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UNITED STATES
ATOMIC ENERGY COMMISSION
WASHINGTON

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MAY 8 1961

Dear Sir:

It is my pleasure to enclose a copy of our latest booklet publication entitled, "Cancer Research," which is one of several being issued describing the biomedical research program of the Atomic Energy Commission. Other publications in this series have been "Marine Sciences Research" and "Genetics Research."

We feel that this is a most useful documentation of an important segment of the Commission's biomedical research program and would appreciate any comments or suggestions you may care to furnish with regard to the enclosed publication.

Sincerely yours,

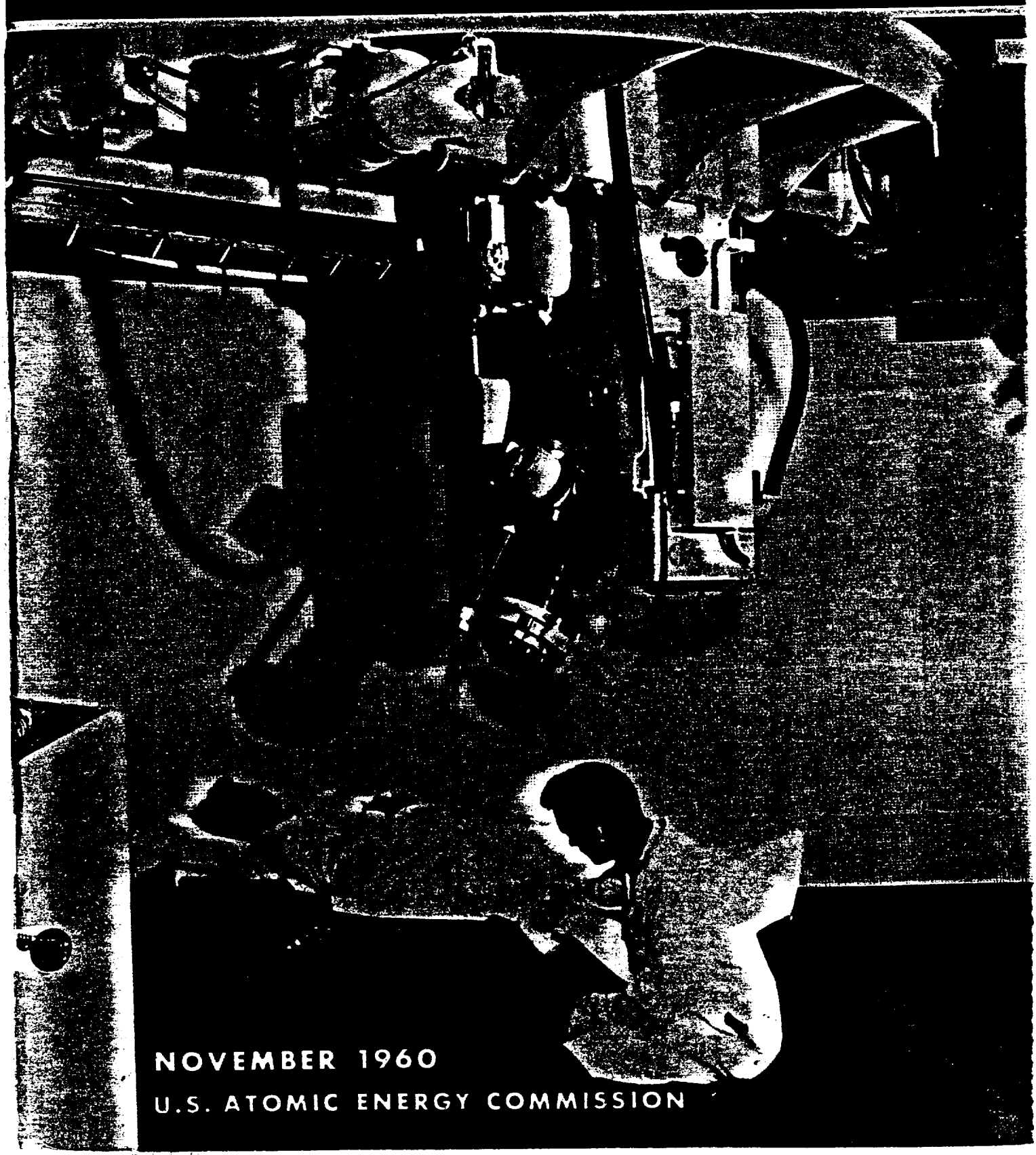
Chas L. Dunham

C. L. Dunham, M. D., Director
Division of Biology and Medicine

Enclosure:
As stated above

CANCER RESEARCH

Division of Biology and Medicine



NOVEMBER 1960

U.S. ATOMIC ENERGY COMMISSION

Subject Category: Biology and Medicine.

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CANCER RESEARCH PROGRAM OF THE DIVISION OF BIOLOGY AND MEDICINE

Division of Biology and Medicine
U. S. Atomic Energy Commission
Washington, D. C.

THIS DOCUMENT HAS BEEN PREPARED WITH THE COOPERATION AND ASSISTANCE OF THE VARIOUS LABORATORY DIRECTORS TO SERVE AS AN INFORMATION SOURCE FOR THOSE INTERESTED IN THE CANCER PROGRAM OF THE UNITED STATES ATOMIC ENERGY COMMISSION

James F. Haggerty, Ph.D.
Biochemist, Medical Research Branch
Division of Biology and Medicine

Foreword

With the passage of the original Atomic Energy Act of 1946 by the 79th Congress of the United States, the Division of Biology and Medicine was established as one of the seven original divisions of the U. S. Atomic Energy Commission. By this Congressional Act (Public Law 585) the Commission was empowered to conduct research in accordance with the following:

> "Section 3 (a) authorizes and directs the Commission to conduct research and development activities relating to, among others, "(3) utilization of fissionable and radioactive materials for medical, biological, health or military purposes;" ... and "(5) the protection of health during research and production activities."

Because cancer may be both caused and treated by radiation, the Atomic Energy Commission has interpreted Section 3 (a), referred to above, as containing a clear mandate, and imposing a definite obligation on the Commission, to undertake cancer research, exploiting these special properties of atomic energy for this purpose. Furthermore, the Independent Office Appropriation Act of 1948 stipulated that "there shall be available to the Commission for cancer research work such sums as the Commission believes can be efficiently used without duplicating the cancer research of other public and private agencies." In February of 1948 the Commission approved the establishment of a cancer research program within the Division of Biology and Medicine.

The problems of cancer etiology are as highly complex as its treatment, and radiation is but a single facet of a systematic approach which involves every discipline of modern medical science. Thus, our particular sphere of activity in oncological research is a circumscribed one embodying studies into the causes and prevention of cancer as an occupational hazard in atomic energy operations and, in addition, the development, with the tools of atomic energy, of new approaches to the study and treatment of cancer.

The major portion of cancer research supported by the Atomic Energy Commission is conducted in seven major installations, five

of which are associated with national laboratories or special AEC projects. In addition to these major facilities, modest research programs are supported at several universities, medical schools, and hospitals throughout the United States.

