-198, lutecium-177 emits both beta particles and gamma rays, but each at much lower energy levels.

Lutecium and other rare elements present chemical characteristics which suggest study for internal use by mechanical localization within cavities and tissues and possibly by metabolic presentation to tissues. In the former, the hydroxides and a few salts are highly insoluble and are adaptable to preparation as colloids. In the latter, there are some quite stable soluble complexes which are simple to prepare. Also, reports indicate a tendency of the rare earths to associate with nucleic acids.

Procedures for processing lutecium-177 and for its radiochemical assay have been tested. The stability of three complexes has been studied in buffer series of different composition. The distribution of lutecium-177 in the rat administered intravenously as the chloride and as the sequestrene complex is in progress. The distribution pattern in the complex is distinctly different from that of lutecium chloride. A general study of the effect of the type of preparation administered and the route of administration on the distribution pattern in both normal and tumor-bearing animals is contemplated.

Lutecium is one of the heavy rare earths and a relatively scarce member of the series. Its procurement commercially is both difficult and costly, but not to the extent of excluding its study and appraisal as a potential therapeutic agent. The source of the material used in this investigation is by arrangement with F. H. Spedding, Director, Ames Laboratory, U. S. Atomic Energy Commission.

FIGURES

TELETHERAPY DESIGN PROBLEMS

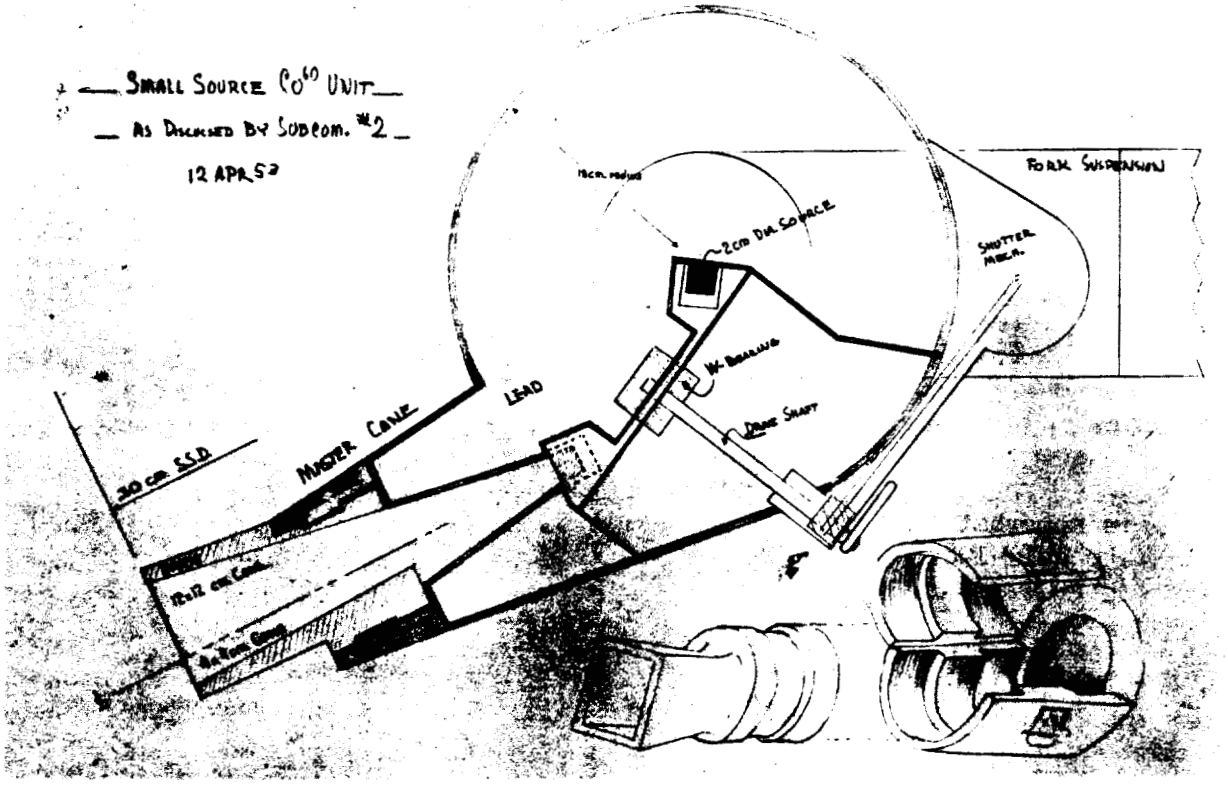


Figure 1. The essential design features of the small curiage machine.

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SKIN DOSE FROM A CO^{60} TELETHERAPY UNIT

ELECTRON BUILD-UP CURVES WITH EXPERIMENTAL CONES

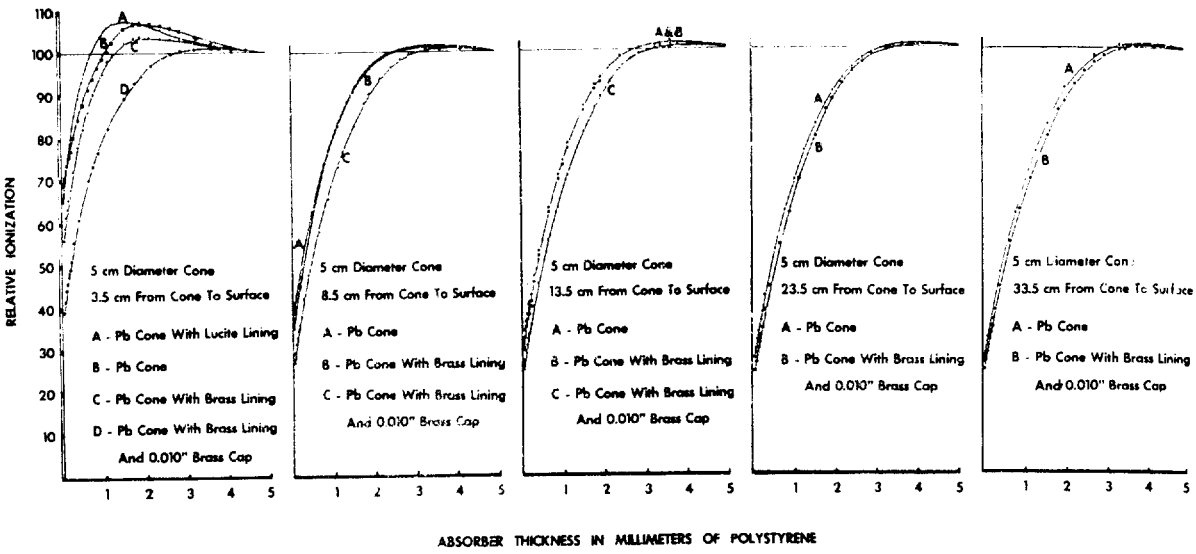
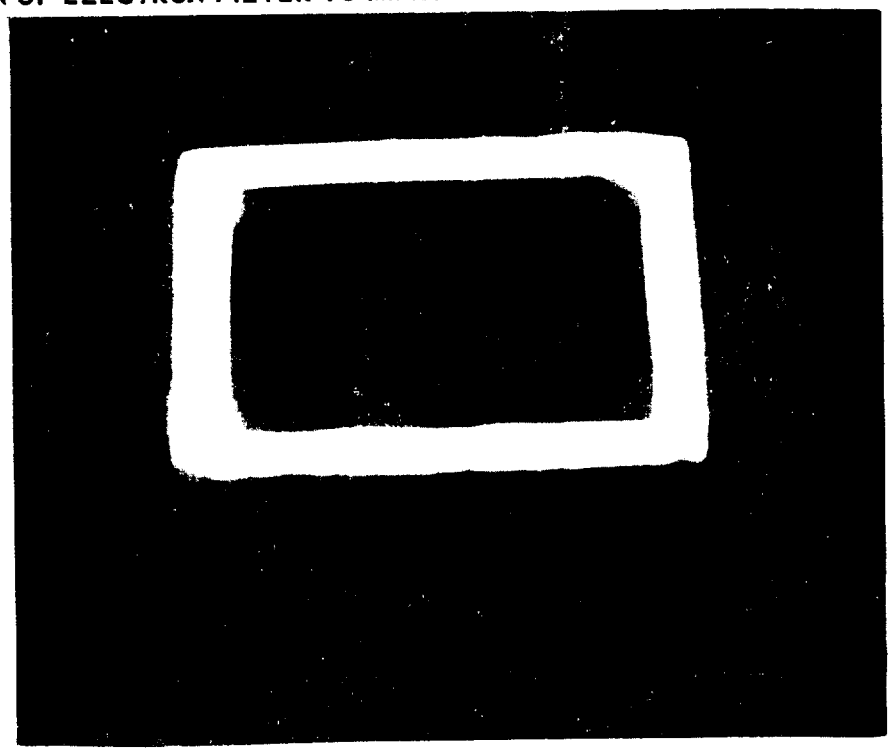


Figure 1.

MODIFICATION OF ELECTRON FILTER TO IMPROVE LIGHT LOCALIZATION OF A COBALT-60 BEAM



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OPEN AIR MEASUREMENTS OF A LARGE Co^{60} SOURCE

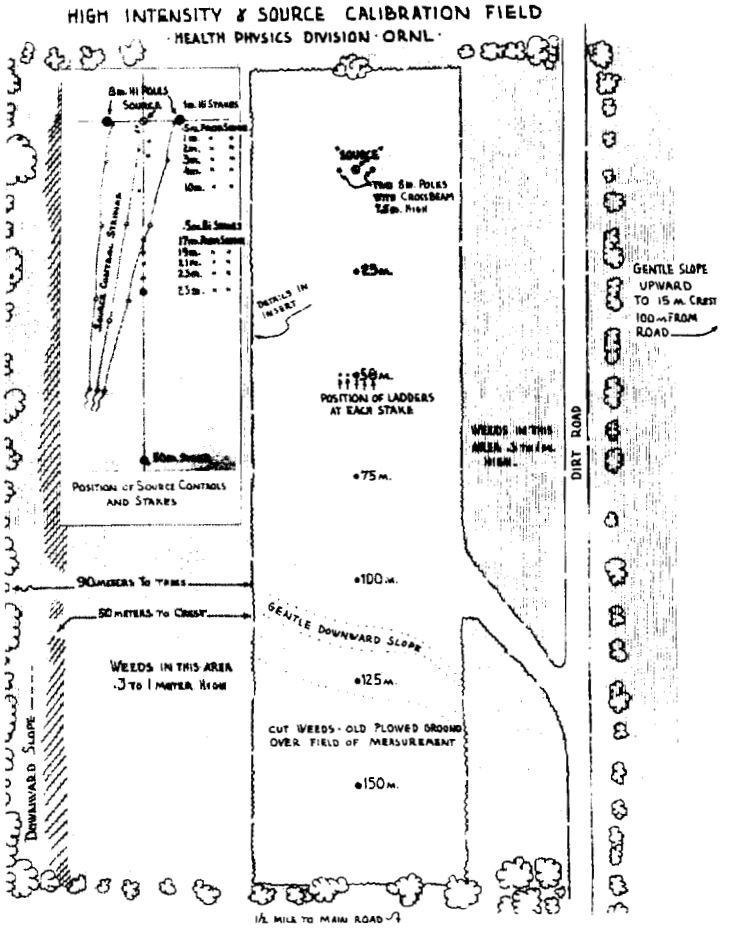
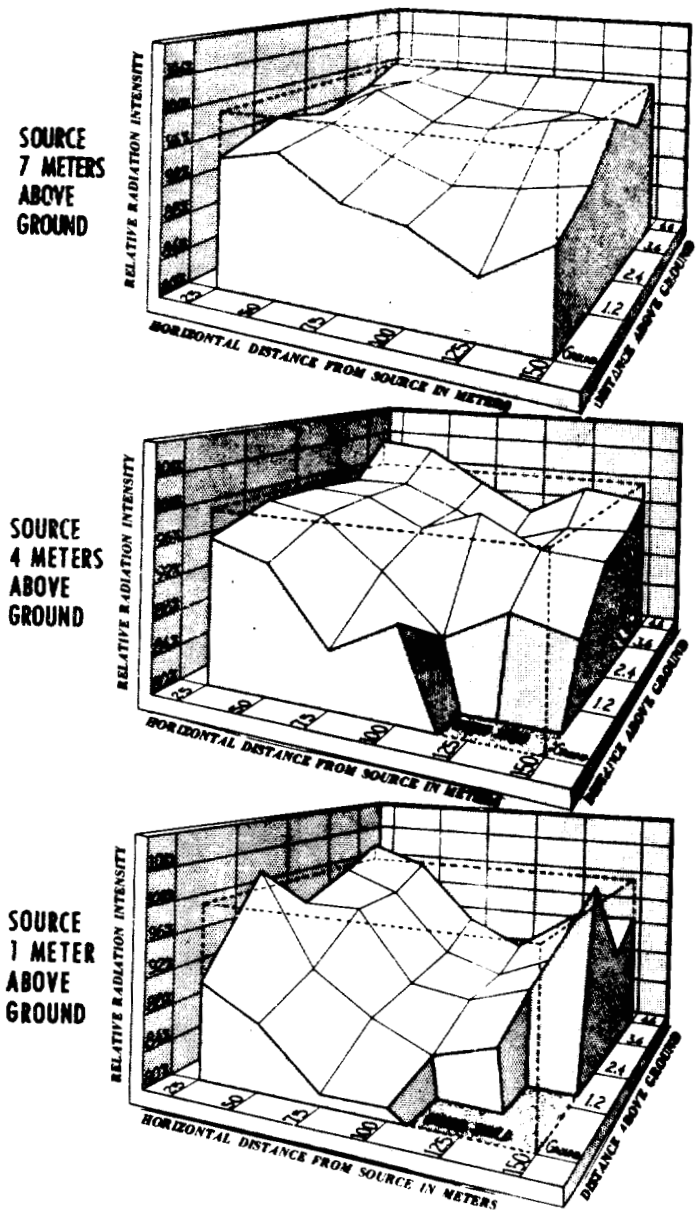


Figure 1.

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Relative Radiation Intensity From A Multicurie Co^{60} Source

source at 7 meters, electroscope at 4.6 meters = 100 %

Figure 2.

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PRELIMINARY REPORT ON THE USE OF THE SCINTISCANNER IN STUDYING THE DISTRIBUTION OF RADIOACTIVE GOLD

by
Charles E. Montgomery, M.D.*

The Medical Division has recently purchased a scintiscanner, an instrument made by R. C. Instruments Company of Playa Del Rey, California. This apparatus consists of a well-collimated scintillation crystal which moves back and forth above a source in such a way that a systematic survey of a whole area can be made. A special recording device produces a small mark for each selected number of impulses so that the final record is a map of the area surveyed, the density of the pattern indicating the degree of radioactivity.

Following a series of preliminary studies on the mechanical action and collimation of the scintiscanner, the machine has been used to survey the distribution of radioactive gold in a number of patients undergoing various types of treatment. The following brief case reports are presented as an illustration of the surveys which are resulting from the preliminary use of this machine. Certain technical problems have been encountered and the recording device has sometimes failed to respond at higher counting rates. Correction of these difficulties is in progress and the general value of the equipment is already apparent. The outlines of the patients are obtained by first locating a number of reference points on the body and then placing a sheet of lucite over the patient and sketching out necessary land marks.

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*Work done under Institute Resident Physician Contract. Present address: Department of Radiology, University of Kansas, Medical Center, Kansas City.

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PRELIMINARY REPORT ON THE USE OF THE SCINTISCANNER IN STUDYING THE DISTRIBUTION OF RADIOACTIVE GOLD

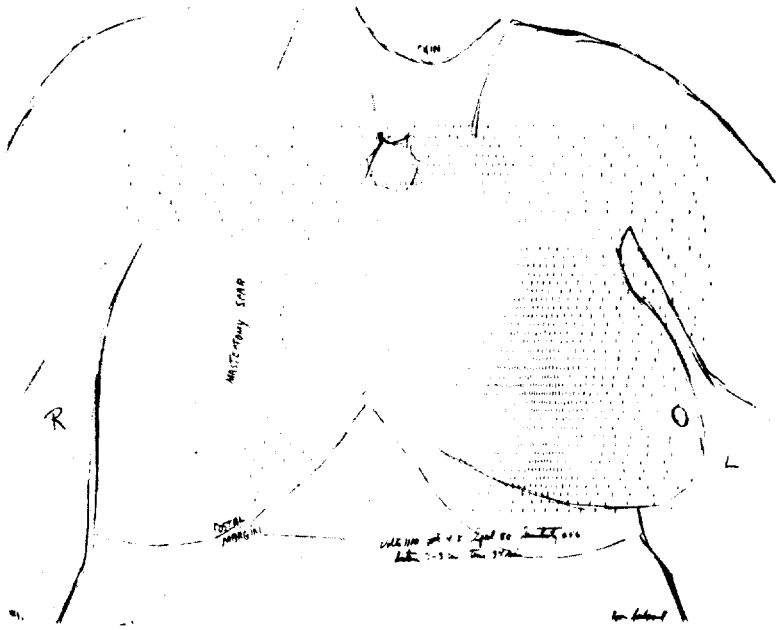


Fig. 1. The patient with carcinoma of the breast was given 75.5 millicuries of radioactive gold two days prior to the survey. The gold was given intrapleurally on the left at the mid scapular line in the ninth interspace for treatment of pleural effusion. Approximately 1800 cc fluid was removed from the left pleural cavity prior to the instillation of radiogold. It required approximately 34 minutes to complete the survey.

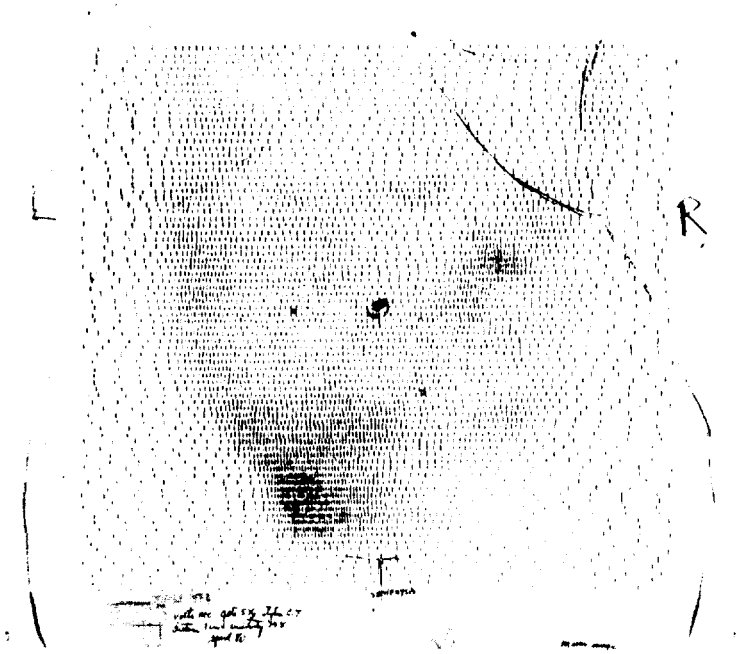


Fig. 2. The patient was given 144 millicuries of radiogold eight days prior to the survey. The gold was introduced intraperitoneally into the lower left quadrant of the abdomen through a polyethylene tube. The treatment was given in an effort to control ascites due to carcinomatosis. On this record only, of the present series, left and right sides are reversed. The small blank spots in the left cul-de-sac are due to an excess counting rate which was faster than the machine could record at the sensitivity setting used. The patient had been moved around following the instillation of the gold and the areas of greatest concentration can be due either to a folding of tissues with a uniform absorption, or a puddling of gold in various areas.

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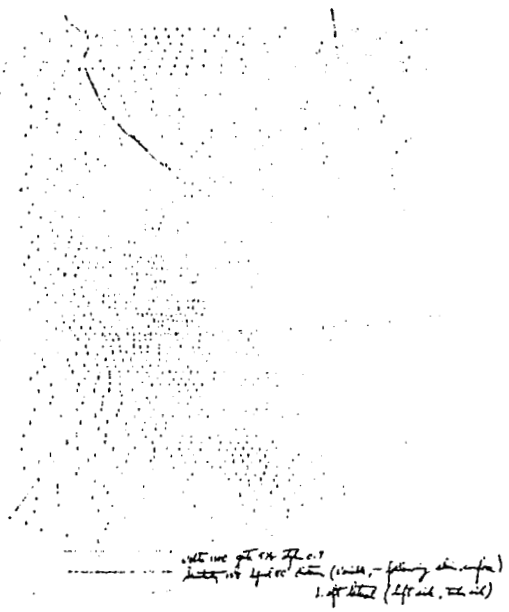


Fig. 3. Here is shown a left lateral projection of the same patient. There is a factor of an increased distance from the site of deposition, with the same sensitivity as in Fig. 2.

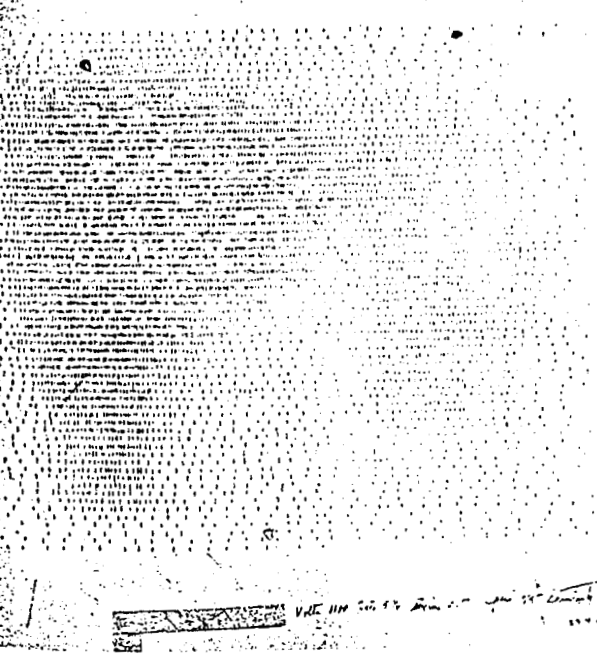
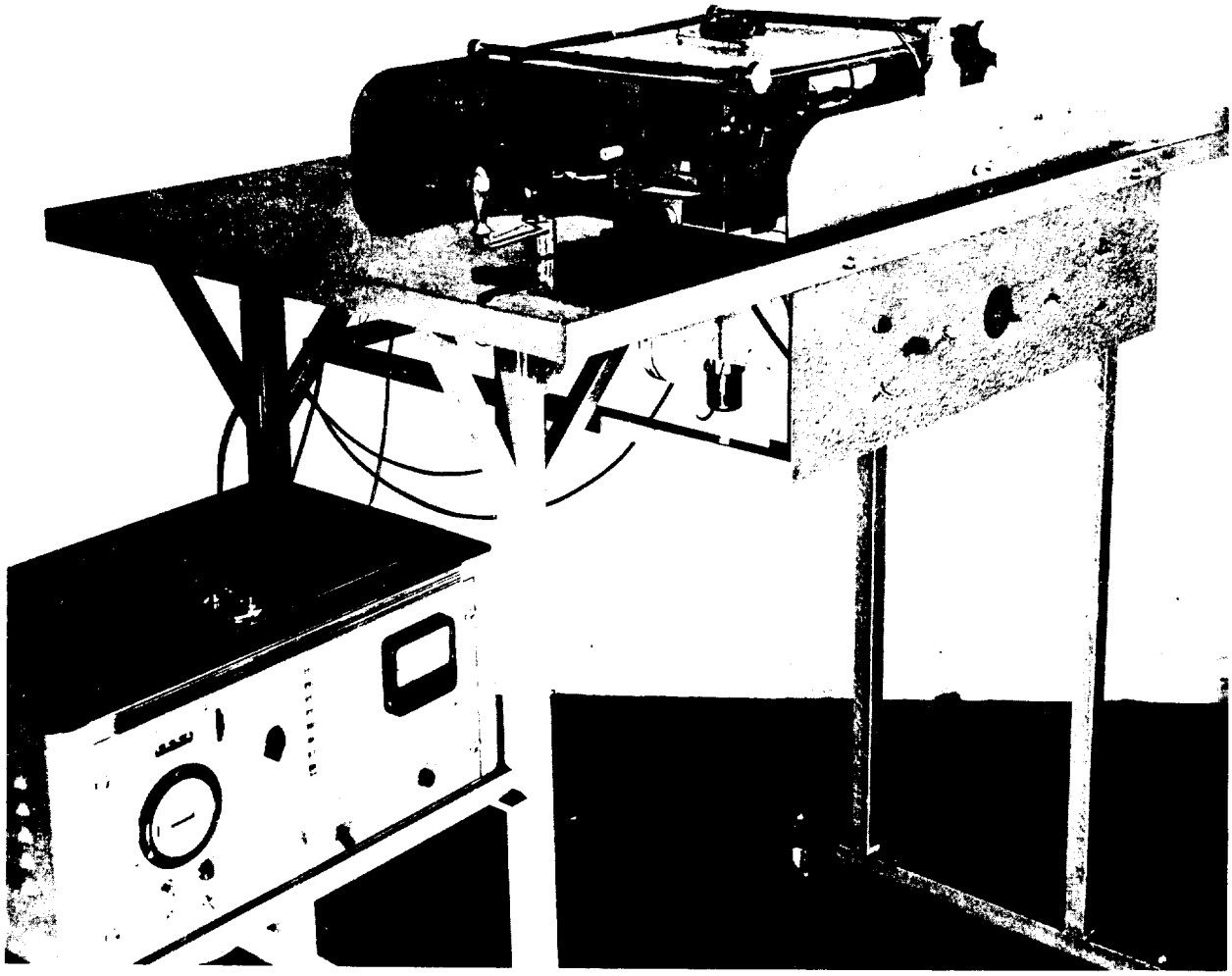


Fig. 4. Here is shown a survey of a patient with chronic granulocytic leukemia who had been given 23.4 mc of gold intravenously. The deposition of the gold in the liver and spleen is well shown. The blank spots over the areas of highest concentration in the liver represent areas where the counting rate was too high to record. These should be viewed as spots of intense concentration rather than areas of decreased concentration.

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Scintiscanner

AEC, Oak Ridge, Tenn. 5-12-53-400-W-21746

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Dr. Bunce

OAK RIDGE
INSTITUTE of NUCLEAR STUDIES

Quarterly Progress Report

April 1 - June 30, 1953

Operating Under Contract AT-40-1-Gen-33
with the
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Not for Re-publication

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AEC, Oak Ridge, Tenn. 300-9-28-53-W-22762

INTRODUCTION

This is the fourth quarterly progress report published by the Institute, the first three having outlined the research from July 1, 1952, until March 31, 1953. The first three reports contained information from all divisions of the Institute.

Since the Medical Division is the only division of the Institute organized for research as a primary objective, it has always been this division which has consumed the most space in past quarterly reports. It is a logical consequence of this situation that this report deals with the Medical Division exclusively.

Future reports also will be essentially those of medical research.

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MEETING OF THE BIOMEDICAL PROGRAM DIRECTORS

U. S. Atomic Energy Commission

Oak Ridge National Laboratory, Oak Ridge, Tennessee

A meeting of the Biomedical Program Directors was held in the auditorium of the new Oak Ridge National Laboratory Research Building on May 28 and 29. With Marshall Brucer, M.D., presiding, the following papers, representing projects of the Medical Division, were presented on Friday morning:

Radioactive Colloids in Therapy

Gould A. Andrews, M.D.
Malcolm Tyor, M.D.
Ralph M. Kniseley, M.D.
Granvil C. Kyker

The General Aspects of Teletherapy

Marshall Brucer, M.D.

Skin Dose from a Cobalt^{60} Teletherapy Unit

Jasper E. Richardson

MEETING OF THE ORINS MEDICAL ADVISORY PANEL AND THE MEDICAL COMMITTEE OF THE COUNCIL

The Medical Committee of the Institute Council and the ORINS Medical Advisory Panel met in the staff room of the ORINS Hospital on Tuesday, June 9. The Committee, on invitation, attended the meeting of the Medical Advisory Panel in the morning. Business transacted included nomination of members; discussion by Paul Elza, ORINS Manager of Administration, of the building program of the Medical Division; budget statement of Howard Harmon, Medical Division Administration Officer; discussion of staff vacancies; and discussion of the training program for radiological technicians.

After lunch, the members of the Panel attended a brief business meeting of the Committee. The members of the Medical Division staff then reported various phases of their work to both groups.

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ACTIVITIES OF THE TELETHERAPY EVALUATION BOARD

During the quarter the following meetings of the Teletherapy Evaluation Board held:

Subcommittee No. 2	Low Curiage Unit Design	April 12, 1953 ORINS Medical Division
Subcommittee No. 3	Rotational Methods	May 3, 1953 ORINS Medical Division
Subcommittee No. 4	Housing Design	May 24, 1953 ORINS Medical Division
Subcommittee No. 5	Clinical Program	June 2, 1953 New York University
Executive Committee		June 3, 1953 New York University

In the Subcommittee No. 2 meeting, the sizes and specific activities of cobalt^{60} ces currently available or expected to be available in the near future were dis- ed. Several design patterns were drawn up which will allow the build-up of about curies in a 2 cm diameter source. A double overlapping clover-leaf design was idered to be the most economical in space and curiage. The committee agreed that mall therapy unit should be designed for an approximate maximum of 45 r/min at source skin distance to take advantage of the currently available cobalt^{60}. It uggested that if possible there should be provision made for a somewhat larger source gth. There was a review of the advantages and limitations of the small therapy and a comparison of such a unit versus 250 kvp x-ray units. The following factors reviewed to bring out the advantages and disadvantages of a small unit:

1) A high tumor skin dose ratio in tumors approximately 5 cm below the surface of the skin is a possibility.

2) Since the unit must be used in contact, or very close to contact, the inverse square reduction exposure rate is considerable. Such a unit would probably not be suitable for any form of deep therapy.

3) With correct cone designs it is possible to use such a unit in head and neck lesions, and possibly in some intracavitary locations. Possibility of its use in cancer of the breast was brought up.

4) Such a unit can be designed with extraordinary flexibility and manipulation but this will depend directly upon the amount of money allowed for this suspension mechanism.

5) Because of the short source-skin distance, the unit is not practical for any form of rotational therapy.

6) Such a unit would have many of the advantages of a radium pack but would be superior in its depth dose and output.

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7) Such a unit should require very small space for the machine itself. With each increased degree of freedom in motion, however, there would be an additional requirement for shielding in the room.

8) Such a machine should be competitive with a million volt unit at short distances in all respects except exposure rate. A specific unit design was adopted.

USE OF PAPER CHROMATOGRAPHY IN THE STUDY OF IODINE CONTAINING COMPOUNDS

James S. Eldridge

The process of paper chromatography is being investigated in an attempt to characterize the various forms of iodine which might be found in the human after the administration of radioiodine as sodium iodide or as thyroxine. Some preliminary runs with non-radioactive l-thyroxine*, 3:5:3 triiodo-l-thyronine* and diiodotyrosine had shown that these materials could be separated under the conditions employed; therefore, it was decided to test the method on a plasma sample from a dog that had received 16.5 mc of I^{131} as sodium iodide. The plasma sample had been collected six days after administration of the isotope. It has been shown that this period corresponds to the maximum value of total serum radioiodine concentration.**

The method of trichloroacetic acid precipitation of plasma protein showed that the protein contained 54 per cent of the radioactivity of the plasma.

An aliquot of the plasma was extracted with n-butyl alcohol. The extract was evaporated nearly to dryness and an aliquot of the extract was applied to Whatman No. 1 filter paper (approximately 3/4" width cut from large sheets) and developed for 20 hours in a solvent consisting of 20 parts tert-amyl alcohol, 20 parts n-butyl alcohol, and 5 parts 2N ammonium hydroxide. The ascending method was used, with the strips suspended in a one-liter glass-stoppered graduated cylinder which served as the chromatographic chamber. The positions of the iodine containing fractions were determined by autoradiography and by counting, using a mica end-window Geiger-Mueller tube.

The autoradiograph shown in Figure 1 was prepared by placing the paper strip in contact with No-Screen X-ray film for 14 days. There were three zones of radioactivity having Rf values of 0.0, 0.3, and 0.49.***

A duplicate strip was counted (1-cm segments were cut from the strips and counted individually), and a histogram was made from the results. It was found that the activities having Rf values of 0.0, 0.3, and 0.49 were present to the extent of 9.7 per cent, 66.5 per cent, and 23.8 per cent, respectively. It was suspected that the three substances were diiodotyrosine, iodide, and thyroxine, although their identification was not completed.

Figure 2 shows the autoradiograph of another chromatogram which was made using the n-butanol extract from the urine of a patient who had received 188 mc of I^{131} five days before the collection of the sample. Five distinct zones with an indication of two faint ones were present. This chromatogram was included to show that paper chromatography using the solvent consisting of 20 parts tert-amyl

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* Courtesy of Smith, Kline, and French Laboratories, Philadelphia, Pennsylvania.

** Jacob Robbins, J. E. Roll, David V. Becker, Rulon W. Rawson. "The Nature of the Serum Iodine After Large Doses of I^{131}." The Journal of Clinical Endocrinology and Metabolism, XII, No. 7, 856 (1952).

*** Rf value is defined as the distance the zone or band travels divided by the distance the solvent travels as measured from the point of application.

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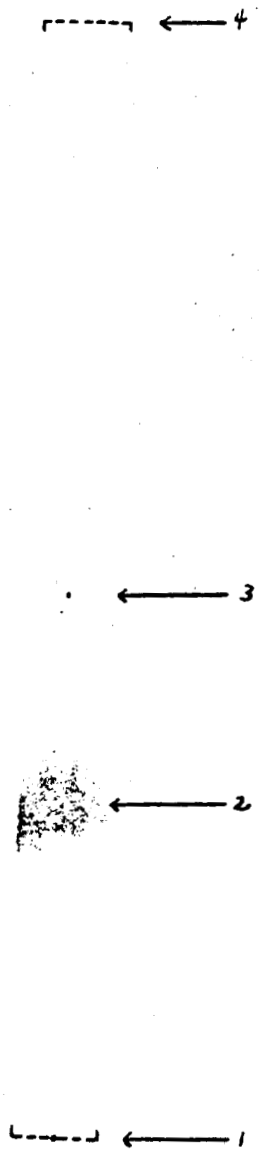


Figure 1. Autoradiograph of chromatogram of plasma from a dog which had received 16.5 mc of I^{131}. Exposure time: 14 days.

1. Indicates point of application and the component having Rf value of 0.
2. Indicates component having Rf Value of 0.3.
3. Indicates component having IRf value of 0.49
4. Indicates solvent front.

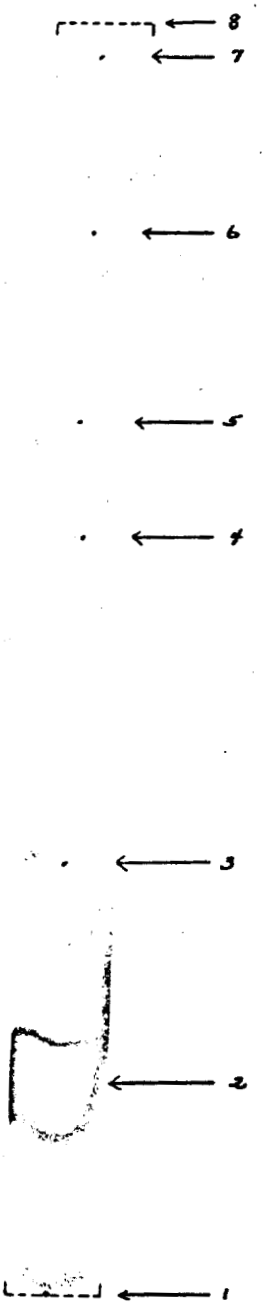


Figure 2. Autoradiograph of chromatogram of urine from patient who had received 188 mc of I^{131}. Exposure time: 14 days.

1. Indicates point of application and one of the components.
2, 3, 4, 7. Indicate the other major zones.
5, 6. Indicate the two faint zones.
8. Indicates the solvent front.

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alcohol, 20 parts n-butyl alcohol, and 5 parts 2N ammonium hydroxide achieves a separation of compounds present in the urine.

The one dimensional ascending method for making chromatograms was chosen because it simplifies the location of the zones both by autoradiography and by counting methods. In addition, the graduated cylinders used as the chromatographic chambers are easily decontaminated. They remain saturated with the solvent vapors, thus eliminating the necessity of an additional solvent saturated strip which is required with larger chambers.

Further investigations using this method are being made.

THE DISTRIBUTION OF INTRAPLEURALLY INJECTED COLLOIDAL CHROMIC PHOSPHATE

Granvil C. Kyker and Joseph H. McAlister, M.D.

(Abstract of paper submitted for presentation by Dr. Kyker at the meeting of the American Chemical Society, Division of Medicinal Chemistry, Chicago, Sept. 7-10 1953.)

Colloidal chromic phosphate labeled with P^{32} was injected into the pleural space of young male Wistar rats. Two series of animals were studied: The first, 21 animals, sacrificed in groups of 3 at 7 intervals varying between 1 and 56 days; the second, 24 animals, sacrificed in groups of 4 at 6 intervals between 1 and 42 days. Each animal was studied separately and the radioactivity of each of the following was measured: (a) washings from the pleural surfaces, right lung, left lung, heart, mediastinum, and external thorax; (b) liver, spleen, kidneys, adrenals, brain, intestine, muscle, bone marrow, blood, and the remaining carcass; (c) urine and feces.

In the first series, approximately 90 per cent of the activity remained in the chest during a period of 2 half-lives, whereas in the second series, approximately 80 per cent remained. Inside the chest, the percentage of activity in the mediastinal tissues increased with time; after one week, this specimen accounted for approximately one-half of the total activity in the chest.

Confirmatory studies were done on 5 dogs. The pattern was similar. The highest specific activity outside the chest was in the liver and spleen. Autoradiographic studies on both the dog and the rat showed the chromic phosphate to be deposited in a randomly splotched pattern on the pleural surfaces.

THE DISTRIBUTION OF INTRAPLEURAL YTTRIUM^{90} IN RATS

Granvil C. Kyker and Edgar A. Cress

In general, metabolic mechanisms fail to provide a means of localizing most radioisotopes exclusively in a particular organ or tissue. Therefore, biologically inert preparations represent an approach of prime importance to the internal use of radioactive substances for therapy. The intracavitary application of colloidal gold^{198} and colloidal chromic phosphate (P^{32}) are prominent examples.

The administration of an unbuffered isotonic solution of a neutral salt of a heavy metal - the hydroxide of which has a very low solubility product - should yield, upon reacting with tissue fluid, materials which are relatively inert biologically. On this basis, the distribution of yttrium^{90} is being studied. This isotope (half-life, 61 hours; beta, 2.18 mev; no gamma) was introduced intrapleurally into a series of 8 rats and its distribution was measured at the following intervals after administration: 18, 67, 138, and 186 hours. The dose consisted of 1.0 ml of an unbuffered saline solution of yttrium chloride containing 98 microcuries of Y^{90} and 410 micrograms of yttrium carrier per ml at an approximate pH of 4 (trace of hydrochloric acid).*

The following specimens from each animal were taken and radioassayed separately: heart, left lung, right lung, mediastinum, external thorax, washings of the pleural surfaces, liver, spleen, kidneys, femurs, blood, residual carcass, urine, and feces.

The pattern of distribution in each animal of the series was quite similar. More than 95 per cent of the total recovered dose remained in the space into which it was injected. The fraction distributed in tissues outside the chest averaged slightly less than 3 per cent of the total dose; from one-third to one-half of this fraction appeared in the liver. The total excreted portion increased gradually and almost linearly to 1.7 per cent of the dose after 8 days, one-fourth to one-third of which appeared in the urine. Within the chest, the activity was fixed to the pleural surfaces rapidly. The different specimens showed an uptake roughly proportional to the surfaces exposed to the injected dose.

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* This preparation was provided by G. I. Gleason, Abbott Laboratories, Oak Ridge, Tennessee.

1033375

PROGRESS REPORT OF CLINICAL STUDIES

Gould A. Andrews, M.D.
Samuel W. Root, M.D.
Malcolm Tyor, M.D.
Ralph M. Kniseley, M.D.
Betty M. Cooper, M.D.

Antimony Studies. A small series of patients has been studied with antimony^{122,124} and detailed autopsy studies have been made in four of them. The antimony was given in the form of an organic trivalent-arsenical, fuadin. Its localization has been chiefly in the liver, where it is deposited in a rather homogenous way, as judged by gross autoradiograms. Microscopic autoradiograms have been unsatisfactory, probably because of the lack of any large amount of low energy beta radiation from the isotope. The concentration of a large portion of the isotope in the liver suggests the possibility that the material is behaving as a colloid. The distribution, however, is quite different from that of most known colloids. For example, there are rather large concentrations of the antimony in the kidney. In addition, studies in rats have shown striking deposition of the antimony in the red cells, particularly after several days have elapsed.

From the results of Dr. Carl Tabb Bahner's work with the rat, antimony is believed to be attached chiefly to the protein portion of the hemoglobin, because hemoglobin isolated from the red cells has a sufficiently high concentration of antimony to account for practically all the activity of the red cells, whereas crystalline hemin split from the protein has little activity. It has been found that the red cells of the rat gradually take up antimony from a solution of fuadin in normal saline. The red cells of the dog seem to have much less tendency to take up and retain antimony than those of the rat. This species difference is easier to explain on the basis of the difference in the protein than on the basis of the difference in the hemin.

Incidental observations in the animal studies this quarter include: (1) the relatively high concentration of antimony in the pituitary glands of rats sacrificed 8 days after injection of fuadin; and (2) the much higher concentration of antimony in the cortex than in the medulla of the kidneys of dogs.

The material used for this study has been somewhat unsatisfactory since there is a mixture of two isotopes. It is now believed that about 2.8 per cent of the activity at the time the material is removed from the reactor is due to the antimony^{124} and the rest is due to the antimony^{122}. It is the latter isotope that is suitable for biological experiments and it would be desirable to have a purer preparation of it. A considerable improvement could be obtained by using an enriched stable isotope with antimony^{121} for the bombardment.

Gold^{198}. During the course of our whole study on colloidal gold^{198}, special efforts have been made to obtain hematologic information following the use of this isotope. Further data on blood and marrow changes are being obtained and the information is being assembled to evaluate the general pattern of response. It appears that the route of administration of the isotope makes a great deal of difference in the degree of hematologic effect.

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A number of patients have been studied after receiving injections of intravenous radioactive colloidal gold. Two of these were individuals in whom it was hoped that some therapeutic effect might be obtained for carcinoma of the liver. Several of the others were individuals with advanced neoplastic diseases to whom the isotope was given shortly before death. The colloidal gold was seen to deposit in the liver to a very large extent and the deposition was quite uniform in areas where the liver parenchyma was unimpaired by vascular damage or cellular infiltration. Areas of damaged liver showed a less uniform concentration. Areas of metastatic neoplasm in the liver were notably lacking in any ability to take up the colloidal material.

Patients with metastatic carcinoma of the liver have been given tracer amounts of the colloidal gold for external counting studies with the scintiscanner, in an effort to delineate metastatic lesions in the liver on the basis of the lack of concentration of the isotope in these areas.

Another study with the intravenously injected colloidal gold^{198} has been the experimental therapy of patients with chronic granulocytic leukemia. Detailed clinical hematologic and biochemical studies are being done with several patients who have been treated with this isotope.

On the basis of animal work done by Harold Berg, M.D., and his associates at Louisville, Kentucky, in conjunction with the Institute Medical Division, clinical studies are now under way with colloidal gold^{198} given by intrabronchial injection at the time of bronchoscopy. It appears that in dogs it is possible to obtain an intense radiation of mediastinal lymph nodes by this method. Up to the present, a small number of patients have been given these injections in doses larger than tracer levels, but probably too low for potential therapy. External counts with the scintiscanner have been the chief method of following the distribution of the isotope. We have also made assays of blood and of urinary excretion and have collected complete sputum samples to determine whether or not there is expectoration of any significant amount of the isotope.

Phosphorus^{32} as Chromic Phosphate. The use of intracavitary colloidal preparations in the treatment of effusions caused by malignant neoplasms is being continued and recent data have been collected on chromic phosphate containing P^{32}. A program to obtain information on the metabolism and distribution of this material after intracavitary injection is being pursued along the lines followed in the work on colloidal gold^{198} previously published from the Medical Division.

The use of radioactive phosphorus in certain cases of polycythemia and leukemia is also being continued.

Gallium^{67}. Clinical studies with gallium^{67} are continuing. The study is concentrated chiefly on patients with osteoblastic types of bone lesions, either primary or metastatic. We are also interested in patients with metastatic osteogenic sarcoma to the lung and are making a cooperative study with George Minor, M.D., of the University of Virignia, in an effort to determine the criteria for the resectability of pulmonary metastases at the same time that uptake studies with tracer doses of gallium are being made.

Studies on Pleural and Ascitic Fluids. A detailed study of the basic factors involved in production of pleural and ascitic fluid by neoplasms is under way. Studies with iodinated albumin injected into the blood and intc the pleural or

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ascitic fluid have shown the pattern of behavior of protein in the two compartments.

Thyroid Studies. The Medical Division is continuing its long range program of studying thyroid carcinoma with radioiodine and has recently treated a small number of selected patients having toxic goiter.

PROGRESS REPORT

Raymond L. Hayes

Aqueous chemical dosimetry has a distinct advantage over ionization dosimetry where integral dosage measurements are of interest. With chemical dosimeters it is necessary only to determine the chemical change per unit volume of irradiated solution. This change multiplied by the total volume of dosimeter solution used then gives a measure of the integral dose received. Irregular geometry of the dosimeter container presents no calculation problems as it would with ionization dosimetry. It is planned to make use of chemical dosimeters in the determination of integral doses obtained with different radioisotopes in which the isotopes are distributed both uniformly and non-uniformly in a standard-man-phantom. It is hoped that the results of these studies will permit much more accurate calculation of total body radiation dosages in patients receiving therapeutic amounts of radioisotopes. Preliminary studies of the application of several different types of chemical dosimeters to these types of measurements are being made at the present time.