Charles L. Dunham, M. D.
Director
Division of Biology & Medicine

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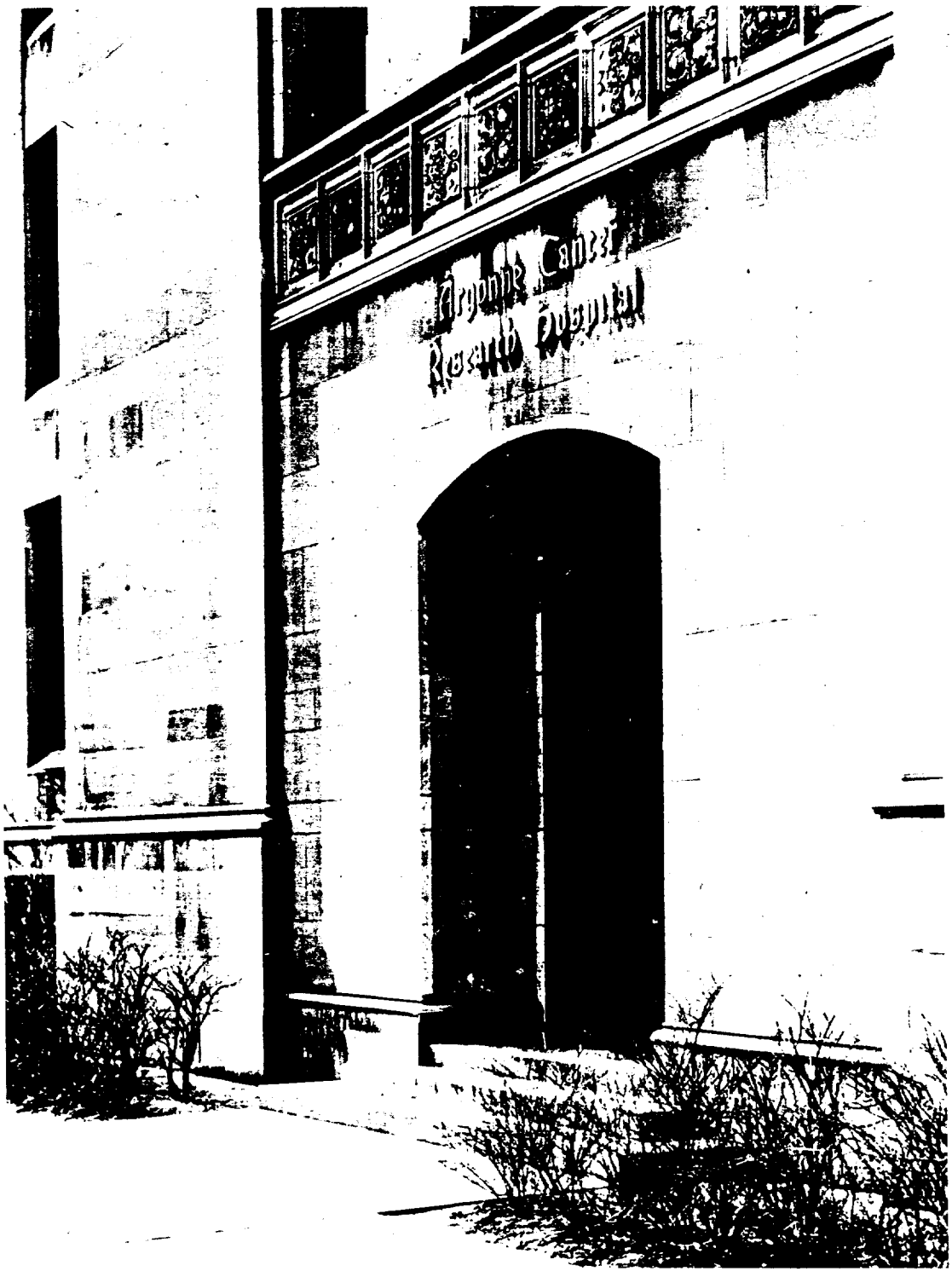
Chicago, Illinois

Leon O. Jacobson, M. D.	Director
Robert J. Hasterlik, M. D.	Associate Director
Edward P. Reedy	Administrative Officer



ARGONNE CANCER RESEARCH HOSPITAL

In 1948 the Atomic Energy Commission approved the establishment of a cancer research hospital with appropriate laboratory facilities at the University of Chicago. It was intended that this hospital be administered by the Medical School and Clinics of the University of Chicago and that its facilities be available to qualified investigators of the Argonne National Laboratory and of institutions associated with it. After nearly three and a half years of building, with an expenditure of approximately three million dollars, the Argonne Cancer Research Hospital was officially opened on January 1, 1953, and the clinical and laboratory experimental program got under way, the following spring. Its purpose and program are directed toward the exploitation of high energy radiation sources for the treatment of malignancies; utilization of radioisotopes in the diagnosis and therapy of disease states; and basic research in oncology and hematology; as well as to the elucidation of certain biologic effects of ionizing radiations.

The physical facilities comprise 58 patient beds available for clinical research, radiochemical laboratories, animal quarters, and three sources of high energy radiations. These latter are a 50-Mev linear electron accelerator, a 2-Mev Van de Graaff accelerator, and a 2800-curie Co^{60} unit designed for rotational therapy. These high energy sources are available for biological experimentation as well as physical research, in addition to the therapy of tumors in patients.

The scientific program of the Argonne Cancer Research Hospital is correlated in general with the broad scientific program of the University of Chicago's Division of Biological Sciences and the University Clinics, of which it is a part. In addition, close liaison is maintained with the scientific program of the Argonne National Laboratory. The operational plan of this research hospital provides for the participation in its facilities and program by the members of the staffs of the Argonne National Laboratory and those universities participating in the Cooperating University Program of the Argonne National Laboratory.

The research efforts of this group are rather broad and, for the most part, interrelated. For this discussion it might be well to review the total program under the following headings:

High Energy Radiation Sources for Therapy and Biological Studies

Certain types of cancer can be removed surgically, whereas other types for one reason or another cannot be so treated; hence, other means of ridding the body of cancer cells must be resorted to. For many years man has known that high energy radiations will destroy the living cell, and this has formed the basis for devising suitable sources of high energy particles for tumor destruction. In establishing a protocol for patient treatment, it is extremely important that normal, healthy tissue be subjected to minimum radiation, at the same time focusing the maximum energy of the high energy beam on the tumor mass. With these points in mind, both the Co^{60} and linear accelerator devices were developed.

There has been considerable activity in this area from the very beginning of this program. A large number of cancer patients have been treated with the two million volt Van de Graaff and the cobalt unit. Patient treatment with the linear accelerator did not begin until mid-June of 1959; consequently, the number so treated to date is small. A total of approximately 1,200 patients have been treated or retreated with the supervoltage equipment at this hospital. Although the overall use of high energy sources in the treatment of malignancies has not been as encouraging as had been hoped, the investigators have found certain advantages in the use of each device, particularly with respect to patient comfort both during and immediately following treatment.

Prior to and paralleling patient treatment with these high energy sources, rather extensive radiobiological experiments with animals have been carried out. Such studies are necessary to determine dosimetry for the treatment of tumors in man. In addition, comparative studies of the RBE of x-rays, gamma rays, and electrons currently in use in the hospital have been and continue to be pursued in an attempt to gain a better understanding of their biological actions. Refinement of the values obtained will continue as more experience is gained in patient treatment, as well as in additional animal studies.