1033378

OAK RIDGE INSTITUTE of NUCLEAR STUDIES

Quarterly Progress Report

July 1 - September 30, 1953



Operating Under Contract AT-40-1-Gen-33
with the
UNITED STATES ATOMIC ENERGY COMMISSION

P. O. Box 117

Oak Ridge, Tennessee

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A. CONTRACT BETWEEN ORINS AND M.D. ANDERSON HOSPITAL

THIS AGREEMENT, made and entered into on this the 19th day of Jul 1950, by and between OAK RIDGE INSTITUTE OF NUCLEAR STUDIES (hereinaft called the "Institute"), an educational corporation, not for profit, o ganized and existing under the laws of the State of Tennessee, and hav its principal office in Oak Ridge, Tennessee, party of the first part, and the UNIVERSITY OF TEXAS (hereinafter called the "University"), an cational institution, not for profit, organized and existing under the laws of the State of Texas, party of the second part.

W I T N E S S E T H:

THAT WHEREAS, the Institute has entered into a written contract wi the United States of America (hereinafter called "Government"), through the Atomic Energy Commission (hereinafter called "Commission"), for the purpose, among other things, of arranging and conducting clinical and re search programs in the study and treatment, with radioactive substances o with radiation, of cancer and allied or other diseases, and

WHEREAS, the University at Houston, Texas, operates and maintains a hospital for cancer research, known as the "M.D. Anderson Hospital for Cancer Research", and

WHEREAS, the parties hereto are desirous of entering into an agreement for the purpose of conducting certain similar or mutual phases of their respective medical research programs.

NOW THEREFORE, in furtherance of their said programs, and in consideration of the faithful performance of the covenants and agreements herein contained, the parties hereto do agree as follows:

(1) That the University, other than as provided in section (2) hereof, will furnish the necessary funds and/or materials and furnish or pay for all necessary labor and services (other than technical services and assistance which the Institute can furnish with its personnel) for the construction of an experimental Telecobalt Therapy unit in accordance with the plans and specifications therefor to be hereafter jointly designed and mutually agreed upon by the parties. The initial installation will be at Oak Ridge, Tennessee.

(2) That the Institute will mount and install said unit in a suitable building therefor in Oak Ridge. In addition, the Institute at its discretion, may provide for minor components and parts for said unit which it can conveniently fabricate in or with its own facilities. Any such components or parts so furnished by the Institute shall be without cost to the University, shall become a part of the unit furnished by the University and shall not be considered, at any time, as being separate and distinct therefrom.

(3) That after the construction and installation of said experimental unit, and so long as it remains at Oak Ridge, the Institute, at its expense, agrees to make all ordinary repairs and provide normal maintenance thereto,

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but the Institute shall not otherwise be liable for the loss, damage, or destruction of said unit.

(4) It is contemplated by the parties hereto that when said unit has been constructed and installed at Oak Ridge, that they will, through the Institute's Medical Division and the M.D. Anderson Hospital, cooperate in experimenting with, testing and measuring the physical and biological characteristics of the experimental unit and its suitability for use in the treatment of cancer or other diseases. Reports and publications of data concerning the project will be made jointly by the Institute and the M.D. Anderson Hospital with due credit to the respective staff members. It is understood that the program conducted under this contract shall be conducted on the same basis as all other programs of the Institute's Medical Division, insofar as medical school participation is concerned.

(5) That if, after testing and measuring the physical characteristics of said unit, and comparing its biological characteristics with present radiation generators, the parties hereto, or either of them, should be of the opinion that the unit should be released for use on human beings, then in that event a committee, composed of five qualified members, two of which shall be named by each of the parties hereto and one named by the Commission, shall be appointed for the purpose of deciding whether or not application should be made to the Commission for the release for human use of the radioactive components of the unit. If, upon such determination, an application for human use is approved by the Commission, that part of the unit provided or furnished by the University shall be delivered at Oak Ridge, Tennessee, to the University; provided, however, that if the University desires to sell, and the Institute desires to buy, the unit, the parties shall negotiate in good faith to mutually agree upon a fair and reasonable price for the unit, which price shall cover the estimated cost of a duplicate unit. In the event that the committee shall decide that release for human use is impracticable or if the Commission shall deny the application for release for human use and the University does not desire to continue development of the unit, the unit shall become the property of the Institute subject to its contract with the Commission.

(6) The parties hereto recognize that in order to accomplish the desired purpose of constructing and experimenting with said unit, a definitive understanding cannot now be reached on all questions which may arise in the future during the period of this agreement, and for that reason, among others, the parties agree that, if, as and when questions and problems arise which relate to the primary purpose of this agreement and which are not specifically covered hereby, they will exert their best endeavors to satisfactorily and mutually dispose of them in accordance with the letter and spirit of this agreement.

(7) All disputes which may arise under this agreement and which are not disposed of by mutual agreement shall be decided by the Manager, Oak Ridge Operation, United States Atomic Energy Commission, whose decisions, or the decisions of his duly authorized representatives or board shall be final and conclusive on the parties hereto. Pending decision of any dispute, the parties shall diligently proceed with the performance of the work under this agreement.

(8) Neither this agreement nor any interest therein or claim hereunder

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shall be assigned or transferred by either of the parties hereto, except that the Institute may assign its entire interest in this agreement to the Government at any time.

(9) The parties warrant that they have not employed any person to solicit or secure this contract upon any agreement for a commission, percentage, brokerage, or contemplated fee.

(10) No member of or delegate to Congress or resident Commissioner shall be admitted to any share or part of this agreement or to any benefit that may arise therefrom.

(11) It is understood and agreed that all services and travel of the University's employees shall be at the expense of the University until completion of initial installation of the unit at Oak Ridge; and that the expenses of travel of the University's employees for the purpose of experimenting with, testing and measuring the physical and biological characteristics of the unit at Oak Ridge shall be compensated by the Institute under and in accordance with the provisions of any personal service or consultant contract now or at any time hereafter in effect between the Institute and personnel of the University and/or its M.D. Anderson Hospital.

(12) The right is hereby reserved on behalf of the Commission, by each of the parties hereto, to inspect, in such manner and at such time as said Commission deems appropriate, all activities arising in the course of the work under this agreement.

IN WITNESS WHEREOF, the parties hereto have caused this agreement to be executed by their duly authorized officers on the day and year first above written.

OAK RIDGE INSTITUTE OF NUCLEAR STUDIES

BY s/ Paul M. Gross
President

ATTEST:

s/ William G. Pollard
Secretary

UNIVERSITY OF TEXAS

BY s/ Theophilus S. Painter
President

ATTEST:

s/ Arthur C. Holt
Secretary

APPROVED AS TO FORM

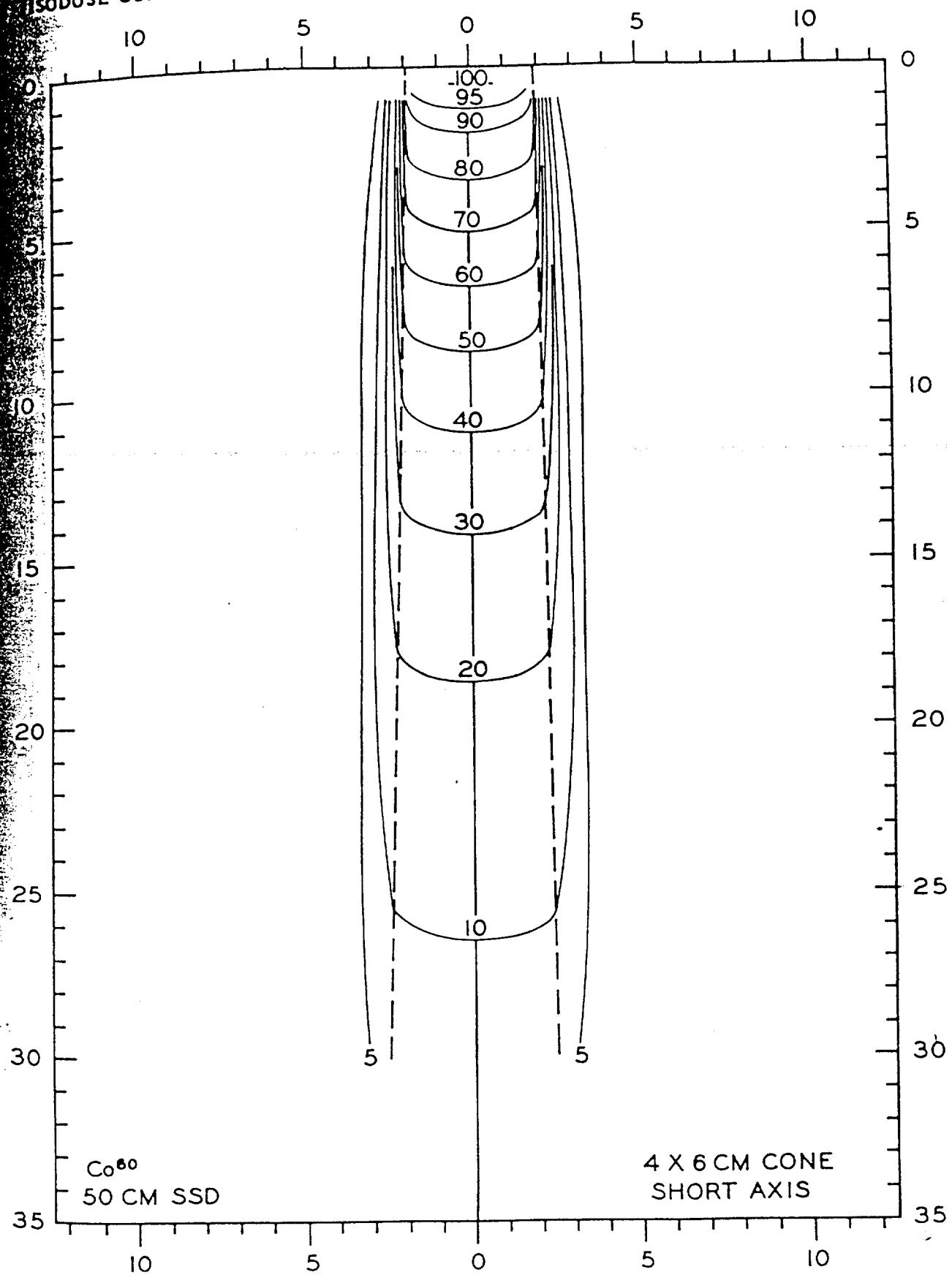
s/ Scott Gaines
Attorney

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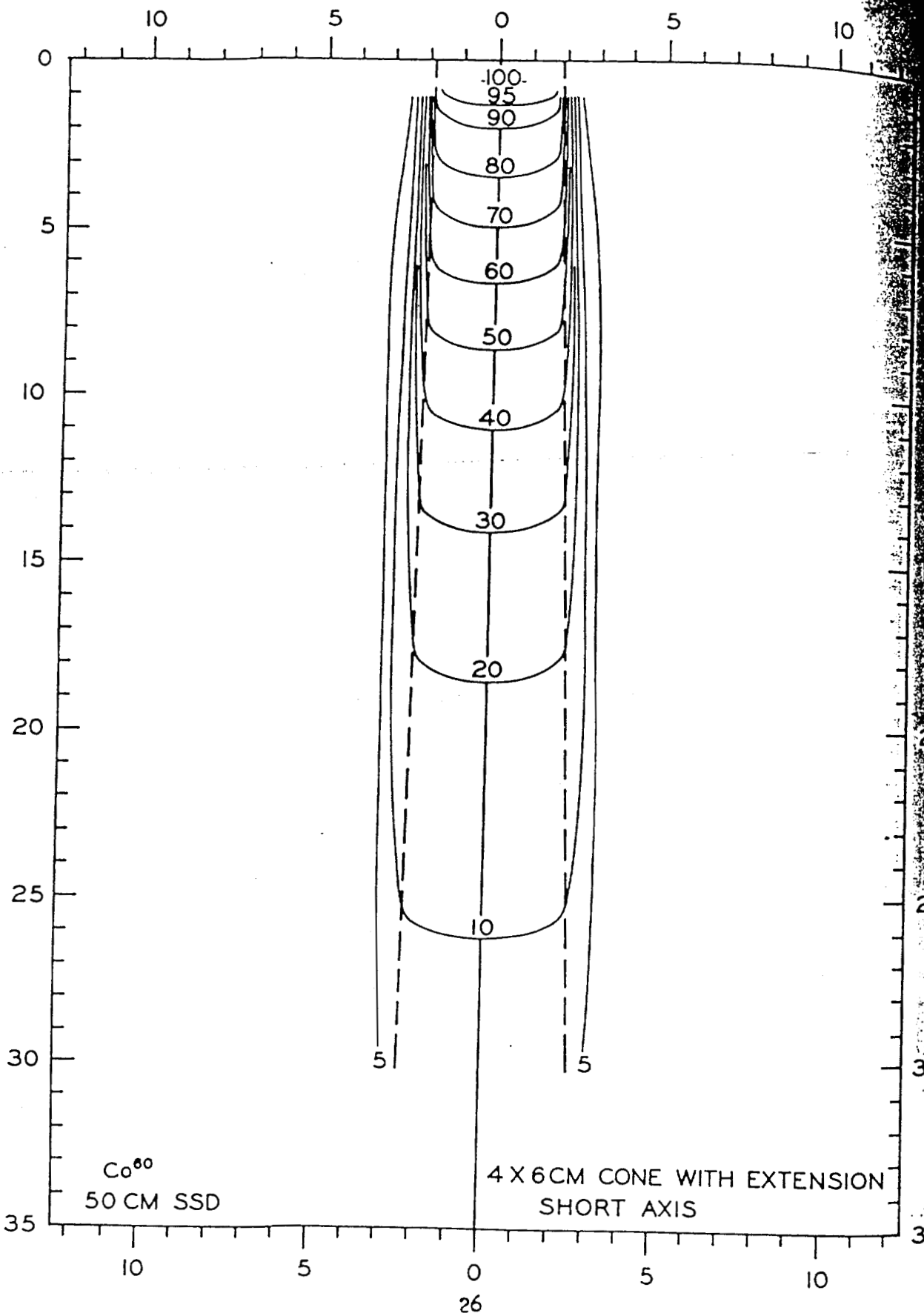
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for Albert H. Holland, Jr., M.D.
Director, Office of Research & Medicine
Authorized Representative of the
U. S. Atomic Energy Commission

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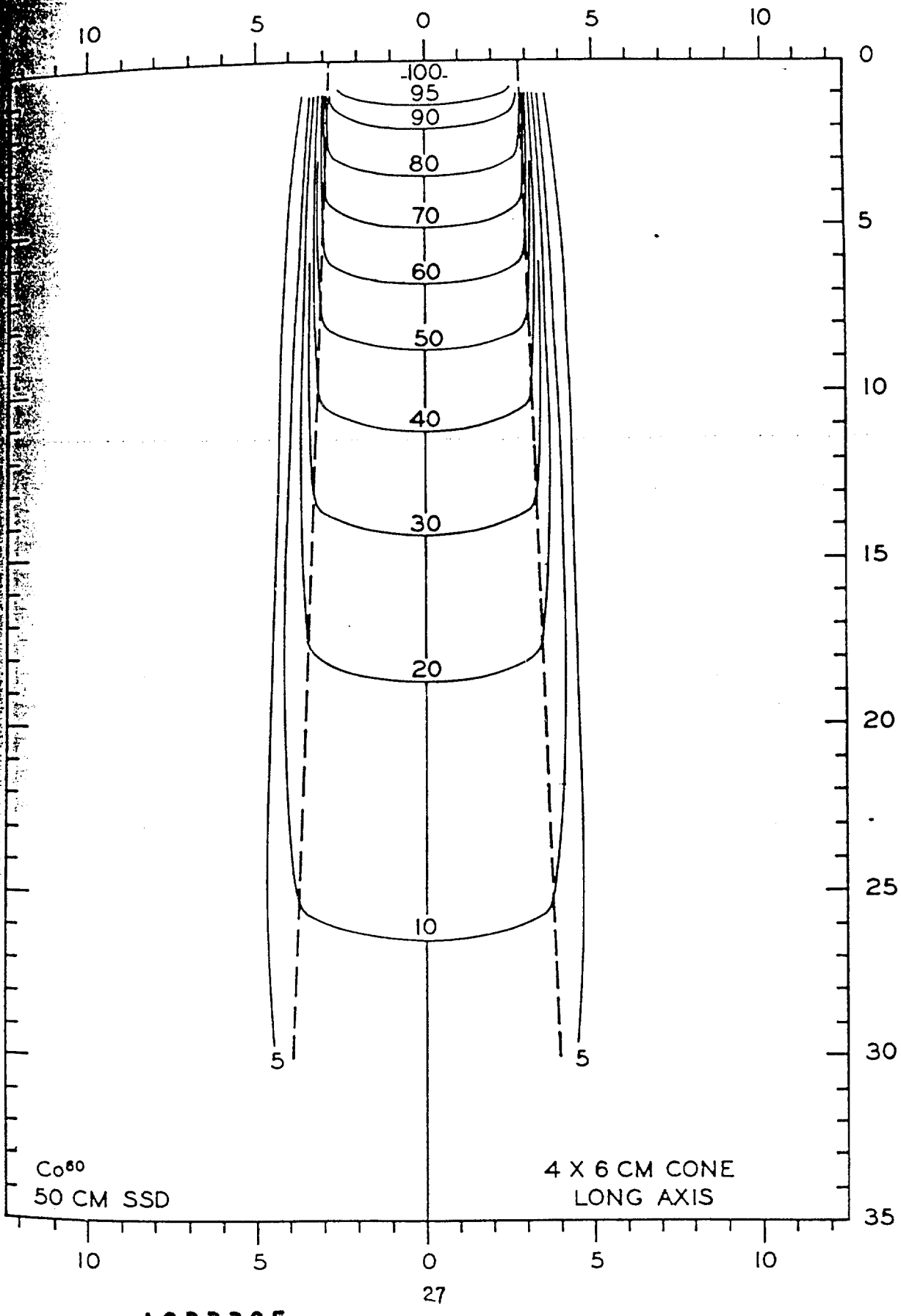
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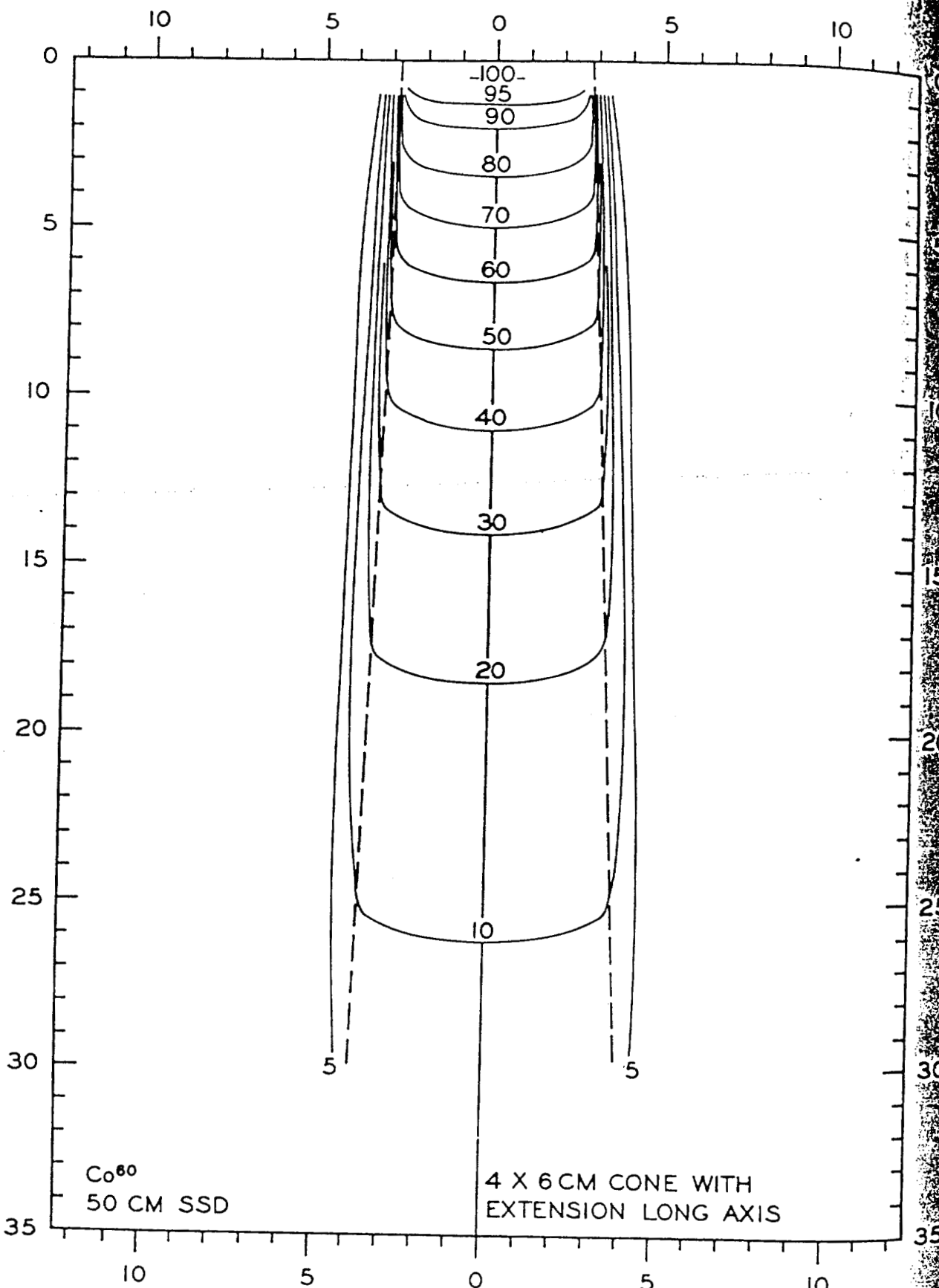
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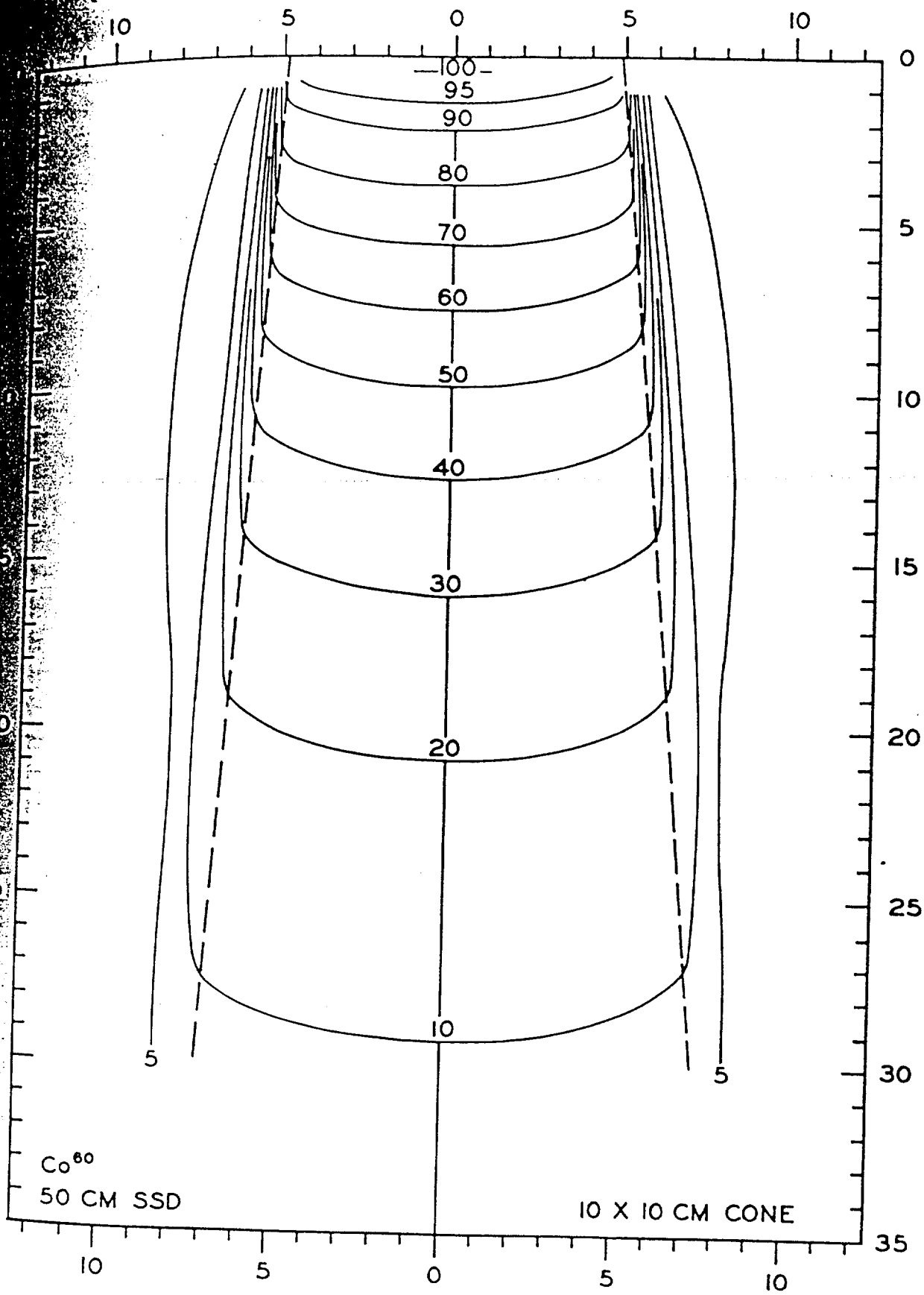
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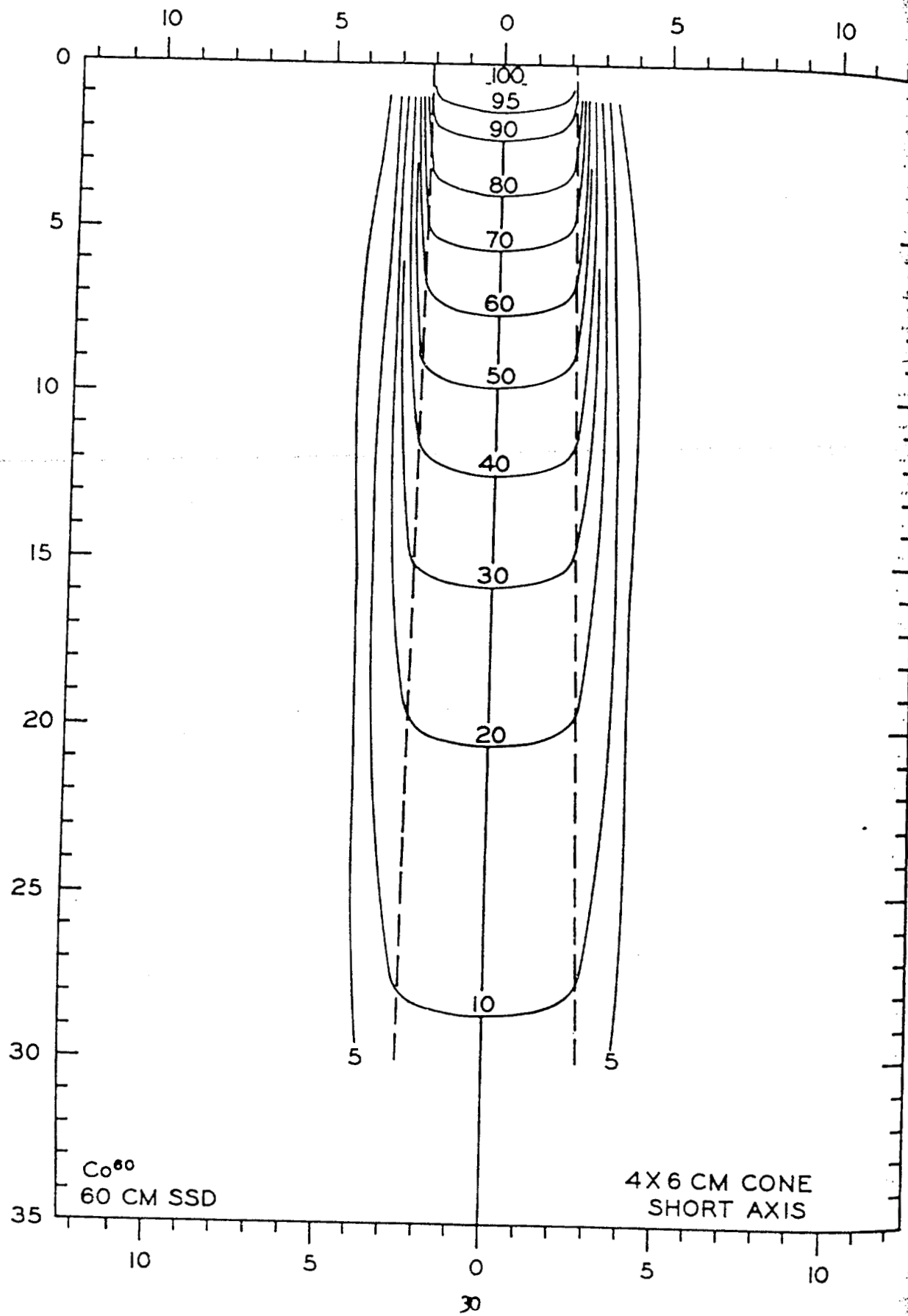
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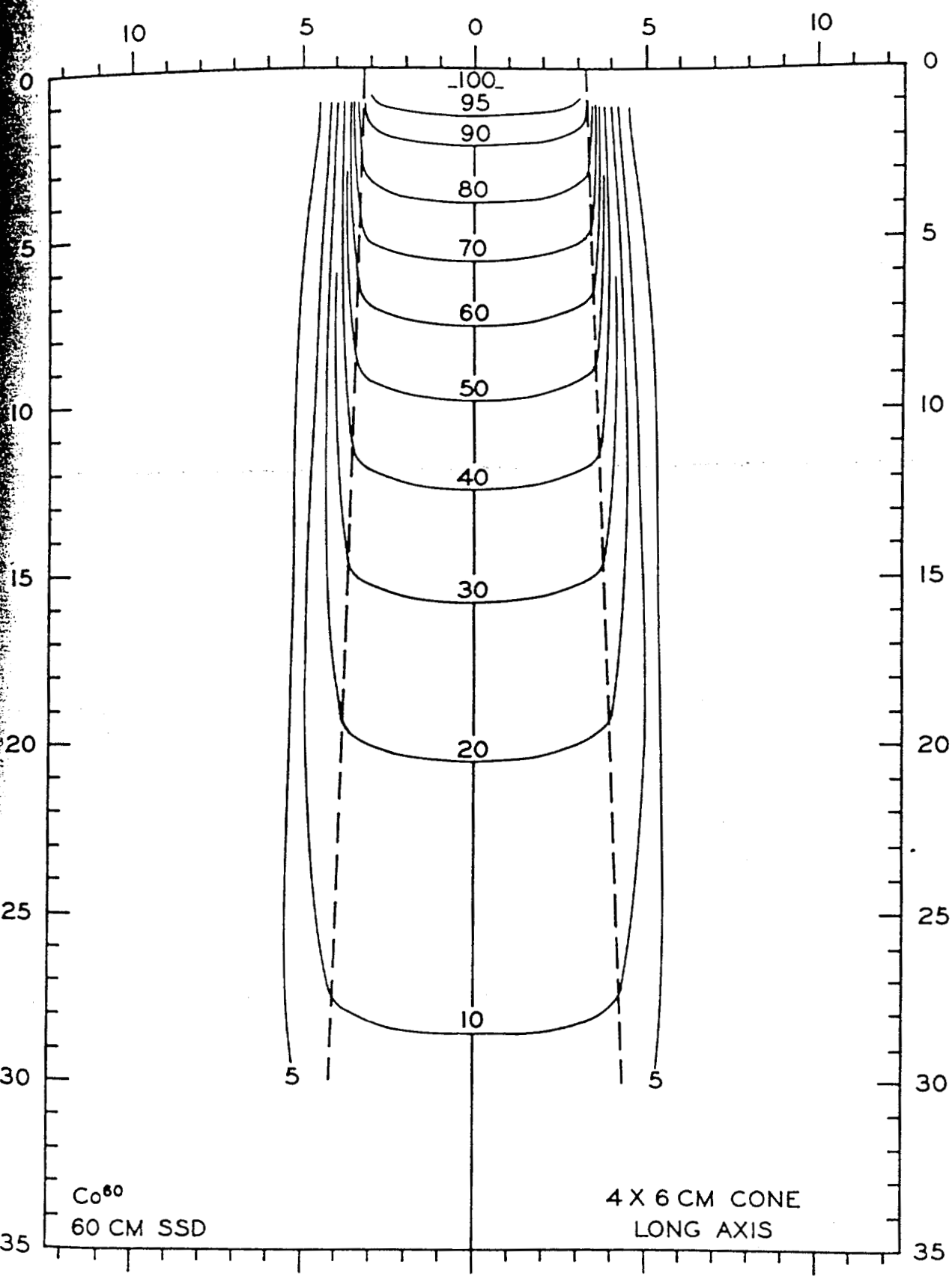
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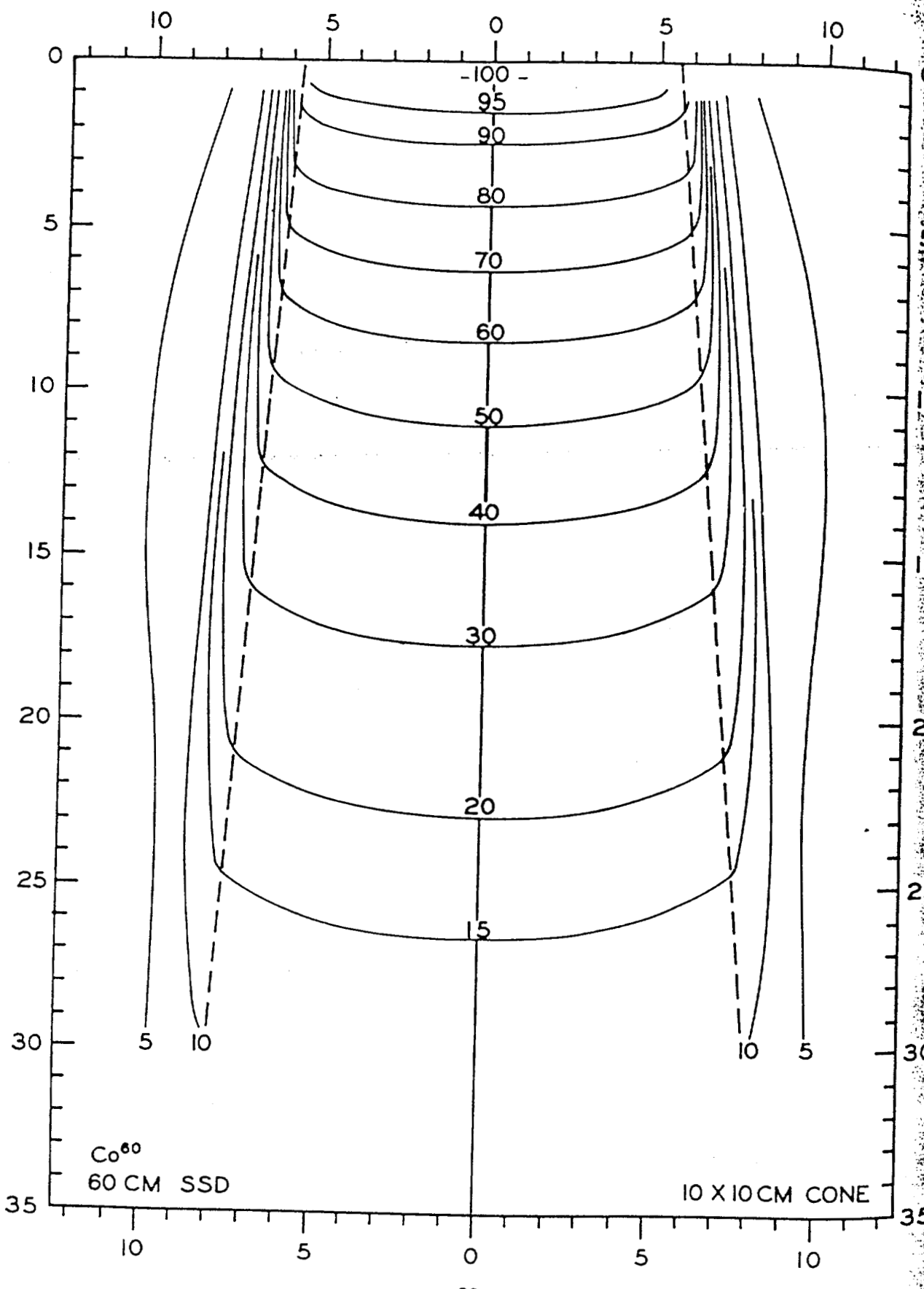
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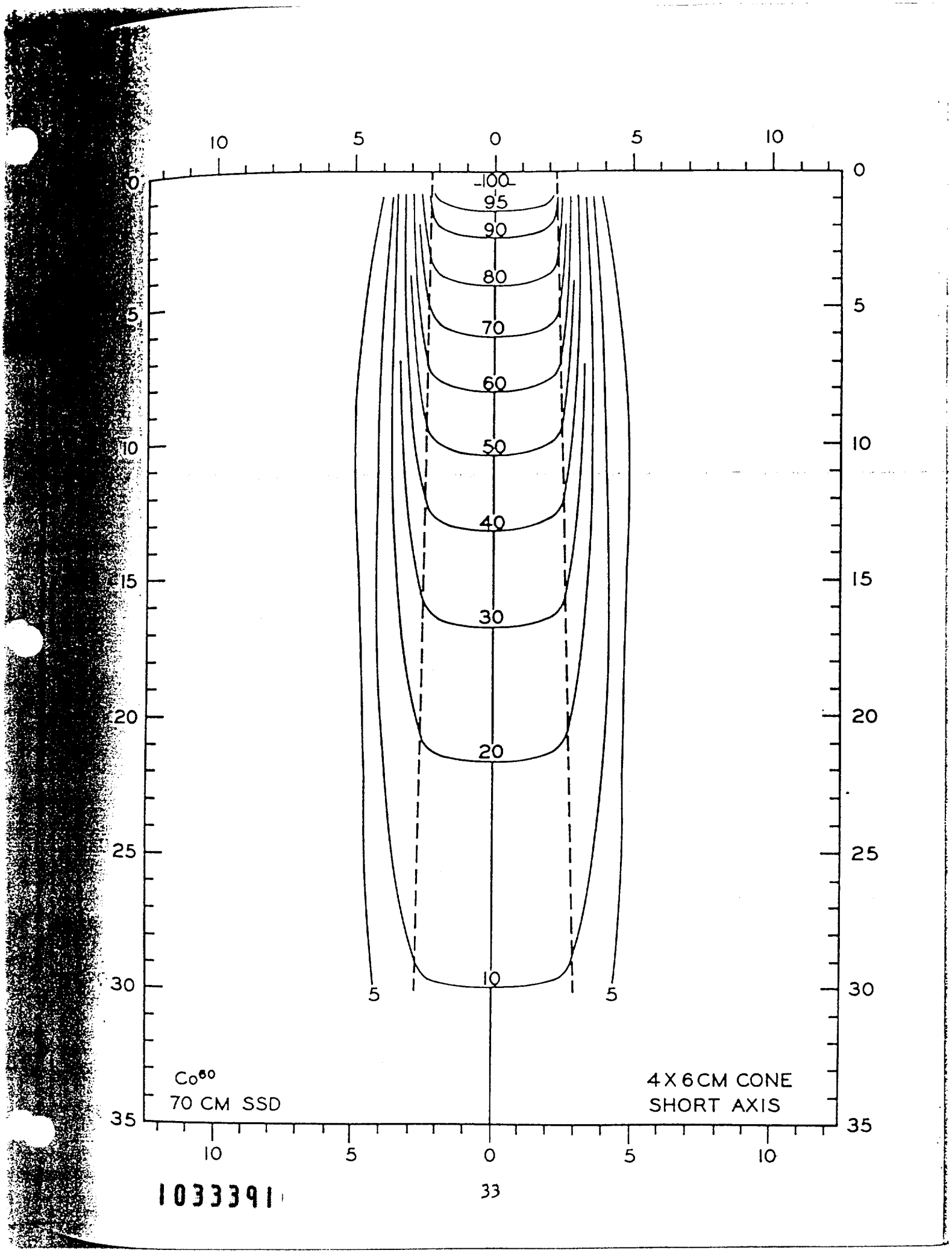
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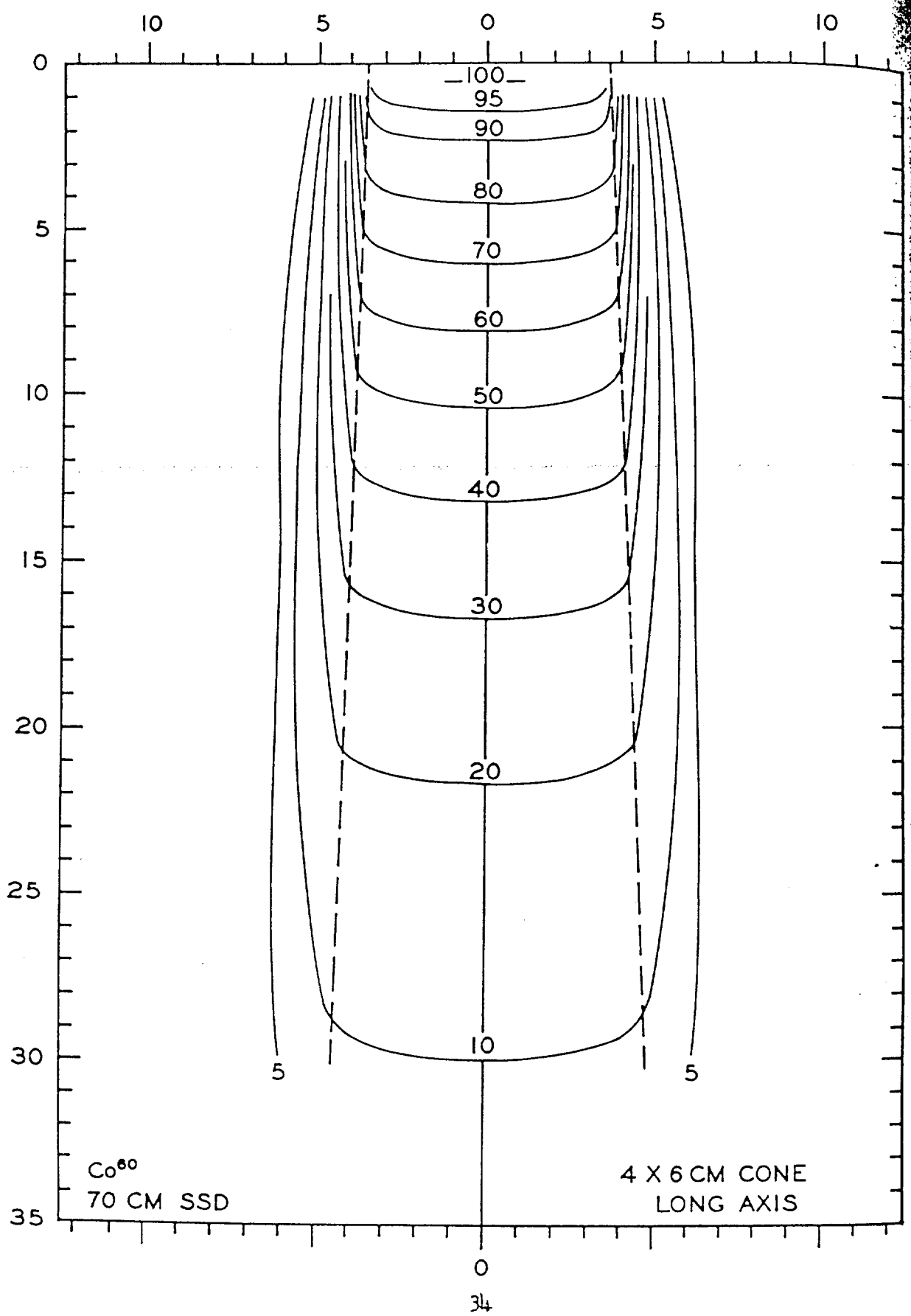
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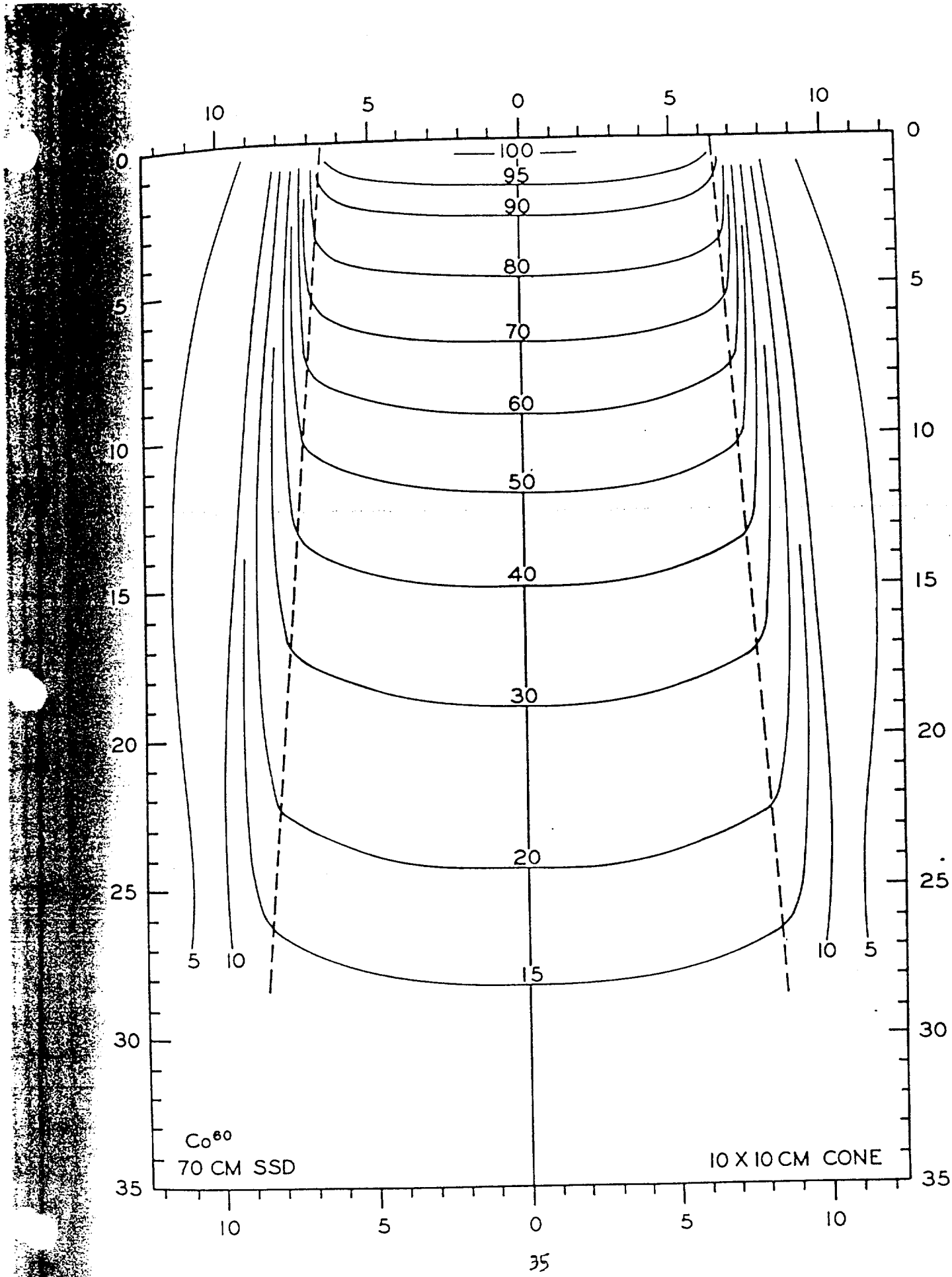
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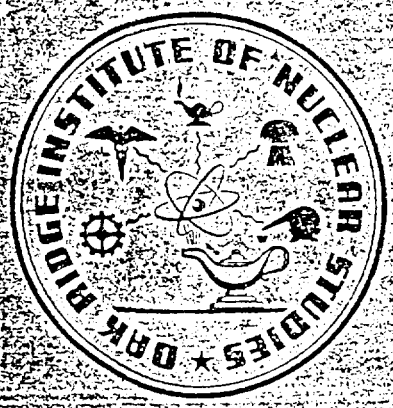
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OAK RIDGE INSTITUTE of NUCLEAR STUDIES

Quarterly Progress Report

October 1 - December 31, 1953



Operating Under Contract AT-40-1-Gen-33
with the
UNITED STATES ATOMIC ENERGY COMMISSION

P. O. Box 117 Oak Ridge, Tennessee

1033395

OAK RIDGE INSTITUTE OF NUCLEAR STUDIES

QUARTERLY PROGRESS REPORT

October 1 - December 31, 1953

Operating under Contract
with
United States Atomic Energy Commission

Not for re-publication
without authorization

AEC Oak Ridge Tenn 5 6 54 400 W 25186

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INTRODUCTION

The Quarterly Report of the Oak Ridge Institute of Nuclear Studies is designed to be a research report. For that reason, it has, in the past, been largely concerned with the work of the Medical Division, the one division of the Institute set up for research purposes. The report for this quarter includes a summary of administrative and other non-research activities of the Medical Division, since it is felt that such activities influence and provide an index to actual research.

In the future, thesis abstracts of Oak Ridge Graduate Fellows who have completed their research work within the reporting quarter will also be published in the Quarterly Report. The first of these abstracts appears in this quarter and is the work of Bowman S. Garrett, Oak Ridge Graduate Fellow from the University of Arkansas, who received his Ph.D. at that university's winter commencement exercises. Dr. Garrett conducted his thesis research in the Chemistry Division of Oak Ridge National Laboratory from September of 1952 until November of 1953. Laboratory members of Dr. Garrett's graduate committee were Henri Levy (research supervisor) and G.H. Cartledge. University of Arkansas members of the committee were R.R. Edwards (chairman), E. Wertheim, E. S. Amis, and Paul C. Sharrah.

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NEUTRON DIFFRACTION STUDIES OF THE CRYSTAL STRUCTURES OF OXALIC ACID DIHYDRATE AND IODIC AC

Abstract of Thesis
by B. S. Garrett

Part One

The crystal structure of oxalic acid dihydrate has been the subject of several X-ray investigations.[1,2,3] Although several attempts have been made to reconcile the sets of experimental data, some of the important features of the structure have remained unanswered. Previous investigators have agreed that the C_2O_4 group of the acid molecule is accurately planar and that the water oxygen makes a close (2.5 A) approach to one of the carboxyl oxygens. The principal points on which they have disagreed are: the carbon-carbon bond length; the equivalence of the two carbon-oxygen bonds in the carboxyl group; and the existence of OH_3^+ in the crystal. The objective of this neutron diffraction investigation was to delineate the hydrogen bond network in the crystal, and to answer as many of these questions as possible, particularly the one pertaining to the existence of OH_3^+.

It was found that the acid molecule is planar, including the hydrogen atoms. The carbon-carbon bond is 1.53 A compared to 1.54 in diamond, or essentially a single bond. The two carbon-oxygen bonds are nearly equal in length indicating considerable resonance within a carboxyl group but very little across the carbon-carbon link. The reason for the planarity was not found. An anisotropic thermal motion was interpreted as a libration by the carboxyl groups about the carbon-carbon bond.

The existence of OH_3^+ was conclusively ruled out by the observation that the dimensions and O-H stretching frequency of the water molecule in the crystal were nearly identical with those of a gaseous water molecule [4,5].

The hydrogen bond network was found to consist of four chains. Two helical chains parallel to the b axis and one parallel to each diagonal of the a-c plane hold the crystal together. These bonds are between water hydrogen and neighboring carbonyl oxygen atoms and are long and non-linear. The short, linear bond between carboxyl hydroxyl and water oxygen is presumably much stronger. The 0.1 A increase of the carboxyl O-H distance above the O-H distance in gaseous water is consistent with the correlation of O-H and O-O distances in hydrogen bonds suggested by the correlation by Rundle and Parasol[6] of O-H stretching frequency with O-O distances.

The chemical formula of oxalic acid dihydrate is $(COOH)_2 \cdot 2H_2O$. It is a soft colorless crystal of the monoclinic system with space group symmetry C_{2h}^5 - $P2_1/n$. The asymmetric unit is one half of a molecule, the molecule lying across a center of symmetry in the crystal. There are two molecules per unit cell with atoms lying in the general fourfold positions: $\pm(x,y,z); \pm(1/2+x, 1/2-y, 1/2+z)$. Space group absences are: $h00, 0k0, 00l$, h, k, or $l \neq 2n$; and $h0l$, $h+l \neq 2n$. The axial lengths are: $a_o = 6.12$ A; $b_o = 3.60$ A; $c_o = 12.05$A. The monoclinic angle β, is $106^o\ 16'$. The calculated and observed densities are 1.63 and 1.653, respectively.

Single crystal diffraction data were taken on a neutron spectrometer similar to that described by Wollan and Shull [7]. Data were obtained with a minimum amount of attention from an operator by use of an automatic programmer

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for scanning twenty reflections in sequence [8]. The techniques for single crystal work described by Levy and Peterson[9] were employed for taking data and calculating structure factors from observed intensities. Cylindrical specimens were used to facilitate making absorption corrections. Single crystal data were compared with data taken on a powdered sample. This comparison indicated secondary extinction in the single crystal specimen to be negligible.

Data were taken from two sizes of crystals in both the (h0l) and (0kl) zones. Ninety-eight reflections were measured in the (h0l) zone and fifty-eight in the (0kl) zone at a wavelength of 1.142 A. An empirical normalization factor was required to bring the data from the two (h0l) specimens into agreement. Agreement between (0kl) specimens was satisfactory without normalization.

The procedure adapted for analyzing the (h0l) data was the Fourier series synthesis method. In order to determine signs of the structure factors to be used in constructing the series, a procedure involving no assumptions regarding hydrogen positions was used. Statistical methods [10] were used to estimate an average temperature factor coefficient for carbon and oxygen. After calculating the structure factor contributions of carbon and oxygen from this temperature factor coefficient and X-ray parameters, signs of two thirds of the experimental structure factors were directly determined by the carbon and oxygen contribution. Signs of most of the remaining structure factors were determined by application of Harker-Kasper[11] inequalities to the residual hydrogen contribution.

A preliminary Fourier map was prepared and atomic coordinates determined. The remaining signs were determined and a final Fourier map was prepared. Artificial convergence was introduced into the data by means of a modification function[12]. Parameters were read by Gaussean interpolation of the peaks, temperature factors were refined by peak shape analysis, and a backshift correction was applied to all atoms except the two water hydrogen atoms. Final refinement of the parameters of these atoms was carried out by the method of least squares.

The problem of sign determination in the (0kl) zone was attacked by assuming the hydrogen atoms to be located on the lines connecting the water oxygen with the three nearest oxygen atoms and to have the z parameters determined in the (h0l) zone. The Fourier map prepared with this set of signs was sufficiently unusual that two additional starts from different assumptions were made, in each case converging on the original set of signs. The agreement between calculated and observed structure factors was poor and worsened with increasing k index. Anisatropic temperature factors were indicated for several atoms including the carboxyl oxygens and the water molecule. Because of poor resolution it was necessary to refine the structure by alternate least squares treatments of the water molecule and the carbonyl group. A backshift correction was applied to the two resolved atoms, the hydroxyl group of the acid molecule. Only y parameters were estimated in this zone.

The final set of parameters and the estimates of their standard errors[13] are given in Table I, interatomic distances in Table II, and bond angles in Table III.

Comparison of these results with the best previous treatment of X-ray data[3] showed satisfactory agreement on atomic positions but general nonconcordance in the analyses of the thermal motion of the atoms. It was concluded that errors in the determination of the photographic intensity scale was probably responsible for the discrepancies.

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Part Two

The crystal structure of alpha iodic acid was determined by Rogers and Helmholz[14] by X-ray diffraction. They deduced iodine and oxygen parameters and found the iodic acid molecule to consist of irregular pyramids of IO_3. An irregular coordination octahedron about each iodine was found to be formed by the three oxygen atoms within the molecule and three more from molecules which approach iodine more closely than in a normal van der Waals contact. They also proposed the existence of a bifurcated hydrogen bond. Wells[15] suggested an alternative hydrogen bond arrangement, in which the bond is not bifurcated but forms strings of molecules parallel to the b axis. The purpose of this neutron diffraction study was to determine the actual hydrogen bond arrangement and to refine the oxygen parameters in order to confirm the unusually short intermolecular contacts.

It was confirmed that the IO_3 group is an irregular pyramid and that there were three short intermolecular iodine-oxygen approaches described by Rogers and Helmholz as completing a coordination octahedron around iodine. The suggestion of Wells that the hydrogen bonds form strings along the b axis was confirmed.

An alternative way of describing the structure is suggested. The crystal is composed of two chains of pentagonal rings. The pentagonal ring is composed of the two sides of the O_1-I-O_2 angle in a molecule, the hydrogen bond between O_2 and O_1' of an adjacent molecule, the I'-O_1' bond and the short (2.50 A) I'-O_1 contact. Adjacent rings are coplanar and share edges. There are two chains in the structure; the angle between their planes is 64° 25'. Binding between the chains appears to result from two close approaches to iodine atoms in neighboring chains by the O_3 atoms which project above and below each chain.

The iodine oxygen bonds in the molecule vary in length from 0.04 A less than a single bond (I-O_2) to that of a double bond (I-O_3). Rogers and Helmholz have interpreted these lengths as evidence of large amounts of double bond character in I-O_1 and I-O_3 and suggest the bonds to be sp hybrids in accordance with the observed angles, which are near 100°.

An attempt was made to correlate information from nuclear quadrupole spectroscopy[16,17] with structural information in order to describe the iodine bonding orbitals more completely. It was found that hybridizations consistent with the experimental observations could be obtained, but not unambiguously.

The O-H distance of 0.99 A was found to be about 0.06 A shorter than a general correlation of O-H and O-O distances would predict. It is suggested that its close contact with iodine reduces the effectiveness of the acceptor oxygen in attracting hydrogen.

With the exception of the necessity for making a correction for secondary extinction in the (0kl) zonal data, the analysis of the diffraction data was straightforward. Data were collected on seventy-five reflections in the (0kl) zone and seventy-two in the (h0l) zone at a wave-length of 1.062 A. Signs were determined in both zones by calculation of iodine and oxygen contributions from the X-ray parameter. Hydrogen was assigned approximate parameters on the basis of its contribution to reflections for which the iodine and oxygen contributions were small or cancelled.

After estimation of parameters from a preliminary Fourier map of the (0kl) zone, comparison of calculated and observed structure factors indicated the necessity of making a correction for secondary extinction. The extinction effect was treated as an isotropic absorption coefficient which was proportional to intensity.

After choosing the extinction corrections which gave the best agreement between specimens and between corrected observed and calculated structure factors, a final experimental Fourier map was prepared. Parameters were read and corrected by the backshift method for termination-of-series errors.

A preliminary Fourier map of the (h0l) zone was prepared and parameters estimated. The iodine and hydrogen peaks were unresolved; it was necessary to use graphical methods to subtract the iodine peak in order to obtain an x parameter for hydrogen. The x parameters for the oxygen atoms were read directly, the iodine X-ray x-parameter and the z parameters from the (0kl) zone were used to calculate a set of structure factors from which a final set of signs was obtained. A final Fourier map was prepared and x-parameters for two oxygen atoms were read and backshifted. The x-parameters of the hydrogen, iodine, and remaining oxygen and the temperature factor of hydrogen were refined by the method of least squares.

The final sets of atomic parameters, interatomic distances are given in Tables IV, V, and VI.

Table I. Atomic Parameters and Estimates of Precision in Oxalic Acid Dihydrate

Atom	x		y		z	
C	-0.0450	0.0013	0.054	0.003	0.0501	0.0003
O_1	0.0817	0.0009	-0.057	0.002	0.1467	0.0004
O_2	-0.2235	0.0010	0.227	0.005	0.0375	0.0005
O_3	-0.0452	0.0013	0.114	0.006	0.3222	0.0003
H_1	-0.1361	0.0032	-0.062	0.009	0.3506	0.0016
H_2	0.0729	0.0032	0.118	0.005	0.3870	0.0016
H_3	0.0227	0.0020	0.015	0.004	0.2180	0.0013

Table II. Interatomic Distances and Estimated Precision in Oxalic Acid Dihydrate

Atoms	Distance (A)	Std. error (A)
C - C	1.533	0.011
C - O_1	1.254	0.008
C - O_2	1.229	0.014
O_1 - O_3	2.518	0.008
O_1 - H_3	1.057	0.016
O_3 - H_1	0.968	0.029
O_3 - H_2	0.945	0.021
O_3 - O_2'	2.840	0.008
O_3 - O_2''	2.856	0.008

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Table III. Bond Angles and Estimated Precisions in Oxalic Acid Dihydrate

Bonds	Angle	
$C-C-O_1$	112°22'	0°41'
$C-C-O_2$	120°54'	0°50'
O_1-C-O_2	126°43'	0°57'
$O_1-H_3-O_3$	175°21'	2°0'
$C-O_1-H_3$	112°56'	1°40'
$H_1-O_3-H_2$	105°41'	3°0'
$O_3-H_2-O_2'$	167°2'	2°30'
$O_3-H_1-O_2''$	156°6'	3°0'

Table IV. Final Parameters of Atoms in Alpha Iodic Acid

Atom	x	y	z
H	0.2340 ± 0.0043	0.3220 ± 0.0015	0.1350 ± 0.0020
I	0.2036 ± 0.0011	0.0861 ± 0.0015	0.1580 ± 0.0010
O_1	0.0712 ± 0.0016	0.5225 ± 0.0011	0.2429 ± 0.0010
O_2	0.3340 ± 0.0014	0.1978 ± 0.0012	0.0864 ± 0.0010
O_3	0.4043 ± 0.0010	0.1566 ± 0.0014	0.4481 ± 0.0010

Table V. Interatomic Distances in Alpha Iodic Acid

Atoms	Distance (A)
$H-O_2$	0.990 ± 0.017
$H-O_1'$	1.700 ± 0.018
H-I	2.407 ± 0.013
$I-O_1$	1.816 ± 0.010
$I-O_2$	1.899 ± 0.011
$I-O_3$	1.780 ± 0.010
O_1-O_2	2.800 ± 0.010
O_1-O_3	2.769 ± 0.009
O_2-O_3	2.686 ± 0.010
O_2-O_1'	2.685 ± 0.010

Atoms	Distance (A)
$I-O_1'$	2.503 ± 0.011
$I-O_3''$	2.879 ± 0.010
$I-O_3'''$	2.767 ± 0.009

Table VI. Bond Angles in Alpha Iodic Acid

Atoms	Angles
O_1-I-O_2	$97^\circ 45' \pm 0^\circ 35'$
O_1-I-O_3	$100^\circ 38' \pm 0^\circ 36'$
O_2-I-O_3	$93^\circ 45' \pm 0^\circ 37'$
$I-O_2-H$	$108^\circ 15' \pm 1^\circ 33'$
$O_1'-H-O_2$	$172^\circ 56' \pm 3^\circ 0'$

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MEDICAL DIVISION

STATISTICAL SUMMARY

Marshall Brucer, M.D.
Howard Harmon
Betty Anderson

The Quarterly Report for the period July 1 to September 30 was entirely devoted to research carried out in the Division over the past several years. Therefore, this Quarterly Report covers the six-month period from July 1 through December 31, 1953.

During the last half of 1953, nine of the thirteen senior staff members attended either a regional or national meeting. There were twenty-three separate visits to twenty-one meetings; seventeen papers were presented. Approximately half of these papers will appear in published form within the next year.

During the six-month period there were nine formal meetings held at the Medical Division. Three of these were subcommittees of the Teletherapy Evaluation Board; one was a combined meeting during which time the new hectocurie cobalt 60 unit was demonstrated for the first time. In two of these meetings a large segment of the X-ray industry was invited to discuss various problems of equipment design involving the use of cobalt 60. Representatives of fourteen different X-ray equipment manufacturers attended the meetings. There were representatives also from Atomic Energy of Canada, Limited, and the Oak Ridge National Laboratory Radioisotopes Production Division. These industrial meetings were held jointly with the Isotopes Division of the United States Atomic Energy Commission.

In cooperation with the Special Training Division, the Medical Division conducted during the last two weeks of September the second advanced course in the medical use of radioisotopes. There were 122 participants in this course and 44 invited lecturers. Proceedings of the advanced medical course are now in preparation for publication. Minutes of the Industrial meetings and Teletherapy Evaluation Board Subcommittee meetings have already been distributed.

During the six-month period, there were 65 professional visitors who spent from one to three days at the Medical Division and many nonprofessional visitors. Nine of these visitors were from foreign countries. Approximately one-fourth of all of the visitors were concerned with setting up consultations and conferences with more than one staff member. In addition to the formal meetings, four visits were made to the Barnes Company in Rockford, Illinois, in connection with the contract to manufacture the large teletherapy machine.

During July and August, Dr. Brucer gave four lectures in various foreign countries and attended the International Radiological Society meetings in Copenhagen. A complete report of this trip has been widely distributed in mimeographed form, and a special report has been sent to the Division of Biology and Medicine, Atomic Energy Commission, Washington, D.C.

Current activities of the administrative staff include the preparation of an average of approximately 20 pieces of mail per day. About one-third of this directly concerns patients, patient referrals, patient summaries, and patient procurement. Another one-third is directly involved in the teletherapy program. The final one-third of the mail involves such items as consultations on radioisotope problems, the preparation of manuscripts, materials dealing with the

advanced course and other courses in medicine, and other matters related to the research program of the Medical Division. The following break-down indicates some thing of the scope of the administrative load:

Month	Purchases	Reproductions
July	51	10,325
August	51	19,343
September	50	20,476
October	57	10,079
November	42	4,288
December	46	3,202
Total	297	67,713

To January 1, 1954, 411 patients have been studied or treated. Experimental work has been performed on 7000 animals. Seventy-three physicians have had residency training for periods of 3 months or more. Eighteen senior staff members of participatin medical schools have been in residency for periods up to 7 months. There have been published 6 Quarterly Reports, 4 Annual Reports, 13 Teletherapy Evaluation Board Reports, and 54 articles in the public medical literature.

Admissions	574
Deaths	130
Patient Days	20,774
Average Daily Census	13.4
Out-patient Visits	406
Parasitological	452
Urinalyses	3,994
Gastric Contents	9
Blood Counts	15,156
Sedimentation Rates	894
Coagulation Time	46
Serological Tests	123
Biochemistry	8,803
Tissue Reports	1,849
Basal Metabolic Rates	360
Electrocardiograms	272
Radioassays	20,182
Occupational Therapy	395

PROGRESS REPORT OF CLINICAL STUDIES

Samuel W. Root, M.D.
Gould A. Andrews, M.D.
Malcolm P. Tyor, M.D.
Etna L. Palmer, M.D.
Ralph M. Kniseley, M.D.
Betty M. Cooper, M.D.

Potassium 42 and Rubidium 86 Studies

Rubidium has been found to behave like potassium in many biologic systems. Since K 42 has a half-life of only 12.4 hours, its use has been limited to a very few institutions. Recently, interest has developed in rubidium 86 (half-life 19 days) as a possible substitute for K 42 as a measure of potassium metabolism. Malcolm P. Tyor, M.D., has been engaged in metabolic studies in a few human

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patients, using K 42 and rubidium 86 concomitantly in an effort to see whether they do follow the same metabolic pattern as determined by following the patterns of excretion and plasma concentration. The well scintillation counter has made it possible to obtain statistically significant counts on very low levels of activity.

Iron 59 Studies

The rate with which iron is cleared from plasma is one index of hematopoietic activity. By obtaining plasma disappearance curves of iron 59 in patients with polycythemia vera, it is possible to obtain more information about their need for further treatment. Etna L. Palmer, M.D., is engaged in following several of the polycythemia patients in this manner. She is also obtaining information on red blood cell survival in polycythemia patients, using the pattern of concentration of iron 59 in the red blood cells. This work is also being done with gamma counting in the well scintillation counter.

Gold 198 Studies

Evaluation of the rather large amount of hematologic information concerning patients who have received Au 198 by the intracavitary, as well as the intravenous, route has been in progress now for some time and is continuing. Several patients with known metastases to the liver have been given small amounts of radioactive colloidal gold intravenously and scintiscan records have been made over this organ. Records have also been made of the liver containing metastatic nodules and removed at autopsy, in order to compare the records in vivo and at autopsy. So far, it seems that this detection method is not very practical clinically, since no nodules have been demonstrated that were not apparent clinically. Radioactive colloidal gold has been used prophylactically by intraperitoneal injection in two patients, in one following the rupture of an ovarian cyst and in the other following the rupture of a pancreatic cyst arising from adenocarcinoma of the pancreas. In these patients, the gold was given to prevent implantation of the malignant cells on the serosal surfaces. Studies are continuing on the use of intravenous colloidal gold in the treatment of patients with granulocytic leukemia.

Phosphorus (P32) as Chromic Phosphate

Several patients with pleural and abdominal fluid caused by neoplasms have received colloidal chromic phosphate, and its metabolism and distribution have been followed in a manner similar to that used in work with intracavitary gold. The patients treated have not been followed over a long enough period of time to allow any evaluation of clinical effects.

Gallium 67

Approximately 40 patients have now received tracer doses and larger doses of gallium 67, with external counting, biopsy, and, in some, autopsy distribution studies. The clinical effects, the metabolism and distribution, the effect of carrier on distribution, and hematologic effects are being assembled.

Iodine 131 Studies

Follow-up studies on patients with thyroid carcinoma treated with radioactive iodine are being continued, as well as follow-up studies on the few patients with toxic goiter who have been treated. Several scintiscan records have been made of patients with thyroid nodules.

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Hematologic Studies

Data are being gathered on the eosinophil response to ACTH and cortisone in patients with leukemia. Two interesting cases with myelofibrosis have been studied clinically and at autopsy. In one case, iron 59 distribution data are available.

RADIOACTIVE IODINE IN MALIGNANT MELANOMA*

Gould A. Andrews, M.D.
Marshall Brucer, M.D.

The theoretical possibility of treating neoplasms, in addition to carcinoma of the thyroid, by means of isotopes which localize specifically in malignant tissue has lead many investigators to consider the metabolic characteristics of various tumors from this point of view. Since malignant melanomas have the unique property of melanin formation, an attempt has been made to find an isotope which would be concentrated in the neoplastic tissue as a result of this metabolic activity. From the onset, the prospect is made discouraging by the fact that these are very radioresistant tumors and that, in many of them, melanin formation is spotty or absent.

Marcus and Rothblat[1] studied the localization of Cu 64, P 32, and I 131 in patients with this disease. They used the I 131 in the form of diiodotyrosine, which, as a percursor of melanin, might be expected to concentrate to some degree in the tumor. Limited studies failed to show any such concentration, however.

Before we initiated our studies, a medical research group at a nearby university announced[2] that I 131 had arrested the progress of malignant melanoma. A report of their work has not yet appeared in any scientific journal.

This present report was made to the Subcommittee on Human Applications of the Atomic Energy Commission Isotopes Division because of the many requests for information on this problem. Our efforts have been to learn the distribution of radioactive iodine in patients with this tumor, both in the presence and in the absence of functioning thyroid tissue.

Case Reports

W.S.D., a thirty-seven year old man, was admitted to the ORINS Medical Division Hospital on February 27, 1951, referred from the University of Virginia Medical School.

In November 1942, after failing vision of one year's duration, the patient's left eye had been removed. Histologic sections had shown a primary malignant melanoma of the retina. Following this, he had been well until late in 1948, when he had begun to have severe attacks of pain in the right upper quadrant of the abdomen. He also had begun to lose weight and strength. In June 1949, a laporotomy had been performed and extensive neoplasm of the liver had been found. A biopsy had been reported as showing metastatic malignant melanoma. Following this operation, the patient had been unable to return to work and had become gradually weaker.

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* Presented by Marshall Brucer, M.D., in December 1951. This report will receive no further publication.

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Upon admission to the ORINS Hospital, the patient showed pronounced cachexia. The left eye was absent and a prosthesis was worn. The liver was tremendously enlarged, and at the upper end of the laporotomy scar there was a small sinus from which black pigmented material was draining.

On March 3, the patient was given 100 microcuries of I 131 orally. At the end of three and one-half days he had retained 52 per cent of this, as indicated by urinary excretion. On March 6, he was given 57.6 millicuries of I 131 orally. External counting studies showed no increased radioactivity over the liver area.

The patient died on March 9. Autopsy showed an extreme degree of enlargement of the liver, which weighed 10,060 grams and was extensively replaced by large masses of deeply pigmented neoplasm. Small metastases were found in retroperitoneal lymph nodes, the pelvis of the left kidney, the left testis, and subcutaneous tissue. Histological sections showed the lesions to be melanotic neoplasm, with extensive necrosis in the larger masses. The thyroid gland weighed 13.68 grams and showed no distinct abnormality. There was phagocytosed melanin pigment in spleen and lymph nodes.

Table 1 shows the levels of radioactivity of tissues having highest activity and of two samples of tumor, which had similar levels of activity. The neoplastic tissue assayed was not grossly necrotic. Many other uninvolved tissues were assayed and showed activities about the same or slightly less than those of the tumor.

M.F.P., a forty-three year old housewife, was referred to the ORINS Medical Division Hospital on April 24, 1951, from the University of Alabama Medical School.

In October 1948, she had begun to have pain in the region of a deeply pigmented nevus on the posterior calf of the left leg. This had been destroyed with some type of local caustic application and the area eventually had healed, leaving a depressed scar. In July 1950, she had noted a hard lump in the left inguinal region and this had been resected. In January 1951, there had been recurrence of the inguinal mass and a few small subcutaneous masses had been noted on the trunk and on one arm. She then had been referred to the University of Alabama Medical School, where a biopsy had been done and had been reported as showing a malignant melanoma.

On admission to the ORINS Hospital in April 1951, the patient was thin but in fair general condition. There were four small subcutaneous masses scattered over the body. In the left inguinal region there was a group of irregular confluent nodular lesions, one of which was ulcerated. The whole group covered an area of about 11 cm by 7 cm.

Routine blood count, serology, and urine examinations were within normal limits.

On April 30, the patient was given 305 microcuries of I 131 orally. In a period of three days, 79 per cent of this dose was excreted. External counting showed about twice as much activity over the inguinal lesions as over the corresponding area on the other side. The level was very low, however, as compared with the thyroid area.

On May 2, a subcutaneous metastatic nodule was removed and assayed for radioactivity along with normal skin and subcutaneous tissue. None of the samples showed measurable activity.

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On May 15, 1951, 69.7 millicuries of I 131 were given orally, with the intention of producing a "radiation thyroidectomy." The patient complained of transient soreness of the throat and neck after this dose. On May 22, the whole group of left inguinal nodes was resected as one mass. A skin pedicle was moved up from the thigh to cover the inguinal defect and a split thickness graft was applied to the area from which the pedicle was removed.

The gross specimen is shown in Figure 1. The nodules of tumor varied from deeply pigmented to pale pink in color. On histological section, they showed malignant melanoma with varying degrees of pigment and with some necrosis.

The gross autoradiogram in Figure 2 shows less activity in most of the areas of tumor than in the surrounding connective tissue stroma. The small irregular areas of heavy density appear to arise in areas of tumor not unlike the other parts of the lesion, and these focal points of activity are not explained. They do not represent blood vessels. They were seen again when another autoradiogram was made from the same tissue and with a new layer of pliofilm between tissue and film. Thus some types of artifacts have been ruled out. Table 2 indicates radioactivity levels of tissues from this specimen and from plasma drawn at the time of operation.

The operative site healed almost completely and the patient was discharged a month after operation. When she returned on August 10, her general condition had not changed greatly. A right axillary lymph node had enlarged to 2 x 2 cm and several black subcutaneous lesions had appeared near the scar in the left inguinal region. She did not show signs of clinical myxedema. Blood cholesterol was 270 mgm per cent. X-rays of the spine showed collapse of several thoracic vertebrae and small patchy areas of decreased density in the vertebrae and in the right pelvis and ischium. The changes shown by the X-rays had become more definite since films taken three months earlier.

On August 14, 1.98 millicuries of I 131 were administered, and on the following day a biopsy of a subcutaneous metastatic nodule was performed. Table 3 indicates radioactivity of this tissue.

Although 75 per cent of this dose was excreted in five days, there was still a considerable amount retained in the thyroid, and an additional 45 millicuries was administered to further irradiate the thyroid tissue.

Discussion

The first patient was given radioiodine when in terminal condition. The autopsy distribution studies indicate the expected very high concentration of radioactivity in the thyroid, with the stomach showing a level somewhat higher than most other tissues. The tumor failed to selectively concentrate the iodine.

The second patient again shows the failure of the iodine to be concentrated to any appreciable extent in this type of tumor. The most recent biopsy did show activity in the tumor almost seven times that of plasma. This finding may represent a change due to atrophy of the thyroid, but since only two samples were assayed, it is difficult to make an evaluation now.

Slight concentrations of activity in the region of the tumor as indicated by external counting in the second case may be indicative of increased vascular permeability in or near the tumor, rather than metabolic localization of the isotope.

Summary

Two patients with metastatic malignant melanoma have been treated with radioactive iodine. Autopsy studies in one patient and biopsy studies in the other failed to show therapeutically significant concentration of radioactivity in the tumor.

These preliminary studies do not suggest that simple I 131 is of any value in the treatment of patients with malignant melanoma.

References

1. Marcus, R., and Rothblatt, J., The Application of Radioactive Isotopes in a Case of Multiple Melanomata. British Journal of Radiology, September 1950, p. 541-549.

2. Ely, J. B., Associated Press Release, February 12, 1951.

Table 1

Autopsy distribution study on patient W.S.D. Death three days after administration of 57.6 millicuries of I 131. Values corrected to time of administration.

TISSUE	RADIOACTIVITY MICROCURIES PER GRAM
Thyroid	424.68
Bladder Wall	1.40
Stomach	1.52
Blood	0.23
Skin	0.20
Tumor from Liver	0.31
Uninvolved Liver	0.14
Abdominal Metastasis	0.17
Heart	0.12
Pancreas	0.23
Colon	0.35

Table 2

Radioactivity levels of tissues from inguinal node resection and of plasma.

TISSUE	MICROCURIES PER GRAM
Skin	0.023
Fat	0.012
Highly pigmented tumor	0.017
Nonpigmented tumor	0.014
Partly necrotic tumor	0.016
Fluid from necrotic tumor	0.029
Plasma	0.044

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Table 3

Radioactivity of metastatic nodule and of plasma.

TISSUE	MICROCURIES PER GRAM.
Metastatic nodule	0.134
Plasma	0.020

A STANDARD-MAN LIQUID PHANTOM FOR DOSAGE STUDIES

Raymond L. Hayes
Henry P. Copeland
Harold E. Bishop
Marshall Brucer, M.D.

A standard-man liquid phantom made up of rectangular compartments is being used by the Medical Division for the experimental determination of integral and differential radiation dosages from external and internal sources distributed in both uniform and nonuniform patterns. Following is a description of this apparatus together with the experimental data on which its construction was based.

Any practical design for a sectionalized standard-man phantom will obviously involve a number of approximations, but even the roughest designs for such a phantom must involve some knowledge of, or assumptions about, the average volumes of different parts of the human body, together with at least two linear dimensions for each section. Although numerous studies involving many different types of human body measurements have been reported in the literature, little is available concerning sectional volumes. In an effort to establish some criteria for the sectional volume design of a standard-man phantom, rather than relying on simple estimation, a limited study was made of the relationship of the volumes of different parts of the male body to the total body volume, preliminary studies having indicated that such ratios might by fairly constant. The subjects of this study were ten male members of the Medical Division staff whose ages varied from 23 to 34 years. The variation in the physical build of the group is indicated in Table 1. Sectional and total body volumes for each individual were determined by water displacement measurements for the different body sections indicated in Figure 1. This arbitrary sectional division of the body facilitated experimental measurements, in addition to dividing the body into solid sections of roughly uniform dimensions. The results of this study are shown in Table 2, together with the results of a height study which was carried out at the same time. Table 3 shows the calculated sectional body volumes based on Table 2 for a 70 kilogram standard-man with a body volume of 66 liters, assuming an average body density of 1.06 grams per cubic centimeter. Included in Table 3 are the calculated heights, also based on Table 2, for each of these sections, assuming a standard-man height of 177 cm.

Narrow coronal sections through the human body in most instances closely approximate geometrically either elliptic cylinders or rectangular parallelopipeds. The incidence of the two types of section with respect to body weight is roughly equal and therefore the choice of either as the basic geometry of a phantom would be equally approximate. It was decided to use a rectangular parallelopiped design in the construction of the desired phantom, since such a design would allow ready access to any part of the phantom and thus simplify experimental techniques. The dimensions of the required rectangular parallelopiped sections or tanks were arrived at in the following manner: The calculated standard-man sectional volumes given

in Table 3 were used as the basic criteria and the various parts of the phantom, with several simpifying exceptions, were assigned these volumes. The calculated standard-man sectional heights given in Table 3, together with measurements from an unpublished somatotype study of 400 male students at the University of Chicago*, were then used as a guide in adjusting the dimensions of each phantom section to fit the assigned volumes. Table 4 gives the dimensions which were finally adopted in the construction of the present phantom, and Figure 2 shows the phantom assembled for use. For comparison, Figure 3 shows the phantom replaced by a man whose proportions are close to those of a "standard" man. Each phantom section was constructed of 1/4-inch and 1/16-inch plexiglass sheet, the 1/16-inch sheet being used where contact would be made between sections. The phantom is supported in a supine position by a stand constructed of plywood designed to minimize back scatter of radiation.

Adoption of the dimensions given in Table 4 necessarily represents a number of approximations. Prominent among these is the assumption that the volume and dimensions of the chest and pelvis sections are equal. Such an assumption, however, makes for simplicity in design and requires only one composite section for the chest-abdomen or abdomen-pelvis portion of the phantom.

* Tucker, W.B., Friedman,A., and Brucer, M. Unpublished.

Table 1

Height	Build	Number
Short	Stout	1
Tall	Stout	2
Short	Thin	2
Tall	Thin	3
Medium	Medium	2

Table 2

Section	Per cent of total body volume	Ratio of height to total height
	Mean std dev	Mean std dev
Head	6.9 ± 1.6	0.106 ± 0.006
Neck	1.0 ± 0.4	0.062 ± 0.006
Arms	8.6 ± 0.9	0.376 ± 0.019
Chest	19.8 ± 1.2	0.124 ± 0.013
Abdomen	14.1 ± 2.2	0.120 ± 0.015
Pelvis	21.6 ± 1.3	0.139 ± 0.013
Thighs	16.5 ± 1.6	0.190 ± 0.015
Lower legs	8.6 ± 1.0	0.233 ± 0.010
Feet	3.2 ± 0.4	0.044 ± 0.013
Total	100.3	1.018 (arms omitted)

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Table 3

Section	Calculated volume for 66.0 liter standard-man	Calculated height for 177 cm standard-man
	liters	cm
Head	4.6	18.8
Neck	0.7	11.0
Arms	5.6	66.6
Chest	13.1	21.9
Abdomen	9.3	21.2
Pelvis	14.3	24.6
Thighs	10.8	33.6
Lower legs	5.6	41.2
Feet	2.1	7.8
Total	66.1	180.1 (arms omitted)

Table 4

Section	Length cm	Width cm	Depth cm	Liquid Depth cm	Volume liters
Head	19	14	26	17.3	4.60
Neck	8	9	20	9.7	0.70
Arms	54	7	20	7.4	(2x) 2.80
Chest	21	32	26	20.3	13.65
Abdomen & Chest or Pelvis	42	28.5	26	19.2	22.95
Abdomen	21	25	26	17.7	9.30
Pelvis	21	32	26	20.3	13.65
Thigh	40	11	22	12.3	(2x) 5.40
Lower legs	40	8	22	8.7	(2x) 2.80
Foot	7	9	26	16.7	(2x) 1.05
Total	177				66.00

TRACES WITH LUTECIUM 177

Granvil Kyker
Elmer A. Greene
E.L. Warren
Martha Stewart

Announcement of preliminary work on lutecium 177 appeared in a recent Quarterly Report (January 1 - March 31, 1953). The project is still in progress and now includes data on the distribution of the isotope in more than 80 rats. Three routes of administration have been used, though most of the animals have received intramuscular doses. A smaller series was injected intrapleurally, and an intraperitoneal series has been started. Two preparations have been used: lutecium chloride and lutecium versenate. Each preparation was adjusted to pH 4.5 - 5.0.

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Prominent differences appear in the pattern of excretion and distribution for the two preparations. Following intramuscular injection, the versene preparation is rapidly excreted. Renal excretion accounts for 90 per cent of the total dose within the first few hours and then increases to approximately 98 per cent in three days. The fraction of the dose retained by the animal is rather general in its distribution. In contrast with the versenate, the inorganic preparation remains largely in the injected site. Observations ranged from three hours to five days after injection. The immobile fraction averaged 95 per cent; the excreted fraction remained less than 4 per cent at all intervals up to five days; and urinary excretion exceeded fecal excretion throughout the series. The liver showed a high relative activity and contained from 10 to 20 per cent of the amount of the retained dose that was distributed outside the site of injection.

STUDIES OF YTTRIUM 90 IN ANIMALS*

Granvil C. Kyker
Edgar A. Cress
John Rafter

The Quarterly Report for the period July 1 - September 30, 1953, presented a summary of the distribution of yttrium-90 in rats following a single intrapleural injection. The study of this radioisotope has continued and includes a comparison of various routes of administration and the effect of variations of the preparation. This summary is based on observations of 102 rats, 4 dogs, and 3 mice.

A preparation containing approximately 100 microcuries of yttrium-90 and approximately 1000 micrograms of stable yttrium as the chloride per milliliter in normal saline and adjusted to a pH of 4.0 - 4.5 has received the most attention. This preparation has been studied by radiochemical assay and by gross autoradiography after single intrapleural, intraperitoneal, intramuscular, intratumoral, intravenous, and subcutaneous injections. In general, observations extended through six days, or approximately two half-life intervals. Blood clearance in one dog included separate determinations on whole blood, plasma, and cells. Effective localization of the dose within the site of administration was observed in each route of administration with the exception of the intravenous dose. In the intravenous dose, the excretion was much greater, approaching one-sixth of the dose in six days; most of the retained dose was deposited in the liver, spleen, and skeleton. By all other routes of administration, the excreted fraction of the dose was small but somewhat variable, ranging from less than 1 per cent to values rarely exceeding 5 per cent. The distribution calculated on the basis of the unexcreted fraction presented a quite regular pattern of 95 to 98 per cent remaining with the site of administration and the rest distributing proportionally in a manner similar to the intravenous dose. In the animals receiving intrapleural injections, more than half of the small mobilized fraction of the retained dose was deposited in the liver. Similarly, in the animals receiving intraperitoneal injections, approximately half of the mobilized fraction was deposited in the mediastinal tissues. Both patterns suggest that the mobilized fraction is behaving as a colloid, the intrapleural representing removal of particles from the blood and the intraperitoneal representing removal from lymphatic drainage of the peritoneal cavity.

The urinary and fecal distribution of the excreted fraction was observed to be similar for different routes of administration. In the rat, excretion is primarily renal at first and then rather rapidly declines in favor of fecal excretion. On the third day, the two are approximately equal, and on the sixth day, fecal excretion predominates. Although only a few dogs were studied, the pattern appears to be the

*All of the radioactive preparations which were used were supplied through the collaboration of G.I. Gleason, Abbott Laboratories, Oak Ridge, Tennessee.

same, except for a slower inversion of the renal and fecal balance.

Two variations in the preparations were evaluated: (1) pH, and (2) concentration of stable yttrium. In the first, preparations adjusted to pH 2, pH 3, and pH 7, and otherwise similar to the previously described preparation adjusted to pH 4.0 - 4.5, were administered intrapleurally and intraperitoneally. No significant effect of pH could be detected. In the second series on the effect of the chemical dose, all preparations were adjusted to pH 4.0 - 4.5 and contained approximately 100 microcuries of yttrium-90 -per milliliter. The concentration of the yttrium ranged in nine steps from 2.5×10^{-9} molar (carrier free) to 5.5×10^{-2} molar (5000 micrograms per milliliter). The effect of the carrier on the pattern of distribution is prominent. Approximately one-fourth of the carrier-free dose is excreted in less than three days and decreases as the amount of carrier is increased. Approximately 40 per cent of the retained dose remains within the site of administration for preparations not exceeding 10^{-6} molar. This percentage increases sharply with concentration to approximately 5×10^{-3} molar yttrium, and then quite gradually to the highest observed concentration.

Numerous earlier studies using carrier-free yttrium have classified this element as a bone-seeker. The observed effect of carrier on its distribution calls for a consideration of the therapeutic potentialities by control of its interstitial and intravacitary localization. The chemical toxicity in animals is based upon a wide range in the use of carrier.

PIPETTE MANIPULATOR FOR USE WITH RADIATION BARRIERS

J.H. Wilde
R.L. Hayes

Many routine procedures performed during the handling of radioisotopes require pipetting. If high curiages are involved, it is usually necessary to employ some sort of remote control device for this operation. Such a remote control pipetter should allow the operator to transfer liquids readily and accurately without loss, by manipulation of the device from an adequately shielded position. To most installations now using radioisotopes for medical and experimantal purposes, the cost of such a device will be an important factor. Therefore, a low cost pipetter meeting the desired requirements has been developed with the following characteristics:

1. Smooth vertical, longitudinal, and transverse manipulation of the pipette with any movement separate, or combined with other movements.
2. Full operability behind a radiation shield. Pick up and release of pipette by remote control. Remote control of all normal pipetting operations.

The accompanying photograph shows the design and operation of the pipetter; construction drawings and details can be supplied by the ORINS instrument shop.

A vertical track and glide provides smooth vertical movement, and a base track on top of a lead barrier provides longitudinal movement. Transverse movement is obtained by the introduction of two pivot points. All action must be reasonably smooth or chatter and vibration will cause the pipette to drip. Trouble was originally experienced with the knee action of the lever when the pipette was raised or lowered. The bending and flexing of the lead line connecting the pipette and pump cylinder tended to move the liquid column as the lead line became taut or relaxed. This was solved by using small diameter polyethylene tubing for the knee action. From the knee to the pump cylinder a stainless steel tube is used; between the air chuck and the tubing an absorption tube for removal of any corrosive acid fumes is

inserted. The air chuck makes possible the rapid changing of different sized pipettes while eliminating the necessity for any exposure to the hands of the operator. In use the air chuck is lowered over the pipette and the top portion of the pipette is gripped and sealed simultaneously by opening the chuck to compressed air. The air chuck alone will seal and support the pipette but a clamp was added for extra support and safety. The pipette may be removed by simply releasing this clamp and the air pressure in the chuck.