The following high energy radiation sources are currently in use at the Argonne Cancer Research Hospital:

Van de Graaff Generator. This device is capable of producing charged particles in the two million electron volt range. It is a standard high energy therapy device which has been available for many years to the medical profession. A large number of cancer patients in this hospital have received and continue to receive treatment from this source.

Cobalt-60 Teletherapy Unit. A kilocurie Co^{60} therapy unit designed specifically for revolution therapy has been in use at the Argonne Cancer Research Hospital since early 1954. This unit was designed to obtain the best characteristics which could be achieved at that time without regard to specifications arbitrarily laid down by others. One of its unique features is the use of uranium rather than other materials for the shield. The result is a large reduction in weight of the shield and consequent decrease in the size and complexity of the device.

The unit consists of a single source which can revolve continuously in a vertical plane about a horizontal axis, as shown in the photograph. A collimated beam of radiation is directed at the axis of revolution. The patient is placed in a recumbent position on the axis of the machine and may be treated by full rotational, sectorial, or stationary fields.

This unit has been in continuous use since 1954, with approximately 800 patients receiving treatment. In November 1957, the cobalt source was replaced with one of 2,800 curies, having a specific activity of 240 curies per gram. This higher intensity source has resulted in a decrease in patient treatment time.

Linear Accelerator. This particular accelerator was constructed by the physicists on the staff, with the assistance and cooperation of scientists at Stanford University who had successfully designed an electron linear accelerator. The unit constructed at the Argonne Cancer Research Hospital represents a modification of the original unit, the operating principle of which is based on two important facts. First, an electromagnetic wave, producedwhen a radio-frequency pulse is directed into a hollow metal tube, can be made to travel through the inside of the tube parallel to its axis in such a way that its velocity is equal to that of electrons injected into the tube. Secondly, a sufficiently high fraction of electrons which are injected will remain in the hollow tube and will be accelerated to the desired energy.

At the Argonne Cancer Research Hospital a beam scanning device was developed which made possible a new approach to electron therapy. This device, more properly called a magnetic deflecting and scanning unit, is capable of directing a high energy electron beam of small cross section to scan over any arbitrary field size and shape. This unit is capable of accepting electrons from 5 to 50 million electron volts with a beam diameter of one centimeter or less. The scanning device includes three

electromagnets which bring about a linear displacement of the horizontal beam and ultimately deflect it through 90°, as shown in the schematic drawing, Figure 1. The following advantages are obtained by using this adaptation to the linear accelerator:

(1) The depth of penetration within a single field can be varied by varying the energy of the electrons in the course of scanning to give any desired changes;

(2) rapid field size selectability including circles, rectangles, as well as irregular shapes, is possible;

(3) single field, multi-port, and revolution therapy can be used; and

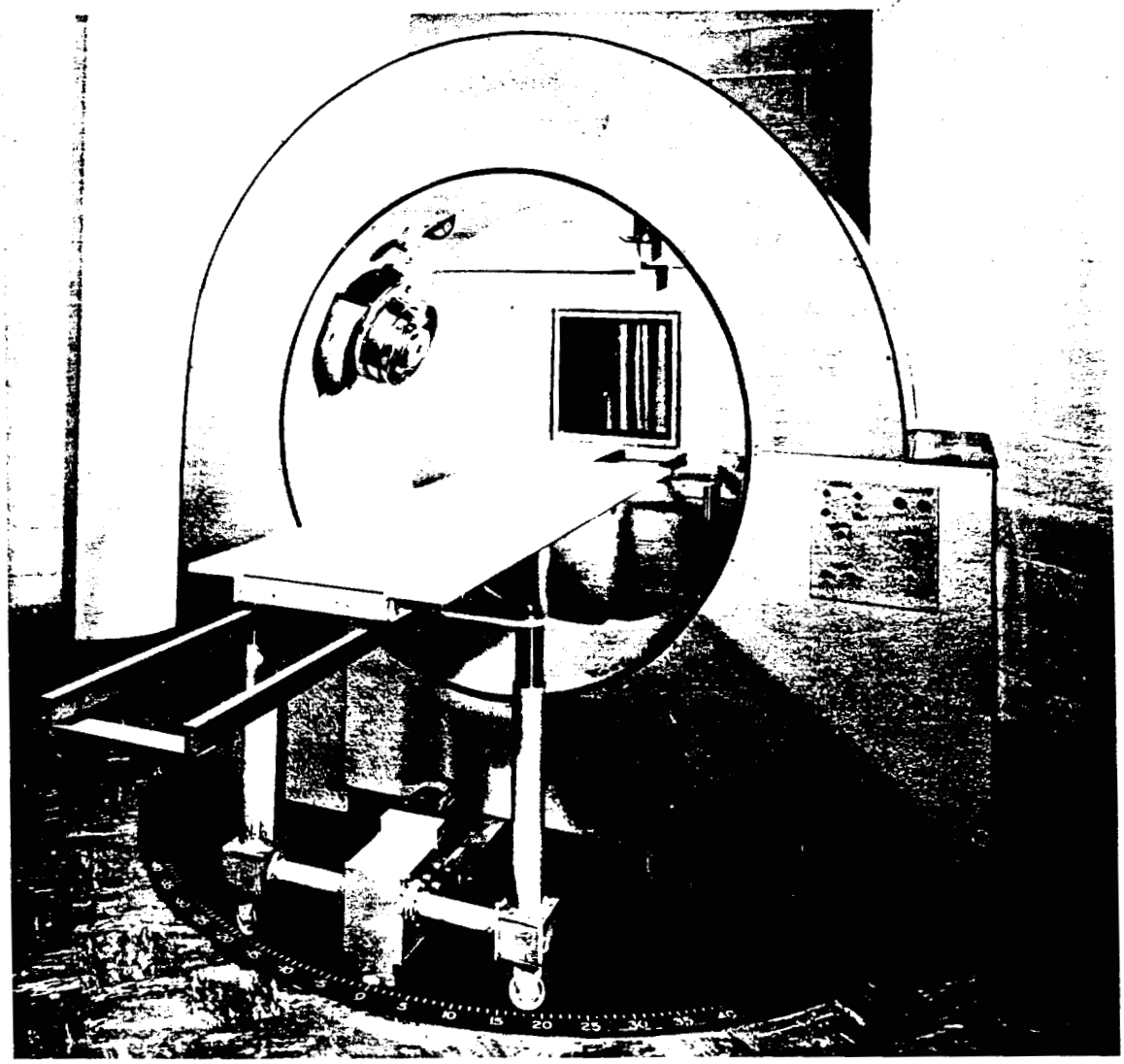
(4) the patient is immobilized in a recumbent position.

This combination of a linear accelerator and beam deflection and scanning unit promises to take full advantage of the unique depth dose properties of high energy electrons. It further provides full flexibility of beam direction in treating a recumbent patient, easy control in selection of field size and shape, conventional single portal as well as revolution therapy, and protection of the patient from stray radiation.

In treating different types of cancer with this linear accelerator, the finite penetration of the electron beam was used to spare the brain or some other critical organ. Experience to date has clearly demonstrated a marked increase in ability to localize the radiation in the tumor itself. Clinical results have been encouraging and skin damage has been less than expected, even less, it appears, than can be explained on the basis of physical dose to the skin.

Though experience with the linear accelerator has so far been limited, it does appear to offer many advantages in treating difficult cases.