A GOLD WIRE IRRADIATION CONTAINER

J.H. Wilde

A gold wire irradiation container has been manufactured to simplify the spacing and make possible more uniform irradiation of small diameter gold wire.

A 2S aluminum tube was cut to dimensions shown in Figure 1. On the periphery of this tube four grooves 5/32 inch in diameter were milled. Tubing lengths of standard 5/32 inch quartz were cut to fit into these peripheral grooves in the aluminum cylinder

The gold wire is cut to length and inserted in the quartz tubing. The quartz tubi is forced by simple press fit into the grooves in the aluminum cylinder and the entire assembly fits a standard aluminum irradiation container. After irradiation, nonirradi gold tubing is forced down the quartz tubing through the flared ends of the quartz tubes. This forces the "hot" gold wire inside of "cold" gold tubing. The quartz tubing is the means for supporting the fragile "hot" gold wire and allowing a tight pressure fit inside the "cold" gold tubing. The gold tubing acts not only as a beta shield, but prevents loss of "hot" gold and contamination of the area.

A MAGNETIC MANIPULATOR FOR LOADING SHORT COBALT WIRE

J.H. Wilde

A manipulating tool has been designed for the purpose of simplifying the problem of inserting short radioactive cobalt wires into needle-type cylindrical containers or, if necessary, into larger containers. This tool is an electromagnetic device which automatically positions the length of cobalt wire and positions the container so that, by breaking the electrical connection, the cobalt wire drops directly into the container

The tool consists of an electrical switch inserted in a long plastic handle. At the end of the handle is a metallic funnel (labeled "A" in Figure 1). At the apex of the funnel is an electrical coil ("B"). The neck of the funnel is slightly larger than the diameter of the wire to be handled and the mouth of the funnel is slightly larger than the length of the wire. The funnel and coil are a separate detachable piece and are replaced for each length of cobalt wire.

When the mouth of the funnel is placed over a piece of wire and an AC current is passed through the coil, the wire is pulled up into the neck of the funnel by the magnetic field as shown in Figure 2. The mouth of the funnel is then placed over the open end of the container (Figure 3). The taper of the funnel aligns the center of the funnel and the cylindrical container so that the cobalt wire is dropped into the cylindrical container when the current is broken. Figure 4 is a photograph of the manipulator.

1033418

A DEVICE FOR MEASURING AND CUTTING RADIOACTIVE GOLD SEEDS

J. H. Wilde

If radioactive gold wire is entrapped in nonradioactive gold tubing, seeds must be manufactured by cutting small pieces of tubing in such a way that the radioactive gold is entrapped within the nonradioactive gold tubing without contamination or loss of activity. Requirements usually call for an approximately 1 mm length and 7 microcuries per millimeter activity or less. The cutting action must be such that the cold gold tubing surrounds and shields out the beta rays. A gold cutter, shown in Figure 1, has been made to accomplish this cutting action. Gold wire is inserted in a groove in a lead pot and is pushed out a distance measured by a micrometer head. An ionization type instrument (not shown in the diagram) gives a quantitative measurement of the amount of activity extending between the body of the shield and the micrometer head. With the correct activity and linear measurement a cutting handle is depressed; by smearing action it cuts the nonradioactive gold tubing and seals the ends. The lead shielding of the cutter protects the operator during the cutting and measuring procedure.

A CONTAINER TO ASSURE UNIFORM IRRADIATION OF COBALT WIRE IN A NUCLEAR REACTOR

J. H. Wilde

In order to assure uniform irradiation of cobalt wire, it is necessary that the wire be placed in a neutron flux in a position to minimize self-shielding. To accomplish this, a cobalt wire irradiation container was made as shown in Figure 1. The container consists of a cylinder 7.5 cm (3 inches) long made of 2S aluminum. On the outside of the cylinder, 40 grooves approximately 0.8 mm (0.033 inches) deep are milled with a 40 pitch rack cutter. The entire cylinder is dropped into a standard aluminum irradiation can and the cobalt wire is loaded individually into the grooves. The standard irradiation can is then sealed. The wires to be placed in the irradiation container can be any length up to 3 inches.

The cobalt wire which is used routinely is prepared from high purity cobalt sponge B.222 manufactured by Johnson-Matthey and Co., Limited, London, England. The cobalt wire is 0.7 mm (0.028 inches) in diameter. Prior to the loading of the irradiation container, the wire is cut into the lengths desired up to maximum lengths of 7.5 cm (3 inches) and is electroplated with gold. With small diameter wires, under approximately 3mm (1/8 inch) in diameter, a thin plate of gold will adhere better than thicker coats. For adequate coverage, the ends of the wire must be slightly rounded. The wire is then chemically cleaned and immediately barrel plated for 30 seconds at 0.5 amps per square foot.

SULFUR STUDIES

Granvil C. Kyker
Martha Stewart

Although chondroiton sulfate was among the first complex biochemicals to receive attention almost a hundred years ago, it remains poorly defined. The classical work of Levene of about thirty years ago is still among the best references. Mild treatment of cartilogenous and collagenous tissues releases a complex glycoprotein of which the prosthetic group is the sulfate ester of a glycuronide-chondroitin sulfate. During recent years, several publications have appeared which indicate a resumed interest in the use of S 35 as an investigative tool. A report that S 35 administered as inorganic sulfate is preferentially taken up in chondrosarcoma was published last year and provided further cause for interest.

Sulfur is unique among the constituent elements of nutriments in the range of valence change of eight electrons, which it undergoes in metabolic oxidation. The end product, sulfate, is excreted rapidly, and consequently appears at very low levels in body fluids. The chondroitins are unique as esters of sulfate because in other sulfur compounds of tissue, with very rare exceptions, the element appears in its lowest valence state of minus two. The mechanism of formation remains obscure. The assumption prevails that esterification follows oxidation, since S 35 administered as sulfate is incorporated. The evidence is inconclusive, however, since the incorporation of sulfate by chondroitin could represent exchange.

During recent months, the exchange of S 35 labeled inorganic sulfate with condroitin sulfate, in vitro, has been under study. Considerable attention to devising adequate methodology was necessary. At first, the separation of sulfate and chondroitin sulfate was attempted by precipitation of the sulfate. This proved unsatisfactory under various conditions. A workable procedure was devised whereby the chondroitin sulfate separated and the inorganic sulfate remained in solution. The procedure is based on a solubility curve which was determined for chondroitin sulfate in increasing concentrations of acetic acid in water. Preliminary studies suggested that exchange does take place. This suggestion derives from the fact that chondroitin sulfate isolated from the reaction mixture contained radioactivity that could not be reduced appreciably by washing. Further study by repeatedly dissolving and reprecipating favors the interpretation that the uptake of S 35 was by adsorption. Analysis of the chondroitin sulfate for its sulfur content in aliquots of solution at various stages in the study showed no occurrence of hydrolysis. Preliminary studies of the uptake of sulfate by homogenized specimens of cartilage, muscle, and liver from the rat have been made. These tissues were chosen to represent a wide range in concentration of chondroitin-like components. The data at the present stage permit no conclusions regarding adsorption of incorporation of the sulfate that was taken up by the tissues.

Continuation of the study contemplates the biosynthesis of radioactive chondroitin sulfate in a suitable animal and the use of this material for investigating the system further.

1033420

CESIUM TELETHERAPY MACHINE

Marshall Brucer, M.D.
L. J. Bulliet

The cesium teletherapy machine is now in the assembly stage at the W. F. and John Barnes Company in Rockford, Illinois.

Figure 1 shows a picture of the test subassembly of the cesium shield and collimating device. In the foreground is the iris diaphragm in an open position. It is attached to the telescoping collimator tube which is attached to the continucusly variable wedge filter mechanism. Behind this is the source shield and the pneumatic shutter device.

In Figure 2 is a partial assembly of the rotating wheel. This rotating wheel is suspended on a temporary support.

FIGURES

RADIOACTIVE IODINE IN MALIGNANT MELANOMA



Fig. 1. Photograph of cut tissue from inguinal node resection. Patient M.F.P. resection seven days after dose of 69.7 millicuries of I 131.

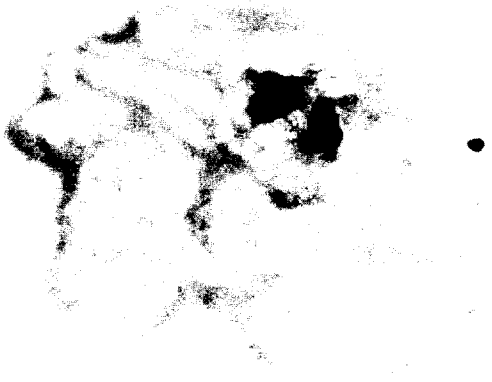


Fig. 2 Gross autoradiogram from the above specimen.

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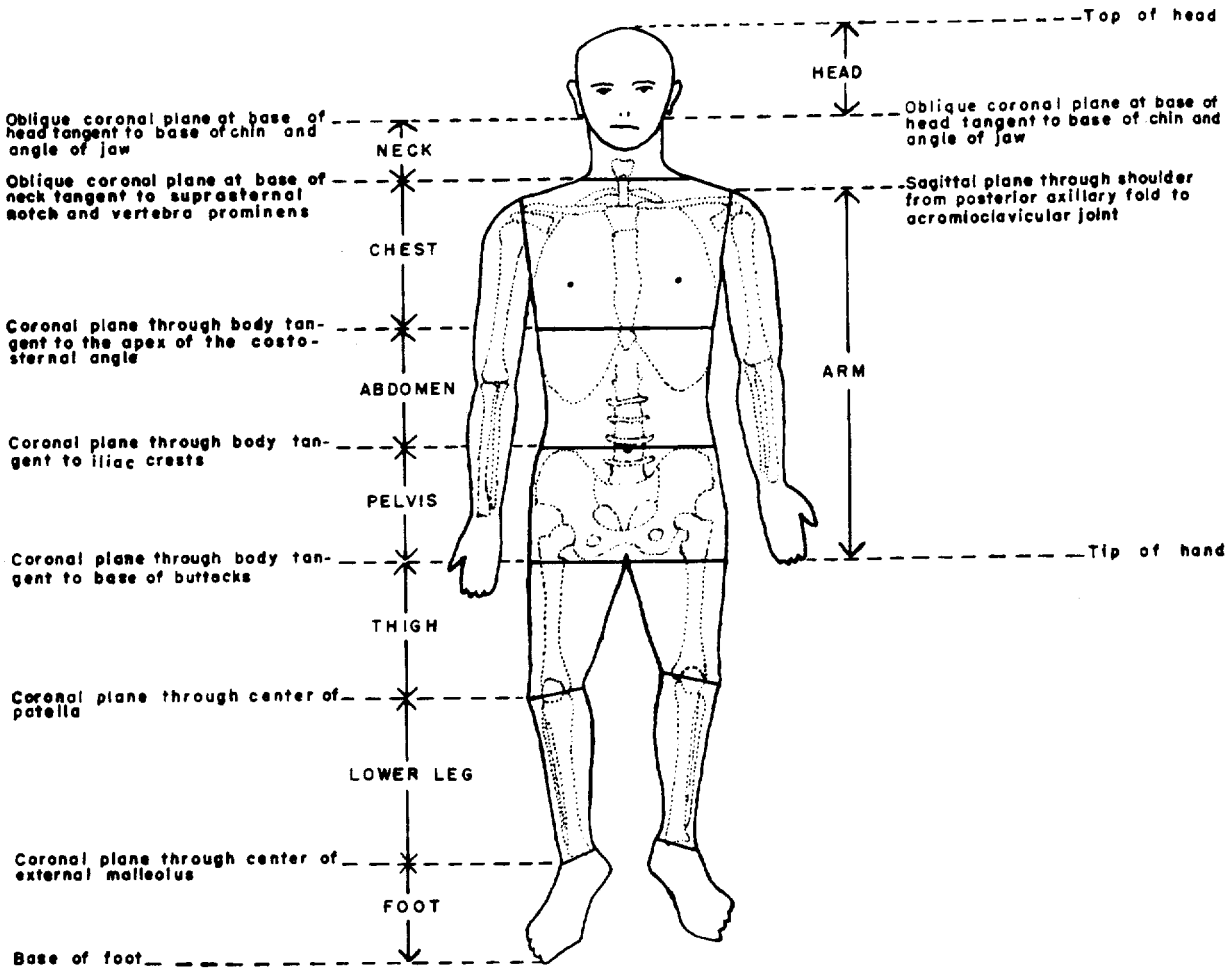


Fig. 1.

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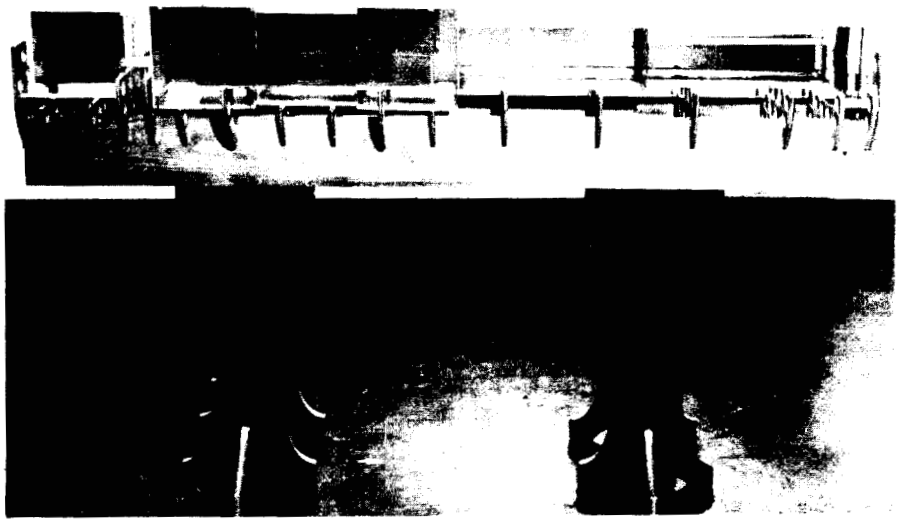


Fig. 2A.

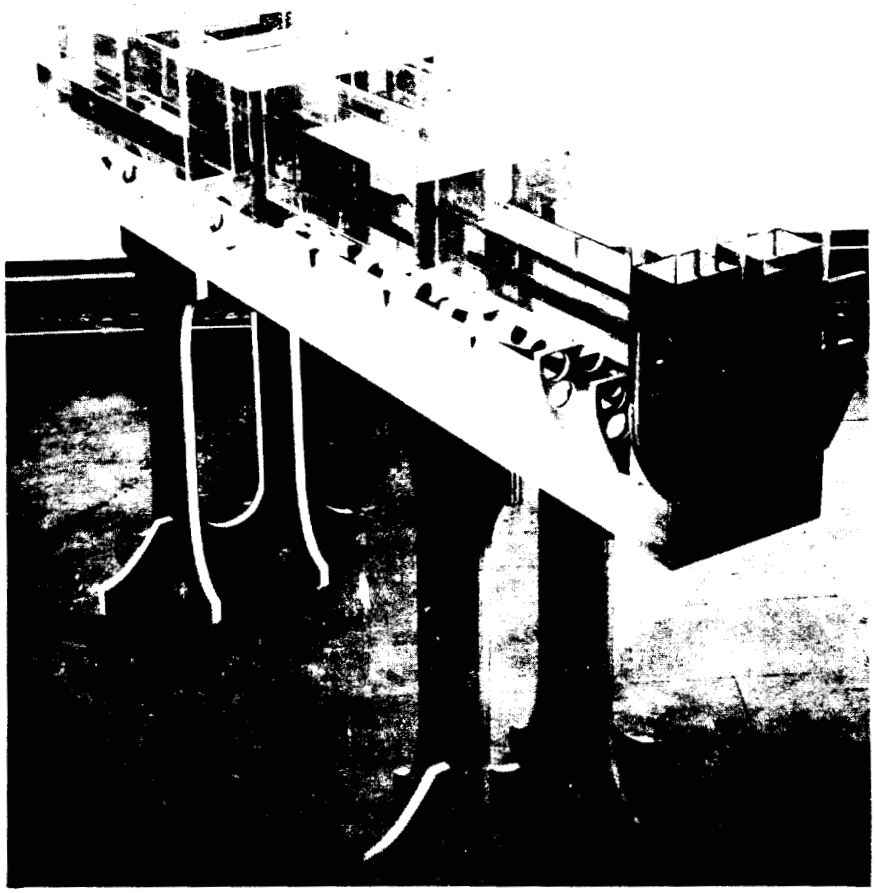


Fig. 2B.

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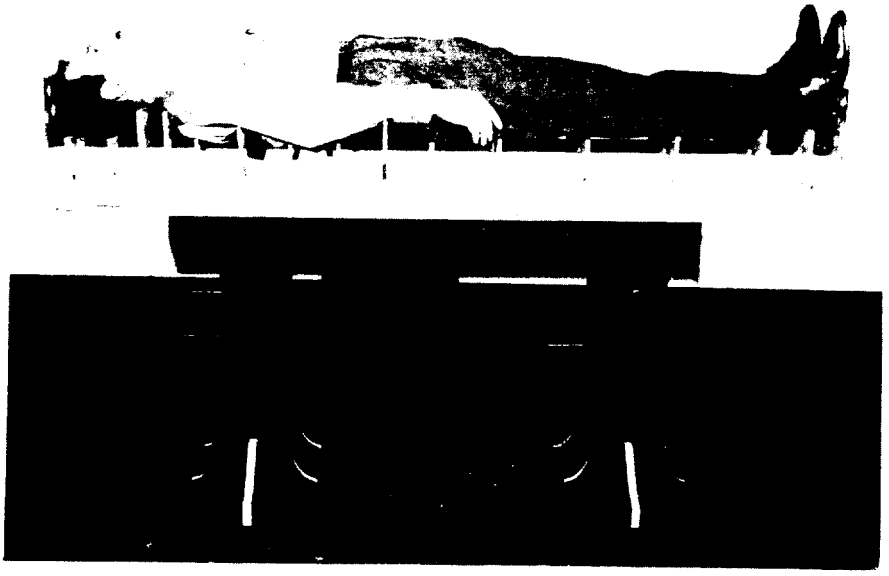


Fig. 3A.



Fig. 3B.

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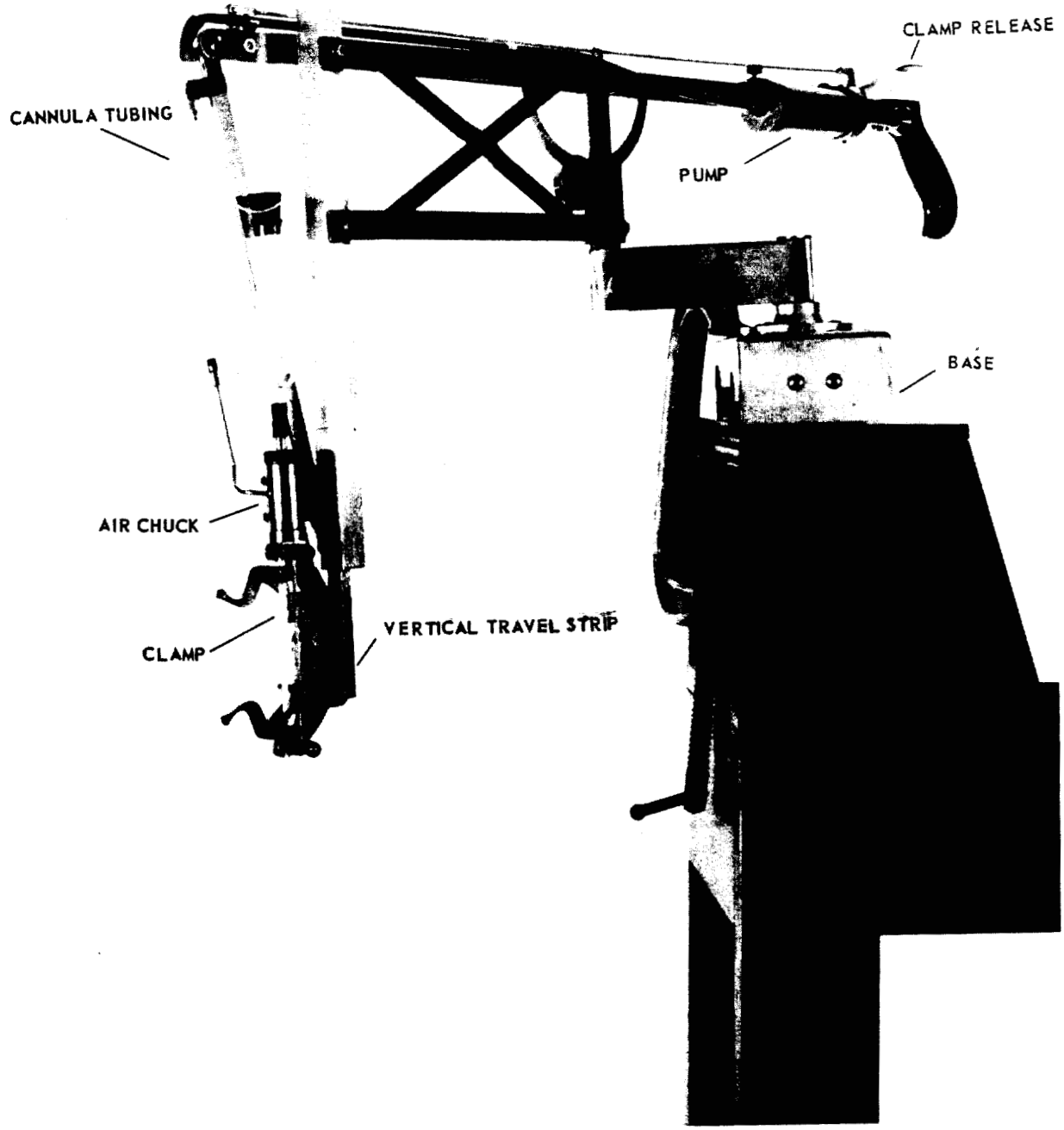


Fig. 1.

103342b

A GOLD WIRE IRRADIATION CONTAINER

GOLD IRRADIATION
INSERT

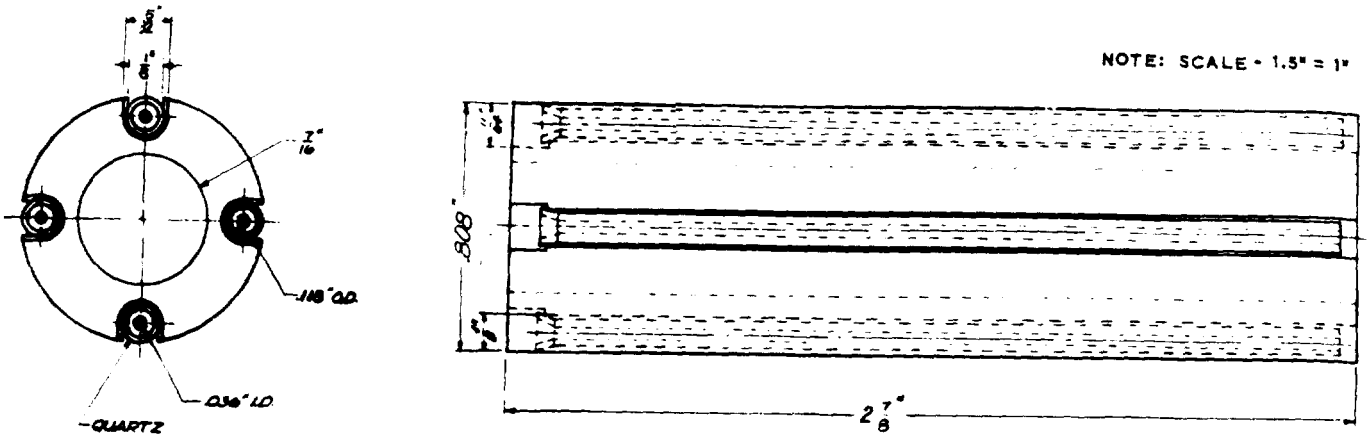


Fig. 1. Container for Irradiation of Gold Wire

A MAGNETIC MANIPULATOR FOR LOADING SHORT COBALT WIRE

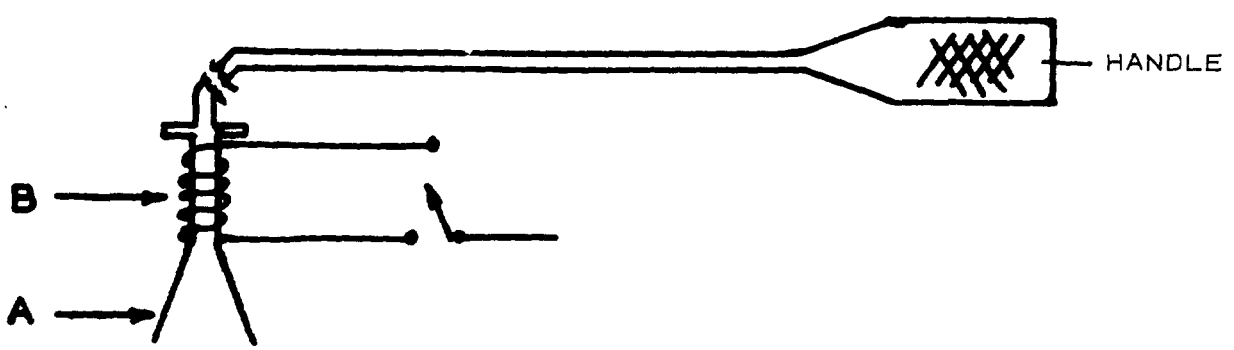


Fig. 1.

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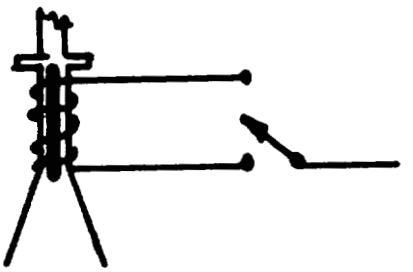


Fig. 2.

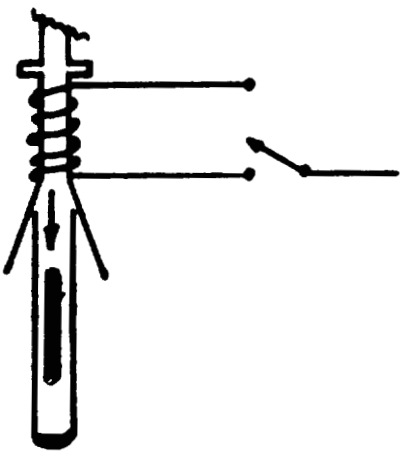


Fig. 3.

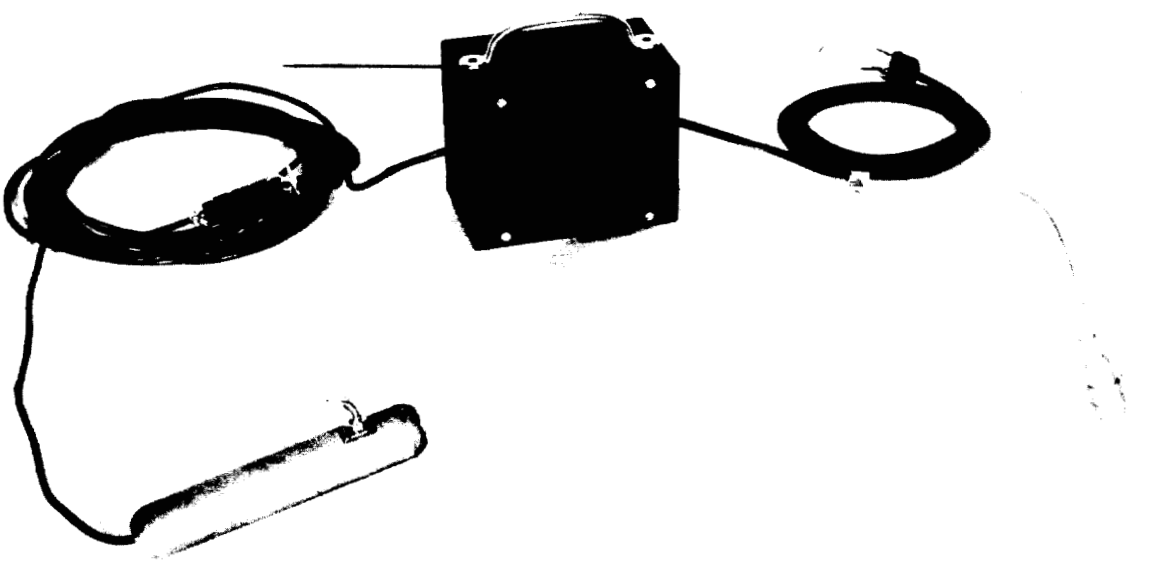


Fig. 4.

1033428

A DEVICE FOR MEASURING AND CUTTING RADIOACTIVE GOLD SEEDS

GOLD CUTTER

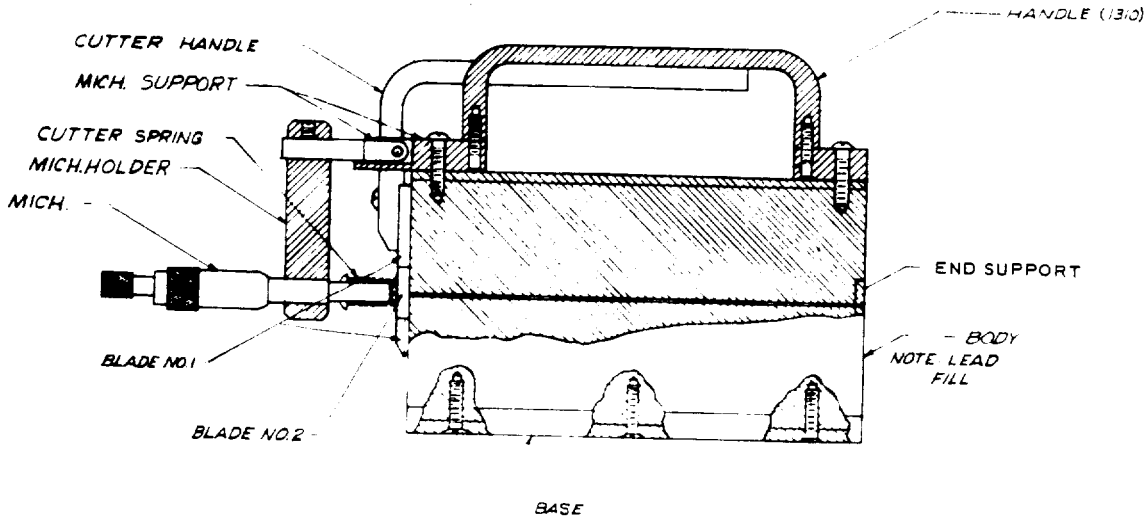


Fig. 1.

A CONTAINER TO ASSURE UNIFORM IRRADIATION OF COBALT WIRE IN A NUCLEAR REACTOR

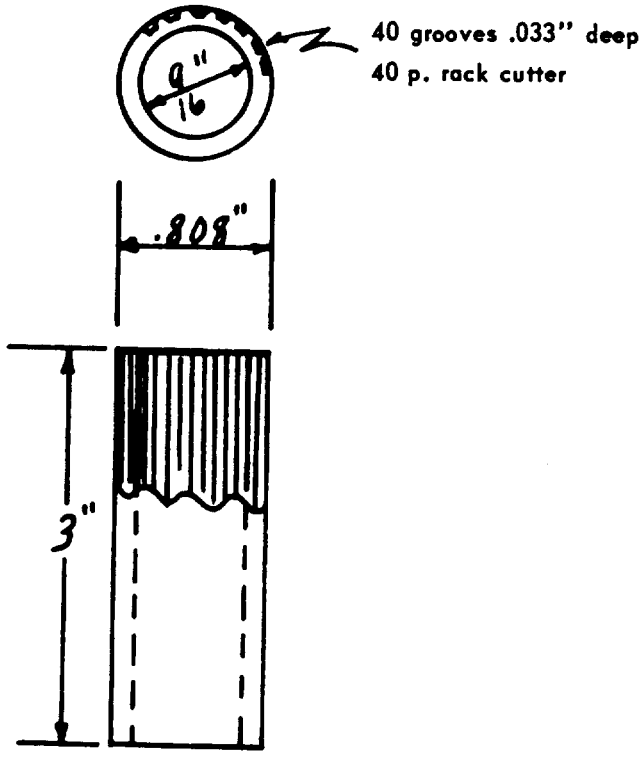


Fig. 1. Diagram showing irradiation container for cobalt wire.

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CESIUM TELETHERAPY MACHINE

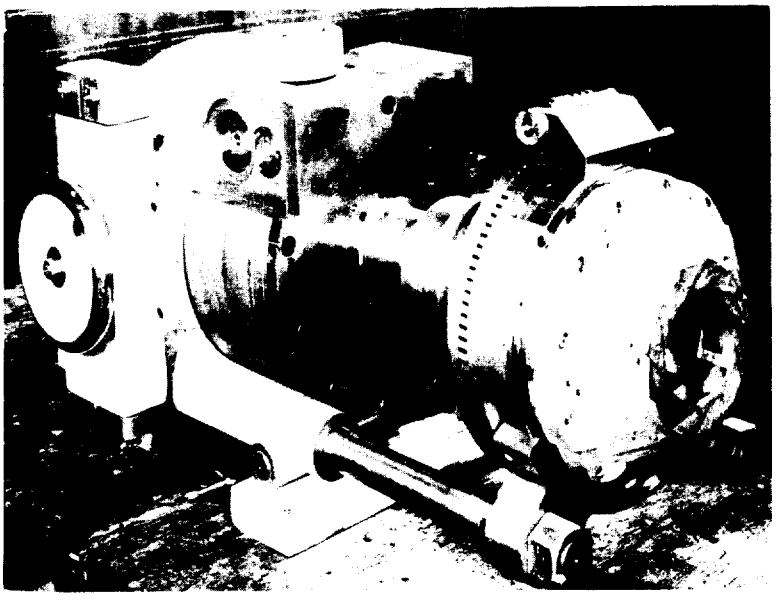


Fig. 1.

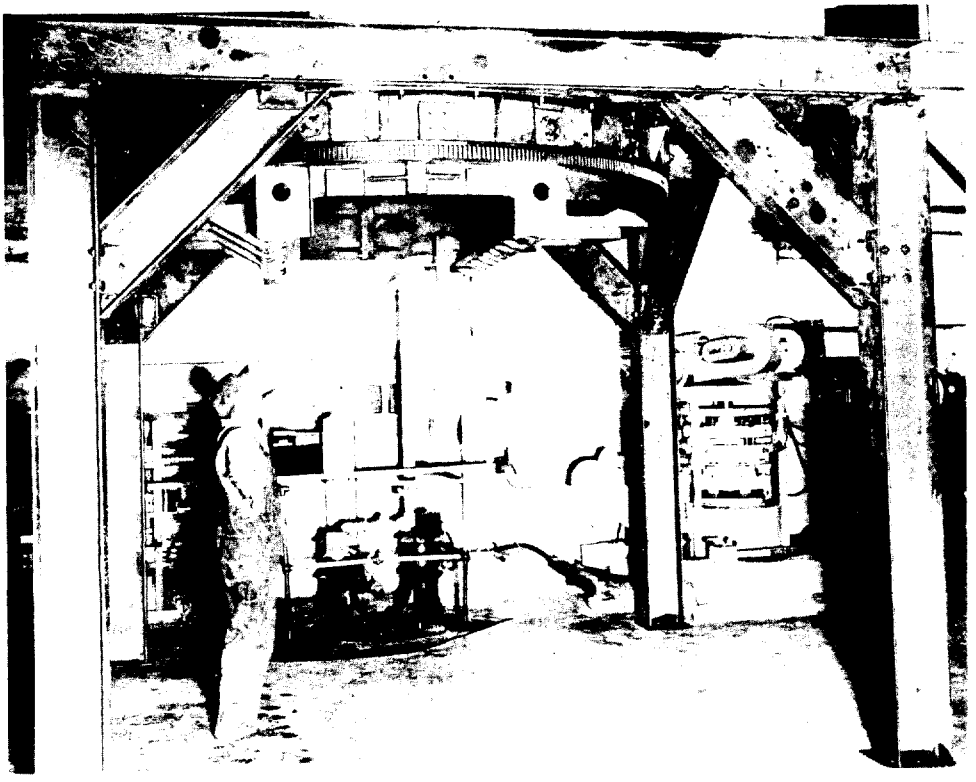


Fig. 2.

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OAK RIDGE
INSTITUTE of NUCLEAR STUDIES

Medical Division

Quarterly Progress Report

Teletherapy Design Problems III

January 1 - March 31, 1954



Operating Under Contract AT-40-1-Gen-33
with the
UNITED STATES ATOMIC ENERGY COMMISSION

P. O. Box 117 Oak Ridge, Tennessee

1033431

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without authorization

AEC, Oak Ridge, Tenn. 7-12-54-550-W-25573

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INTRODUCTION

The Medical Division of the Oak Ridge Institute of Nuclear Studies has pursued a range project for the study of teletherapy problems. Twenty-two medical schools hospitals are cooperating with the Institute in this program.

Teletherapy Design Problems I concerned cesium 137 and was published as an AEC port, TID-5086, first revision, May 15, 1952. Teletherapy Design Problems II told the L. G. Grimmett Teletherapy Unit, and appeared as the ORINS Quarterly Report for period ending September 30, 1953. The present report, Teletherapy Design Problems , is in three sections: It includes some of the work on the cost and availability cobalt 60, which was presented to the Third Industrial Conference on Teletherapy, 14 and 15, 1954; some of the results of the studies of area shielding using marble the type example (to be published by the Marble Institute of America); and the al report on the Grimmett model, which will have no further publication.

Because of the length of this report, progress notes from other sections of the dical Division and the work from the University Relations Division are being held publication in the next ORINS Quarterly Report.

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OAK RIDGE
INSTITUTE of NUCLEAR STUDIES

Medical Division

Quarterly Progress Report

Teletherapy Design Problems III
Supplement

January 1 - March 31, 1954

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P. O. Box 117

Oak Ridge, Tennessee

Operating Under Contract AT-40-1-Gen-33
with the
UNITED STATES ATOMIC ENERGY COMMISSION

PROCEEDINGS OF THE THIRD INDUSTRIAL CONFERENCE ON TELETHERAPY

May 14 & 15, 1954

An informal information conference jointly sponsored by the United States Atomic Energy Commission, Atomic Energy of Canada Limited, and the Oak Ridge Institute of Nuclear Studies. The meeting was held at ORINS Medical Division, Oak Ridge, Tennessee.

ACTING CHAIRMAN

J. R. Mason, Chief
Radioisotopes Branch
Isotopes Division, U.S.-A.E.C.

EDITORS

Marshall Brucer, Chairman, Medical Division, ORINS
J. H. Harmon, Administrative Officer, ORINS Medical Division
Elizabeth B. Anderson, Technical Editor, ORINS Medical Division

1033436

Supplement to Quarterly Progress Report, January 1, March 31, 1954, The Medical Division, Oak Ridge Institute of Nuclear Studies.

This supplement to the Quarterly Progress Report serves two purposes. It supplements material that was prepared and has been published in the last Quarterly Progress Report. It also constitutes the minutes of the Third Industrial Conference on Teletherapy. Since a portion of the material presented to the Third Industrial Conference is published in the regular Quarterly Progress Report, we can see no reason for republishing this in the minutes of the conference. The combined material from the Quarterly Progress Report of March 1954 and these minutes constitute the proceedings of the Third Industrial Conference on Teletherapy.

1033436

Quarterly Progress Report - Teletherapy Design Problems III, January 31, 1954, for the following two papers presented at this meeting by Brucer, Chairman, Medical Division, Oak Ridge Institute of Nuclear

Cobalt 60: Cost, Curiage, and rhm Output.

Review of Final Requirements for Teletherapy Protection (check list).

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STATEMENT OF POSITION OF THE UNITED STATES ATOMIC ENERGY COMMISSION, WITH RESPECT TO THE INDUSTRIAL CONFERENCES ON TELETHERAPY

Chairman Mason

It has been called to the attention of the Chairman that, in the past, [illegible] questions have arisen in connection with the activities of so-called "Industry Advisory Committee" to Government agencies. It is not the position of the AEC that this group is an "Industry Advisory Committee". It is, more characteristically, an informal conference for the purpose of considering or obtaining [illegible] information on specialized technical problems, and for preliminary discussions, relative to the distribution and use of cobalt 60 for teletherapy.

To the end that no such questions are raised in connection with this conference, the following rules are being observed:

1. All sessions shall be under the chairmanship of a full-time employee of the AEC.
2. Complete minutes of the conference shall be kept.
3. All sessions shall be open to the public, and information discussed at the conference may be made public.
4. The group shall act in an advisory capacity only, and all determinations as to actions or decisions concerning the functions of the AEC will be made by the proper officials of the AEC.

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COST OF RADIATION IN HOSPITALS

S. W. Donaldson, M.D.
St. Joseph Mercy Hospital
Ann Arbor, Michigan

conomics of a medical specialty must take into consideration the distribution of the specialists and the populations served, the type or institutional practice, the cost of service to the patient, and A new and significant factor in the field of radiation is that various alth insurance are being offered to the public for the purpose of funds for medical and hospital care. Only in rare instances do any of racts indemnify the subscriber against the expense incident to treatment tion.

diation therapy is a highly specialized branch of medicine and until cent years it has been limited to radium and X rays. With the advent es the field broadened and radioactive cobalt is now available for the of deep seated malignancy. The cost of cobalt 60 therapy must be d in order to compare such a method with conventional agencies.

the present time there are probably less than 50 radiologists who devote ll time to therapy and less than that number outside of the radiothera- o have a particular interest in the treatment of cancer. Patients for radiation therapy (200 PKV and higher) are generally referred to the t from other physicians. Patients for radium therapy are not all treated supervision of a radiologist and many have such treatment administered hs, gynecologists and other specialists.

here are at the present time approximately 4000 American Board of Radiology od radiologists devoting full time to their specialty. There are 156,000 ing physicians (about one half of them are general practitioners) rendering 2,500,000 medical services daily. One patient out of every 30 seen by a im is referred to a radiologist and of those referred 16.2 per cent are for . The therapy patients can be further divided into 80 per cent for high , 19 per cent for low voltage or superficial therapy, and 1 per cent for t therapy.

The practicing physicians who attend the general public in the United States irly uniformly distributed according to the population except in the sparsely d areas. The radiologists are likewise distributed according to population re closely in relation to the number of physicians than are other specialists. st and west of the Mississippi River the ratio of radiologists to physicians radiologist to every 57 physicians.

A total of 5,386 of 6,572 registered hospitals have X-ray equipment, and of the 4,761 general hospitals have some form of equipment. Therapy instal- s are in a few of the less than 100-bed hospitals, and also in some of the linics in this country. The most recent survey showed that there are 1,850 y installations available to the general public and exclusive of those in rental hospitals. As an example a recent check has revealed that there are st 80 installations of 200 PKV or higher in the State of Michigan.

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upervise and operate these units there are certified radiologists in
e hospitals and full time radiologists in all of over 300 beds capacity.
of the large teaching hospitals a radiation physicist is a member of
gy department staff. Forty-eight per cent of all physicians and 57 per
l radiologists are located in cities of 100,000 population or over. If
of 50,000 population or over are included, it is found that 69 per cent
ologists and 56.6 per cent of all physicians reside in these cities.
and daily admissions furnish a daily hospital census of 430,000 patients,
missions per hospital radiologist per day. Considering the fact that
t of the hospitals (mostly small institutions) do not have X-ray equip-
hat 16.2 per cent of all patients referred to a radiologist are for
it can be assumed that there is an admission of at least one therapy
r hospital radiologist per day. Practically all radiation therapy
re at some time during their course of therapy treated as in-patients,
the beginning of the series of treatments.

has been more or less a business axiom in industry that any piece of
should earn an annual gross return of 120 per cent of its cost to justify
se. Applying this business axiom and disregarding the humanitarian
X-ray therapy it is apparent that many hospitals do not have a sufficient
therapy to justify equipping one or more rooms for that purpose. On the
, the cost of operation of a therapy department has always been a subject
ersy. Hospital staff members in some way seem to resent the fact that
of equipment their patients must be sent to another institution for
reatment. Hospital administrators and hospital Boards of Directors, real-
t the volume of therapy patients would not be great enough to justify the
re of money to buy equipment, are often reluctant to provide the space,
and personnel if such service is available nearby.

e cost of operation of a hospital therapy department should include every
pense which is to be charged against the income. The most recent cost
ve been obtained from private offices and these are not applicable to all
radiology therapy departments. Many of the large hospitals have a suffi-
ber of therapy patients to warrant a separate therapy department with full
nical and medical personnel. The smaller hospitals must pro rate expenses
ries between the radiographic department and the therapy department

distributing costs common to both departments some accounting methods
a percentage factor based on relation of square footage in each department
otal square footage in use. Some private office accounting systems use a
e factor based on the relation of departmental collections to total col-
. The square footage system appears to be the best method for prorating
enses as space, heat, light and janitor service in keeping the ordinary
calculating office or store room space rental. When operating an office
private practice of radiology, either as a partnership or as a group, every
business expense is usually included, such as entertainment for business
, travel expense to medical meetings, donations made in the name of the
surance and any other expense the partnership has which is to be charged
the gross income. The hospital radiologists' income is derived from a
a percentage of the department income, or he operates the department on a
ntal agreement with the hospital. Many of the items considered as a busi-
ense for group private office operation, such as expense of attendance to
meetings, are for taxation purposes deductible items from the radiologist's
income.

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of the fixed charges such as space, depreciation, interest on the equipment, and insurance vary greatly dependent upon the extent of the installation. Salaries, laundry expendible supplies, and administrative fairly constant in those therapy departments which operate full time. repair, and replacements may vary tremendously in studies covering t period of time, but in studies over longer periods these costs ow a comparable average per installation. It has been estimated that t of income be allowed as the cost of the electrical energy for operbe equipment per treatment.

one accepts the manufacturers guarantee of tube life as a base line, it nd that $1.00 per hour for 200 PKV machine and $2.50 per hour for 400 nt can be considered as the tube operational cost. The guarantee is ly low in order to provide a profit for the tube manufacturer and under conditions most tubes will exceed the guaranteed number of running time The gain from the additional usefulness above the guarantee of the tube fficient to take care of cable and valve tube replacements. Linen or pense in a therapy department is an item usually completely disregarded ible, but may prove to be far in excess of tube and maintenance cost. ltable for a treatment table cost as much as $30.00 per dozen and the life ital sheet has been determined as 80 washings. The average over-all need ral hospital is 17-18 lbs. of fresh linen per patient per day, and that rtment of radiology is 1-2 lbs. per patient per day.

e actual cost of radium therapy can be disposed of more easily than cost or cobalt 60. The major expenses attendant to the application of radium a cost accounting point of view, allotted to the department of surgery rm of a set charge for the use of the operating room and to the department thesiology as a fee for the anaesthesiologist. If hospital owned radium ded in the same manner as X-ray equipment, then everything which has been d and has any relationship to radium therapy, as well as standby radium not ring a particular treatment must be considered as an investment and treatch. For the physician using radium there is the additional expense of a remium for malpractice insurance.

If it were not for the hidden subsidy in the production of radioactive co- e cost of obtaining it from private industry would not be competitive with The cost of X-ray therapy equipment is within the financial possibilities mall hospitals and radiologist's private offices, and for that reason 200 apy is accessible to every community. More than 90 per cent of all X-ray in the United States is administered by the general practitioner radiolo- Several factors are involved in such a situation: 1. Cost of equipment is hibitive; 2. Distances in this country are not comparable to those in where large treatment centers have been developed; 3. An adequate supply ologists with training in therapy are available; 4. The demand of the profession is that equipment be available to treat patients locally.

The recently trained radiologist has received as thorough a training and ly more complete training in some instances, then the young trainee of some other medical specialties. For that reason he is in most instances com- to serve his community as a therapist. Most of them do not like therapy cept it as a necessary part of their specialty. They recognize the fact that much time is required to earn X dollars in therapy as in diagnosis and that

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the medical care of the patient have often been depleted before he was to the radiologist. They also know that, except in few instances, therapy benefit in the same manner as diagnostic services under any of the pro- insurance plans, and that therapy patients are all potential malpractice

1929 there were 400 medical malpractice claims filed in the United States. re were 4,000 such claims, or one for every 39 of the 156,000 practicing . The 4,000 certified radiologists were not the leading target for those damage due to therapy was the most frequent allegation against radiolo- has long been a recognized fact that malpractice insurance rates are radiologists than for any other physician. Fear of the court room may some radiologists to under treat their patients. The absence of extensive ions following cobalt 60 therapy in the conventional manner may also tend this timidity, and result in better treatment of patients.

additional expense to the operation cost of X-ray therapy has occurred in medical centers since the introduction of so-called super voltage. This se is the remuneration for a radiation physicist who is necessary if high the rotational method of administration is used. Even though the expense icist is usually borne by one institution the benefits of his knowledge and ion is eventually passed along through publications and attendance to to those who are doing therapy in more or less isolated communities.

recently published compilation of cost figures set each 200 PKV treatment ate office practice at $4.99. Of this amount $1.10 was the cost of the per treatment and the cost of the treatment was 67 per cent of the charge tient. This same study in the diagnostic department of the same office on coast showed the cost of each radiographic examination to be $10.04, which per cent of the charge to the patient.

nother study in the midwest had shown the general over-all expenses includ- diagnostic and therapy departments in hospitals was 55 per cent of the In another study of a private office in New England with diagnostic work cost per examination was 60 per cent of the charge, or, in other words, was 60 per cent of income.

ot only do the available figures on cost accounting show a wide variation cost per treatment for radiation therapy, but there also appears to be ethods on which charges are based. The most common basis for charges is a for a series of treatments according to the anatomical location of the ith post irradiation check-up examinations included in the original charge. ee schedules may be based upon a unit charge per 100 r administered or a for each area or portal to which radiation is applied.

Inasmuch as therapy is on a strictly time basis for both medical and lay el who participate in the treatment of patients it seems more logical to te costs on a time for the "job" basis rather than according to square foot- a percentage of collections as has been done by some offices and hospitals. ed charges such as rental allowance for space, interest on equipment invest- depreciation and obsolesence, etc., would be constant and comparable among installations. The variable factors would be salaries of technicians, clerical help, nurses, orderlies and expendible supplies. Even though

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...should be individualized the fact remains that certain routine pro-...been set up and are followed in most departments of therapy. The ...patients with like conditions are treated in the same manner in order ...the same tumor dose in each patient. A known number of portals of known ...will receive a known number of r-units in a known number of days and a ...of time will be consumed at each visit. The actual cost of administer-...lete series of treatments to two separate individuals with the same ...al condition located in the same anatomical part would be the same ir-...of the income received for administering the treatments. The physical ...of the patient during treatments or the skin reaction would probably be ...easons for deviating from the prescribed formula.

...ith each set of cost figures which has been released for publication there ...n plea for a uniform system of cost accounting in order that factual data ...ld be of advantage to others could be obtained. In none of these has ...a suggestion that therapy cost be computed on a time basis and stated ...and cents in the same manner as the fee charged is stated to the patient ...m in vague percentages of income according to square footage occupied by ...y department or of departmental collections. The information radiolo-...nufacturers of equipment, hospital administrators and the patient want to ...how much does it cost to treat what?

HOSPITAL CAPACITIES, FACILITIES, AND SERVICES

4761 - General Hospitals
2257, 50 beds or less - 77% have X-ray equipment
991, 50 to 100 beds
786, 100 to 200 beds
357, 200 to 300 beds
370, 300 or more beds
} All have X-ray equipment

15,000,000 Hospital admissions per year
50,000 Admissions daily
430,000 Hospital patient daily census
4,000 General Hospitals diagnostic equipment
10,000 Diagnostic units 2.5 each
1 Unit per 5 daily admissions

150,000 Physicians render 2,500,000 medical services daily
16 Services per physician per day
3,500 Radiologists and 600 residents - 20 patients per day - 82,000
610 Physician patient services per radiologist
20 Patients per radiologist per day - 1:30
1:30 Refer to radiologist of 2,500,000 services equals 83,333
(57) Physicians at 16 patients per day - 912 services
18,000 X-ray units-hospitals, radiologists, clinics
140 Physician patient service per X-ray unit

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000 Radiologists full specialty or certified
500 Part specialty or non-certified
500 Full or part specialty services 4,000 hospital X-ray departments
4.3 Hospital admissions per hospital radiologist per day

X-RAY EQUIPMENT UNITS

20,000 Gen. Pract.	1 unit each
3,000 Radiologists	2.5 units each
12,000 Specialists	1 unit each
2,000 Clinics	2 units each
13,000 Hospitals	3 units each
50,000 (1,800 therapy duplicated)	

1 X-ray unit per 3,000 population

OWNERSHIP OF MEDICAL X-RAY EQUIPMENT

Diagnostic and Therapeutic Installations in U. S. Hospitals
Diagnostic 5,170
Therapeutic (Duplicated) 1,850
y Installations Owned by Private Physicians (under 65 years of age) in the U. S. 32,250
Total Medical X-ray Installations 37,420

RADIOLOGISTS			PHYSICIANS			
Full Specialists	Att. to Spec.	Total	G.P.	Full Specialists	Att. to Spec.	Total
1,828	326	2,154	49,306	38,169 (57)	16,271	103,746
788	101	889	22,613	5,209 (57)	6,662	45,208

RATIO OF RADIOLOGISTS TO POPULATION IN U. S.

Year	Population	Radiologists	Pop. per Radiologist
1931	122,775,041	1,005	122,164
1938	128,877,000 (est.)	2,191	58,821
1950	150,697,361	3,559	42,342

1033444

PERCENTAGE DISTRIBUTION OF RADIOLOGISTS IN THE UNITED STATES

	Radiologists	Physicians
...000	3%	17.1%
25,000	16%	16.9%
50,000	12%	9.4%
100,000	12%	8.4%
...000	57%	48.2%
...ic Area		
...land	8%	7.9%
...tlantic	27%	28.4%
...	32%	27.4%
...d Southwest	20%	21.9%
...n and Pacific	13%	14.4%

ESTIMATED DISTRIBUTION OF DOCTORS OWNING X RAY

By City Size

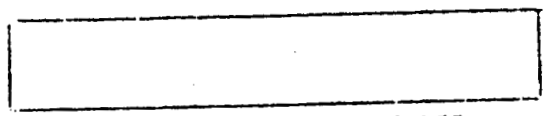
...ze	General Practice	Specialist	Total
...,000	6,490	--	6,490
25,000	4,530	1,890	6,420
50,000	980	2,150	3,130
100,000	1,770	1,740	3,510
...,000	5,910	6,790	12,700
	19,680	12,570	32,250

By Geographic Area

...phic Area	General Practice	Specialist	Total
...gland	1,260	920	2,180
... Atlantic	5,150	4,230	9,380
...al	6,200	2,610	8,810
... and Southwest	4,310	2,620	6,930
...cin and Pacific	2,760	2,190	4,950
	19,680	12,570	32,250

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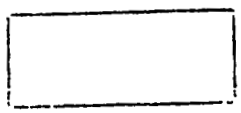
DISTRIBUTION OF X-RAY USE

Examination  43.3%

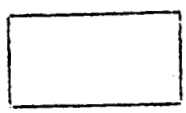
Number of examinations, 30,355

Photofluorogram  28.2%

Number of photofluorograms, 19,677

Treatment  16.2%

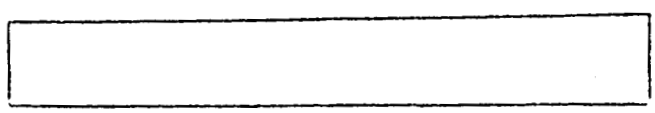
Number of treatments, 11,465

Fluoroscopy  12.1%

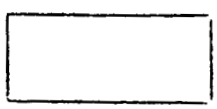
Number of fluoroscopies, 8,465

(X-ray Department, University of Minnesota Hospitals. 1947-1948)

COMPARATIVE DISTRIBUTION OF X-RAY THERAPY

Deep X-ray Treatments (400-220 KV)  79.0%

number patients 9,063

Superficial X-ray Treatments  20.2%

number patients 2,290

Contact Treatment  0.8%

number patients 103

total patients 11,465

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OAK RIDGE
INSTITUTE of NUCLEAR STUDIES

Quarterly Progress Report

April 1 - June 30, 1954

Operating Under Contract AT-40-1-Gen-33
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P. O. Box 117 Oak Ridge, Tennessee

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AEC, Oak Ridge, Tenn. 400-7-30-54-W-25679

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INTRODUCTION

Because the ORINS Quarterly Report for the period ending March 31, 1954, was devoted entirely to teletherapy design problems, the material in this report covers the six month period from January 1, 1954, to June 31, 1954, for both the University Relations Division and the Medical Division of the Institute.

1033449

AN AUTORADIOGRAPHIC STUDY OF THE DISTRIBUTION OF POLONIUM IN THE RAT DURING 24 HOURS AFTER INTRAVENOUS INJECTION

John C. Gallimore
George A. Boyd
J. N. Stannard

Anatomical Record 118: 253-274, February 1954

The distribution of polonium chloride in the liver, spleen, kidney, muscle, and blood of rats after intravenous administration was studied autoradiographically and radiochemically.

It was found that the polonium in the blood, immediately after injection, exists in two systems: a system of polonium aggregates, characterized by sunbursts in the autoradiograms; and a system of nongrouped singly-dispersed atoms or molecules.

The aggregates were removed from the blood stream over an approximate two-hour period and were deposited in the liver and spleen.

It was observed that the nonparticulate polonium concentrated in the proximal convoluted tubules of the kidney and that no particulate polonium was deposited in this organ.

The polyatomic groupings deposited in liver and spleen became diffuse and gradually disintegrated, beginning at about 10 hours after administration and continuing until the end of the observation period (24 hours).

The conclusion drawn from this study is that the aggregates are taken up by elements of the reticuloendothelial system. The study infers that distribution, excretion, and toxicity may be affected by the relative number of aggregated and dispersed atoms present under any given conditions.

TELETHERAPY DESIGN PROBLEMS

Marshall Brucer, M.D.

Radiology 62: 91-98, January 1954

A review of the current status of the production of multicurie sources indicates that there are two outstanding isotopes having a combination of advantages that make them suitable for teletherapy units: cesium 137 and cobalt 60. Cobalt 60 sources can be produced in specific activities ranging from 20 to 30 curies per gram. It is apparent that, within the next few years, activities up to 100 curies per gram could be made available. Cobalt sources must be replaced every five to ten years. There is a significant change in output from year to year.

Cesium sources can be produced with specific activities not exceeding 23 curies per gram. Cesium is a waste product in the neutron economy and, once a manufacturing plant is set up, it should be the cheapest of all sources. The source must be replaced only every thirty to fifty years, and there is no significant change in output from year to year. Cesium, however, must be produced as a Cs_2SO_4 salt and must be pressed into a sealed housing. Cesium sources can be housed in shields one-fourth as massive as can equal cobalt sources.

Which of these sources can be considered "best" for the teletherapist is debatable. Only a long-range program, using each to its best advantage in the actual clinical practice of radiotherapy, will give a reasonable comparison and evaluation of the sources for teletherapy machines.

A NON-LEACHING TECHNIC FOR AUTORADIOGRAPHY

John C. Gallimore
E. C. Bauer
George A. Boyd

Stain Technology 29: 95-98, March 1954

The following non-leaching technic for autoradiography has been developed:

A paraffin ribbon is fastened on a perforated metal plate having a rectangular hole wide enough to allow the ribbon to be suspended freely. The desired histologic section is centered over the hole and is straightened by softening the paraffin over a hot plate and blowing gently on the section. The section is then cut loose on the end of a rubber stopper under a safelight and pressed against the albuminized photographic emulsion. Mayer's albumin does not affect the sensitivity or produce chemical fog in the emulsion.

1033451

PATHOLOGIC CHANGES IN NORMAL HUMAN THYROID TISSUE FOLLOWING LARGE DOSES OF I-131

Gould A. Andrews, M.D.
Ralph M. Kniseley, M.D.
Robert R. Bigelow, M.D.
Samuel W. Root, M.D.
Marshall Brucer, M.D.

American Journal of Medicine 16: 372-81, March 1954

The early histologic changes that occur in normal thyroid tissue after relatively large doses of I 131 have been noted on the basis of information obtained from ten patients. Because of variations in size of the gland and differences in concentration and retention of the isotope, the radiation dose to the thyroid tissue is not closely correlated with the total dose administered. Even when all of the factors known to influence tissue radiation dosage are considered, it is not possible to predict the biologic response on the basis of dosage. The accomplishment of complete destruction of the thyroid by means of a single, safe dose of radioiodine is a rather uncertain procedure. In some cases, large total doses have failed to cause complete necrosis of the gland.

BIOMEDICAL CONSIDERATION OF DISTRIBUTION

Granvil C. Kyker

American Journal of Medical Sciences 227: 572-88, May 1954

"Biomedical Consideration of Distribution" deals with major factors that influence the distribution of foreign substances. It emphasizes elemental substances that afford potential usefulness in the internal application of radioisotopes for medical purposes. Major factors given attention include: Elemental relationships within periodic groups; the "radiocolloidal" behavior of many metals; the size of the chemical dose; complexed or chelated structures; route of administration; and stress. The considerations find limited illustration in certain data from the study of yttrium. Appraisal of factors affecting distribution serves to evaluate approaches to the study of both the effective localization of radioactivity and the removal of relatively inert substances that have been deposited in some organ or tissue.

1033452

INTRACAVITARY USE OF COLLOIDAL RADIOACTIVE GOLD

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Samuel W. Root, M.D.
Ralph M. Kniseley, M.D.
Herbert D. Kerman, M.D.

Radiology 61: 922-29, December 1953

Radioactive colloidal gold has been used by intracavitary injection in an attempt to reduce the reaccumulation of pleural effusions and ascites that develop secondary to neoplasm. During the past two years, 39 patients who have collected intracavitary fluid have been treated. The optimal dosage has not been determined; recently, 150 millicuires for ascites and 75 millicuries for pleural effusion have been used. Radioactivity levels of the pleural and abdominal fluids were determined serially after injection of the isotope. An early fall in concentration (probably due to adsorption in serous surfaces) was demonstrated. Blood and urine levels of radioactivity were very low, demonstrating that practically all of the isotope remains in the injected cavity. Autoradiograms made at autopsy from the serous surfaces, liver, and spleen are included in the complete paper.

Of the 39 cases treated, 16 showed a distinct decrease in fluid accumulation, seven showed some decrease, 10 were unsuitable for evaluation because of early death, and four were unsuitable for evaluation because of combined therapy.

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HUMAN SERUM ALBUMIN TAGGED WITH I 131 IN PATIENTS WITH ASCITES CAUSED BY ABDOMINAL CARCINOMATOSIS AND PORTAL CIRRHOSIS: THE RATES OF INTERCHANGE BETWEEN THE VASCULAR COMPARTMENT AND PERITONEAL CAVITY

Malcolm P. Tyor, M.D.

To be published in the Journal of Laboratory and Clinical Medicine, July 1954

Tracer amounts of human serum albumin, 5 to 10 mg, labeled with I 131 were injected intravenously or intraperitoneally into nine patients with abdominal carcinomatosis and ascites. The rates of decreasing concentration of the tagged albumin in the injected compartment and increasing concentration in the other were similar after the initial 12 to 24 hours. In two patients with cirrhosis and ascites, the patterns of exchange between compartments were similar to those seen in patients with carcinoma. The specific activity of albumin in the injected compartment and in the other — either the vascular compartment or the peritoneal cavity — approached a common value in all subjects studied. Complete equilibrium of the injected tagged albumin between compartments occurred in four patients during the period of study. Equilibrium time between compartments was approximated from the slope of the linear plot obtained from the differences between the specific activities of the plasma and ascitic fluid. The half times were found to be 11 to 52 hours for intraperitoneal injections and 18 to 66 hours for intravenous injections.

Although there were many individual factors that influenced the complex disturbance of ascitic fluid accumulation, these studies suggest that the ability to differentiate between molecular size is maintained and that similar mechanisms are at play in the two disease states studied. Accumulation of ascitic fluid must be due to an imbalance between inflow and outflow from the peritoneal cavity. Either inflow or outflow, or both, could be responsible. A decrease in ascitic fluid accumulation is frequently evident following various forms of therapy. These studies suggest that the measurement for half time of interchange of tagged albumin might reflect the over-all defect in the mechanisms causing ascitic fluid accumulation and that repeated determinations in the same patient before and after treatment may help to clarify these problems.

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LARGE DOSES OF I 131 IN DOGS: RADIATION DOSAGE CORRELATED WITH HISTOLOGIC AND AUTORADIOGRAPHIC CHANGES

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Accepted for publication by the American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine

Pathologic changes in human thyroid tissue following large doses of I 131 have been reported and emphasis has been placed on the variability of response. There are also a number of comparable studies in small laboratory animals. Observations in larger animals in which the thyroid gland approaches the size of that in the human being have been limited. Since the distribution of ionization produced by I 131 is dependent on the volume and dimensions of the thyroid and adjacent structures, pathologic changes induced by I 131 can well be studied in the dog, which has a thyroid gland closely comparable in size to that of man.

Eight mongrel dogs were given I 131 intravenously with the dose calculated at 1.5 millicuries per kilogram with 10 micrograms of carrier iodine added. Daily 24 hour urine samples, as well as daily blood samples, were collected. Radioactivity over the thyroid region was measured daily by means of a collimated Geiger tube. On the 3rd, 4th, 5th, 6th, 9th, 12th, 20th, and 30th days after the administration of I 131, one animal was killed by exsanguination under anesthesia. Immediately after removal, each pair of thyroids was assayed against the same standard using both the collimated Geiger tube and Lauritsen electroscope. The glands were then weighed and histologic and autoradiographic preparations were made. Sections of the trachea and parathyroids were also prepared for routine histologic study.

The initial uptake of radioiodine by the thyroid glands varied from 12.9 to 22 per cent, with the exception of one dog, in which it was 49.5 per cent. Between the 3rd and 5th days after the I 131 injection, a sharp decline in the thyroid radioactivity was noted; a pronounced secondary rise in urinary I 131 excretion followed within the next 24 hours. Histopathologic changes were correlated with calculated tissue dose and have been prepared in tabular form. The I 131 content of the thyroid gland, determined by external counting and by the radioassay of the digested tissue, showed good correlation.

The histologic features following large doses of I 131 can be divided into three stages: There is a latent period of approximately three days during which no changes are apparent; this is followed by the period of beginning reaction and breakdown (from the 4th to the 6th day) without frank necrosis; after the 6th day, necrosis is diffuse and severe. Detailed histologic descriptions have been prepared. Autoradiograms in the three-day animals showed the expected uneven follicular distribution of the isotope with somewhat greater concentration in large follicles. By the 6th day, much of the isotope had felt the main bulk of the gland with residual focal areas of high activity localized in the intact follicles in the capsular region. This appears to confirm the fact that release of iodine is closely correlated with the process of

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necrosis. A similar situation was seen on the 9th day; by the 12th day, there was no remaining rim of preserved follicles. On the three animals killed at later dates, there were no longer any areas of preserved follicles.

Since the cells of the outermost follicles are not subjected to radiation from all directions (as are those more centrally located), they receive a smaller amount of energy from the beta particles. These factors combine to produce a sharp decrease in beta dosage to the peripheral follicles and presumably account for the histologically observed "protected zone." Since the maximum range in tissue of beta particles emitted by I 131 is 0.22 cm with an average range of approximately one-third of this, the zone is a narrow one. This rim of protective tissue tends to emphasize the fact that the gamma radiation accounts for only a small portion of the total dose absorbed by the thyroid. This phenomenon would probably not occur as a result of the gamma emission alone, since the fall-off of gamma radiation from center to periphery is quite gradual.

DISTRIBUTION OF COLLOIDAL RADIOACTIVE CHROMIC PHOSPHATE AFTER INTRACAVITARY ADMINISTRATION

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Accepted for publication by Radiology

A study was made to gather data on the metabolism and distribution of colloidal radioactive chromic phosphate after intracavitary injection into patients with pleural effusion or ascites on the basis of carcinoma. Because of the fact that the chromic phosphate has only beta emission (from the P 32), it has some theoretical advantages over the use of colloidal radioactive gold, which has a significant gamma emission. Although the extent of the contribution of the gamma emission of the gold 198 to the therapeutic effect is not known, it does produce a total body effect that is undesirable.

Four patients with pleural effusions and six with ascites, all of whom had cancer proven histologically, were selected. Following intracavitary administration of the isotope, levels of radioactivity in the blood, pleural and peritoneal fluids, and urine were measured at intervals. On three patients who died at varying intervals after administration of the colloid, autopsies were performed and tissue distribution data were obtained. Microscopic and gross autoradiograms were prepared from the tissure of these three patients.

Plotting the concentration of radioactivity in the pleural and abdominal fluid against time revealed that in six patients — after the first hour, in which there was an erratic variation of concentration — there was a fairly rapid decrease in concentration in the fluid. Since there is little absorption from the cavity, this decrease must result from the settling out of the colloid on the serous membranes. In three patients, fluctuating high levels of activity in the fluid were obtained for several days. The reason for these variable levels was not clear. The radioactivity levels

on whole blood, washed red blood cells, and plasma were obtained. Most of the radioactivity was seen to concentrate in the red blood cell portion. Upon hemolysis and dialysis of these red blood cells, 41 per cent of their radioactivity passed into the dialysate, which indicates that they contain ionic phosphate. The total amount of P 32 circulating in the blood at any time is actually very small. In three patients, the maximum amount obtained by multiplying the concentration of P 32 per ml of blood by the estimated blood volume showed that slightly less than 1 per cent of the administered dose was present in the blood at any time. Urinary excretion of the chromic phosphate averaged approximately 5 per cent of the administered dose over a period of 11 days.

Autopsy distribution showed two items of particular interest: First, the highest concentration of radioactivity is on the serous membranes of the injected cavities; and, second, uptake in lymph nodes adjacent to these cavities is relatively good.

Autoradiograms prepared from the liver of a patient given intraperitoneal chromic phosphate showed deposition of radioactivity in both tumor and liver, suggesting that the chromic phosphate distributes both like phosphate ion and like a colloid.

These studies provide information on only a small number of patients, but the results seem fairly consistent. There is good evidence that most of the radioactivity remains on the walls of the injected cavity after the injection of chromic phosphate. Only a small percentage of the injected dose is present in the blood at any one time, but it is a larger proportion of the injected dose than is seen after administration of gold 198. Three points of interest in which the behavior of the chromic phosphate differs from that of gold 198 after its intracavitary injection are: (1) the high concentrations of radioactivity in the red blood cells; (2) the higher urinary excretion; and (3) the greater deposition in neoplastic tissue. These results suggest fairly strongly that some of the radioactive phosphorus breaks away from the colloidal complex and distributes like phosphate ion.

LOCALIZATION OF ANTIMONY IN BLOOD

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Accepted for publication in The Proceedings of the Society for Experimental Biology and Medicine

Labeled fuadin prepared from neutron irradiated antimony trioxide has been used in a study of the localization of antimony in the red cell fraction of rat blood. The results are consistent with the hypothesis that the antimony is attached to the globin portion of hemoglobin.

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THE DISTRIBUTION OF INTERSTITIAL AND INTRACAVITARY INJECTIONS OF CERTAIN RADIOCHEMICAL PREPARATIONS OF MEDICAL INTEREST

Granvil C. Kyker

Accepted for publication in the Bulletin of the Medical Association of Puerto Rico

The problem fundamental to the successful internal use of radioisotopes in therapy is one of distribution. Almost without exception, the metabolic processes cannot be relied upon to afford the pattern necessary for the control of a localized abnormality without also producing injury elsewhere in the body. Certain factors do influence the distribution of internally administered foreign chemicals. The more influential factors include the size of the chemical dose, the radiocolloidal nature of many heavy metal ions at very low concentrations, the use of complexing agents, and the route of administration. These effects are illustrated by recent studies of "colloidal" chromic phosphate, yttrium chloride, and lutecium in simple and complex ionic preparations.

THE DISTRIBUTION AND RADIATION EFFECTS OF INTRAVENOUSLY ADMINISTERED RADIOACTIVE COLLOIDAL GOLD 198 IN MAN

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Accepted for publication in Cancer

Clinically, radioactive colloidal gold has been administered interstitially, intracavitarily, and intravenously. The distribution and effect are greatly influenced by the route of administration. The present report is concerned only with intravenous injection of this material. The study was undertaken to investigate a repeatedly suggested possibility of using gold 198 in the treatment of neoplasms located in the liver, and to obtain additional general information on its distribution and effects in man.

Six patients, whose case histories and autopsy reports are presented in the complete report, received the isotope intravenously. Information was obtained about the metabolism and distribution of the radiogold by external counting with a collimated Geiger tube over the patient's liver and spleen; by obtaining plasma and urine levels for radioactivity; and by obtaining tissue distribution data, as well as histologic data and gross autoradiograms at autopsy. Complete blood counts and careful clinical observations of all patients were included in the study.

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Despite a considerable amount of unavoidable error, it is possible to make some rough estimates of the distribution of the total dose of intravenously administered gold: The normal liver tissue contained approximately 60 to 94 per cent of the administered dose. The spleen contained from 5 to 16 per cent (except one that contained only 1.2 per cent). The amount in the bone marrow was in the same range as that in the spleen. The kidneys retained from 0.05 to 0.24 per cent, the lungs from 0.8 to 0.2 per cent, the adrenals less than 0.1 per cent, and the total plasma from 0.1 to 0.7 per cent.

There was a very rapid fall in plasma radioactivity as the gold was deposited in the reticuloendothelial organs. This was shown by external counting over the liver and spleen of the patient during administration of the gold while, at the same time, serial samples of plasma for radioactivity content were being obtained. The total urinary excretion was very low, with the largest amount appearing during the first day.

The intravenous injection of the radioactive colloid produced no immediate clinical reactions.

The patients died, as a result of their underlying disease, at intervals of 12 hours to 23 days after injection of the gold. Distribution data in the tissues of the radioactive gold showed the largest amount of the gold to be in the liver, spleen, and marrow, in that order. There was extremely low retention in the nonreticuloendothelial organs. At autopsy, none of the livers examined showed evidence of radiation damage; assay of tissues and gross autoradiograms showed practically no uptake of the radiocolloidal gold in neoplastic tissue.

This study has not ruled out the possibility that diffuse neoplastic tissue in the liver might be effectively irradiated by intravenous colloidal gold. In some cases, such as lymphosarcoma with extensive diffuse liver involvement, it might be a more effective form of therapy than would other means. Patients in whom the disease is localized mostly in lymph nodes would not be expected to respond, because of the low concentration of the isotope even in normal lymph nodes.

Although the therapeutic possibilities of intravenously administered radiocolloidal gold appear exceedingly limited, the unique behavior of colloid materials and their concentration in reticuloendothelial tissues are the basis of worth-while experiments now being carried out in several institutions. Experimental cirrhosis in animals has been produced by several workers. The rate of removal of isotopes from the blood may eventually give information on blood flow in the liver or on reticuloendothelial function. The absence of concentration of colloidal gold 198 in tumors in the liver — with the resulting area of low activity in a field of high activity — suggests the possibility that external counting studies might reveal unknown areas of neoplasm in the liver. Studies based upon the information in the present report are in progress.

Summary

1. Radioactive gold in colloidal form can be injected intravenously into the human being without immediate untoward reactions.

2. The isotope promptly leaves the blood stream and deposits largely in reticuloendothelial organs.

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3. Neoplasms that replace reticuloendothelial tissue in liver do not concentrate the isotope and these lesions contrast strikingly with surrounding tissue having high levels of activity.

4. This information in a small number of cases suggests that intravenous colloidal radiogold holds no promise in the treatment of discrete primary or metastatic lesions in the liver, but does not rule out the possibility that very fine diffuse lesions could be treated advantageously.

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EARLY RESULTS OF THE TREATMENT OF CHRONIC GRANULOCYTIC LEUKEMIA WITH INTRAVENOUS COLLOIDAL GOLD 198

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Read by title before the Central Society for Clinical Research, Chicago, November 1953

Six patients with previously untreated chronic granulocytic leukemia were given colloidal gold 198 intravenously and have been observed for periods of from three to eight months. Two additional patients with late treated granulocytic leukemia were also given this isotope.

In the previously untreated patients, initial injections of from 23 to 45.5 millicuries were administered. Three patients have had a second dose, administered at an interval of from two and one-half to five months. There were no untoward or toxic reactions except that of mild nausea. Less than 0.5 per cent of the isotope was excreted in the urine during the first week. Plasma radioactivity fell precipitously to a low level within the first half hour. Levels of radioactivity in the white and red cells were determined for one patient. It was found that the leukocytes contained somewhat more of the isotope than did the plasma, whereas the red cells showed negligible radioactivity. External counting studies and "scintiscan" records verified the high concentration of the isotope in the liver, with a significant but lesser concentration in the spleen.

General clinical improvement was definite in five of the six previously untreated patients. All six showed regression in the size of the liver and spleen. Hematologic studies showed a distinct fall in the total white count in all of the previously untreated patients, with an associated increase in the maturity of the granulocyte picture. In five of these cases, an improvement in the red cell values occurred after the maximal fall in leukocyte count. Liver function tests were abnormal in most of the group before treatment. Subsequent studies showed no uniform change. In two patients for whom data are available, the total blood cholesterol increased from abnormally low levels, and an elevated basal metabolic rate decreased after treatment.

One patient with late previously treated leukemia showed no benefit from therapy. The other patient, who was in terminal condition when the isotope was given, died two days later. Autopsy studies, including tissue radioactivity assays and autoradiograms, were performed.

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DIAGNOSTIC STUDIES WITH COLLOIDAL AU 198

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Read by title before the Southern Society for Clinical Research, New Orleans, January 1954

Earlier work has shown the striking concentration of intravenously injected colloidal radioactive materials in reticuloendothelial tissues. Autoradiographic studies and radioassays of tissues obtained at autopsy have indicated that areas of neoplasm in the liver and bone marrow are characterized by an almost complete absence of the isotope and represent clearly demarcated zones of low radioactivity in a field of high radioactivity. With the availability of a method for obtaining a visual record of the distribution of gamma emitting isotopes in the body of the living patient, efforts have been made to use colloidal Au 198 as a diagnostic method for neoplasms in the liver. After intravenous administration of the isotope, it has been possible to show, in general, the size and configuration of the liver and, in some cases, of the spleen. Large areas of metastatic neoplasm in the liver are demonstrable because of their low concentration of the radioisotope. The method is limited by the irregular shape of the organ and the respiratory movement of the patient. The size of the lesion and its location in the liver are important in determination of detectability. To the present time, only large metastases, which were usually clinically obvious, have been demonstrated.

THE DISTRIBUTION OF YTTRIUM ADMINISTERED BY VARIOUS ROUTES

Granvil C. Kyker
Edgar A. Cress

Presented before the Federation of the American Society for Experimental Biology, Atlantic City, April 1954

Many previous studies of the distribution of carrier-free yttrium emphasize the bone-seeking nature of this element. This study places the emphasis on the chemical dose. After a single injection of a preparation of radioactive yttrium, the pattern of distribution was observed in more than 100 rats and a few mice and dogs. Administration included intrapleural, intraperitoneal, intramuscular, intratumoral, intravenous, and subcutaneous routes. The preparation contained approximately 100 microcuries of yttrium 90 and 1000 micrograms of the stable isotope as yttrium chloride per milliliter dissolved in physiological saline and adjusted to pH 4.0 - 4.5. A quite similar pattern was observed for all animals except those of the intravenous series. The excreted fraction was small but somewhat variable, generally accounting for less than

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1 per cent but ranging as high as 5 per cent of the dose during the first half life of the isotope. Practically all of the unexcreted fraction was retained within the site of administration and about 3 per cent appeared elsewhere. In the intrapleural and intraperitoneal series, the liver and mediastinum, respectively, accounted for more than half of the small mobilized fraction. In the intravenous series, the rate of excretion was approximately five times as fast. The radioactivity of the blood fell rapidly during the first 24 hours. Liver and both femurs accounted for 70 and slightly less than 2 per cent, respectively, after two half lives. Renal excretion was always greater at first, but fecal excretion predominated before the 6th day.

THE EFFECT OF PH AND CARRIER ON THE DISTRIBUTION OF RADIOYTTRIUM

Granvil C. Kyker
Edgar A. Cress

Presented before the Division of Medicinal Chemistry and Division of Biological Chemistry of the American Chemical Society, Kansas City, March 1954

A study was undertaken to evaluate the effect of pH and of the quantity of carrier on the distribution of radioyttrium in rats.

In the first series, four unbuffered preparations of yttrium 90 (beta, 2.25 Mev, $t_{\frac{1}{2}}$, 65 hours) were adjusted to pH 2,3,4, and 7, respectively, and were administered intrapleurally to one group of animals and intraperitoneally to another group. Each preparation contained 1000 micrograms of stable isotope per milliliter as yttrium chloride in physiological saline. No effect of pH was observed. Excretion was consistently low for all animals of both groups and averaged 0.9 per cent for a period of three days. Ninety-five per cent of the unexcreted fraction remained within the injected cavity. Approximately half the activity outside the cavity appeared in the liver and mediastinum, respectively, for the two groups.

In the second series, nine unbuffered preparations of yttrium 90 in physiological saline were similarly administered to two groups. Each preparation was adjusted to pH 4.0-4.5 and ranged in concentration of carrier from 2.5×10^{-9} molar (carrier-free) to 5.55×10^{-2} molar yttrium. Intracavitary retention and excretion was similar for the intrapleural and intraperitoneal groups. At concentrations below 10^{-6} molar, carrier exhibited no significant effect. At higher concentrations, the effect of carrier was prominent. Excretion decreased rapidly from 2.5 to 1.0 per cent as carrier increased from 10^{-6} to 2.8×10^{-3} molar. Further increase of carrier to 5.5×10^{-2} molar decreased the excretion slowly to 0.1 per cent. Conversely, the percentage of the unexcreted fraction, which remained within the injected cavity, increased from 47 to 89 to 97, respectively.

A COMPARISON OF THE METABOLISM OF RB 86 AND K 42 FOLLOWING SIMULTANEOUS INJECTION INTO MAN

Malcolm P. Tyor, M.D.
James S. Eldridge

Read by title before the American Society for Clinical Investigation, Atlantic City
April 1954

The physical characteristics of K 42 ($t\frac{1}{2}$, 12.4 hours) have limited its widespread use.

Studies indicate that rubidium may replace potassium in several biological systems. The physical characteristics of Rb 86 ($t\frac{1}{2}$, 19 days) are suitable for tracer studies in man.

Simultaneous intravenous injections of K 42 and Rb 86 were given to four patients with leukemia and carcinoma. Stable rubidium injected varied between 0.25 mE and 1.52 mEq to determine any effect of "carrier"; potassium injected was 0.07 to 1.04 mEq.

Multiple samples of plasma, red cells, and urine were obtained from all patients; white cells were separated in one patient. Each sample was assayed in a well scintillation counter. Counts of Rb 86 and K 42 were determined by taking advantage of their half lives and were analyzed statistically.

The percentage of total counts of Rb 86 and K 42 in each sample of plasma, red cells, and urine was relatively constant within each patient. When the ratio of Rb to K 42 in the plasma and red cells of individual patients was compared with the ratio of the mixture injected, they were found to be similar. The ratio for white cells also agreed closely with that of the administered dose.

In contrast, the ratio of Rb 86 to K 42 in the urine of each patient was constantly lower than it was in the mixture injected. The lower values, however, bore a consistent relationship to the ratio of the dose injected in each patient. The ratios of percentage of total counts of Rb 86 in urine to the percentage of total counts of Rb 86 injected were similar in all patients.

In individual patients, the data indicate a constant ratio of Rb 86 and K 42 in plasma, red cells, white cells, and urine. The ratio is similar to that of the injected dose in all fractions except urine, which showed less Rb 86 and more K 42.

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STUDIES OF RARE EARTH ELEMENTS USING LUTECIUM 177

Granvil C. Kyker

To be presented before the Division of Biological Chemistry of the American Chemical Society, New York City, September 1954

Lutecium chloride containing lutecium 177 as a tracer was administered intraperitoneally to about 150 young adult rats. The animals were divided into three series. In the first series, the size of the chemical dose was varied. In the second, the chemical dose of rare earth was increased by adding yttrium chloride to the labeled lutecium chloride. The third series was analogous to the second and employed lanthanum chloride instead of yttrium chloride. In all animals, the dose of radioactive lutecium was similar. Groups of animals in each series were studied at various intervals up to 21 days after administration. Five specimens from each animal were assayed for lutecium 177, as follows: abdomen, mediastinum, remaining carcass, urine, and feces.

The data indicate that the retention of radioactive lutecium in the injected cavity is increased by increasing the dose of rare earth element. The size of the dose ranged from less than 1 microgram of lutecium per rat in certain groups of the first series to more than 5 milligrams of total rare earth in the two other series. Usually less than half of the smaller doses remained within the injected cavity after one week, whereas 97 per cent or more of the larger doses were similarly localized. Retention elsewhere in the body and excretion were related also to the size of the dose. When more than 1 milligram of rare earth per rat was administered, extracavitary retention always exceeded excretion. With a dose of 0.1 milligram or less, this retention exceeded excretion at first, but this relation was reversed after three days. Urinary excretion exceeded fecal excretion regularly at first. The duration of this excess indicated an inverse relation to the size of the dose. Fecal excretion of large doses was frequently greater within one day, but for very small doses increased after eight or ten days.

The data emphasize the fundamental importance of the size of the chemical dose and the biochemical similarities of the rare earth elements.

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Progress Reports

THE PATHOLOGY SECTION

Ralph M. Kniseley, M.D.

Autoradiography

The Pathology Section has assumed the responsibility for presentation of the material on autoradiography in the basic course in radioisotope techniques, which is conducted by the ORINS Special Training Division. Through modification of the laboratory experiment, presentation of autoradiography has been reduced to a one half-day session.

A general orientation lecture in gross autoradiography is followed by an experiment that exposes slices of formalin-fixed rat organs containing intravenously administered Au 198 and the plated disc of cobalt prepared as an earlier laboratory exercise by the class. Concomitantly, demonstrations of various microscopic autoradiograms are presented in another laboratory room. Following this demonstration, a second lecture stresses details of technique and sources of material. Emphasis is on microscopic autoradiography.

Microscopic Autoradiography

Several new methods of microscopic autoradiography have been adopted and several important modifications of existing methods have been devised. The wet mounting technique of Evans has been modified by William Gibbs, and involves the following steps:

1. Process sections in the routine histological manner.
2. Cut sections at the desired thickness.
3. In the dark room with lights on, float individual sections in warm water (37° C).
4. After wrinkles smooth out, take up section with a clean glass rod and refloat on cool (68° F) 95 per cent ethyl alcohol.
5. Dip the photographic plate into the alcohol and pick up the section.
6. Allow alcohol to evaporate for about one minute.
7. Turn plate emulsion to side down and press firmly on a clean rubber stopper. This fixes the section firmly to the emulsion.
8. Place plate in plastic slide box and seal with black tape.

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9. Place in the refrigerator for exposure.

The substitution of 95 per cent alcohol in place of water for floating the sections prevents absorption of water by the emulsion and subsequent latent image fading.

Gibbs has also found that the substitution of several more readily available materials works equally well in preparing high resolution microscopic autoradiograms in accordance with the technique proposed by Gomberg in Nucleonics, October 1951. Plexiglass slides, 1 by 3 by 1/16 inches coated with 5 per cent polystyrene in benzene have been prepared in the shop. After drying, the slide is dipped in a 0.1 per cent solution of chrome alum prepared in 1 per cent gelatin. This technique is then followed by the usual stripping film technique. The method is applicable to blood and fluids for examination of single cell autoradiograms, such as sulfur labeled methionine leukocytes, and phagocytes containing Au 198 in paracentetic fluid.

Other innovations include substitution of No Screen and Type A microscopic slide emulsions in place of NTB plates. These have usefulness in giving higher sensitivity ranges, though with some sacrifice in definition in comparison with NTB plates. A liquid coating method, employing a modification of previously described techniques has also been adopted. Stripping film (35 mm) of Eastman Kodak has been melted at 37° C and placed over the section with an eyedropper. It is brushed out to a uniform thickness and subsequently treated in a manner similar to a stripping film method.

One major advantage to this method is that the danger of displacement of the emulsion giving artifactual localization is virtually eliminated; this method gives a rather high resolution microscopic autoradiogram.

Gross Autoradiography

Several modifications in the equipment for preparation of gross autoradiograms have been devised by the technical members of the section. William Fields has designed a plastic mold for use in plaster embedding of bone in preparation of gross bone autoradiograms. The plastic mold is in the shape of a frustrum of a rectangular pyramid, measuring 5 by 9 inches at the base and 4 1/2 by 8 3/4 inches at the top (outside dimensions). It is 4 inches deep in the smaller end, and is fitted with a removable bottom that greatly reduced the hazard of tissue breakage during removal of the plaster of Paris and bone from the mold. The mold is constructed of 1/16-inch Lucite.

Another difficulty in obtaining good gross autoradiograms has been in providing a firm uniform pressure of film against the specimen. The press boards that have been in use tend to produce greater pressure around the periphery of the tissue. Spring clamps of brass with a 2 1/8-inch opening have been designed by Fields and have been found to provide a more uniform pressure.

Still another of the problems in gross autoradiography has been in the determination of proper exposure times. Exposure tables for tissues containing Au 198 worked out by Gibbs and Fields have proved reliable with a number of specimens. The technique, in brief, is as follows: The end window of a Tracerlab laboratory monitor, Model SU3-A, is placed in contact with the pliofilm covering of the specimen. The tissue is scanned for the area of most intense activity and the number of counts per minute is recorded. The

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subsequent exposure is then based on the decay curve for Au 198. Such a chart can be devised for any isotope, using almost any laboratory monitor. It should be noted that the counts per minute obtained with one isotope probably will not produce the same quality of autoradiogram or give the proper exposure with a different isotope.

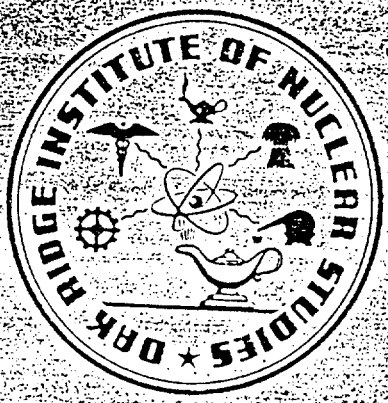
Counts/minute	Exposure time
20000	2 hours
15000	3 hours
10000	4 hours
7500	6 hours
5000	8 hours
2500	17 hours
200	21 hours
1000	47 hours
800	64 hours
600	102 hours
400	4 half lives
200	4 half lives
100	4 half lives

OAK RIDGE INSTITUTE of NUCLEAR STUDIES

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RARE-EARTH STUDIES

INTRODUCTION

Granvil C. Kyker

The studies of rare-earth elements have continued throughout the period of this report. Representative elements of the lanthanide group were used in animals. Yttrium-90, yttrium-91, lutecium-177, and holmium-166 in combination with natural isotopes of yttrium, lutecium, holmium, lanthanum, neodymium, and samarium were included. This selection was made in order to determine the distribution in laboratory animals of certain radionuclides of medical interest, to evaluate the effect of the size of the chemical dose, and to compare the biochemical properties of elements in this series. These aims were in part projected by the abstracts that appeared in a recent ORINS Quarterly Progress Report (pp. 14, 15, and 17, April 1 - June 30, 1954). The studies are at present in a transition that anticipates the study of certain biochemical reactions of these elements in order to interpret their distribution. The abstracts that follow summarize present status.