It is realized by many physicians that the use of radiation alone is not the answer to the successful treatment of certain tumors. Accordingly, an intensive effort is being made to find a means of potentiating the effect of radiation on the tumor while at the same time minimizing the overall effect on the patient. The compound, triiodothyronine (T-3), among others, has been



Cobalt 60 revolution therapy unit showing source shield, treatment cot, and auxiliary control panel.

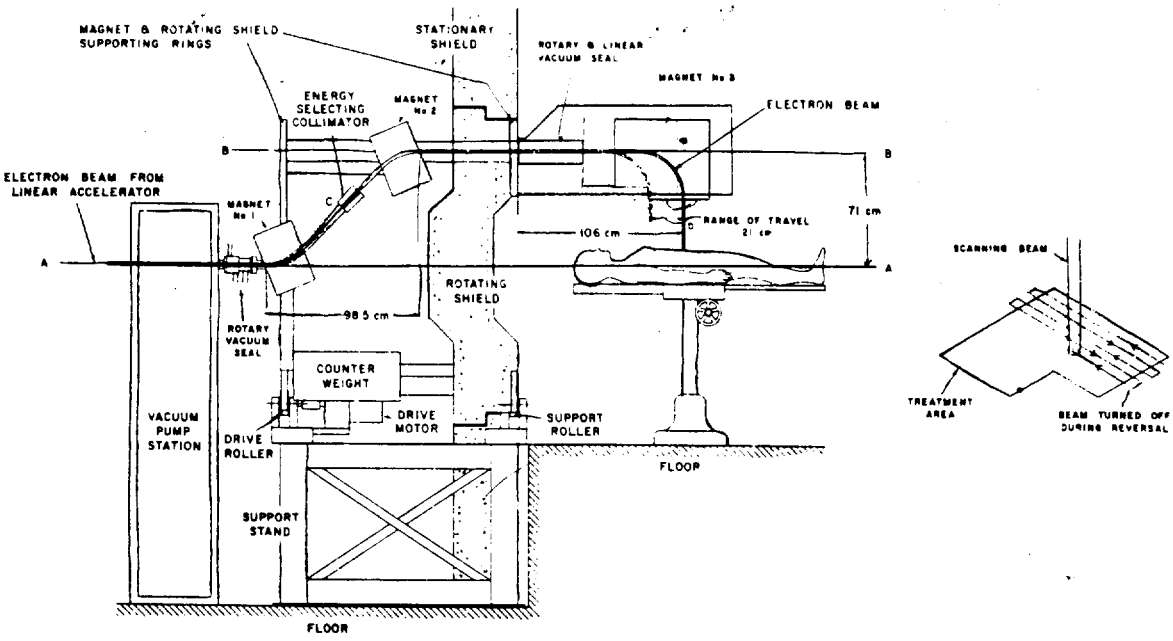


Figure 1

This schematic drawing of the deflecting and scanning unit shows the arrangement of the triple magnet system, counterweight, rotating shield, treatment cot, and patient. The electron beam is contained within a vacuum chamber which is not shown in this drawing. The inset on the right side illustrates scanning over a single portal field.

given some consideration. The use of l-triiodothyronine in conjunction with radiation in the control and ablation of various tumors has been found to be effective both in clinical patients and in experimental animals, although some toxicity has been noted in patients subjected to prolonged treatment. In an attempt to discover a method of eliminating the deleterious effects of prolonged, continuous use of the drug, it was administered alternatively with x-rays at various intervals to treat various animal tumors, and results suggest that there is a very definite relationship between times of administration of the drug and x-irradiation.

Favorable results have also been obtained using colchicine; other drugs are currently under investigation.

Radioisotopes in Diagnosis and Therapy

Sometimes tumor diagnosis and precise localization of cancerous lesions pose a difficult problem for the physician. This group continues to explore the various radioisotopes in search of an improved technique with respect to this problem.

Octo-iodofluorescin (OIF) labeled with iodine-131 has been studied as an agent for brain tumor localization. The labeled OIF is considered by this group to be superior to other agents because of its greater persistence in tumor tissue, thus affording a longer period of time for normal tissues to eliminate the dye. Over 100 patients at the University of Chicago Clinics have been scanned using OIF. The electronics group is developing a high efficiency scanning device which will be operational by December, 1960.

Preliminary investigation indicates that phthalocyanine, when labeled with a radioactive metal (mercury-197 or 203) and injected into experimental animals, may prove a useful diagnostic tool in revealing specific sites of tumor localization. The use of soft x-ray emitters in this connection may well improve the resolution in liver scanning.

Clinical and experimental work continues with the various soft x-ray emitting isotopes which have been found to be well suited as a means of delivering interstitial radiation for the treatment of malignancies. Among them, palladium-103 has been used without immediate harmful effects to treat several patients with advanced tumors; yttrium-90 is still being used with success to destroy the hypophysis of patients who have metastatic carcinoma of the breast. Various organic carriers are being tested for use with different isotopic sources in liver and brain scanning.

Fundamental Studies in Oncology

The major effort of this scientific group in the area of basic cancer studies is directed toward problems associated with immunity. The possibility of effectively treating tumor metastases as well as the tumor itself by immunological means has intrigued many investigators. However, the difficulties inherent in such an approach require that emphasis be placed first on elucidating mechanisms at a very fundamental level.

The use of radioisotopes, fluorescence microscope, and immuno-electrophoresis in studying the localization of antibodies and also in tracing virus particles into tumor cells continues. In addition, radioisotopes are used as tracers to study the origin and fate of the antibody-forming cells. Studies also are continuing on the changes produced by x-rays on the immune response in animals, and the effects produced by these changes on tumor sensitivity and the tissue transplantation mechanism.

Much of the biochemical effort has been directed toward fundamental studies involving ribosenucleic acid. It is hoped that a better understanding of ribosenucleic acid synthesis may lead to an insight into the transmission of genetic information to other cytoplasmic particles which will in turn contribute to our understanding of normal and cancerous cells.

In addition to the work on ribosenucleic acid, considerable effort has been directed over the past three years toward studies of a substance known as "erythropoietin." This hormone-like material has been shown to stimulate red blood cell production, and the main objective of this research has been to isolate and characterize this substance with the hope that it might prove useful in alleviating certain blood discrasias that are sometimes associated with certain cancerous conditions.

Biological Effects of Radiation

The effects of ionizing radiation on the skin has been of appreciable concern to clinicians in relation to patient therapy. A number of studies have been carried out to determine the effects of long-term, low intensity, total body radiation on the skin of experimental animals. In addition, the effects of various types of radiation on the metabolism of the skin of dogs have been followed with interest. The quantitative response of the eccrine glands of the human skin to small doses of radiation has also been studied by this group. All of these studies take cognizance of the possible carcinogenic properties of radiation.

In cooperation with members of the staff of the Argonne National Laboratory, clinical studies of the radium patients continue in an effort to determine the long range effects of internal emitters. Radiographic skeletal analysis has now been completed on 181 former radium dial painters from the Ottawa, Illinois area, and determination of the radium body burden of these individuals has been accomplished.

Of especial interest is the increasing frequency of occurrence of epidermoid carcinomata arising in the mastoid air cells of patients carrying a body burden of radium. Two new cases of epidermoid carcinoma have been seen and proven at surgery in the past year and a third suspected on radiographic grounds. This brings the total to six under cognizance of this group.

Special techniques have been devised for study of the intimate vasculature of bone in an attempt to elucidate the mechanism of bone destruction in radium-bearing humans. Histologic study of the bone and epithelium of the mastoid process will continue in order to understand better the mechanism of carcinogenesis in this specific site in radium patients.

Metabolic Studies

The Argonne Cancer Research Hospital, with its 58 research bed capacity, offers a unique opportunity for a team of medical scientists to carry out extensive studies on cancer patients, as well as patients with abnormalities of carbohydrate or lipid metabolism. Major emphasis has been placed on studying the pattern of excretion of carbon-14 labeled carbon dioxide following the administration of metabolically important substances labeled with carbon-14 in human subjects, as well as in experimental animals. These substances include bicarbonate, formate, acetate, glucose, and ribose.

Studies on experimental animals involve the determination of normal patterns and the effect of whole body radiation injury on such patterns.

As patients with appropriate diseases (carcinoid, gout, essential hyperlipemia, adrenal carcinoma, etc.) are located, they are admitted to the metabolic unit for pilot studies of various aspects of metabolism using carbon-14 and tritium-labeled materials. Particular attention is devoted to the metabolic interactions of the principal pools--carbon dioxide, urea, acetate, and the like.

Two programs on the study of experimental cancer are under way, one involving the study of the effect of a developing cancer on metabolism of carbon-14 labeled intermediates. To date, alterations in metabolism of glucose and acetate have been demonstrated in mice with solid Ehrlich cancer. The second program is an investigation of the hormonal influence of the biosynthesis and turnover of proteins and nucleic acid in normal mice and in mice with a hormone-dependent transmissable mammary cancer.

* * * * *

The Argonne Cancer Research Hospital represents the Atomic Energy Commission's greatest effort in the area of cancer research. Its integration with the University Medical School and associated Clinics makes possible a sizable influx of patients. In this way, the medical staff is able to select patients most suitable for study and intensify their efforts for the solution of specific problems. The Hospital also enjoys a close relationship with nearby Commission facilities at the Argonne National Laboratory. This mutually collaborative atmosphere has been a tremendous asset to the medical staff in carrying out its research responsibilities.

ARGONNE NATIONAL LABORATORY

Division of Biological and Medical Research

Argonne, Illinois

Austin M. Brues, M. D.	Director
E. L. Powers, Ph.D.	Assistant Director

ARGONNE NATIONAL LABORATORY

Division of Biological and Medical Research

Cancer research is intimately related to many problems in radiobiology, and it can be said that important observations on cancer production are made in the various toxicity programs. These are complemented in the cancer research program by several lines of investigation directed more specifically to fundamental differences between normal and neoplastic states. Studies are made of carcinogenesis by radiation and other agents, growth characteristics of tumors, and physiologic and immunologic relationships between tumor and host. Applications of radiations and other agents to the modification of tumor growth represent an important part of the research.

Carcinogenesis

Studies of carcinogenesis include detailed histological examination of pre-neoplastic changes in tissues of irradiated animals. These observations also provide information concerning the latent period for induction of tumors as a consequence of various patterns of external and internal radiation.

Mechanisms of carcinogenesis are being investigated in biochemical and cytological studies of liver during prolonged administration of the hepatic carcinogen 2-acetylaminofluorene (AAF). Others have shown that administration of the carcinogen need not be continued until tumors are grossly visible. Tumor incidence will be high if administration is continued through a relatively short critical period; if the carcinogen is withdrawn before this critical period, very few animals develop tumors. The present results show that during continuous administration of the carcinogen, rapid cell division begins suddenly in the liver at a time which corresponds to the critical period just mentioned. Apparently, "successful" malignant cells are not produced until a physiological threshold is reached which results in active cell division in the liver. The time of onset of rapid cell division depends on the age (liver size) when carcinogen administration begins. Present experiments will determine whether onset of cell division in these livers is affected by the carcinogen liver in the diet. When the timing of the onset of cell division can be controlled, its relationship to the carcinogenic process can be determined more precisely. In addition to the unusual degree of cell division in these livers,

there is a synthesis of protein and ribosenucleic acid (RNA) at a steady rate, which appears to be independent of age. Synthesis of protein and RNA continues at a constant rate for many weeks, during which time liver weight may increase threefold. The relationship of this abnormal synthesis to the "threshold" effect described above and to the carcinogenic process is being investigated.

Experiments to examine some implications of the somatic mutation hypothesis are in progress. Under comparable conditions of carcinogen dosage and of specific mutation rate, the point-mutation concept implies that exposure of a large number of cells (a large animal) to a carcinogen should produce more mutations and, therefore, more tumors than exposure of fewer similar cells (a small animal). This is being investigated by the administration of plutonium or methylcholanthrene to mice, rats, and rabbits (ratio of body weights, 1:8:80).

In another experiment on carcinogenesis, it was found that late effects of X-irradiation in mice were not additive with methylcholanthrene applied some months after irradiation; in fact, fewer tumors were produced in the irradiated, methylcholanthrene-painted animals. Moreover, the late effects of the irradiation were not comparable to a simple increase in age.

Preliminary results of still other experiments suggest that administration of growth hormone increases the incidence of bone tumors after gamma irradiation and that thyroxine shortens the latent period.

The role of sunlight (ultraviolet irradiation) in the production of skin tumors in man is indicated by the results of a study of incidence of skin tumors in several American cities; the incidence rate doubles for about each 265 miles farther south.

Chronic consumption of arsenic is known to produce skin tumors in humans; attempts are being made to produce comparable skin tumors in mice by chronic administration of arsenic in the drinking water.

Growth Characteristics of Tumors

Properties of tumors are being studied using a subline of the MGIM fibrosarcoma, adapted to the ascitic form, in which the individual cells grow separately in fluid that accumulates in the peritoneal cavity of the host. It has been shown that the solid form contains almost one-third more calcium than the ascitic form. This finding is of interest because calcium is believed to play a

role in the cohesion of cells in normal tissues. Various lines of evidence indicate that cell proliferation in some ascites tumors may be carried on by only a fraction of the total cell population. This complicates interpretation of estimates of the intermitotic time; the incorporation of tritiated thymidine into the individual cells of an ascites tumor cell population is being studied by autoradiography in order to determine the fraction of mitotically active cells.

Earlier results in another ascites tumor study pointed to an increase in tumor cell size a few days after injection of mouse ascites into a rat. Although the cells grow larger, there is no increase in the quantity of DNA per cell. When previously irradiated mouse tumor cells are introduced into a normal mouse, the cells become larger than normal and there is some increase in DNA. The basis for the increase in cell size appears to be somewhat different in the two cases.

Tumor-Host Relationships

Present efforts in tumor therapy include study of various aspects of neutron capture therapy, as well as exploratory investigation of other potentially useful factors. Reference has already been made to hormonal influences in carcinogenesis. In neutron capture therapy, destructive irradiation of a tumor is accomplished by neutron activation of a stable nuclide selectively concentrated in tumor tissue. For any reasonable expectation of success, it is necessary that the selected nuclide be combined very firmly with an organic compound that will be concentrated in the cells or stroma of the tumor. Conditions must be chosen so that only the administered nuclide will have an appreciable cross section for neutron capture. Experiments in several laboratories have centered mainly on efforts to utilize activation of lithium-6 or boron-10 by thermal neutrons to take advantage of the destructive alpha decay which follows. This approach has had limited success because it has not been possible to prepare sufficiently stable combinations of these nuclides with organic compounds. Theoretical studies indicate that application of resonance rather than thermal neutrons will increase the number of useful nuclides and permit the use of nuclear fission rather than alpha decay. This may provide a great increase in destructive effect and may facilitate monitoring during the course of treatment by measurement of the gamma rays produced during the nuclear fission. Organic compounds containing some of these nuclides in extremely stable combinations have been prepared.