RADIOYTTRIUM-91 WITH NEODYMIUM CARRIER IN RATS

Granvil C. Kyker
Martha Stewart

A heterogeneous carrier, radioyttrium-91 with neodymium carrier, is similar in purpose and design to other combinations that have been under study. The prominent effect of the chemical dose of yttrium on the distribution of intracavitary radioyttrium-90 was reported in March 1954 to the American Chemical Society (ORINS Quarterly Progress Report, April 1 - June 30, 1954, p. 15). Concurrent studies suggested a similar behavior as a function of the dose of other rare-earth elements. The practical application of using one rare-earth element as carrier became of obvious importance, as some lanthanide radionuclides of medical interest are now quite rare and expensive. The extent to

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which the animal fractionates or handles differently two or more rare elements in a mixed dose was of theoretical interest, also.

Yttrium-91 was used because of the convenience of its longer half life. The preparation was free of carrier yttrium. Neodymium was chosen as a carrier to represent the lighter lanthanide elements. Young adult white rats were used. In each experiment, the intraperitoneal dose was of similar volume, pH, ionic concentration, and radioactivity. The tracer dose of radioyttrium-91 was approximately 25 microcuries per 200 grams of rat. The level of carrier in each of four series differed as follows: 0.0, 0.1, 1.0, and 10.0 mg of neodymium as the chloride per milliliter. Each series contained four groups of four rats in which the excretion and intra- and extracavitary retention was studied at 1, 5, 10, and 20 days, respectively.

The effect of neodymium carrier was observed to be practically identical with the previously reported effect of yttrium carrier. That is, without carrier, mobilization of the dose was immediately quite rapid and then slow; at the different intervals, from only a third to a fourth of the dose remained inside the injected cavity. At the 1.0-mg level of neodymium, 90 to 95 per cent of the radioyttrium was localized in the injected cavity, even at the longest intervals in the series. As compared with the 1.0-mg level, the retention with 0.1 mg was considerably less and with 10.0 mg, slightly greater. Excretion and extracavitary retention paralleled intracavitary retention.

INTERSTITIAL YTTRIUM IN THE PROSTATE AND THE PARAMETRIUM

Granvil C. Kyker
Julio Torriello, M.D.*
Ralph M. Kinsely, M.D.

(An abstract submitted to Federation Proceedings, Volume 14, 1955, and to be presented before the American Society of Biological Chemists, San Francisco, April 1955)

The Medical Division has previously emphasized the availability

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and potential usefulness for internal radiation of several radionuclides of the rare earths and has reported on certain biochemical similarities among elements in this group. Their study with yttrium offers advantages since this element is readily available, has suitable radioisotopes, and conveniently delineates the metabolic pattern of the heavy lanthanides. Two milliliters of 0.01 molar yttrium chloride adjusted to pH 4.0 in isotonic sodium chloride and containing approximately 125 microcuries of radioyttrium-91 (half life, 57 days; beta, 1.54 Mev) per milliliter was injected in the prostates and the parametria of five male and five female dogs. Three of each sex were killed at three days and the remaining four animals at seven days. The mobilization of the dose was determined by radioassay of the tracer in ten tissues remote to the injected area and in approximately 30 samples from autoradiographically mapped retroperitoneal tissues. A similar lymphatic pattern near the site of injection was observed in each animal. Some nodes within 5 to 10 cm showed a concentration of yttrium approaching that in the primary site of injection and 1000 times that of immediately adjacent tissue. Microautoradiography of the representative specimens showed a diffuse but somewhat irregular distribution of yttrium in the parametrium. The pattern in iliac and para-aortic nodes was not uniform. Variations in the prostate appeared to indicate localization in injected lobules and interstitial tissues.

THE EFFECT OF ASCITES ON INTRAPERITONEAL RADIOYTTRIUM (WITH CARRIER) IN MICE

Granvil C. Kyker
Edgar A. Cress

The intracavitary studies of radioyttrium (with carrier) in rats partially failed to anticipate the behavior of somewhat similar preparations in the first clinical cases studied at the Medical Division. Whereas the total intraperitoneal retention was similar in normal rats to that observed in human patients with ascites, deposition on serosal surfaces was distinctly different. In the normal animals, practically all of the fraction retained by the cavity deposits on surfaces so that thorough rinsing with saline does not remove it. In contrast, the ascitic fluid of patients contained a fourth to a half of the large intracavitary fraction of the dose. It was therefore of interest to compare the effect of ascites on intraperitoneal yttrium in the same organism.

A solution of yttrium chloride containing 1 mg of yttrium per milliliter and yttrium-91 tracer, and adjusted to approximately pH

4, was injected intraperitoneally in 25 normal mice and in 60 mice with Ehrlich ascites tumor. The mice with tumor were divided into seven groups that were injected with yttrium at 0, 1, 2, 3, 4, 5, and 6 days after inoculation with the tumor. All animals were killed three days after receiving the yttrium. Distribution between the cavity and the rest of the body, distribution within the cavity, and the excretion, were measured.

Excretion was always small, ranging from 0.1 to 1.0 per cent of the total dose. Retention within the cavity was always high and, on the average, exceeded 95 per cent. The whole pattern of distribution in mice with tumor was similar to that observed in normal mice, and that previously observed in normal rats except for the ascitic fluid. The yttrium that appeared in the ascitic fluid varied from one-fourth to one-half and averaged approximately one-third of the intracavitary fraction of the dose. The volume of ascitic fluid, measured by isotopic dilution, varied also at different stages of tumor growth. The specific radioactivity of the fluid decreased rapidly at first and then quite slowly as the age of the tumor increased. Ways in which the yttrium is held by the ascitic fluid remain for further study.

TOXICITY STUDIES OF RARE EARTHS

Granvil C. Kyker
Edgar A. Cress

There are very few reports to be found on the toxicity of the rare-earth elements. The limited information available indicates much variation between different routes of administration and the particular compound used. These differences are probably related to the low solubility of the rare-earth hydroxides that are formed at the pH of tissue fluids and the very limited capacity of the body, which have been observed in other studies, to mobilize and transport these elements from the administered site. By parenteral routes it appears that the toxicity is relatively low and offers no problem in the use of lanthanide isotopes of medical interest. No explanation of the mechanism of the toxic action of the elements is available. The present study is preliminary and is continuing.

The survival of 80 rats and 40 mice has been observed following intraperitoneal doses of rare earth. A solution of the chloride containing 60 milligrams of the rare earth per milliliter adjusted to approximately pH 3.5 was used. The levels of dosage that have

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been included at present range from 25 to 300 mg/kg. For yttrium, the rate of mortality for a survival of 30 days is approximately 20, 80, 100, 100, and 100 per cent for 25, 50, 75, 150, and 300 mg/kg doses respectively. The LD_{50} was observed at 45, 8.5, and 5.5 hours for 75, 150, and 300 mg/kg respectively. A lower toxicity was found for lanthanum. The LD_{50} occurred at 4.5 days and at 18 hours and the LD_{100} at 18 days and 42 hours for doses at 150 and 300 mg/kg respectively.

Study of radiochemical toxicities as well as a continuation of the study of chemical toxicities is planned.

RADIOYTTRIUM-91 WITH A BODY POOL OF STABLE YTTRIUM

Robert A. Woodbury*
Granvil C. Kyker
Ernest A. Daigneault*

Other studies have regularly emphasized the importance of the chemical dose on the distribution of many of the radioisotopes of medical interest. Practically none of these isotopes represent elements that occur naturally in tissue. This study was undertaken to show what effect a previously induced body pool of stable isotopes of a foreign element might have on the pattern of a subsequent dose of a radioisotope of the element.

Sixty rats were divided into eight groups. The control group received only yttrium-91. Four groups received 1, 4, 10, and 22 injections (1.0 mg in 1.0 ml, twice weekly on the third and seventh days) prior to a final injection of yttrium-91. One group received, at similar intervals, four injections of a more concentrated yttrium solution (12.5 mg/ml) and one yttrium-91 injection. Remaining groups received yttrium-91 and yttrium carrier combined in the same solution. All injections were intravenous by the tail vein. The excreta and 16 tissues were surveyed by radioassay of specimens.

Although rigid conclusions require continued study with larger groups of animals, the results set up a number of problems. The uptake of yttrium-91 tended to decrease with an increased pool. The adrenals showed a prominent increase in uptake with an increased number of stable yttrium injections. The increase in adrenal uptake

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was more pronounced in one-day than in four-day animals. Micro-autoradiography indicated a diffuse uptake throughout the adrenal cortex. The circulating radioyttrium was significantly lower at one day for the groups that received the heaviest treatment with stable yttrium but not at four days. Toxicity of yttrium by the intravenous route required very slow injection of the more concentrated solution and some of the more heavily treated animals showed prominent hematuria.

RADIOLUTECIUM-177 WITH SAMARIUM CARRIER IN RATS

Granvil C. Kyker
Lewis Warren

The prominent effect of the size of the chemical dose and of other rare-earth carriers on the distribution of radiolutecium was first reported to the American Chemical Society in September 1954 (ORINS Quarterly Report, April 1 - June 30, 1954, p. 17). The series of animals that was studied with yttrium and with lanthanum carrier has been extended to include other dose levels to intervals of three weeks to cover at least three half-life periods of lutecium-177. In addition, samarium has also been studied as a heterogeneous carrier for this radioisotope. The three carriers with atomic numbers 57, 62, and 39 (yttrium, chemically quite similar to 67-69) represent in general the effect of heterogeneous carriers from the lanthanide series of elements for a radioisotope of the heavy lanthanide elements.

The experimental scheme was similar to that outlined in a separate abstract in this report on neodymium as a carrier for yttrium. Three series of rats were studied intraperitoneally at 1, 5, 10, and 20 days with three levels of samarium carrier that differed by a factor of 10. The concentrations of carrier were 0.1, 1.0, and 10.0 milligrams of samarium per milliliter of the dose, prepared as the chloride at approximately pH 4.0. The three series were compared with the highest specific activity lutecium preparations that were available. The four levels of dosage were of the order of 10^{-3}, 10^{-6}, 10^{-5}, and 10^{-4} moles per kilogram. Intracavitary retention was observed to be approximately 70, 90, 98, and 99 per cent of the dose after one day and approximately 50, 70, 90, and 98 per cent after 20 days. The retention as a function of dose and time is therefore quite similar to other examples of heterogeneous carriers that have been studied.

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INTERSTITIAL RADIOLUTECIUM-177 IN DOGS

Harold F. Berg, M.D.*
Granvil C. Kyker

A study of radiolutecium similar to that summarized separately for radioyttrium in the prostate and the parametrium is in progress. Two groups of dogs have received tracer levels of radiolutecium-177 and one group has received the radioisotope at a level comparable to estimated therapeutic doses. Each preparation contained carrier at a concentration selected on the basis of previous studies in small animals to provide efficient localization of the dose near the site of interstitial administration. Yttrium was used as carrier in one of the tracer level preparations and lutecium carrier was used in the other two preparations. In each case the concentration of carrier was approximately 10^{-2} molar. The study in its early stages affords a preliminary indication that the spread of an interstitial dose in the breast of a dog follows a lymphatic pattern and that immediately adjacent tissue contains no appreciable amount of the dose. The distribution within lymph nodes appears by microautoradiography to be rather diffuse and more favorable than that of radiogold colloid similarly administered.

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RADIOHOLMIUM-166 WITH OTHER RARE-EARTH CARRIERS IN MICE AND RATS

Granvil C. Kyker
John Rafter

Studies with holmium presently include 140 animals: 104 mice that were injected intraperitoneally and 36 rats that were injected intravenously. The two series of animals were each divided into

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groups that received holmium, holmium with yttrium carrier, and holmium with lanthanum carrier. The experimental scheme simulated that of the study of heterogeneous carriers with yttrium and with lutecium, which appear in other abstracts in this report. The intravenous series included the fourth group that received an injection of yttrium chloride prior to the administration; the study of this group is somewhat analogous to the study of the effect of a "body pool" of stable yttrium on the distribution of radioyttrium summarized separately.

The groups of mice receiving intraperitoneal holmium with or without additional heterogeneous carrier were subdivided further for study at 24, 48, and 72 hours after injection. The results were quite similar to those observed for yttrium and for lutecium. Abdominal retention was increased from 90 to 98 - 99 per cent by each carrier. Yttrium appeared slightly more effective than lanthanum at similar levels based on weight, but no differences appeared on a molar basis. Each carrier was studied at a concentration of 1.25, 2.5, and 5.0 mg/ml and the doses were equal in volume. Most of the increase in cavitary retention was accomplished by the lowest of the three levels of carrier. One apparent difference may be the 90-percent retention of holmium, which was higher than the retention of yttrium or of lutecium by the same cavity. A comparison of the doses on a molar basis explains the difference. Yttrium-91 was available without carrier. Both lutecium-177 and holmium-166 were produced by nuclear reaction with neutrons and the radioactive preparations contained significant amounts of carrier. Holmium preparations had a much lower specific radioactivity than those of lutecium because of a smaller cross section of the starting material and a more rapid decay of holmium-166.

The groups of rats receiving intravenous doses were subdivided into groups that were studied 15 minutes and 1, 4, 24, 48, and 72 hours after the injection. The limited number of animals restricts conclusion, but the results suggest a distinct difference for each carrier. The fraction of the dose deposited in the liver illustrates the difference. With approximately 10^{-5} moles of holmium per kilogram of body weight composing the dose, the removal from blood was rapid and two-thirds of the dose deposited in the liver during 15 minutes and roughly 80 per cent during an hour. When the total dose of rare earth was increased approximately five times, by adding yttrium or lanthanum, it was removed during the first four hours at about one-half the previous rate. Some difference appears for the two carriers: with lanthanum, deposition in liver persists at a somewhat slower rate throughout the longest interval of 72 hours. Some reduction in the deposition of radioisotope in the liver is suggested when prior treatment of the animals with an intravenous dose of stable yttrium is followed three days later by holmium-166.

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PRELIMINARY STUDIES OF CERTAIN LANTHANIDE ELEMENTS

Granvil C. Kyker
Martha Stewart

Samples of readily available commercial grades of the oxides of yttrium, praseodymium, and neodymium sealed in evacuated quartz ampoules were activated in the Oak Ridge National Laboratory nuclear reactor. The purpose of the work includes the study of yield and purity of the radioisotopes produced and the application of procedures that are used routinely for holmium oxide and lutecium oxide. (Pertinent physical data appear in Table I, below.) Considerable medical interest in yttrium-90 has recently developed. Isotopes of praseodymium and neodymium present properties of interest and provide convenient examples of the lighter lanthanide elements for comparison with the heavy lanthanides.

TABLE I

Radioisotope	Abundance of Parent Isotope, Per Cent	Activation Index	Half Life	Energy of Emissions	
				Beta	Gamma
39 Yttrium-90	100	140	65 hours	2.26	---
59 Praseodymium-142	100	1100	19.3 hours	2.21 - 2.14	0.13 - 1.74
60 Neodymium-147	17.2	172	11.6 days	0.4 - 0.8	0.09 - 0.53
60 Neodymium-149	5.7	17	1.8 hours	1.4	0.5
60 Neodymium-151	5.6	11	12 minutes	1.9	1.14

The activated oxide was converted to the chloride with hydrochloric acid. A routine procedure was used for each oxide and the yield of recovered radioactivity was measured. The procedure consisted

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of warming gently with a heat lamp 1.5 ml of 3 M hydrochloric acid with the oxide to a temperature near the boiling point and maintaining this temperature for 5 minutes. The solution was transferred to a 5-ml volumetric flask. The treatment was repeated twice. The rare-earth chloride in about 4.5 ml of solution was diluted to 5.0 ml and labeled as Extract I. Extract II was prepared by the same steps. Extract III was made in a similar manner except that 3 M nitric acid in twice as large portions and finally diluted to 10 ml was used. The procedure has been used on the samples of oxides of rare-earth elements ranging from less than 1 mg to more than 50 mg with similar results. The results in Table II, below, summarize the yields calculated on the assumption that the three extracts approach 100-per-cent recovery.

The decay curves for praseodymium-142 and for neodymium-147 were observed to be in excellent agreement with published half-life values. The curve for yttrium-90 indicated a significant amount of longer-lived material. The impurity was not identified. Quite different thermal-neutron cross-sectional values have been reported. The specific activity of neodymium-151 was much lower than that indicated by the activation index, which is the product of the cross section and the relative abundance of the parent isotope.

TABLE II

Radioisotope	Activation Data			Per Cent Recovered in Processing			Specific Activity Mc per Mg of Element
	Compound	Labeled Purity Per Cent	Time in Reactor	Ext. I (HCl)	Ext. II (HCl)	Ext. III (HNO_3)	
Yttrium-90	Y_2O_3	99.8	3 weeks	99.06	0.15	0.79	0.114
Praseodymium-142	Pr_2O_3	99.8	1 week	98.71	1.26	0.03	0.541
Neodymium-147	Nd_2O_3	99.9	4 weeks	99.85	0.12	0.03	0.023

The pH at which solutions of the three isotopes showed instability was studied. Suitable aliquots were added to a series of buffers. Sedimentation by gravity during four hours and centrifugation at about 2000 rpm for five minutes gave similar results. The pH at which precipitation occurred was observed to be similar for the three isotopes, to appear sharply with increasing pH, and to be practically complete at pH 6.2 to 6.6.

The chelation of the three isotopes was studied in systems containing increasing amounts of Versene from which the excess rare

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earth was removed by precipitating with alkali and centrifuging. The molar ratio of Versene to rare earth that was required to give complete complexing increased with decreasing concentration of rare earth. Two moles of Versene per mole of yttrium was required when the system contained 0.27 mg of yttrium and 16 moles of Versene, when a similar volume contained only one-twelfth as much yttrium. Intervening values confirmed this effect of concentration.

Gamma-counting of standardized solutions by means of a well scintillator showed a higher efficiency than beta-counting with praseodymium and neodymium.

A SURVEY OF THE ALKALI METALS IN VARIOUS TISSUES OF THE RAT

Malcolm P. Tyor, M.D.*
Granvil C. Kyker
James Eldridge
Edgar A. Cress
Lea Keller

Previous studies indicate that it may be practicable to replace potassium-42 with rubidium-86 in clinical tracer studies of potassium metabolism in man (ORINS Quarterly Progress Report, April 1 - June 30, 1954, p. 16). Further comparison of the alkali elements was carried out in animals.

One series of rats received intravenous injections of potassium-42 and rubidium-86. Similarly, another series received potassium-42 and cesium-134. Each series contained 18 rats subdivided into three groups of six animals. The groups were killed at 15 minutes, 1 hour, and 17 hours after injection. Twenty specimens were taken from each animal to survey widely the comparative behavior of the different tracers. The specimens included: plasma, red cells, bladder urine, skeletal muscle, pelt, femur, jejunum, large intestine, adrenals, pancreas, kidney, spleen, liver, lung, heart, mediastinum, eyes, brain, urine, and feces. The specimens were assayed for both of the isotopes by counting in a well scintillation counter. The radioactivity attributable to each isotope was determined separately by measurements before and after the decay of the short-lived potassium. The precision attainable for potassium-42 was less than that for the other tracers since its measurement was by difference. Also, the very convenient procedures

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that were chosen for a preliminary survey of the whole body were less accurate for potassium in specimens of unequal weight. Whereas the beta emissions of rubidium-86 and cesium-134 are not sufficiently energetic to vitiate appreciably the activity detected by the gamma-counting system, this does not apply completely for potassium-42.

A tentative summary of the results includes the very rapid movement and the similar behavior for the three elements that were observed. Even at five minutes the pattern of concentrations in various tissues resembled closely that which was seen at the 17-hour interval. Specimens from the excretory systems showed higher concentrations, and the brain lower concentrations, than skeletal muscle and most other tissues. The differences were largest at first and decreased, but persisted, as the tracers approached equilibrium with the stable potassium of the body. The data raise important questions on which quantitative interpretation is presently limited. Further study is scheduled to continue during the summer of 1955.

A METHOD FOR DETERMINATION OF THE pH OF RADIOCHEMICAL PREPARATIONS

Granvil C. Kyker
Martha Stewart

A method for determination of the pH of radiochemical preparations undertaken by the Medical Division is acessory to biological studies of rare-earth radioisotopes. Solutions of inorganic salts of these elements require a slight excess of acid to prevent their hydrolysis to insoluble hydroxides. Therefore, preparations for internal use require careful adjustment of pH to maintain stable solutions and to avoid unnecessary administration of acid. Test papers and other visual methods lack accuracy. The widely used glass electrode endangers cross contamination of radioactive preparations. This method has many of the advantages of spectrophotometric methods and also independence of the concentration of indicator over considerable range.

One drop of the appropriate indicator solution is added per 2 ml of the solution to be measured. The optical density is then measured spectrophotometrically at each of the two wave-length settings that correspond to the absorption maxima of the acidic color and of the basic color of the indicator. The ratio of the two optical densities is a function of pH. A Beckman model-B spectrophotometer was used, but previous experience with the method has shown various photoelectric colorimeters to be adequate. Sulfonphthalein indicators were chosen for their stability and prepared by accepted procedures for

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colorimetric methods. The treatment of the measurements as a ratio compensates for differences in concentration of indicator. The use of 3, 5, and 8 drops of an indicator reagent per 10 ml of solution gave results that agree closely. Six indicators were used to cover the range from pH 2.0 to pH 9.0 The pertinent data are tabulated. (See Table III, page 14.)

The empirical calibration consisted of ratios of optical densities at intervals of 0.2 unit of pH. Intermediate values were interpolated linearly. Both prepared buffers (Clark and Lubs series) and commercial buffer tablets (Coleman) were used for duplicate measurements. The calibration was checked at close intervals in the titration of acetic acid and of chloracetic acid against sodium hydroxide. The pH of the buffer mixtures at various stages of the titrations were calculated by the Henderson-Hasselbalch equation. Agreement between observed and calculated values was usually within 0.05 units of pH.

LOW-LEVEL COUNTING FACILITIES

C. L. Comar

Techniques and facilities are being developed for relatively low-level beta and gamma counting. The initial objectives are concerned with: (a) metabolism of strontium-89 and calcium-45 in patients, with emphasis on relation between excretory pattern, renal function, and body burden; (b) possible effects of background levels of fission products upon medical diagnostic tests; (c) metabolism of ruthenium in patients; and (d) development of special sources and techniques for routine clinical use of radiosodium and radiopotassium.

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STUDY OF THE CIRCULATORY SYSTEM OF BONE MARROW

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Several approaches have been used in studying the circulatory

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TABLE III

Indicator	Thymol Blue	Bromphenol Blue	Bromcresol Green	Bromcresol Purple	Bromthymol Blue	Meta cre Purple
Color and accepted range, pH	(R) 1.2 - (Y) (2.8-8.0) - (B) 9.0	(Y) 3.0 - (B) 4.6	(Y) 3.8 - (B) 5.4	(Y) 5.2 - (P) 6.8	(Y) 6.0 - (B) 7.6	(Y) 7.4 - (P) 9.0
Absorption maxima, wave length:						
- acidic color	425, 540**	435*	445*	430*	435*	430*
- intermediate color	435*					
- basic color	590	590**	610**	560**	615**	575**
Calibrated range:						
- pH	2.8 - 8.0	2.8 - 4.6	3.8 - 5.4	5.2 - 6.8	6.0 - 7.6	7.4 - 9.0
- optical density ratio	1.3 - 5.1	6.5 - 0.1	5.4 - 0.2	6.1 - 0.2	4.2 - 9.2	3.5 - 1.6

(R) - red; (Y) - yellow; (B) - blue; (P) - purple.

*Setting for optical density used in numerator of ratio.

**Setting for optical density used in denominator of ratio.

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system of the bone marrow: (a) casts of the circulatory system of the marrow have been made by injecting a plastic material, latex, and an alloy, Cerrolow-117; (b) X rays have been taken of rabbit bone injected with various substances including mixtures of latex and radiopaque material; (c) microautoradiographic studies have been done using potassium-32, chromium-51, iron-59, as red-cell labels, and iodinated serum albumin iodine-131 as a plasma label; (d) the fresh bone marrow has been observed under the microscope; (e) serial histologic sections of the bone marrow have been prepared after injections of Helly's solution and India ink; (f) microradiograms have been prepared after injection of barium sulfate with particle sizes from the angstrom level to one micron, by means of a low-voltage X-ray unit.

With these approaches, especially the microautoradiographic technique and the India-ink injection, the anatomical structure of the sinusoids of the bone marrow has been studied.

The technique of making stereoscopic microradiograms is already being developed, and by this method a study will be made of the three-dimensional structure of the circulatory system of the bone marrow of normal, leukemic, anemic, and irradiated animals.

CELLULAR IMMUNITY IN AVIAN COCCIDIOSIS

P. P. Levine*

Experiments with radiophosphorus administered to fowls and designed to "tag" coccidial oocysts were unsuccessful, despite the high activity of the intestinal epithelium in which the parasites developed. Suspending the coccidial oocysts in radiophosphorus at room temperature caused adsorption of radioactivity onto the oocyst wall. The activity could not be washed off. This was not the result of metabolic activity, since heat-killed oocysts also adsorbed radioactivity. Autoradiograms of these dead oocysts confirmed these findings.

Phosphorus-32 was metabolized by Escherichia coli B when the organisms were grown in the broth with the phosphorus. Heat- or formalin-killed E. coli that had been grown in normal broth also picked up activity when the dead organisms were suspended in broth containing potassium-32. This activity could not be washed off. However, the dead organisms picked up only one-tenth as much

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activity as was found in the live organisms.

Experiments with sulphur-35 administered to fowls failed to "tag" coccidial oocysts parasitizing these birds. Oocysts suspended in sulphur-35 did not pick up any activity. Oocysts suspended in iodine-131 also failed to pick up any activity.

Experiments to demonstrate the passive transfer of humoral antibodies are in progress, and attempts are being made to demonstrate localization of immunity in different parts of the intestinal tract parasitized by different stages of the same species.

STUDY OF ANTITUMOR COMPOUNDS

Carl Tabb Bahner*

A series of dyes synthesized at Carson-Newman College has been selected for investigation because of the discovery, at the Wistar Institute, that some of them cause regression of a particular type of tumor in rats. Colorimetric analyses showed that 13 to 74 per cent of the dye administered to rats and mice in ground food was excreted in the feces, but that nearly all the rest was converted quickly into other substances. A preliminary study of the effects of variations of the structure of the dye molecules has led to finding a compound capable of causing large tumors of this type to regress almost completely within three days. This compound is so potent that, even at a dose level of 1 part in 10,000 of rat food, it caused the tumors to disappear within seven or eight days. Only one variety of rat tumor is known to respond in this way to the treatment, and there is no evidence that human tumors will do so. However, it seems that further investigation of the action of these substances with the aid of tagged compounds may bring to light information that will be of value in tumor chemotherapy.

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A STUDY OF YTTRIUM-90 CHLORIDE AND YTTRIUM-91 CHLORIDE IN THE POSTERIOR MEDIASTINUM OF DOGS

Dabney M. Ewin, M.D.*
Betty M. Cooper, M.D.

Doses of yttrium-91 chloride varying from 200 to 400 microcuries with 1 mg/ml stable yttrium chloride carrier were injected into the posterior mediastina of five dogs. The dogs were autopsied at intervals of 3 to 30 days and specimens for assay were taken of muscle, liver, kidney, plasma, red cells, adrenal gland, brain, pericardium, lungs, heart, bone marrow, spleen, and mediastinal lymph nodes. Assay showed that an average of about 2 per cent of the activity was in the liver, 0.1 per cent was in the spleen, and the rest of the recovered activity was in the mediastinum and regional lymph nodes.

Three different methods of introducing the isotope into the mediastinum were studied. The mediastinum was approached through a right thoracotomy incision and a plane was developed between the superior vena cava and the trachea. In three dogs, Gelfoam pledgets soaked with yttrium-90 chloride solution were implanted in the space between the vena cava and the trachea. In two dogs, yttrium-90 solution was injected through polyethylene tubes placed in the mediastinum at surgery and brought out through the anterior chest wall. In two dogs, the yttrium chloride was painted in the mediastinum with a water-color brush. All dogs were autopsied on the third day and each mediastinum was removed in block, frozen, and cross-sectioned at 0.5-cm levels for autoradiographic distribution studies. By each of these methods the activity was found confined to the area in which it was placed.

Experiments were done to study the effect of injection of relatively large doses of yttrium-90 chloride. A solution containing 7 mc yttrium-90 per ml and 8 mg stable yttrium per ml was used. In three dogs, 1 ml of solution was injected into the pericardial sac and 0.5 or 1 ml was injected into the paratracheal tissue and the perivascular sheath of the superior vena cava. The dogs were autopsied on the

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*Resident in Surgery, Ochsner Clinic, New Orleans; University of Alabama.

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twelfth day and all had developed rather severe inflammatory changes localized to the site of injection. All urine and feces were collected and assayed for the full 12 days, and a total of less than 1 per cent of the injected dose was recovered.

A STUDY OF YTTRIUM-90 CHLORIDE AND YTTRIUM-91 CHLORIDE INJECTED INTO RAT TUMORS

Dabney M. Ewin, M.D.*

Wistar rats with a two-week-old subcutaneous Walker S-256 carcinosarcoma were used for this study. In 16 rats, injections of 0.25 ml and 0.5 ml of a solution containing 30 microcuries yttrium-91 chloride and 1 mg of stable yttrium carrier per ml were made into the center of the tumor. Three days later the rats were killed, and the tumors were frozen and cut in half. Autoradiograms showed that the yttrium distributed fairly evenly over an area about 2 cm in diameter.

Four rats with two-week-old tumors (averaging about 3 cm in diameter) were then injected with 0.5 ml of solution containing 3.5 millicuries yttrium-90 chloride and 4 mg stable yttrium carrier. Twelve control rats died between the 25th and 34th days. The average date of death was 29 days after injection. The injected tumors regressed in size to about $1\frac{1}{2}$ cm diameter and have shown no subsequent growth. The treated rats were still alive at 60 days and in apparent good health. A biopsy of one of these tumors at 60 days showed complete central necrosis with spotty areas on the periphery where cancer cells were still present three or four cells deep. These cells showed some evidence of injury; they have been transplanted to other rats in an effort to determine their viability. The study is still incomplete.

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*Resident in Surgery, Ochsner Clinic, New Orleans; University of Alabama.

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TWENTY-CHANNEL PULSE-HEIGHT ANALYZER

Jack Trombka
Marshall Brucer, M.D.

A 20-channel pulse-height analyzer following the Oak Ridge National Laboratory design and manufactured by the Atomic Instruments Company has been put into operation. There has been considerable difficulty with the breakdown of registers, but with the cooperation of the manufacturer these difficulties are being corrected. A new set of registers of a different make and design has been installed. A series of sodium iodide crystals and photomultiplier tubes has been tested to find a matched set that will give the best resolution. An iodine spectrum run with the completed setup is shown in Figure 1, page 20. A large part of the program is currently directed toward the mock-iodine program. As soon as this is completed, the 20-channel analyzer will be put on the problem of spectrometry of the cobalt beam in water phantoms.

BRACHYTHERAPY DEVICES

Marshall Brucer, M.D.
Henry P. Copeland

In the hearings before the Subcommittee on Research and Development of the United States Joint Committee on Atomic Energy, on June 2, 3, 4, 1954, a detailed statement of the program of the Medical Division was presented. Copies of these hearings, entitled "The Contribution of Atomic Energy to Medicine," are available from the United States Government Printing Office. This document describes the preparation of a number of experimental brachytherapy devices for application to specific types of cancer therapy.

A small number of these devices have been completed, have been irradiated and measured, and are ready for distribution to

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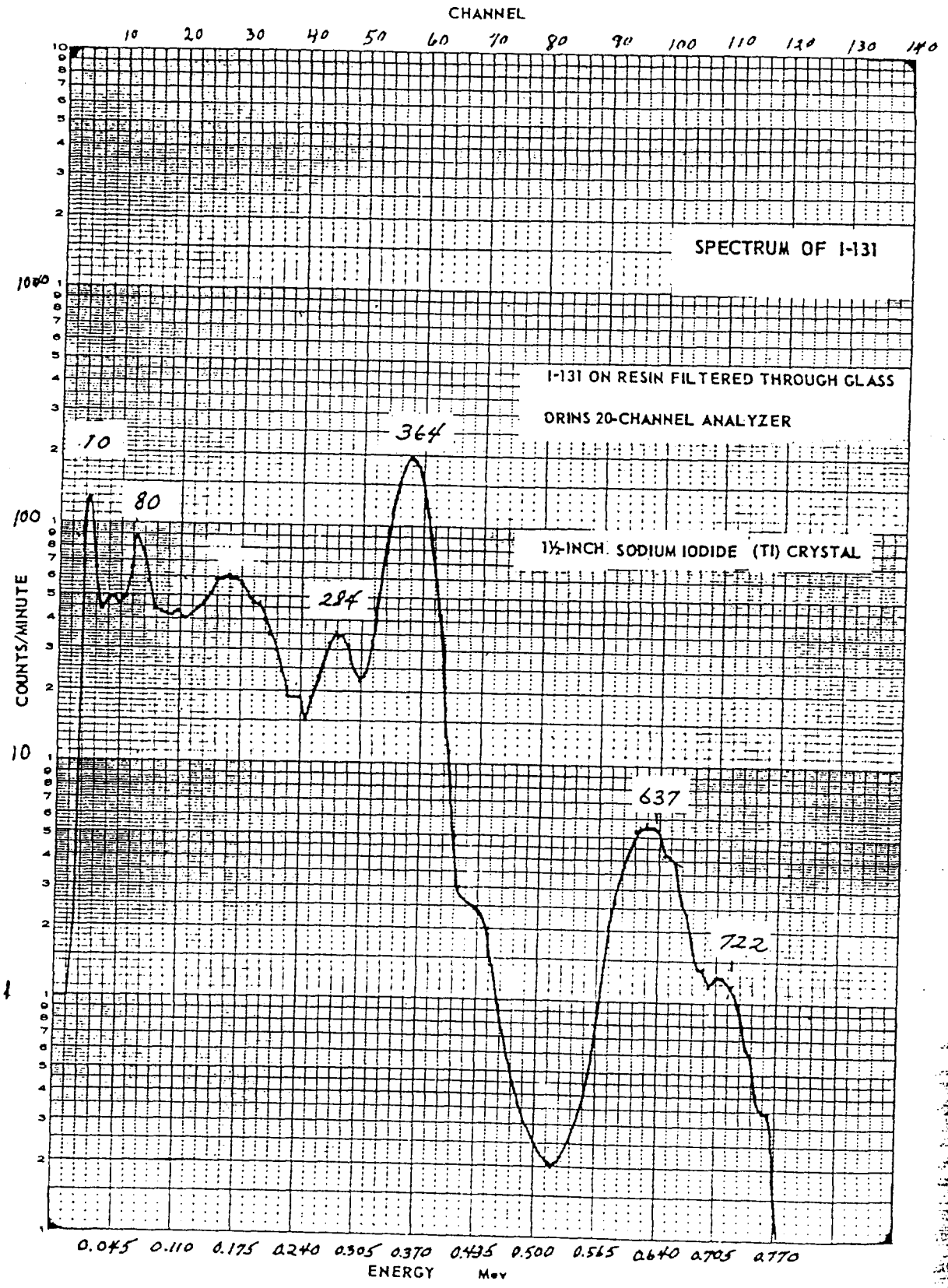

CHANNEL
10 20 30 40 50 60 70 80 90 100 110 120 130 140
SPECTRUM OF I-131
I-131 ON RESIN FILTERED THROUGH GLASS
ORINS 20-CHANNEL ANALYZER
1½-INCH SODIUM IODIDE (TI) CRYSTAL
364
284
637
722
80
10
COUNTS/MINUTE
1000
100
10
1
0.045 0.110 0.175 0.240 0.305 0.370 0.435 0.500 0.565 0.640 0.705 0.770
ENERGY Mev

Figure 1

Medical Division consultants. There are two primary problems in these brachytherapy devices: One is to use a cobalt alloy that is corrosion-resistant to ordinary body fluids; the other is to minimize the primary and secondary electron scatter from the surface of the device. With the cooperation of the International Nickel Company, a number of highly corrosion-resistant metals have been prepared; tests indicate that with small cobalt devices the problem of corrosion resistance is not serious, provided the correct alloys are used. It appears that any alloy containing a high proportion of cobalt alloyed to any except the precious metals is sensitive to ordinary body fluids and will lose a high proportion of radioactive cobalt from the alloy. It appears that with low concentrations of cobalt in the alloy, a number of nickel, cobalt, and chromium alloys can be used with a high degree of corrosion resistance. On a number of tests performed in the subcutaneous tissues of the rat, exposure of the corrosion-resistant metal to corrosion of the tissue juices resulted in less than 1 part in 1,000,000 of the activity being lost to the body of the animal from the source.

The problem of the electron contamination of the beam close to the surface of the source is more difficult to measure. By means of a very small anthracene crystal insensitive to gamma rays, a comparison was made of the electron activity near the surface of the devices as compared to a standard radium needle. It appears evident that, when measured in this way, the field of electrons around a cobalt-alloy needle is of the same order of magnitude as that around a standard radium needle. However, the method of measurement is open to question and other methods will have to be found. From the preliminary results available, it seems that in the brachytherapy devices thicker than a few millimeters the secondary-electron problem is insignificant. In the very small devices, however, secondary electrons may pose a serious problem.

THE CESIUM MOVING-FIELD TELETHERAPY MACHINE

Marshall Brucer, M.D.
Howard Harmon

The cesium moving-field teletherapy machine was demonstrated to a number of subcommittees of the Teletherapy Evaluation Board in July 1954. The mechanical construction was completed, but considerable difficulty was experienced in the controlling mechanism. The W. F. and John Barnes Company redesigned and reconstructed the control circuits and by October the entire mechanism was operating in Rockford according to specifications.

During the last three months of 1954 the teletherapy room was redesigned and reconstructed to hold the cesium teletherapy machine. This consisted primarily in adding supports to the ceiling so that the heavy machine could be moved with complete freedom and without changing the focal point of the beam. By the end of the year the mechanism was shipped to Oak Ridge and installation of the machinery into the teletherapy room was started.

One of the first problems in the use of the cesium moving-field teletherapy machine will be the design of cams to control the automatic computer mechanism. Since the cam design will be quite complex for anything other than very simple rotational motions, a cam design computer has been constructed. This computing mechanism has been completed and was in operation by the end of the year.

CHEMICAL DOSIMETRY AND INTEGRAL DOSE

Raymond L. Hayes
Edward Arakawa

Work is continuing on the development of a chemical dosimetry technique for measuring integral radiation dosages resulting from nonuniform distribution of internal radiation sources in phantoms. The insensitivity of chemical dosimetry measurements in such systems constitutes the main problem at the present time. With external sources, however, no such problem exists; by means of chemical-dosimetry techniques a simplified phantom study of integral dosages from external radiation sources has been initiated. Studies are being made of the integral dose relationships as a function of the primary photon energy employed, the distance of the phantom from the source, the size of the phantom volume under "treatment," and the size of the "total-body" phantom. Various rotational patterns as well as stationary positionings are being investigated. Figure 1 (page 23) shows the type of apparatus that has been used in an initial study of integral dosage relationships resulting from cobalt-60 teletherapy with the prototype hectocurie machine.* Figure 2 (page 24) shows a portion of the results of this study. In addition to teletherapy dosage studies with cobalt-60, similar studies of cesium-137 will be initiated with the moving-field cesium teletherapy

*This is the cobalt machine designed by the ORINS Teletherapy Evaluation Board and built by the W. F. and John Barnes Company of Rockford, Illinois.

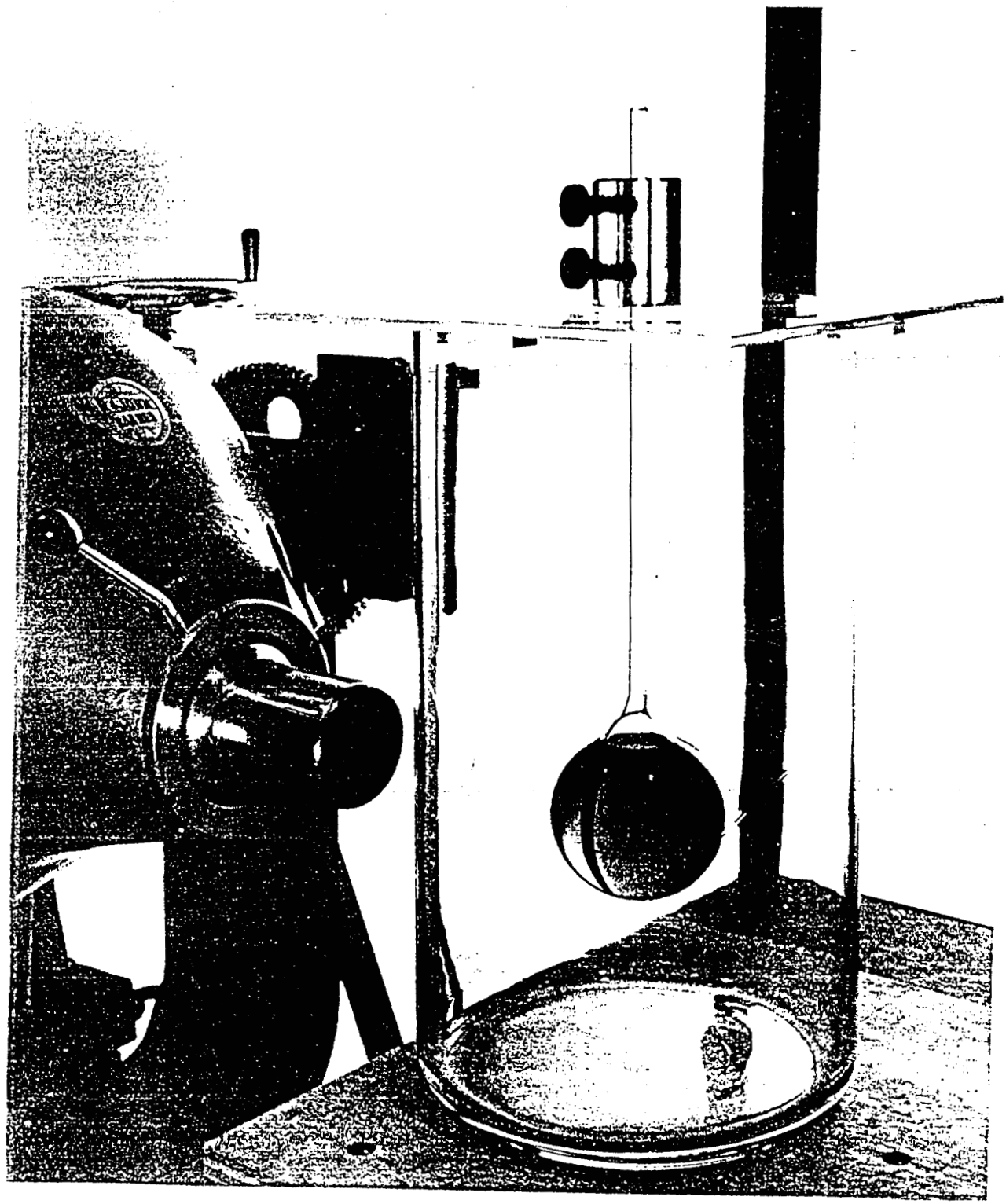


Figure 1

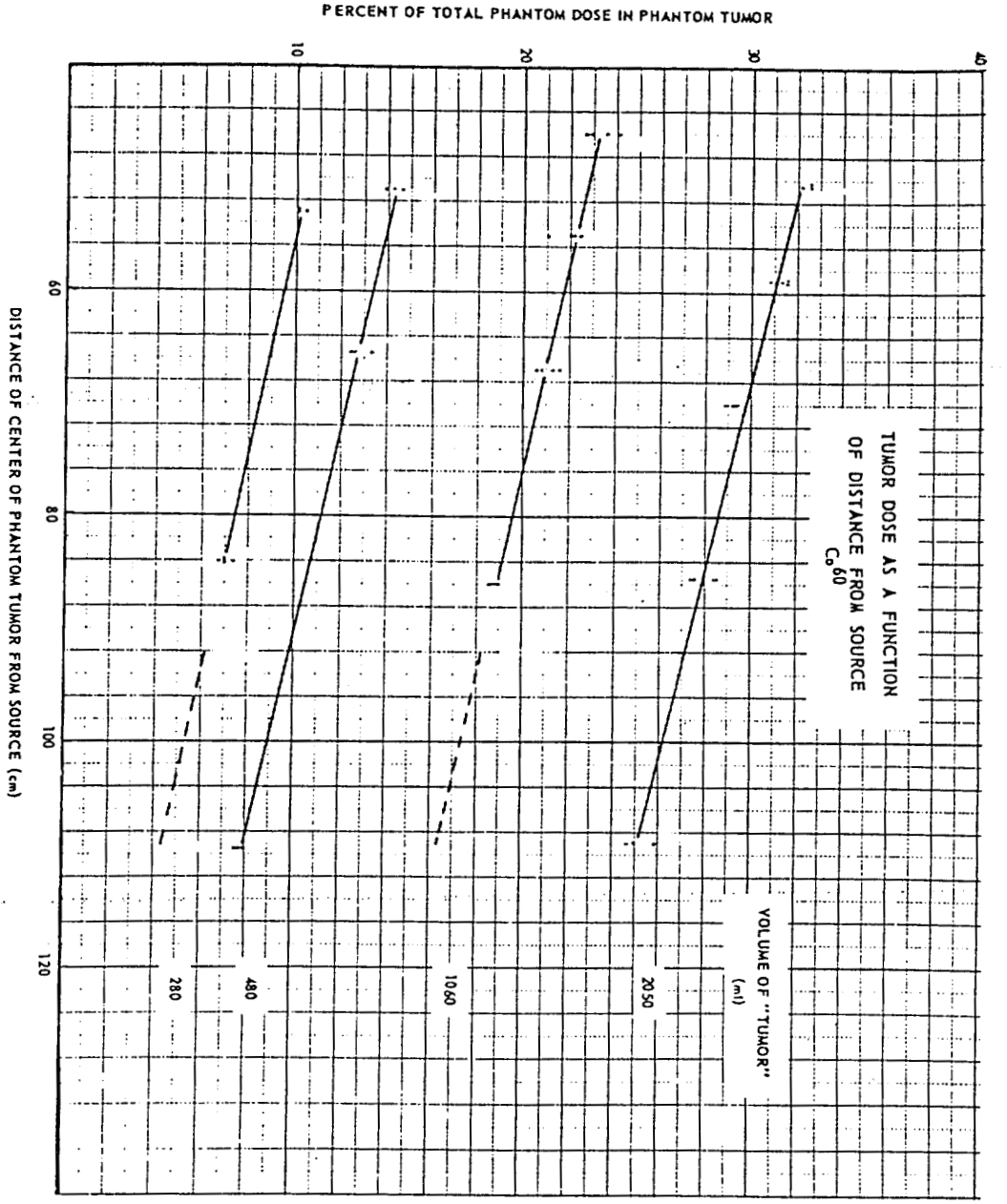


Figure 2

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machine which is now being installed.*/ A study with 250-kvp X rays is also planned.