In another study, inhalation of oxygen during irradiation increased the initial regression of well implanted solid ascites tumors. However, this procedure alone or in combination with certain antimetabolites, e.g., 2-deoxy-d-glucose or cyanide, did not significantly increase the number of non-palpable tumors observed six weeks after irradiation over that obtained with radiation in air. Other work is concerned with the possible application of far-red irradiation. It is known that chromosome damage in irradiated plant tissues is increased considerably if the tissues are subsequently exposed to far-red radiation. Preliminary results suggest that this occurs also in animal tissues. Chromosome abnormalities in Krebs ascites tumor cells were increased when irradiation was blanketed or followed immediately by exposure of the cells to far-red radiation.

During ensuing years, studies of the latent period in induction of tumors by bone-seeking radioelements will be extended. Detailed biochemical and cytological studies will be continued on the response of liver and the "threshold" effect in chemical carcinogenesis by AAF. Further investigation will be made of the role of hormones in carcinogenesis by ionizing radiation. Studies of the somatic mutation hypothesis will be expanded to include other forms of radiation and other animal species. The possibility that tumors are produced by indirect rather than direct action of ionizing radiation will be examined by transplanting normal tissue into an irradiated field.

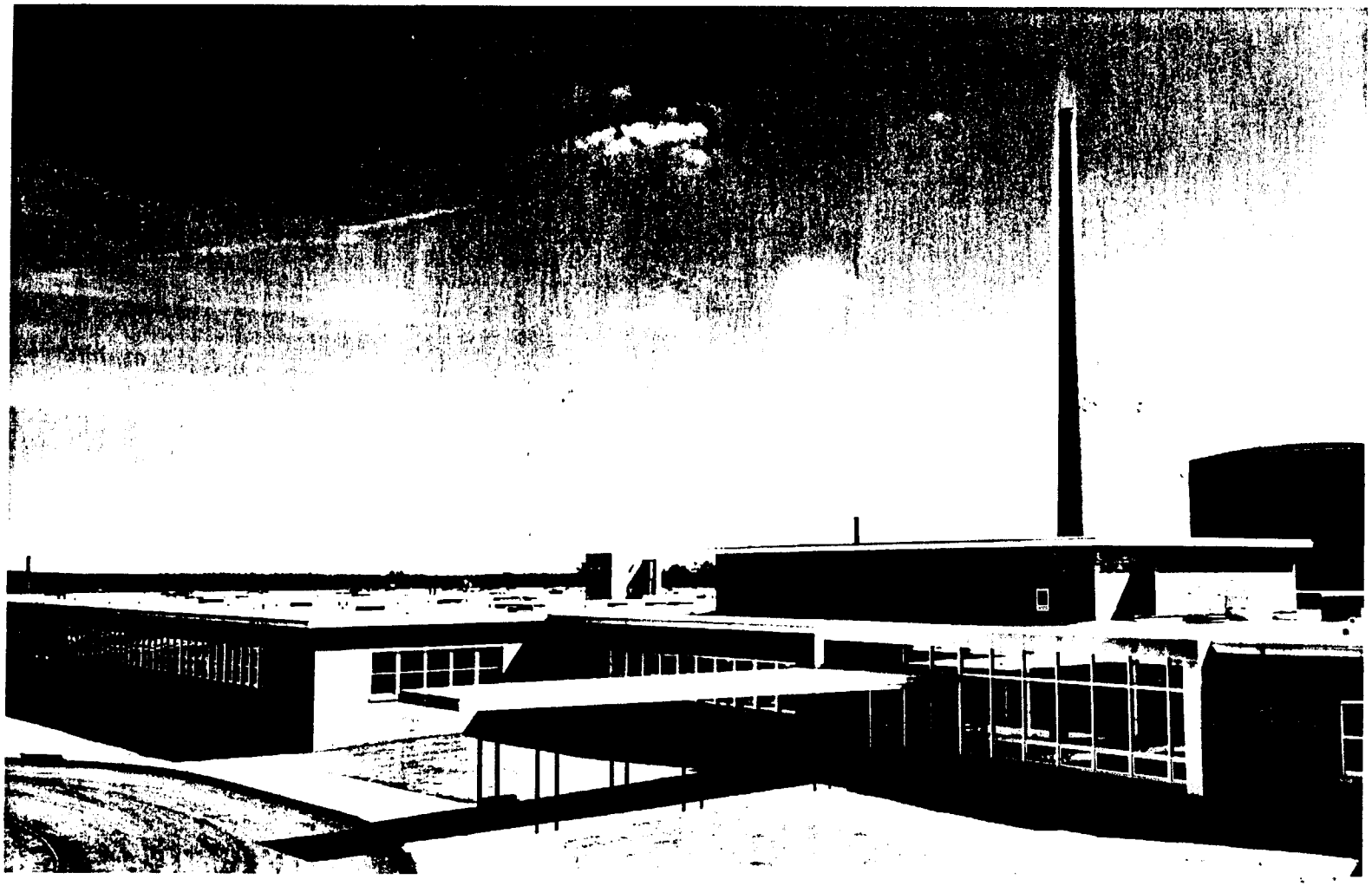
Comparative studies of the solid and ascitic forms of tumors will be continued, particularly in terms of factors that may influence the cohesiveness of the cells. An understanding of these factors may have ramifications to processes controlling metastasis. Other investigations will consider the mechanisms underlying the immune response of heterologous ascites tumor cells. Experiments on neutron capture therapy will be continued, and other applications of neutron capture activation will be explored. Neutron activation will be evaluated as a possible method for determining arsenic distribution in tissues of animals receiving arsenic for extended periods of time. Study of the potentiating effect of far-red irradiation on x-ray induced chromosome damage will be extended to tissue culture of Chinese hamster organs, which are more favorable for determination of chromosome aberrations.

BROOKHAVEN NATIONAL LABORATORY

Medical Department

Upton, Long Island, New York

Lee E. Farr, M. D.	Medical Director and Chairman
W. Alvord Finn	Executive Assistant and Hospital Administrator
Lewis K. Dahl, M. D.	Chief of Medical Service



The Main Entrance to the Medical Research Center, Brookhaven National Laboratory

BROOKHAVEN NATIONAL LABORATORY

Medical Department

The Brookhaven National Laboratory is operated by the Associated Universities, Inc. under contract with the U. S. Atomic Energy Commission. This Laboratory is a national research center for fundamental and applied research in the nuclear sciences and related subjects and is an integral part of the AEC's nationwide program. Its major objectives are:

(1) To seek new knowledge in the nuclear sciences and other related fields;

(2) To encourage appropriate use of its facilities by qualified scientists of universities and other laboratories and industrial research groups;

(3) To assist the Atomic Energy Commission in the solution of specific problems;

(4) To aid in the training of scientists and engineers in nuclear science and technology.

The biomedical program at Brookhaven was supported initially in fiscal year 1949, and the following year the first funds were made available for research in the cancer field. Since the inception of this medical program in fiscal year 1949 there has been considerable intensification of activity and expansion of the program. The completion of the new medical center in December 1958 marked a high point of construction activity and makes possible the attainment of a stable and well integrated medical program.

This modern, well equipped, Medical Research Center, built at a cost of 6.5 million dollars, includes twelve individual patient rooms in four identical circular nursing units. This arrangement provides a forty-eight bed hospital with a central area (see photograph) for ancillary services housing occupational therapy and day rooms, central supply, emergency operating room, x-ray, pharmacy, medical photography, and hospital division offices.

The laboratory sector of the building is shown in the photograph and contains modern, completely outfitted laboratories for scientific research.

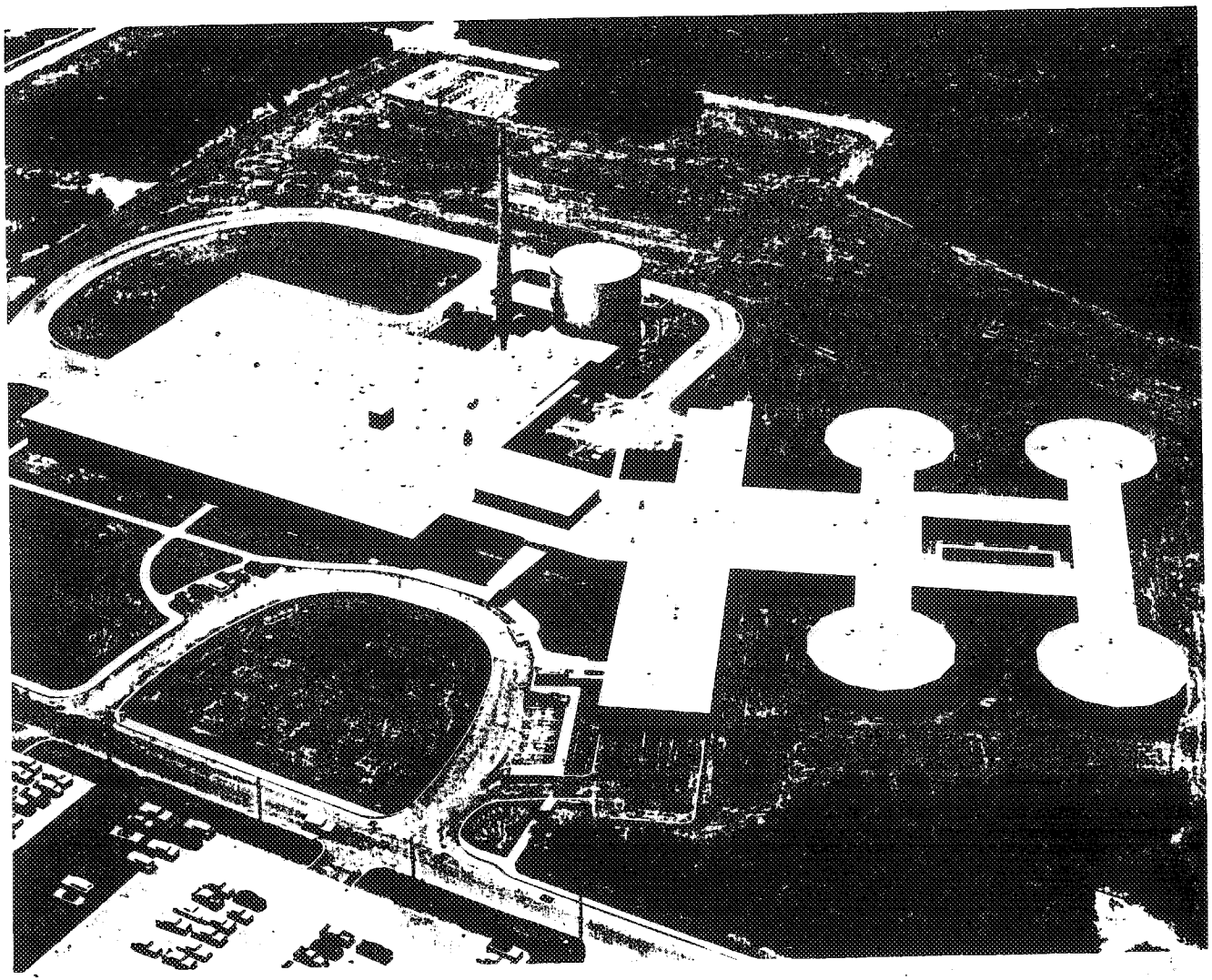
The research program of the Medical Department concerns itself with the biological effects of radiation and, in particular, with particle radiation of very short range. Although the program is not primarily that of research on cancer, its problems are intimately related to the problems of cancer. This is necessarily so since the use of radioactive isotopes offers a most promising possibility for the treatment of cancerous conditions as yet beyond ordinary medical therapy. Furthermore, in attempts to utilize radioisotopes in this fashion, precise testing of capacity to control the movement of the radioactive isotope within the body is carried out. This knowledge is of the utmost importance in the utilization of radioactive isotopes for general diagnostic procedures. Finally, since cancer may be provoked by radiation exposure, it becomes not only of interest but of great moment to the users of radiation and radioactive isotopes to learn under what conditions and to what degree these types of tissue experiences may lead to malignancies.

The Medical Research Reactor

A nuclear reactor specifically designed for a program of investigation in medical problems has been built into the Medical Research Center as an integral part. The reactor can be seen in the photograph, located at the rear of the Center. Its uniqueness is based largely on the planning of its radiation shielding and the particular way in which the research conveniences are provided. Additional advantages accrue simply because of its physical location contiguous with the medical laboratories and the research hospital of the Department, and because control of scheduling and operation are directed exclusively toward the medical research program.

The design specifications for the Brookhaven Medical Research Reactor (MRR) called for a capability of continuous operation at a power level of one megawatt. The fuel elements each contain an average of 140 grams of uranium, and the reactor is critical when 17 of them are in use. The moderator is pure, natural water, and the core is cooled by circulating the moderator water through a heat exchanger. Outside of the core is an air-cooled graphite reflector in the shape of a cube and fitted around the core tank as tightly as possible to a thickness of about three feet. After filtering, the cooling air is exhausted up a 150-foot stack. When operating at one megawatt, the MRR has a core flux of fast and thermal neutrons of the order of 10^{13} $n/cm^2/sec$.

Shutters have been built into the neutron apertures leading to the experimental irradiation rooms. The shutters incorporate flexible beam-directing and neutron-moderating arrangements in a hydraulically operated device weighing some 20 tons with an effective opening interval of about three seconds. Two irradiation rooms are



Aerial view of the Medical Research Center, Brookhaven National Laboratory, with Medical Reactor in the rear of center

provided to sustain a standardized therapy program and to accommodate development of procedure improvement and associated animal studies. Since these rooms are enclosed within shielding walls and also are equipped with neutron activation tubes passing directly to the reactor core, they also may be employed to investigate diagnostic and therapeutic possibilities of radioactive isotopes of very short half life. Preparation for either of these purposes thus can be carried out without interference from other reactor activities and under hospital conditions.