A summary of current results was given at the Los Angeles meeting of the Radiological Society of North America in December 1954 and was published in the January 1955 issue of Radiology.

THYROID-UPTAKE CALIBRATION COMMITTEE

Marshall Brucer, M.D.
James Eldridge

For a number of years it has been realized that iodine-uptake measurements, as performed by many different techniques over the country, are highly variable. Interest in attempting to unify methods of measuring thyroid uptake has been widespread.

The Medical Division has designed a phantom that represents the head and torso of a patient — a mannequin with a suitable thyroid and with suitable body background iodine activity. A simulated radioiodine has been developed out of a mixture of barium-133 and cesium-137. This matches the spectrum of radioiodine remarkably well and has a useful life of about five to ten years. To assist in a program designed to measure the degree of variation of uptake measurements over the country, a Thyroid-Uptake Calibration Committee was formed consisting of the following persons: Dr. Benedict Cassen, University of California at Los Angeles; Dr. Raymond L. Libby, Los Angeles Veterans Administration Hospital; Dr. A. Stone Freedberg, Harvard Medical School; Dr. Robert T. Neiset, Tulane University; Dr. Edgar S. Gordon, University of Wisconsin; Dr. Samuel W. Root, Jacksonville, Florida; Dr. Herbert D. Kerman, University of Louisville Medical School; Dr. S. M. Seidlin, Montefiore Hospital, New York City; Dr. S. Allan Lough, Francis Delafield Hospital, New York City; Dr. T. H. Oddie, University of Arkansas; and representatives from the Isotopes Division of the Atomic Energy Commission and the Medical Division of the Oak Ridge Institute of Nuclear Studies.

The first meeting of this committee was held on October 1 and 2 at ORINS. A set of minutes of this meeting has been prepared. A preliminary report of preparation of a mock-iodine source has been

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*This is the cesium machine designed by the ORINS Teletherapy Evaluation Board and built by the W. F. and John Barnes Company of Rockford, Illinois.

mimeographed and will be published shortly.

After considerable discussion, the committee decided it would be of value to conduct a nationwide survey of the methods of measuring thyroid uptake. The purpose of this survey is to correct what are felt to be unnecessary errors in technique. If current methods turn out to be as unsatisfactory as expected, then the results of this survey should be published and a concerted attempt should be made on the part of some national organization to standardize methods. The survey is to be conducted in local areas under the sponsorship of area representatives who form the ORINS Thyroid-Uptake Calibration Committee.

The plan of the survey is to lend to a group of physicians a half-body mannequin complete with a thigh section and a series of total-dose, 100-per-cent standards. Assuming that the total-dose standard is given 24 hours previously, the physician, using his own routine methods, will be asked to measure the thyroid uptake. A "urine" sample is included if the physician cares to assay it. The physician will be asked to assay the curiage of the total-dose standards if he has the equipment necessary for such a measurement.

The mannequins have been made to resemble a human patient as closely as possible, to emphasize the point that the test is to be conducted as though it were being done on a human being and not as a special test in physics. There was considerable difficulty in deciding on total-dose standards. The standards currently used throughout the country are so different that all methods cannot be mimicked, but a good sampling of the most commonly used standards has been chosen and these will mimic actual devices as closely as possible.

Seven mannequins have been prepared for the first survey. Three will have approximately 10-microcurie total doses and three will have approximately 50-microcurie total doses. The committee felt that any physician who needed more than 50 microcuries for his total diagnostic dose is already proved to be using a faulty method. Within each dose range, a euthyroid, hyperthyroid, and a hypothyroid simulated patient will be prepared.

It is expected that the test mannequins will be sent to the area representatives early in 1955. Each of the area representatives will distribute the mannequins to ten or more physicians in his area. The mannequins will then be shipped to the next area. It is expected that in about one year the results of about 60 measurements each on six different mannequins should be available. This should allow for an estimate of the state of thyroid-uptake measurements. It is hoped that the preliminary survey will be completed before the third advanced course in the medical uses of isotopes early in 1956. An attempt will be made during this course to bring together many of the users of radioiodine to discuss the problems of standardization and calibration of methods.

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CLINICAL STUDIES

Gould A. Andrews, M.D.
Etna Little Palmer, M.D.
Arthur L. Kretchmar, M.D.

Further opportunities for studies on thyroid carcinoma have occurred and current studies emphasize the measurement of uptake in the tumor at various intervals after administration of radioiodine. The scintiscanner is being used to advantage in association with these external counting studies. Further detailed histologic studies and autoradiograms of functioning thyroid carcinoma have recently been obtained.

Miscellaneous types of thyroid disorder have been studied with radioiodine with emphasis on correlation of clinical and pathologic data. The value and limitations of the scintiscanner are being explored, especially in conjunction with autoradiographic studies on surgical specimens. These comparisons tend to bring out the relative crudeness of the information derived from the scintiscanner as compared with the detailed distribution information shown by gross autoradiography. A few hyperthyroid patients are being treated with iodine-131. Histologic data on the effects of such treatment on the thyroid gland are being obtained when possible, and special serial studies of blood iodine-131 levels are being made.

Special patients with malignant plasmocytoma have been studied with radioiodine, following the report of Kriss, et al. Instead of blocking the thyroid with stable iodine, as was done in the original work, the staff has attempted to ablate the function of the normal thyroid with iodine-131 and then to study the distribution of subsequent doses of iodine-131 by external counting and by assay of tissue obtained by biopsy or at autopsy.

The value of colloidal gold-198 for interstitial, intracavitary, and intravenous use has led to efforts to find still better isotopes with similar colloidal behavior. At the present time a preliminary study on the distribution of yttrium-90 injected into the body cavities has been almost completed. The isotope is administered as yttrium chloride with added carrier. It stays well localized in the region of the cavity of injection and, in fact, a considerable portion of it remains suspended in the fluid. Another isotope of similar chemical properties but different radiation characteristics

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is lutecium-177. Studies are being undertaken to evaluate the suitability of this isotope for intracavitary use and for interstitial injection. Colloidal gold-198 is still being used for more routine intracavitary therapy and its intravenous use in a small series of carefully studied patients with chronic leukemia is being continued.

A number of long-range programs not mentioned in this report are also in progress. Several of these depend upon the chance to study certain types of patients. Additional work is being done in these categories as opportunity arises.

A long-range trend in the clinical program is the increase in number of patients, many of them from nearby communities, who are seen as out-patients. The majority of these are followed for hematologic disorders. The opportunity to follow these patients increases the amount of interesting hematologic data obtainable, but, on the other hand, there has been an increasingly apparent deficiency in facilities for caring for these patients. It is expected that the out-patient facilities to be provided in the new wing of the Medical Division will be of great help in this problem.

PATHOLOGY AND AUTORADIOGRAPHY

Ralph M. Kniseley, M.D.

The experiment that has been of primary interest to the Pathology Section during the period covered by this report has been concerned with metabolic and histologic changes produced in the thyroid glands of dogs after large doses of X irradiation.* This work is 90 per cent complete with interpretation of some special stains of the sections of thyroids remaining to be done.

The services of the pathology and autoradiography section have also been made available to other visiting residents and research participants. Principally this has involved histologic and autoradiographic data in connection with experiments with yttrium-90 and

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*The study was done in conjunction with Paul St. Aubin, M.D., visiting resident from Massachusetts General Hospital, and Gould A. Andrews, M.D., Medical Division staff.

yttrium-91.* Interstitial yttrium was injected into the prostatic and the parametrial regions of dogs. Autoradiographic distribution of this material has been studied in the injection site and in the draining iliac and para-aortic lymph nodes. This work is also nearing completion. Gross and microscopic autoradiographic facilities have been provided for Dr. Dabney Ewin, visiting resident from the Ochsner Clinic, whose experiment has dealt with the effects and distribution of yttrium-91 injected into the mediastinum and peribronchial regions of dogs. Similarly, microscopic autoradiograms were prepared as an adjunct to the distribution study on the effect of carrier on intravenous yttrium injected into rats, work carried out by Dr. Robert A. Woodbury.

The work involving patients has centered on continued interest in gathering and interpretation of data relating to the effects of iodine-131 in patients with thyroid disease and the distribution of iodine-131 in patients with advanced multiple myeloma. Continued follow-up data have been accrued after gold-198 therapy. Also, a series of patients who received yttrium-90 has been studied pathologically following intravenous and intracavitary dosage of the isotope. Until now no headway has been made in interpretating and analyzing for publication the data on patients who have received yttrium.

PROCEEDINGS OF THE SECOND ADVANCED COURSE ON THE USE OF ISOTOPES IN MEDICINE

Elizabeth B. Anderson

The proceedings of the second advanced course in the use of isotopes in medicine (given in September 1953) is being published under the title "Radioisotopes in Medicine." The manuscript, edited by Dr. G. A. Andrews, Dr. M. Brucer, and E. B. Anderson, has been completed and turned over to Technical Information Services of the United States Atomic Energy Commission. The book will be printed by the United States Government Printing Office and sold through the Superintendent of Documents.

Forty-two speakers submitted manuscripts or edited the Stenotyped transcripts of their talks. All discussions were taken in Stenotype, and the edited transcripts were sent to the discussants for approval or further editing. The book also includes the material

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*One project was conducted in collaboration with Granvil C. Kyker, and Julio Toriello, M.D., visiting resident from Massachusetts General Hospital.

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presented at the three evening clinics, more than 480 illustrations, and an extensive bibliography on the use of isotopes in medicine.

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Dr. Glenn Davis

ORINS - 27

OAK RIDGE INSTITUTE of NUCLEAR STUDIES

Medical Division

Midyear Report

For The Period Ending December 31, 1958



Operating Under Contract AT-40-1-Gen-33
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UNITED STATES ATOMIC ENERGY COMMISSION

1033502

P. O. Box 117 Oak Ridge, Tennessee

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INTRODUCTION

Marshall Brucer

The year 1958 represents a transitional year in the Medical Division. This transition was not started in 1958, nor will it be completed in 1959. We are trying to keep this period of change as slow and orderly as possible, but it does represent a large number of changes from the early days of the Medical Division. For example, in the early days we were concerned mostly with the development of methods and equipment basic to the clinical study of radioisotopes in human beings. This period is now almost complete. Most of the basic equipment and methods are now clinically available in hundreds of hospitals. We are undergoing a transition of effort toward the improvement of this basic equipment to the point where it is truly clinical and not a problem in physics. The change, for example, from ordinary counting equipment to spectrometry marks a major change in emphasis. Spectrometry is not yet a standard clinical technique, but progress over the past five years has been sufficient that all experts in the field are now sure that all external gamma counting and calibration ultimately will be done with some instrument similar to a spectrometer. This is no longer a prediction; it is almost an accomplished fact.

Ten years ago we were very much concerned with the application of new radioisotopes to clinical problems. The gallium study of 1952 is an excellent example of a very necessary phase that had to be passed through. We no longer look at isotopes in the same light as we did in 1952. Now, everything has shifted to complex compounds of elements. It is no longer a prediction that this will occur; it is an accomplished fact. The Medical Division has had to change, and is changing, its investigative program from the field of inorganic to the field of organic chemistry.

Ten years ago we were concerned primarily with diagnostic and therapeutic results. These results that can be seen and applied immediately are now pretty well finished as research projects. Now we have to change back to the age-old problems of toxicity, metabolism, and biochemical methods of transport. Only a few years ago the relatively simple adaptation of a gamma-ray emitter to a practical teletherapy device was an important problem. This problem is not yet solved but it is so close to solution that teletherapy is now a part

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reporting. The only reason they are selected is that these were the specific items that received the most attention during the year. The fourth section is a brief report on the training program. The fifth section gives the 1958 publications.

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teletherapy unit early next year.

ORGAN RESPONSE TO INTRAVENOUS YTTRIUM

Ernest A. Daigneault* and Granvil C. Kyker

These experiments are concerned with the distribution and toxicity of yttrium by intravenous administration to rats. It is recognized that carrier-free yttrium-91 is a bone seeker. Preliminary evidence indicated that large doses of stable yttrium carrier (yttrium-89), administered simultaneously or independently, altered the usual distribution. (Woodbury, Kyker, and Daigneault: Semiannual Progress Report, Medical Division, ORINS, Dec. 31, 1954, p. 5.) These experiments were designed to establish what changes occur in yttrium-91 distribution after repeated pretreatment with stable yttrium. All doses (stable and radioactive) were administered intravenously (tail vein). The additional information on toxicity included both chronic and acute administration of stable yttrium.

The study used male Wistar rats. Tracer distribution (yttrium-91) was compared in three dose groups. The three groups were given 3.33 mg/kg of $Y^{89}Cl_3$, pH 4, twice a week for different periods (2, 5, or 11 weeks). A fourth group received 12.5 mg/kg twice weekly for two weeks; this group was also used to study intravenous toxicity. One day after the last dose of stable yttrium, approximately 50 microcuries of carrier-free yttrium-91 was administered intravenously. Animals were then killed with ether at 24 and 96 hours after the dose of radioyttrium. Tissue samples were taken for gross autoradiograms, microautoradiograms, pathologic examination, and a limited number of liver samples for lipide analysis. Yttrium-91 was counted in wet ashed samples.

Normally doses of carrier-free yttrium-91 are found predominantly in bone and urine, and approximately 15 per cent of the retained dose is in the liver. The pretreatment with four doses of 3.33 mg/kg of $Y^{89}Cl_3$ drastically reduced the quantities of yttrium-91 in the bone and elevated that in the spleen, liver, and adrenals. Ten and 22 doses similarly altered the distribution; a difference was a decrease in spleen activity. This was shown to be correlated with spleen pathology from these larger doses. In the group receiving the largest dose, approximately 65 per cent of the yttrium-91 was found to be in the liver. Pathologic sections and microautoradiograms are being studied to attain specific information concerning these specific changes.

A range of 12.5 to 60 mg/kg doses of $Y^{89}Cl_3$ was administered

trial appears favorable when compared with inorganic preparations of radioyttrium at the same elemental dose; further studies are planned for next year.

* By courtesy of Abbott Laboratories, Oak Ridge, Tennessee.

THE EXCRETION OF YTTRIUM AND CERIUM IN DOGS

Granvil C. Kyker and John J. Rafter

The renal and fecal excretion of rare earths varies with the time after the dose, the route of administration, and the quantity administered. Fecal excretion predominates at late stages and with large doses. Excretion at various levels throughout the gastrointestinal tract and tissue concentration in various organs were measured in groups of operated and intact dogs that received intravenous doses of yttrium or cerium. Biliary excretion, urinary excretion, blood level, and localization in liver and in spleen were also compared. The intravenous dose of element with radioisotopic tracer varied from 10^{-11} to 10^{-5} M/kg. Intestinal excretion occurred at all levels of the tract and decreased with increasing dose of the element; a similar effect of dose was more prominent on urinary excretion. Localization in liver and in spleen and the circulating fraction in blood increased with the dose. Biliary excretion was quite low in all groups and rarely exceeded 1 per cent of the rare earth in the intestinal contents.

(Abstract of a paper presented at Southeastern regional meeting of the Society for Experimental Biology and Medicine, Nov. 7-8, 1958, Bowman Gray School of Medicine, Winston-Salem, North Carolina.)

CHARACTERIZATION OF LIVER-LIPIDE RESPONSE TO INTRAVENOUS RARE EARTHS IN RATS

Fred Snyder, E. A. Cress, N. Stephens, and Granvil C. Kyker

Fatty infiltration of liver in female rats occurs as early as 24 hours after a single intravenous injection of cerium (3.5 mg/kg body weight) with a maximal elevation of total lipides occurring 48 hours after administration. Choline or methionine does not prevent the fat deposition. Kidney and muscle lipides are increased and decreased, respectively, in cerium-treated rats. Using silicic acid column chromatography, we determined that the elevated liver lipides are a result of an increased deposition of neutral fat. Fatty acid ester equivalents in the neutral fat fraction of the liver of cerium-treated

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In vitro studies:

Initial studies were conducted with a selected group of enzymes that were available commercially. These were alpha amylase, invertase, acid phosphatase, urease, and pepsin. Cerium tends to be precipitated from solution at pH values above 6. It is for this reason that only enzymes were studied whose pH optima are near or below pH 5.

After developing a satisfactory activity assay for a given enzyme, assays were carried out with cerium added at different final molar concentrations. Adequate activity controls and reagent controls were used.

Some inhibition of the activity of each of the enzymes by cerium was observed. The activities of acid phosphatase, invertase, and pepsin were inhibited by cerium concentrations as low as 10^{-4} molar, but amylase was inhibited by 10^{-6} molar cerium. Urease was not appreciably affected by concentrations of cerium below 10^{-2} molar.

The nature of the inhibition was investigated only incidentally and not generally. It appears that the inhibition observed is a rather nonspecific one.

In vivo studies:

Cerium was administered (by tail-vein injection at a level of 3.5 mg/kilo) to female rats of the Sprague-Dawley and CFN strains. Reference animals were injected simultaneously with normal saline. At 6-, 24-, and 48-hour intervals after injection, animals from each group were decapitated and estimation of enzymic activity was made.

Acid and alkaline phosphatase were determined in serum; liver slices were used in the manometric estimation of the hydrolysis of ethylacetoacetate, and of monopropionin (lipase activity); phosphatidic acid phosphatase was estimated in a 10 per cent homogenate of liver in 0.02 M Tris buffer.

There was little significant variation in the serum alkaline phosphatase of cerium- and saline-treated animals; however, serum acid phosphatase was significantly higher in the cerium-treated animals, by 28 per cent, 60 per cent, and 135 per cent at the 6-hour, 24-hour, and 48-hour assays, respectively. The lipase activity of the livers of test animals was not significantly altered from that of the controls; the rate of hydrolysis of ethyl acetoacetate by liver slices from cerium-treated animals was greater than that effected by slices from saline-treated animals by 50 per cent and 180 per cent at the 24-hour and 48-hour assays, respectively; phosphatidic acid phosphatase activity showed no significant variations between test and control animals.

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received high doses of total-body irradiation did show changes in total protein that were largely reflected by the albumin fraction. In general these changes consisted of a hyperproteinemia shown by the first specimen (fourth day) from each patient, followed by an irregular decrease during the next two weeks to a normal level (7.5 to 8.0 per cent). These normal levels persisted for about two weeks and then gradually rose to a hyperproteinemia level as high as, or higher than, that shown by each patient on the fourth day (9.0 to 9.5 per cent). The protein level returned to this peak value during the eighth week and again dropped gradually to a normal level during the next three weeks. No further changes appeared during the last three months of observation. The three patients that received a lower dose of radiation also showed total protein levels that resembled the other five patients during the first two weeks only; after a normal level was reached within two weeks or less, no further change was evident.

RESPONSE OF LINEAR SCANNER TO VARIOUS RADIOISOTOPES IN RATS

John J. Rafter and Granvil C. Kyker

The applicability of a linear scanner for small animals (previously described, ORINS-23, p. 23) to the study of internal radioactivity was surveyed in 60 rats with five radioisotopes that differ widely in metabolic behavior and in radiation characteristics. Each radioisotope was compared by the intravenous, the intraperitoneal, and the subcutaneous routes of administration. The isotopes included sodium-24, potassium-42, scandium-46, niobium-95, and cerium-144. An animal in each of the 15 groups was killed at 0, 1, and 2 hours after injection. In addition, scandium-46 and niobium-95 were given to larger groups and the experimental periods were extended to 48 hours or longer.

An automatic recorder plotted radioactivity as a function of its position in the animal. The chart and animal speeds were the same. According to a model of body segments from head to tail that were marked off on the abscissa of the chart, the localization and translocation of radioactivity as a function of time was studied by planimetric measurements of the areas under segmental parts of the curve.

The intravenous profiles for sodium-24 and potassium-42 were the same for all experimental periods; the intraperitoneal and subcutaneous patterns of these radioisotopes became similar to the intravenous pattern during the first hour. With scandium-46 and cerium-144 the somewhat similar patterns of early localization in the abdominal segment suggested reticulo-endothelial uptake in liver and

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follows:

A small part of the injected cerium-144 chloride localized mainly in the liver within 24 hours, but the larger proportion of the dose remained at the site of injection. Reaction of cerium-144 chloride with the disodium salt of ethylenediaminetetraacetic acid increased the size and mobilization speed of the mobile component; this reaction also resulted in rapid excretion of some of the dose, as could be noted by a rapid increase in localization in the bladder. Localization in the liver increased slowly, and at 24 hours the liver and the injection site contained approximately the same amount of radioactivity. Injection of cesium-134 chloride resulted in a comparatively rapid distribution from the site of injection. Initially, the major concentration of the mobile component was in the liver; after 24 hours, the distribution mirrored the body mass with only a very small component remaining at the injection site.

In preliminary attempts to obtain a measure of quantitation with the scanner, the radioisotope zinc-65 chloride was used. This was given by stomach tube combined with various agents, and then the amount of absorption was determined by use of recordings of both the rate-meter deflections and the integrator deflections. After 48 hours the animal was killed, and the amount absorbed, as estimated by the scan, was compared with the amount determined by dissection and counting on a scintillation well counter. This composite picture was then reconstructed in the phantom. The correlation was found to be semiquantitative in simple applications, but beset with too many variables in less simple systems (such as intravenous injections) to be of use at the present time.

* Visiting scientist; present address: Department of Pharmacology, Medical Branch, University of Texas, Galveston.

SILICIC ACID CHROMATOGRAPHY OF LIPIDES

Fred Snyder and Nelson Stephens

Silicic acid column chromatography was used to investigate the liver lipide response caused by cerium. Separation of the neutral fraction from the phosphatide fraction has been accomplished by the method of Borgstrom. The separated lipides were quantitated by ester, phosphorus, or cholesterol determinations. This method has clearly shown the fatty infiltration of liver caused by cerium to be a result of neutral fat accumulation. More detailed studies of specific lipides present in the accumulated liver fat of cerium-treated rats are in progress.

LABORATORY ANIMALS USED DURING 1958

Rats:

The effect of rare earths on total liver lipides. The effect of sex, strain, hormones, and various compounds on fatty livers.	320
Study of the distribution of iodine-131, cerium-144, scandium-46, zinc-65, and niobium-95 with the linear scanner for small animals.	130
The effect of various rare earths on respiration of rat-liver slices.	108
The effect of cerium on the choline oxidase activity of rat-liver homogenates.	90
Rats provided to the Special Training Division for use in the basic radioisotope course.	64
The effect of body pool of yttrium on yttrium-91 distribution.	60
The distribution of yttrium-90-gelatin-phosphate.	50
Pathological study of rat lungs.	42
Autoradiographic liver distribution of gold-198 (for isotope courses).	40
Effect of cerium on liver lipase, urease, and serum phosphatase.	32
Acute toxicity of yttrium after intravenous administration.	30
Yttrium-91 distribution in liver fractions.	14
Total	980

Dogs:

Gastrointestinal distribution of orally administered yttrium-90.	24
Gastrointestinal and bile distribution of cerium-144 and yttrium-91 after intravenous administration.	19
Principle of radioisotope distribution. Two pathology course laboratory sessions.	10

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the element is present in excess of the amount that can be bound in the supernatant and the sedimentation of aggregates of the element formed at the pH of the tissue. Further studies are planned with high-speed centrifugation.

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appointment in conjunction with the Oak Ridge Hospital.

The permanent clinical staff (medical and nursing), the short-term residents, postresidents, and visitors from abroad are listed in the section on staff at the end of this report. The projects described in the clinical section represent the combined work of this group.

IODINE-131 STUDIES

Clinical Staff

Carcinoma of the Thyroid

There has been a further extension of our series of cases of patients, with well-differentiated carcinoma of the thyroid, who have areas of iodine-concentrating tissue in the neck after presumed total thyroidectomy. Repeated surgical procedures have been done in some of these patients with the probe counter used for locating the functioning tissue. In the majority of cases it has been found difficult or impossible to remove the last remnant of functioning tissue. Histologic studies have been of great interest, but often puzzling, because it is difficult to differentiate normal thyroid from tumor in some instances. In general, this study seems to indicate that radical neck dissection for carcinoma of the thyroid is not a very satisfactory procedure. The areas of remaining tumor are often in the region of the thyroid bed or closely associated with the larynx and trachea; because they are in these locations they are not necessarily more adequately resected by radical neck dissection than by more conservative surgery.

Other cases of carcinoma of the thyroid not falling into the foregoing group have been investigated, with special emphasis on scintiscans at various intervals after test doses, in an effort to show the iodine-131 turnover rate of tumor tissue. Studies of surgical specimens with autoradiography and assay have helped correlate histologic type with iodine metabolism. The use of larger test doses of iodine-131 than were formerly used have made it possible to reveal poorly functioning metastases by external measurements. New observations have been made on areas of iodine-131 concentration on nonthyroidal tissue.

We have followed a small number of patients who have been given large doses of thyroxin for carcinoma of the thyroid. The lesions have shown lack of progression but have not shown regression.

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TOTAL-BODY IRRADIATION

Clinical Staff

Leukemia

Studies of total-body irradiation followed by attempted marrow transplantation in leukemia have diverged in two directions. First of all, it seems clear that in some patients with acute leukemia a remission occurs that is probably not caused by the marrow infusion but is a result of the radiation itself. This is cause for renewed interest in the subject of the effect of irradiation alone on acute leukemia. This is important as a possible palliative therapeutic means, and it is also important because there is danger that remissions due to irradiation alone will be misinterpreted as evidence of success of marrow transplantation. To prove the latter, more specific information is necessary than simply that there is development of a remission. There are scattered previous references in the literature to success with total-body irradiation in acute leukemia, although in general it has been thought to be a worthless therapeutic procedure. It appears now that with large doses of radiation it may be possible to produce remissions in some patients. We are attempting to determine which types of patient this applies to. It appears that it is applicable in the primitive-cell leukemias in children, and that it is much less likely to succeed in the subacute leukemias in older age groups. There is no doubt that the leukemic cells are exceedingly radiosensitive, and that rapid tissue breakdown occurs after total-body irradiation in acute leukemia. Of greater concern are the problems relating to regenerative phenomena, and why these occur in certain patients and not in others.

The attempts to transplant bone marrow seem, up to the present, to be unsuccessful, or at best to have shown only a transient and dubious graft in one case in our series. Radiation doses up to 800 r were reached (in one case), higher than we had given previously. Attention has been focused on several factors that may have to do with the success of the marrow transplantation.

Y-12 Plant Accident Patients

During six weeks in June and July, the major portion of the time and effort of the clinical staff was directed toward the treatment and study of patients exposed to an excessive amount of radiation in the Y-12 plant accident of June 16, 1958. Five patients were admitted at 1:00 AM on June 17, and three patients who received much smaller doses of radiation were admitted on June 18. The admission of these patients posed a bed-space problem, which was solved by discharging some patients from the hospital earlier than would have been done otherwise and

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The blood-platelet count showed a suggestion of an initial rise followed by a return to approximately normal levels, where they remained until about 16 days after the radiation. Then they began to fall strikingly, with the minimal values reached in about 25 days. All five patients had blood-platelet counts below 40,000 per cu mm at some point, and in two patients the blood platelet count fell to exceedingly low levels. The counts remained at their low levels for a few days and then increased rather rapidly. Normal levels had been attained again six weeks after the irradiation.

Red cell values showed considerable variation from patient to patient. In two patients a definite anemia developed, with the lowest values occurring about 36 days after the radiation exposure.

The reticulocyte count showed a tendency to fall during the first eight days, but reticulocytes were never totally absent in any case. Between the 13th and 25th days there was an abortive rise, and then a distinct rise after the 30th day. The highest reticulocyte count occurred around the 45th day.

Serial bone marrow studies showed a tendency toward progressive decrease in cellularity. In the early stages there was a relatively greater drop in red-cell precursors, so that on the 5th day a relative granulocyte predominance was present, with the red-cell precursors being less than one-fifth of the nucleated elements. Three to five days after the irradiation, giant neutrophil forms were prominent. A pronounced decrease in megakaryocytes occurred, becoming most severe 24 days after the irradiation. This was preceded by the presence of many degenerating megakaryocyte forms. At the point of greatest marrow depression, 33 days after the accident, there was a pronounced increase in unidentifiable mononuclear cells, and plasma cells were prominent in certain cellular areas of the marrow samples. After the period of greatest hypocellularity, there was rather rapid regeneration to normal or increased cellularity by the 54th day.

No serious infections occurred in any of the patients. There were several episodes of minor infections such as furuncles, upper respiratory infection, acute pharyngitis, and acute tonsilitis. The only elevations in temperature occurred in two patients, at the time of acute pharyngitis on one and acute tonsilitis in the other. Both of these patients were treated with tetracycline for 10 days. Otherwise there was no use of antibiotics.

The results of biochemical studies are reported elsewhere.

During the early part of the treatment, the use of bone-marrow infusions in the five patients receiving the larger doses was considered; however, it was decided not to use this measure unless the subsequent condition of the patient became precarious. Donors were obtained for

evidence also suggests that a change in serine excretion follows total-body irradiation.

BONE-MARROW AUTOTRANSPLANTATION AFTER NITROGEN MUSTARD

Clinical Staff

An effort is under way to make use of an autograft of bone marrow in conjunction with large doses of nitrogen mustard. This project is related to the total-body irradiation experiment in acute leukemia, and the same method of obtaining and infusing marrow is used. A group of patients (selected because their neoplastic disease has progressed beyond conventional therapeutic measures and because there is a lack of demonstrable metastases to bone) are being given large doses of nitrogen mustard intravenously. The dose rate is 1 mg/kg body weight, all given within a period of 5 to 10 minutes. The procedure, including general anesthesia and aspiration of bone marrow, is conducted in the same way as with the bone-marrow donors for the acute-leukemia program. The diluted bone marrow, in its plastic bag, is stored for 4 to 6 hours at icebox temperature, subsequently warmed to approximately body temperature, and infused intravenously. Control members of this series have been selected from a table of random numbers, and the decision to include a patient in the series is made independently of a knowledge of whether the subject will fall in the bone-marrow or control group. No conclusions with regard to bone-marrow transplantation can be drawn at this time. Two patients have responded encouragingly, with marked regression of lesions, to this large dose of mustard.

CONTINUING PROGRAMS

Clinical Staff

Certain long-range programs have continued to occupy a part of the clinical activity of the Medical Division. Some of these are carried on chiefly for purposes of teaching the resident staff and offering a variety of clinical experience to the permanent staff. Certain of these projects have specific research value; others do not.

Study of thyroid disease, in addition to the specific projects mentioned, includes a long-range investigation of carcinoma of the thyroid. Some patients with hyperthyroidism and cardiac or pulmonary insufficiency are also treated with iodine-131. There is a continuing interest in early and late histologic effects of iodine-131 on thyroid tissue, and additions to this group of specimens have been made during

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360° rotation) both sources can be in the "on" position at the same time, doubling the dose rate. The net effect is that of having a hectocurie unit, with its small size and mobility, with an output corresponding to that of a kilocurie machine.

Whether the patient is treated with stationary fields or by arc or circular rotation, the tissue doses are calculated by making use of the tumor to air ratios. With this method, attention is focused mainly on tissue doses, rather than skin dose, which in cobalt teletherapy is of little significance. To obtain tumor to air ratios a simple experimental setup was used. It consisted of a Lucite water phantom in which a Victoreen 25 r-meter was submerged. The r-meter was fastened to the frame of the machine and the phantom was laid over the treatment table. By moving the phantom laterally, the water thickness between source and probe was reduced at 1-cm intervals, and the ratios between dose rate in air at the center of rotation and dose inside the water phantom were plotted. Measurements were made for several field sizes. Our data agree within 3 per cent with one set of published values.

The treatment table is of aluminum alloy in order to minimize the attenuation of the cobalt-60 beam when it points upward. To determine the degree of attenuation, a Victoreen r-meter was placed at the center of rotation of the machine, 8 and 10 cm above the surface of the table, and measurements were taken with the cobalt beam traversing the table at different angles. The maximum attenuation amounted to about 15 per cent at 30° from the horizontal. At 90° it was about 8 per cent, small variations being due to the area of the field. On the average, the intensity of the beam at the center of rotation is reduced 8 per cent when the machine is moving through a 180° arc under the table. For 360° the over-all reduction is taken as 4 per cent.

Twenty-two patients with several types of malignancy have so far been treated.

AUTORADIOGRAPHY

William D. Gibbs

The response of a large number of commercially available X-ray films to sulfur-35 and chromium-51 has been determined. In conjunction with data previously obtained from phosphorus-32, iodine-131, and mercury-203, it seems that the range of linearity for any type of film decreases as the beta energy becomes lower. Analysis of all data is not complete as yet.

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MEDICAL PHYSICS

D. A. Ross

Therapy

Cesium-137.

The cesium teletherapy unit has been coaxed back into operating shape and Dr. Comas can use it for basic studies and for tumor irradiation in selected cases. A series of experiments is planned in which the local spectral constitution of the ionizing radiation will be determined at various depths and positions in artificial body phantoms, since this has a bearing on the effectiveness of the radiation in therapy. Another experiment will compare cesium with cobalt in respect to the risk of causing skin injury during the course of deep therapy.

Westinghouse Twin-Source, Co-60 Unit.

This machine, and the cesium unit also, were put out of action in September by a small leak in one of the source capsules, and the cleanup and repair processes have unavoidably been slow. The leaking source has been removed, examined, re-encapsulated, and reinstalled, each procedure requiring remote handling. Appropriate steps have been taken to improve the safety of capsules of this sort, so that such leaks will not recur. Work is still being done on the Westinghouse unit to provide a more effective (and reasonably quiet) air compressor to hold the sources in the "on" position when required, and the contaminated area is now nearly ready for the therapy program again, part of which has been set back several months by the leaking capsule. It is expected that the machine will be in operation early in 1959.

Total-body Irradiation.

The research program on acute-leukemia patients is continuing (see Dr. Andrews' discussion in the clinical section). Current indications are that with moderately high total-body dosage (300 to 500 r) it is often possible to produce a clinical remission in the disease, but that nothing in the nature of a permanent "cure" can be expected from this procedure. On the basis of small-animal studies it seems reasonable to believe that doses of around 800 r and more should

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Distribution Around Deeply Placed Radium Sources.

Water phantoms have been used to estimate the tissue doses at various locations in the neighborhood of buried radium sources. (See Dr. Hayes's discussion.)

The Cobalt-60 Temporary Irradiator and Total-Body Phantoms.

Ionization-chamber studies have been made to determine the depth dosage delivered by a cobalt-60 source to various points within water phantoms having the general size and shape, in stylized fashion, of a human body. Such studies (see Dr. Hayes's discussion) have a bearing on the effectiveness of total-body irradiation, especially in deeply buried structures. The temporary irradiator delivers its radiation to one side of the patient, so that problems of absorption require careful consideration, and the data obtained will be of help in the planning of the actual procedure to be used in irradiating a total-body patient-e.g., how he should lie on the cot, whether he must be turned around frequently, and so forth.

Spectra From a Buried Cesium-137 Source.

One way to approach the question of local-dose spectrum in deep cesium therapy is to do the converse experiment of burying a small cesium-137 source at numerous locations in a water phantom and examining each spectrum from outside with a pulse-height spectrometer. Dr. Umegaki is currently making measurements of this sort.

Tumor Oxygen Tension vs. Radiation Sensitivity.

Since the ease with which a tumor can be injured by radiation is often related to its oxygen content, it might be helpful to know how oxygen tension within a tumor varies during procedures calculated to interfere with the circulation or otherwise change the availability of oxygen. We are currently constructing an experimental arrangement that will convert oxygen tension at the tip of a platinum needle electrode into a minute but measurable current, and the plan is to record these currents during the proposed interfering procedures. After a series of such tests, the most promising procedure can be tried out during actual radiation treatment. Dr. Comas and Dr. Umegaki are working on this problem.

X rays

Self-contained, Portable X-ray Sources.

Several persons have suggested that portable X-ray sources could be constructed to use radioisotopes, and the Medical Division has

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DOSIMETRY AND RADIOCHEMISTRY

Raymond L. Hayes

Dose to the Intestinal Tract.

Additional concentration-time studies on dogs administered doses of nonabsorbable radioisotopes (such as yttrium-90) have shown that the decrease in the total radioactive content of the stomach with time is approximately exponential. The half-emptying time was found to be about two hours. Similar studies have previously shown that the concentration-time relationships for the radioactive content of the lower large intestine of dogs involves a half-build-up time of approximately the same period. If it is assumed for man that the concentration build-up in the large intestine is a direct reflection of the emptying of the stomach, as it appears to be with dogs, it should then be possible to make dose approximations on human beings by using simple tracer techniques. It is assumed that the emptying half-time of the stomach could be determined by profile scans of the subject during the first few hours after ingestion of the tracer dose.

With dogs, previous studies using implanted glass dosimeters have shown wide variations among individual animals. Further, the results of the studies emphasized the great differences in dose produced by variations in rate of passage of intestinal content. It is highly desirable from the standpoint of health physics that the limits of dose variation for human beings be established. The planned tracer studies with human beings should be most valuable, since they will involve actual measurements on subjects of varying habits and will not involve the usual assumptions concerning average behavior.

Radium Treatment of Carcinoma of the Cervix.

Measurements have been made of the dose received outside the pelvic-compartment in the treatment of carcinoma of the cervix with radium. Measurements were made with three water-filled phantoms simulating women of different heights. The routine radium treatment (8000 mg-hr) for carcinoma of the cervix was shown to result in quite high doses to tissues outside the pelvic compartment. As would be expected, the dose was greatly affected by the over-all height of the "patient." This study was made in connection with a survey of the incidence of leukemia among women who had had radium treatment for carcinoma of the cervix. The results of the dose study indicate the desirability of expanding the measurements to include a comparison of radium with other sources of radiation.

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TRAINING

J. Howard Harmon

Two training courses were given in 1958. Both were for pathologists and involved a great deal of time for most members of the senior staff, but particularly for Dr. Steffee and Dr. Nelson. These courses were jointly sponsored by the Medical Division and the American Society of Clinical Pathology. The program was arranged to meet the needs of certified pathologists who wanted to meet the requirements of the U. S. Atomic Energy Commission. The first week was largely on fundamental techniques and the second week was clinical.

Because it is difficult for a physician to be away from his work for more than a week at a time, the course was given in divided form: The first course was begun November 11-15, 1957, and finished February 10-15, 1958. The second course, a repetition of the first, was given September 22-27 and December 8-13, 1958. The separation of the two weeks gave the hoped-for benefit of an interim period for absorption of the material presented during the first week, as well as time for additional reading.

Persons desiring further information should write to Mr. William D. Jones, the administrative assistant assigned to the work of arranging for these courses.

From the beginning of the Medical Division's activities, the training of resident physicians has been a vital part of the program. The short-term residencies (three or four months) have served many young physicians. Residencies in experimental medicine and postresidencies in radiology are for one year. For a list of those in residence in 1958, see the list at the end of this report.

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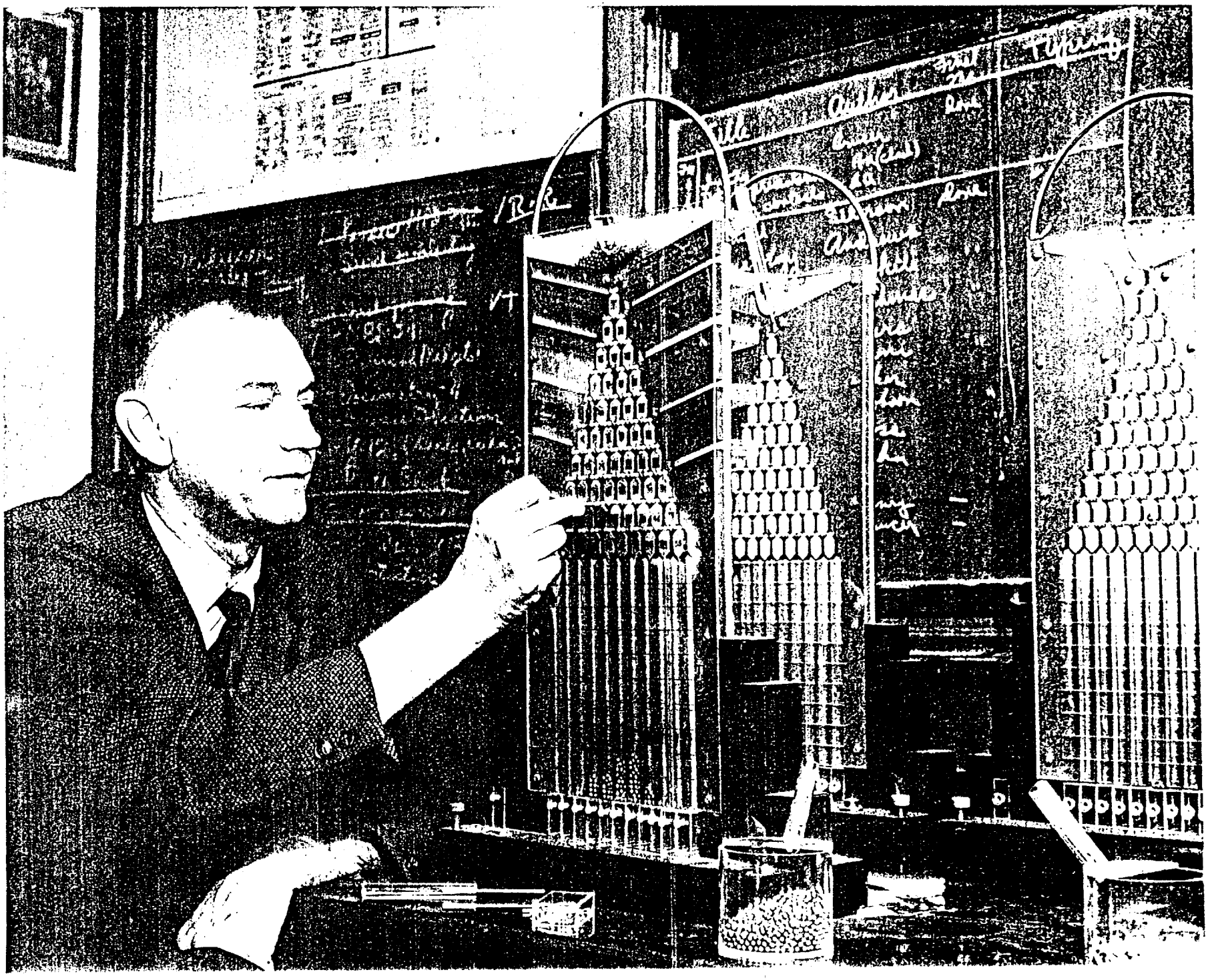
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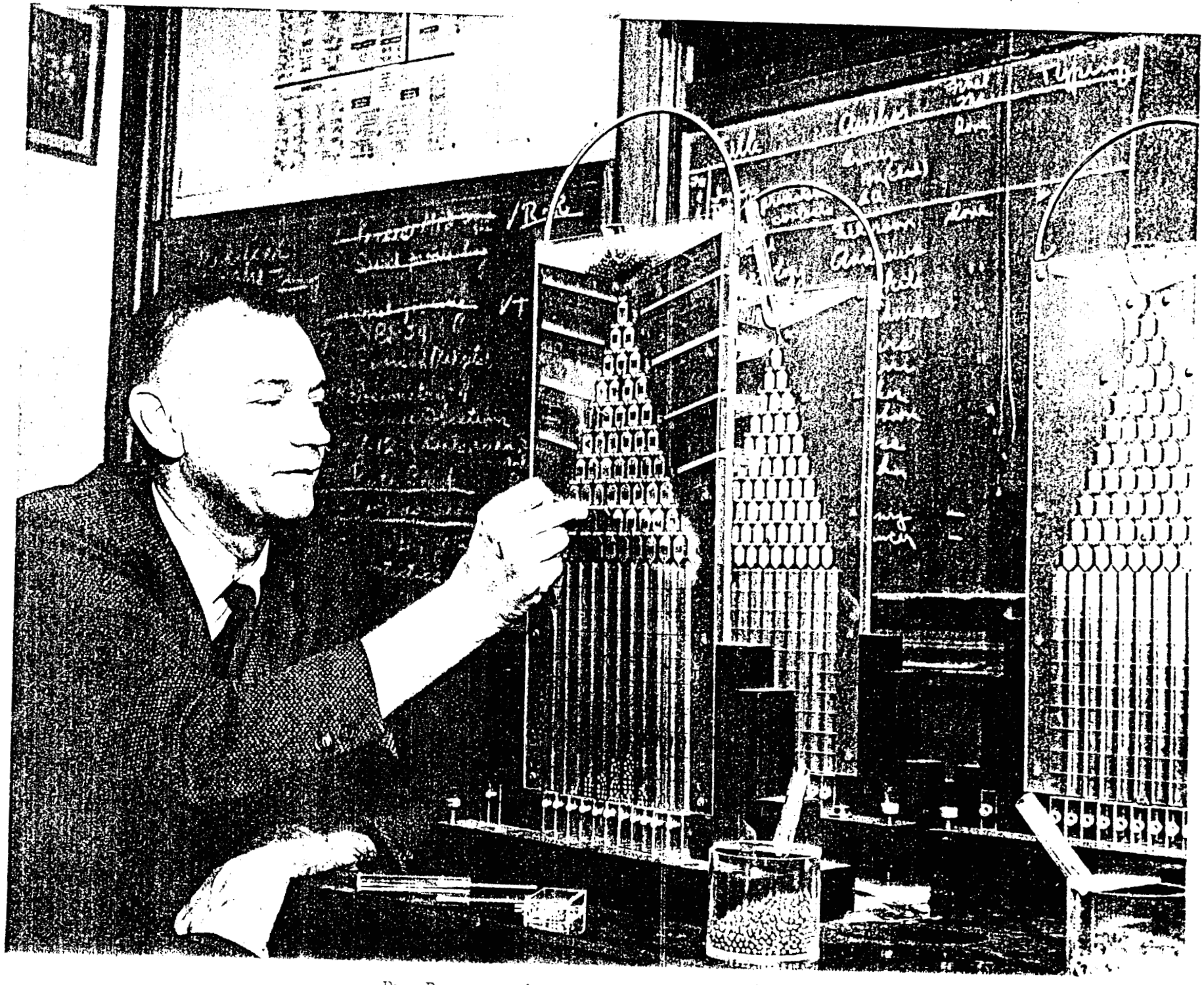
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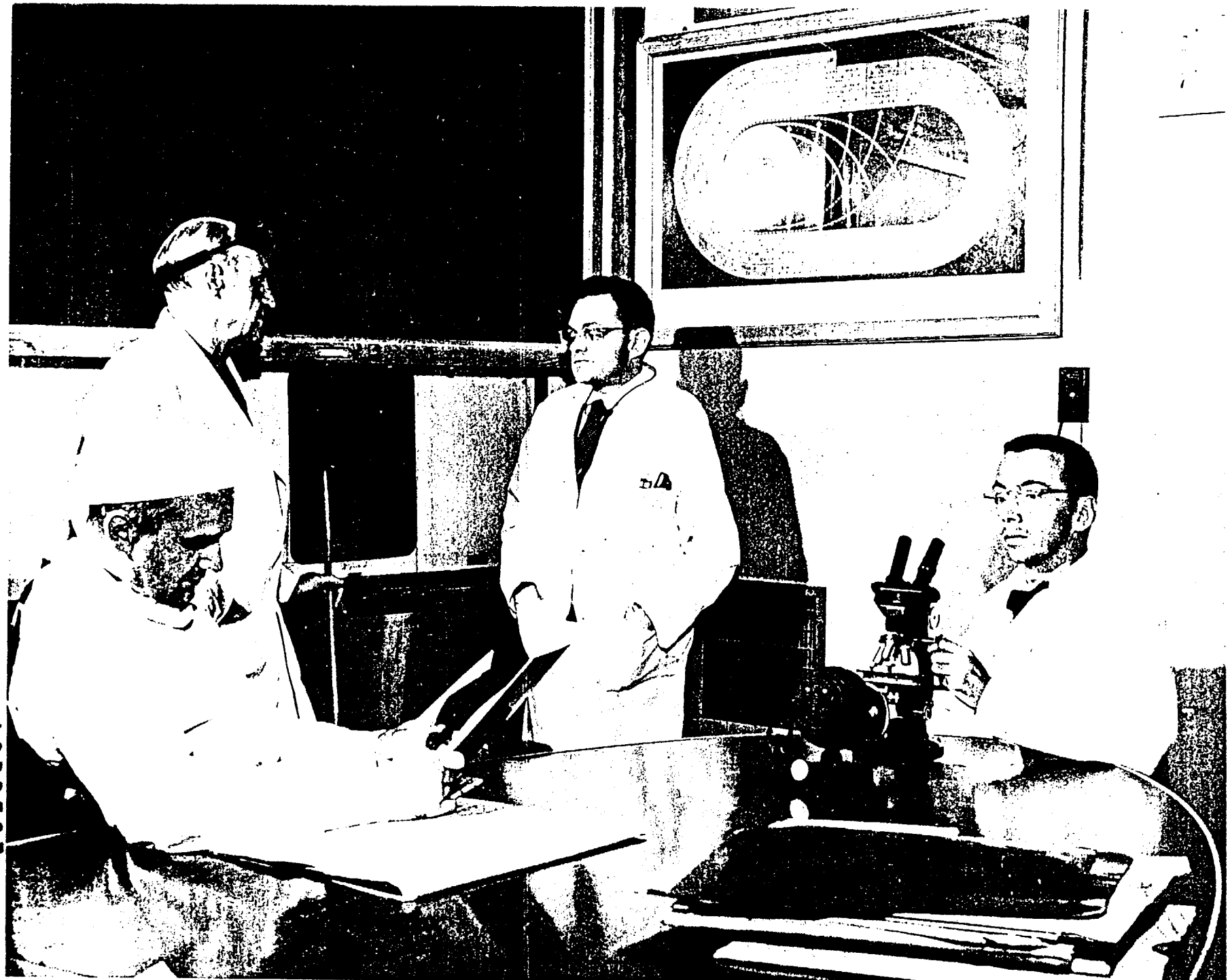
Dr. Brucer and one of the newly developed
training aids (statistics board)

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Dr. Brucer and one of the newly developed



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From left to right, Dr. R. R. Bigelow ...geon) and Dr. Robert P. Ball (radiologist) ...

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Mayo Foundation, Rochester, Minnesota, Pathologist, 1944-1946
Tilton General Hospital, Valley Forge General Hospital, Phoenixville, Pennsylvania, Pathologist, 1946-1948
Mayo Foundation, Rochester, Minnesota, Pathologist, 1948-1949
Lovelace Clinic, Albuquerque, New Mexico, Pathologist, 1949-1951
ORINS Medical Division, Pathologist, 1951-1955
Eden Hospital, Pathologist, 1955-1959
ORINS Medical Division, 1959 ----

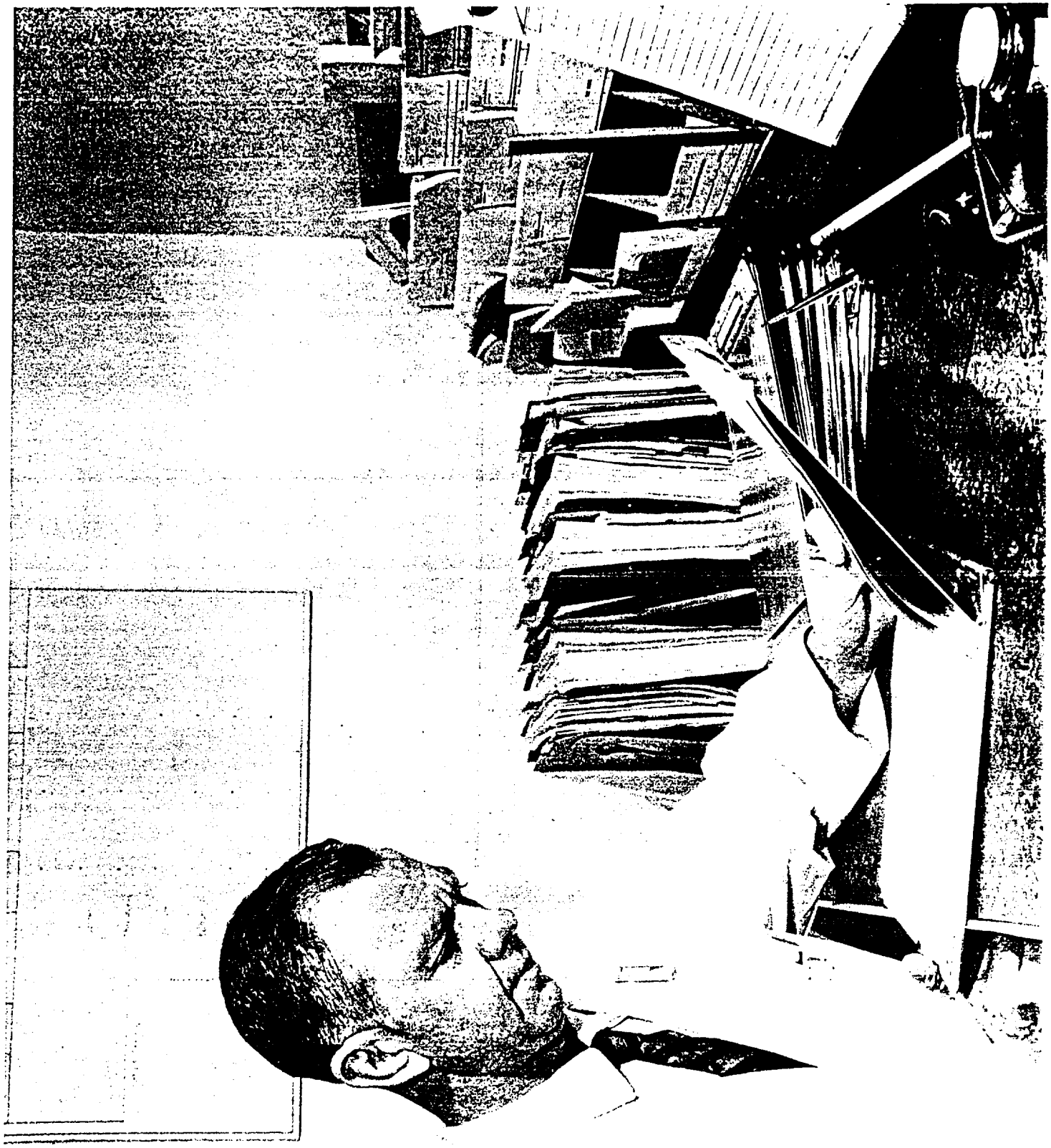
Memberships:

American Medical Association
College of American Pathologists
American Society of Clinical Pathologists (member of Council on radioisotopes)
Alumini Association of Mayo Foundation for Medical Education and Research
Alpha Omega Alpha
Society of Nuclear Medicine
American Association for Cancer Research
American Association for the Advancement of Science

Current Work and Interests:

Pituitary irradiation, safety in blood transfusions, importance of nonbiological contributions to isotopic diagnosis; clinical training.

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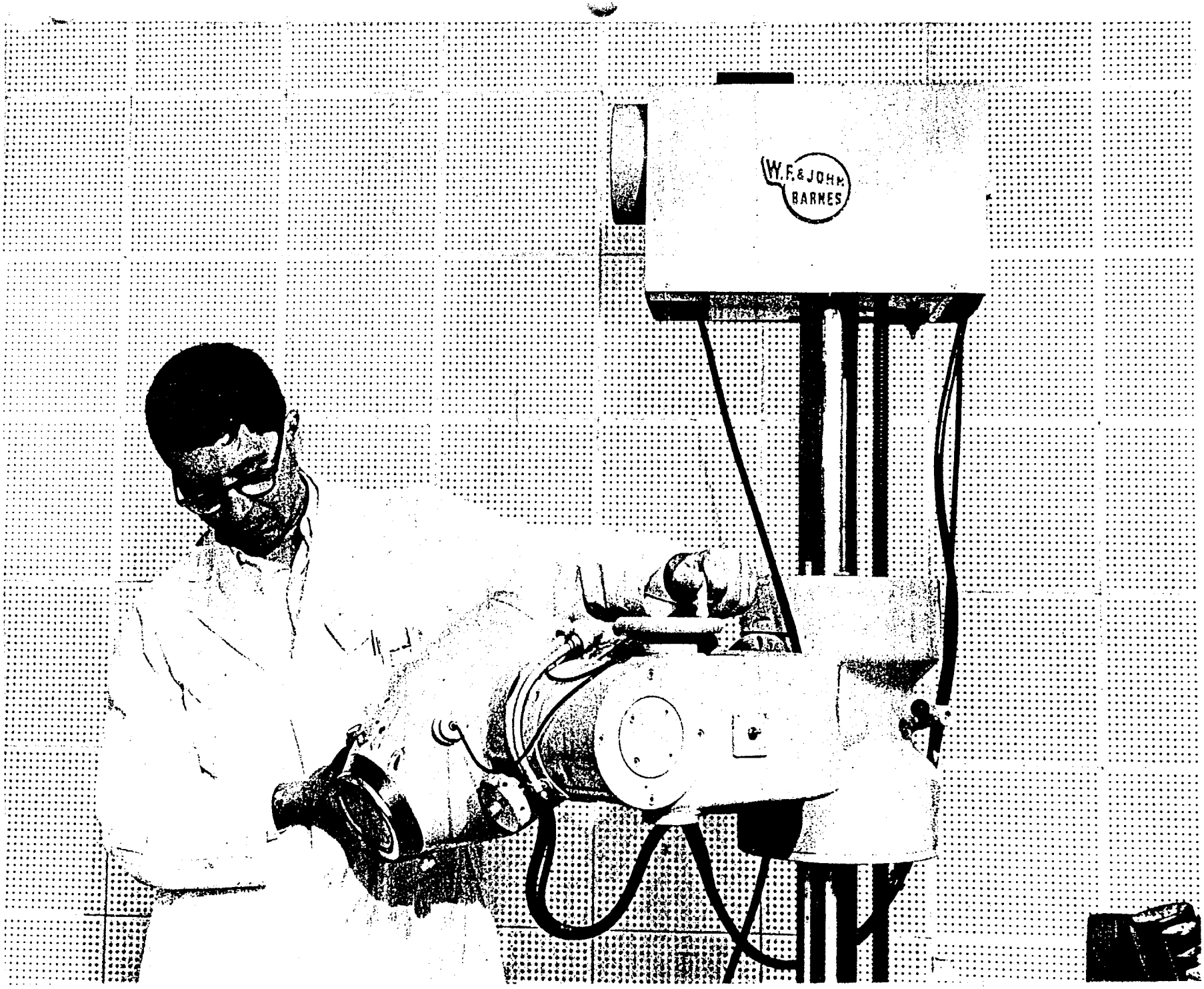
Dr. Kratchman operating the amino acid analyzer

Dr. Nolan preparing a frozen section

1033531

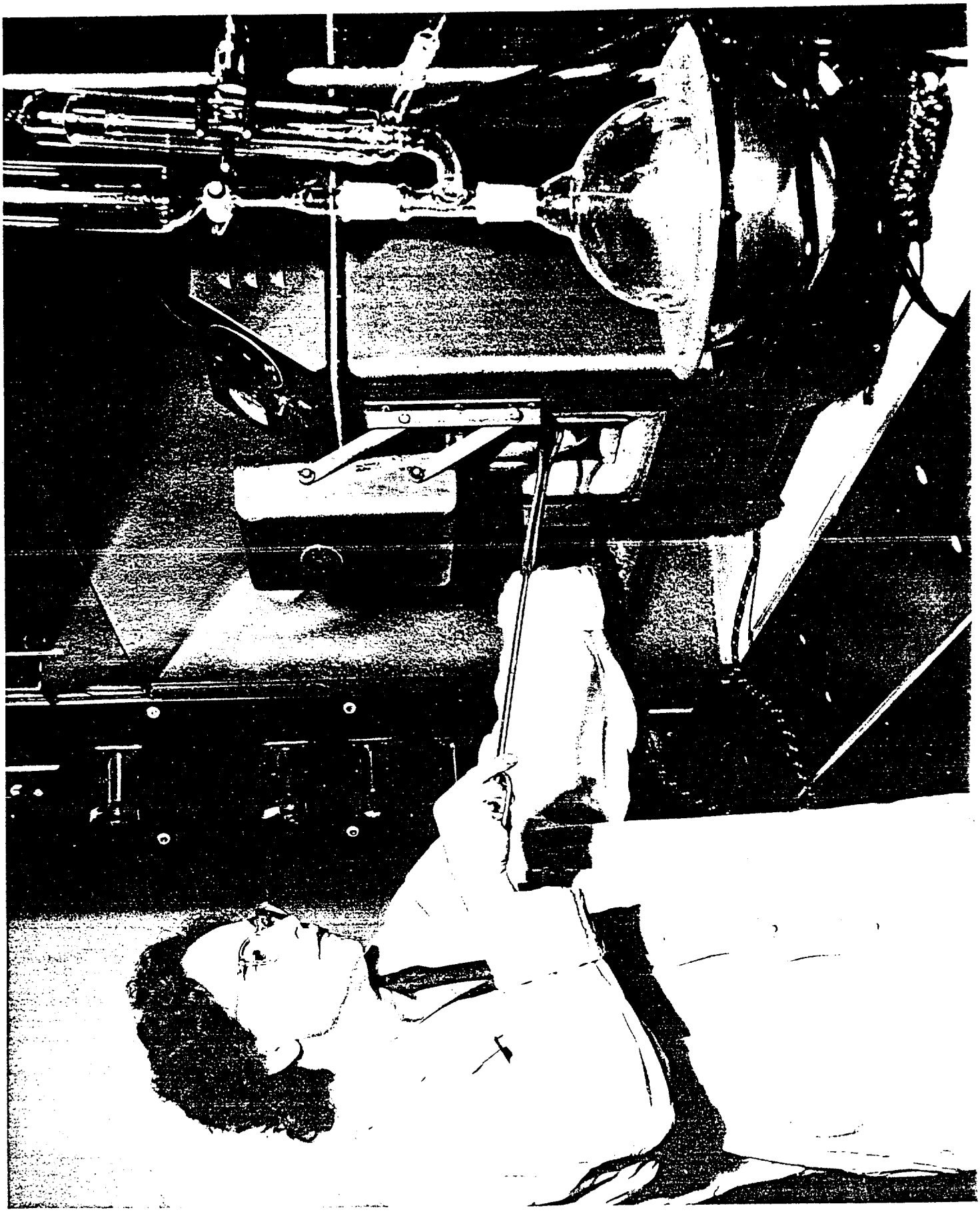
Dr. Nelson measuring a person's reaction

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Dr. Comas and the interchangeable-source teletherapy machine

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Dr. Palmer administering medication orally

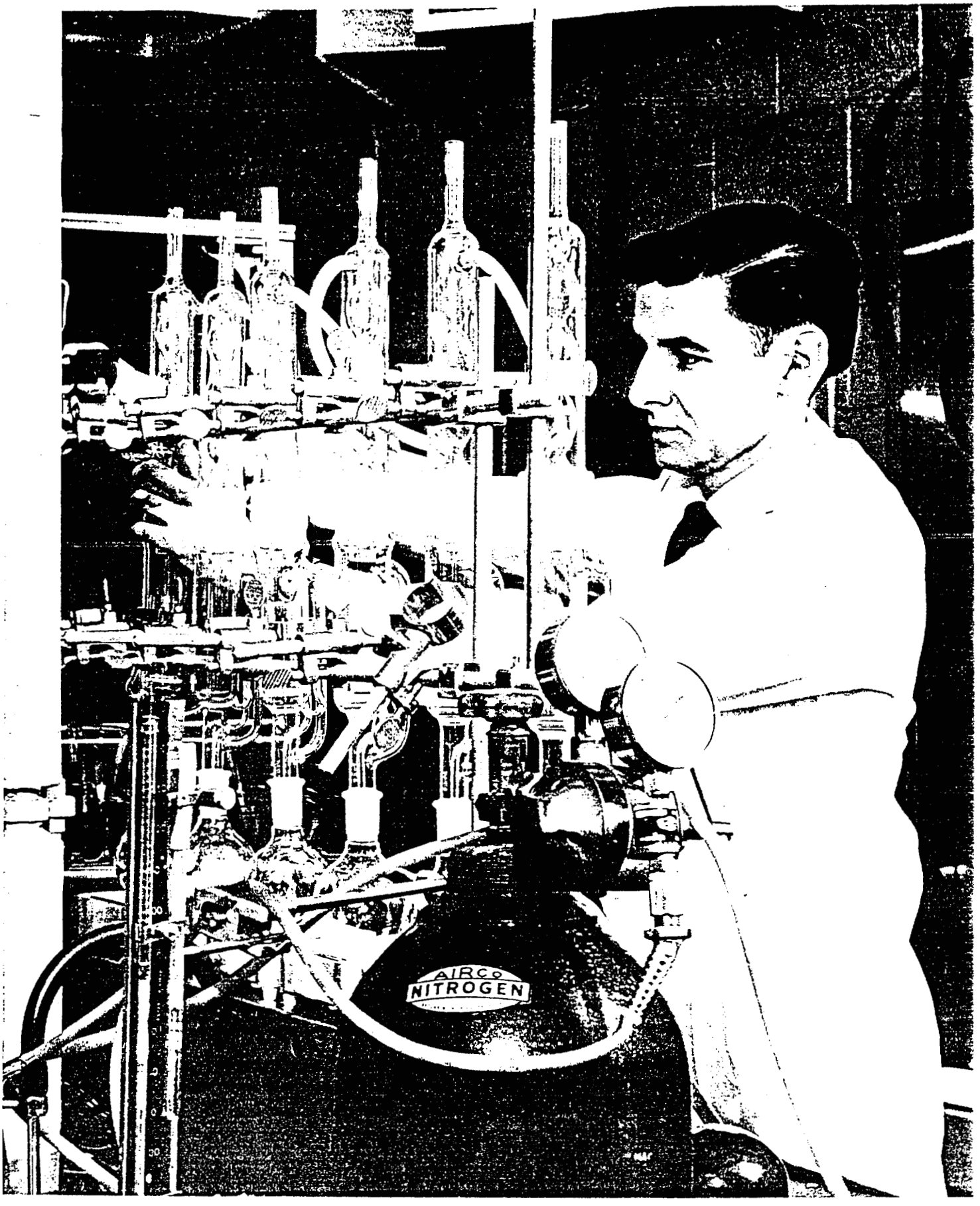
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Mrs. Suttle of adjusting the 67cm of an Astrograph

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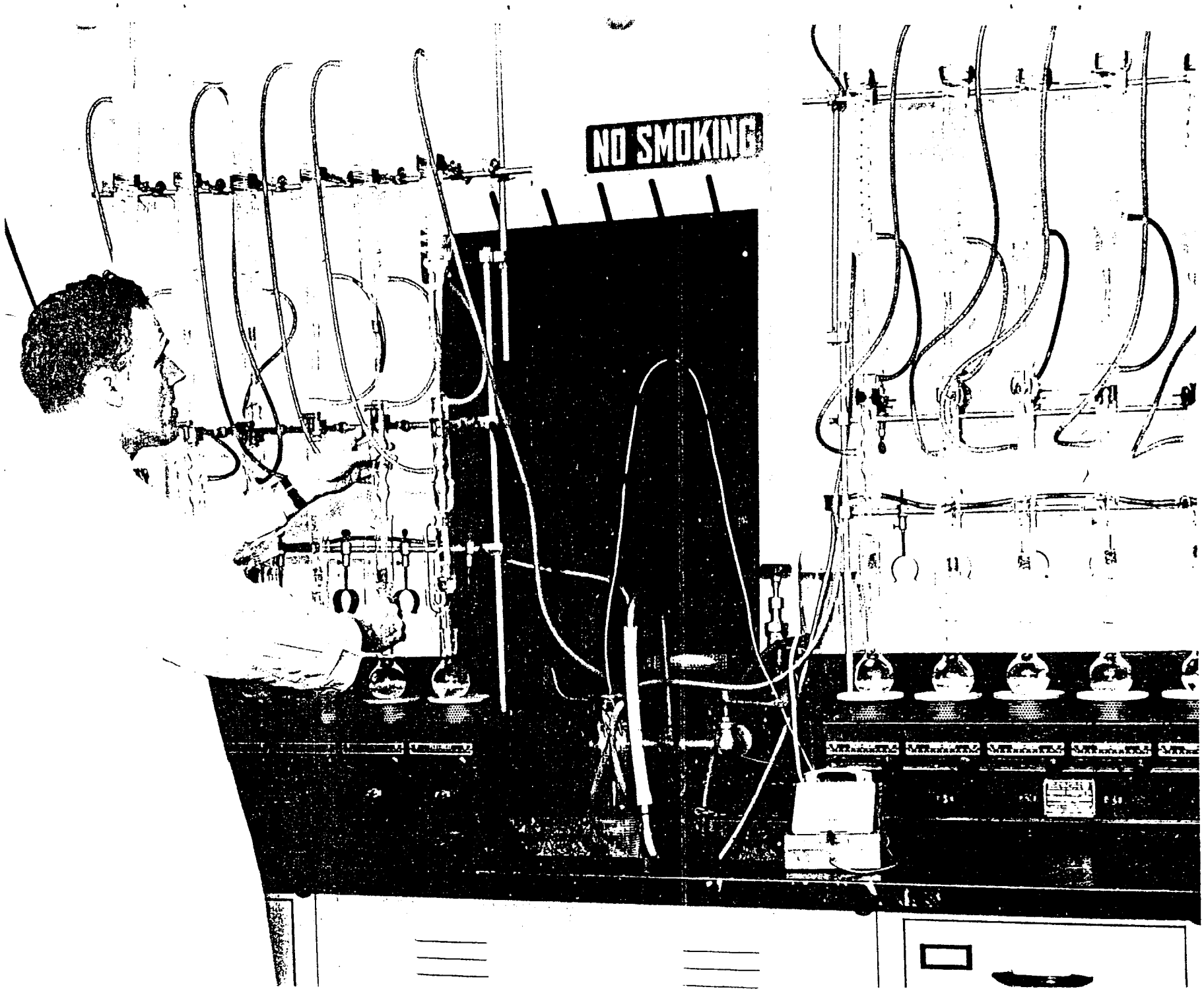
Dr. Kyker preparing a sample for separation by centrifugation

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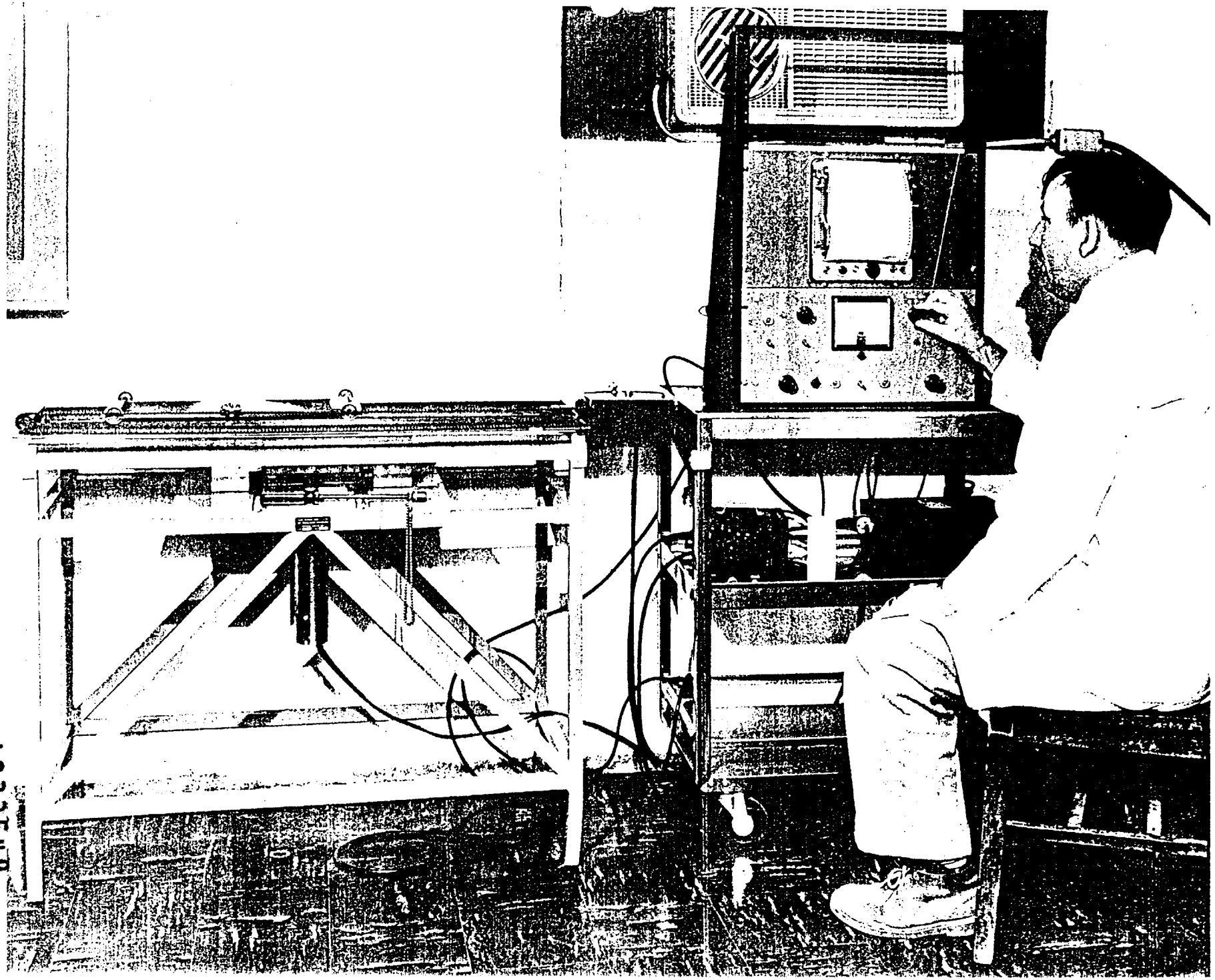
Dr. Snyder getting ready to extract lipides with the Soxhlet continuous extraction apparatus.

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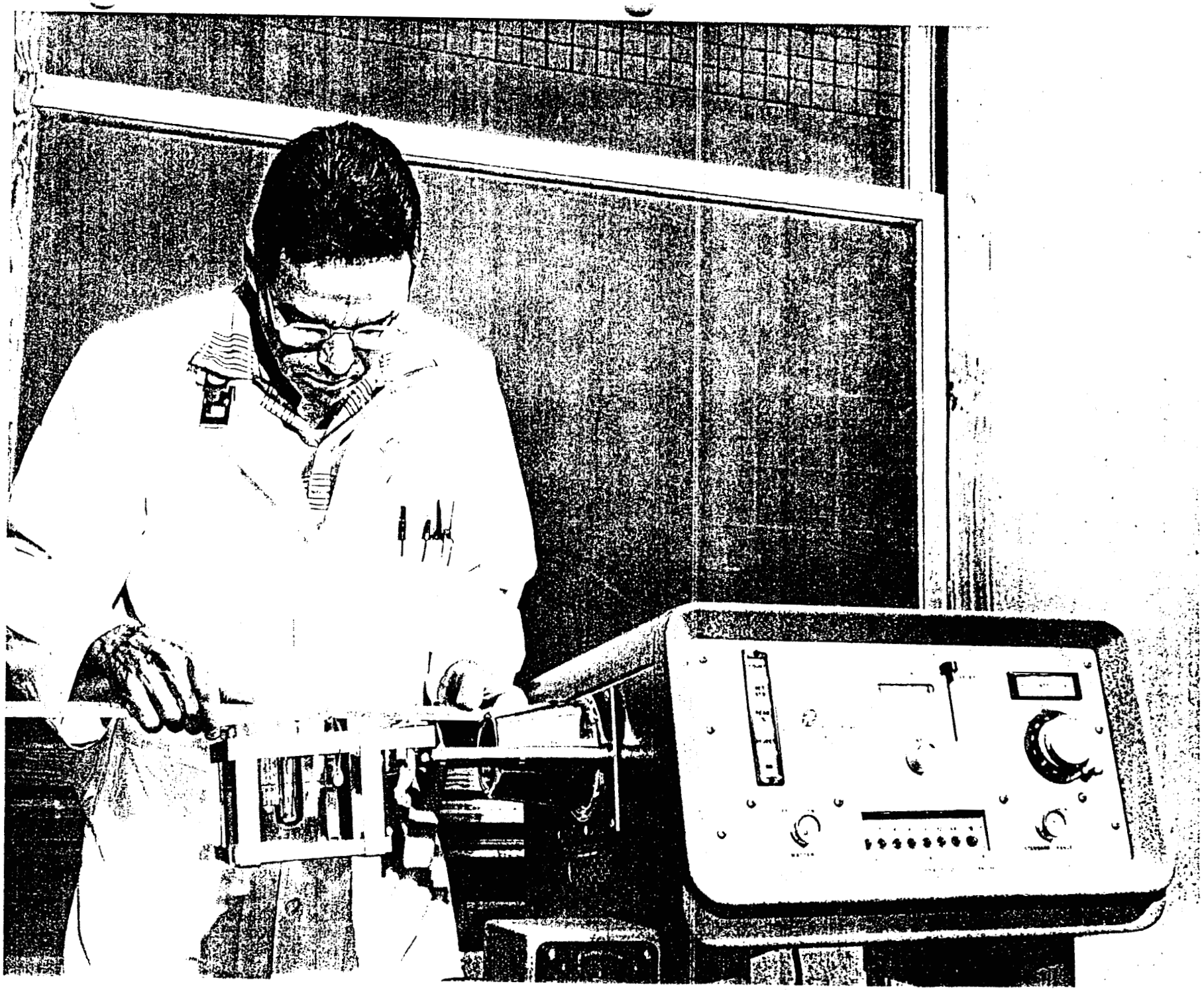
Mr. Cress adjusting an extractor unit used in

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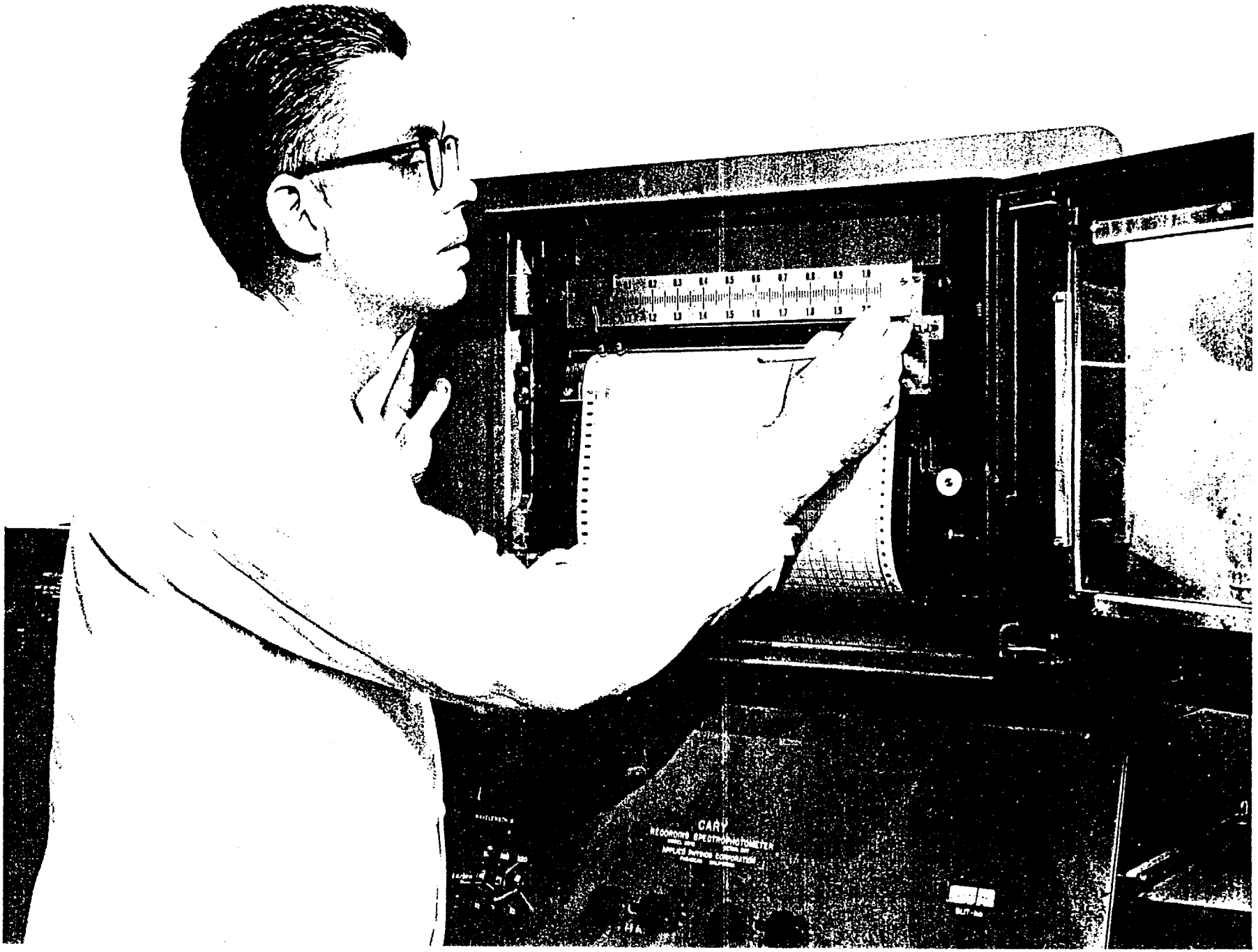
Mr. Rafter and the small-animal linear scanner.



Dr. Ross demonstrating an experiment with a neck phantom.

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Dr. Hayes using the automatic recording spectrophotometer.

Mr. Morris adjusting the recorder on the linear scanner.

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Mr. Harmon (left) and Mr. Jones (right) discussing the budget.

BIOGRAPHICAL SKETCH

Name: William D. Jones

ORINS Title: Budget and Procedures Assistant

Address: 4208 Landon Drive, Knoxville, Tennessee

Born: 1925, Spray, North Carolina

Marital Status: Married

Children: One son, one daughter

School:

University of North Carolina, 1949-1950
University of Tennessee, 1952-1953
Knoxville Business College, Diploma, Higher Accounting and Business Administration, 1953-1954

Positions:

U. S. Navy, 1943-1946
Shipping Clerk with Fieldcrest Mills, Leaksville, North Carolina, 1946-1949
ORINS Medical Division, 1956 ----

Current Work and Interests:

Hospital administration; training courses and seminars for research personnel.

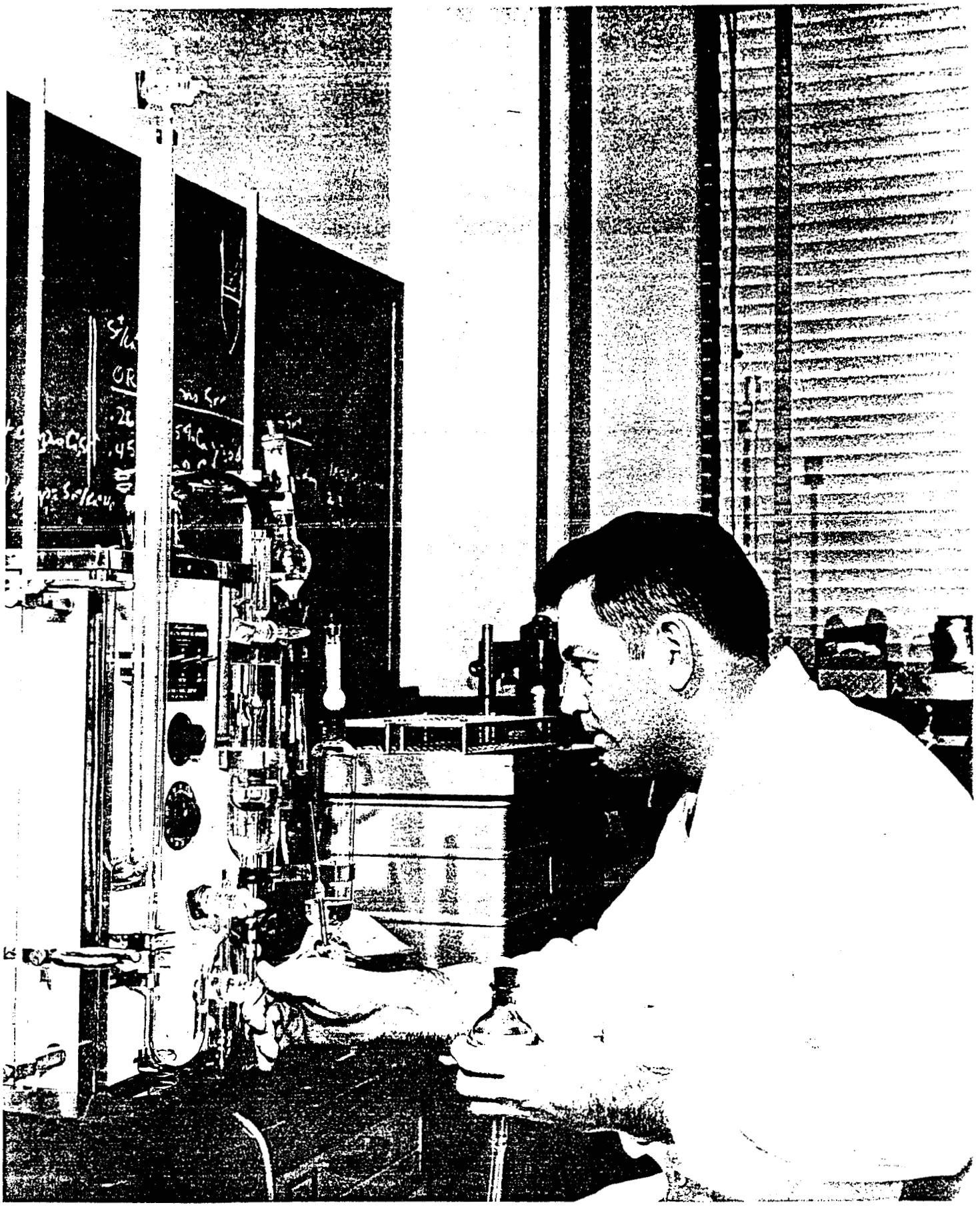
1033545



Mrs. Anderson (left) and Mrs. Mott (right) checking a manuscript.

1033546

Mr. Gibbs grinding an undecalcified bone section.



1033548

Mr. Byrd measuring total alpha-amino nitrogen with the Van Slyke manometric apparatus.

PERMANENT CLINICAL STAFF

Clinical

G. A. Andrews, M.D.
B. W. Sitterson, M.D.

Clinical Biochemical Research

A. L. Kretchmar, M.D., Ph.D.

Radiotherapy

F. Comas, M.D.

Pathology

Bill M. Nelson, M.D.

Anesthesiology

Betty M. Cooper, M.D.

Outpatients

Etna L. Palmer, M.D.

Supervisor of Nurses

Mary Sutliff, R.N.

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SHORT-TERM RESIDENTS

Name	Hospital
Ryosaku Tanida, M.D.	Misericordia Hospital 531 E. 86th Street New York 28, New York
Alvin Segel, M.D.	Cleveland City Hospital Cleveland, Ohio
Alfred L. Weber, M.D.	Massachusetts General Hospital Boston, Massachusetts
Jean Guy Tessier, M.D.	McGill University Montreal, Quebec, Canada
B. B. Bach, M.D.	E. T. Baptist Hospital Knoxville, Tennessee
M. Perez-Reyes, M.D.	Prince George's General Hospital Cheverley, Maryland
E. B. Andrews, M.D.	University of Michigan Ann Arbor, Michigan
John T. Pollard, M.D.	Massachusetts General Hospital Boston, Massachusetts
Syed A. Hafiz, M.D.	Presbyterian Hospital Pittsburgh, Pennsylvania
Enrique Leon, M.D.	Boston City Hospital Boston, Massachusetts
David G. Millard, M.D.	Massachusetts General Hospital Boston, Massachusetts
Stefan Schatzki, M.D.	Massachusetts General Hospital Boston, Massachusetts

POSTRESIDENTS

Orren Hyman, M.D.	St. Mary's Hospital Knoxville, Tennessee
Jose B. Briones, M.D.	Meriden Hospital Meriden, Connecticut

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POSTRESIDENTS - Cont.

C. G. Papavasiliou, M.D.	Boston City Hospital Boston, Massachusetts

RESIDENT IN EXPERIMENTAL MEDICINE

Robert Nightingale, M.D.	Iowa Methodist Hospital Des Moines, Iowa

VISITORS FROM ABROAD

Efraim Otero, M.D.	Instituto Nacional de Cancerologia Colombia, South America
L. Chiang, M.D.	National Taiwan University Hospital Taipei, Taiwan Republic of China Formosa
Kandiah Shivanandan	Royal Melbourne Technical College Melbourne, Australia
Yoichiro Umegaki, M.D.	Medical School of Shinshu University Matsumotoshi, Japan
Akira Tsuya, M.D.	Yokohama Municipal University Minami-ku Yokohama, Japan
N. U. Ahmad, M.D.	Department of Pharmacology Nishtar Medical College Multan, West Pakistan

VISITING SCIENTIST

William B. Stavinoha, M.D.	University of Texas Medical Branch Galveston, Texas

RESEARCH FELLOW

Felix J. Pircher, M.D.	University of Michigan Ann Arbor, Michigan

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SUMMER PARTICIPANTS

Isaac Miller, M.D.	Meharry Medical College Nashville, Tennessee
David Camp, Ph.D.	University of South Sewanee, Tennessee
Ernest Daigneault, Ph.D.	University of Tennessee Memphis, Tennessee

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