Neutron Capture Therapy

Neutron capture therapy is an experimental radiation treatment which uses energetic heavy particles created inside the diseased tissue. It is based on localizing, in some fashion not as yet understood, a target atom, in this case non-radioactive boron-10, within and throughout the tissues marked for destruction by the treatment and then passing a stream of slow neutrons through that region. The neutrons trigger disintegration of the boron-10 atoms already in the tissues. For best effects, the target element is so chosen that the decay of the excited isotope is immediate and results in energetic heavy particles as indicated in the formula:

$$_5B^{10} + {}_0n^1 \text{ --- } {}_5B^{11*} \text{ --- } {}_3Li^7 + {}_2\alpha^4 + 2.79 \text{ mev.}$$

*(The boron-11 is in an excited intermediate state formed by neutron capture which immediately decays to lithium with the release of an energetic alpha particle.)

Further, the distance traveled by the heavy particles for best effects should be of the order of a cell radius assuming a spherical cell. Thus the entire energy of the reaction will be released and absorbed within an average cell volume. Experiments with mice suggest that, for equal amounts of boron, sodium pentaborate would be less toxic than sodium tetraborate, and accordingly the pentaborate has been used in all of the latest series of patients.

Further studies are proceeding on the distribution of both borax and sodium pentaborate in normal and neoplastic tissues in mice as a function of time. By this means it is hoped to determine the interrelationships of neutron exposure and boron atomic distribution for sure destruction of viable neoplastic cells while maintaining a high level of discrimination between normal and neoplastic structures. Of the boron compounds used, it

appears that their distribution and concentration within the neoplasm and its several parts do not follow a smooth curve but proceed stepwise. The significance of this result is being investigated.

In general studies on the efficacy of neutron capture therapy, an extensive investigation is being made on the various structures of the central nervous system for morphological effects of this procedure utilizing thermal neutrons. Serial sections of CNS obtained from patients at autopsy are being studied in collaboration with the Department of Neuroanatomy at Harvard and the Department of Neuropathology at the Armed Forces Institute of Pathology. It has become necessary in this study to devote considerable effort to elucidation of the biology of the tumor, that the effects due to the disease per se and those due to the therapeutic manipulation may be clearly separated. The results of this study have been encouraging to date in that they indicate an absence of effects on normal structures and suggest some radiation effects on neoplastic structures. The desired and sought for chemical and biological discrimination can be rather clearly demonstrated in the mouse experiments, although as yet it is only suggested in patient studies.

Fundamental Research

The development of tritiated thymidine as a suitable label which can be demonstrated by proper radiographic techniques has had immediate application, particularly to the study of the genesis of the various cells of the blood. It has always been of importance to determine in leukemia whether or not an increased rate of synthesis or decreased rate of removal was the primary cause of the increase in cells in the peripheral blood. To a degree the same problem obtains with polycythemia vera. Utilizing this compound, it was found that the labeling of neoplastic cells in the marrow of patients with multiple myeloma or chronic lymphatic leukemia was rare and that leukemic cells in blood of chronic lymphatic leukemia would not incorporate thymidine. Labeling was extensive in the marrow and peripheral blood of patients with acute and chronic myelogenous leukemia. The marrow of patients with infectious mononucleosis showed intensive labeling of primitive stem cells, and an increased number of labeled large mononuclear cells were present in the peripheral blood. The significance of these distinct differences in the different hematopoietic disorders studied and the potential value of these differences in establishing diagnosis, therapy, and/or prognosis are for further and continuing consideration.

With the demonstration that small doses of tritiated thymidine could be administered safely to patients, it was also possible to study patients with malignant diseases who had no disturbances in the hematopoietic system.

In another study, which has been to a considerable extent concerned with multiple myeloma but which also has included a variety of other malignant diseases, a detailed investigation of the physico-chemical nature of crystalline albumin and of gamma globulins and physiological studies on the rate of disappearance of these proteins labeled with radioactive iodine (I^{131}) have been carried out. Certain differences have been observed in patients with multiple myeloma, the significance of which is still under study.

Previous work both here and elsewhere demonstrating that a significant single exposure to sublethal whole body radiation of the young Sprague-Dawley female rat is followed by the relatively rapid appearance of mammary neoplasms has been confirmed and extended. The incidence of breast neoplasia rises linearly with dose between 23 and 400 roentgens of 250 KVP x-rays, measured at 11 months after exposure. Above dosages of 400 r the response does not increase. Ovariectomy preceding or following exposure to 400 r reduces but does not eliminate neoplasia of the breast. Intact males respond to the same degree as ovariectomized females, whereas castrate males give a response intermediate between that of intact males or castrate females and intact females. It would thus appear that the maximum induction of breast neoplasia following irradiation of these animals was affected by the level and type of gonadal hormones. Four distinct histological types of breast tumors have been observed - adenocarcinomata, adenofibromata, fibroadenomata, and fibrosarcomata. Mixed types of breast tumors are seen also. Shielding experiments have shown that neither the pituitary nor the ovary need be irradiated for induction of breast neoplasm. Results on effects following selective irradiation of the breast are not yet complete. Facts suggest that a single hit somatic mutation theory and an indirect or abscopal theory of induction of neoplasia are not necessarily mutually exclusive.

LAWRENCE RADIATION LABORATORY

University of California

Berkeley, California

John H. Lawrence, M. D.	Director
James L. Born, M. D.	Associate Director

LAWRENCE RADIATION LABORATORY

The Biology-Medicine Program at the Lawrence Radiation Laboratory consists of research in three general areas: biological effects of radiation, treatment of the detrimental effects of radiation, and the beneficial applications of atomic energy. The program utilizes the campus facilities of Donner Laboratory and the Donner Pavilion of Cowell Hospital, plus the 184" cyclotron on the hill. It is the 900-Mev alpha particle beam of the cyclotron that is utilized in the irradiation of the pituitary in patients with certain malignancies. In addition, a small amount of space has been provided at the Livermore laboratory for biologic studies involving reactors.

The unique combination of facilities, personnel, and established research programs in the Laboratory's Biology-Medicine Division has attracted advanced students from every part of the world. This year nearly thirty foreign postdoctoral fellows are in residence. The training provided these visitors by the Laboratory, in cooperation with the University, stands out as a valuable contribution to the advancement of worldwide knowledge in biology and medicine.

Although there is an extensive research program in the biomedical area supported currently, the cancer program in this Laboratory is limited for the most part to basic considerations.

The current investigation of the use of high energy particles in the study and control of certain malignant and endocrine-mediated diseases through selective irradiation of the pituitary gland is of wide interest.

The unique properties of the high energy particle beams of the 184" cyclotron enable the localization of large doses in the pituitary gland. Hypophysectomizing, as well as suppressive doses of irradiation, can be given. Clinical findings are closely corroborated by gross and histologic evidence of pituitary destruction. Satisfactory evidence of arrest or remissions in metastatic carcinoma is observed in approximately 40 per cent of the patients. The effect of pituitary irradiation on patients with acromegaly and diabetes mellitus shows promise and will be continued. Alpha particle irradiation is proving comparable in its effectiveness to proton irradiation in ablation of the pituitary.

The underlying metabolic factors, particularly those relating to endocrine control and function, will be investigated, and it is

expected that some clarification of the biochemical processes will be obtained. A continuing search will be made for possible biochemical and metabolic factors that may modify the course of these diseases.

Further information should be available which may indicate whether complete ablation of the pituitary is essential for control of hormone-dependent diseases.

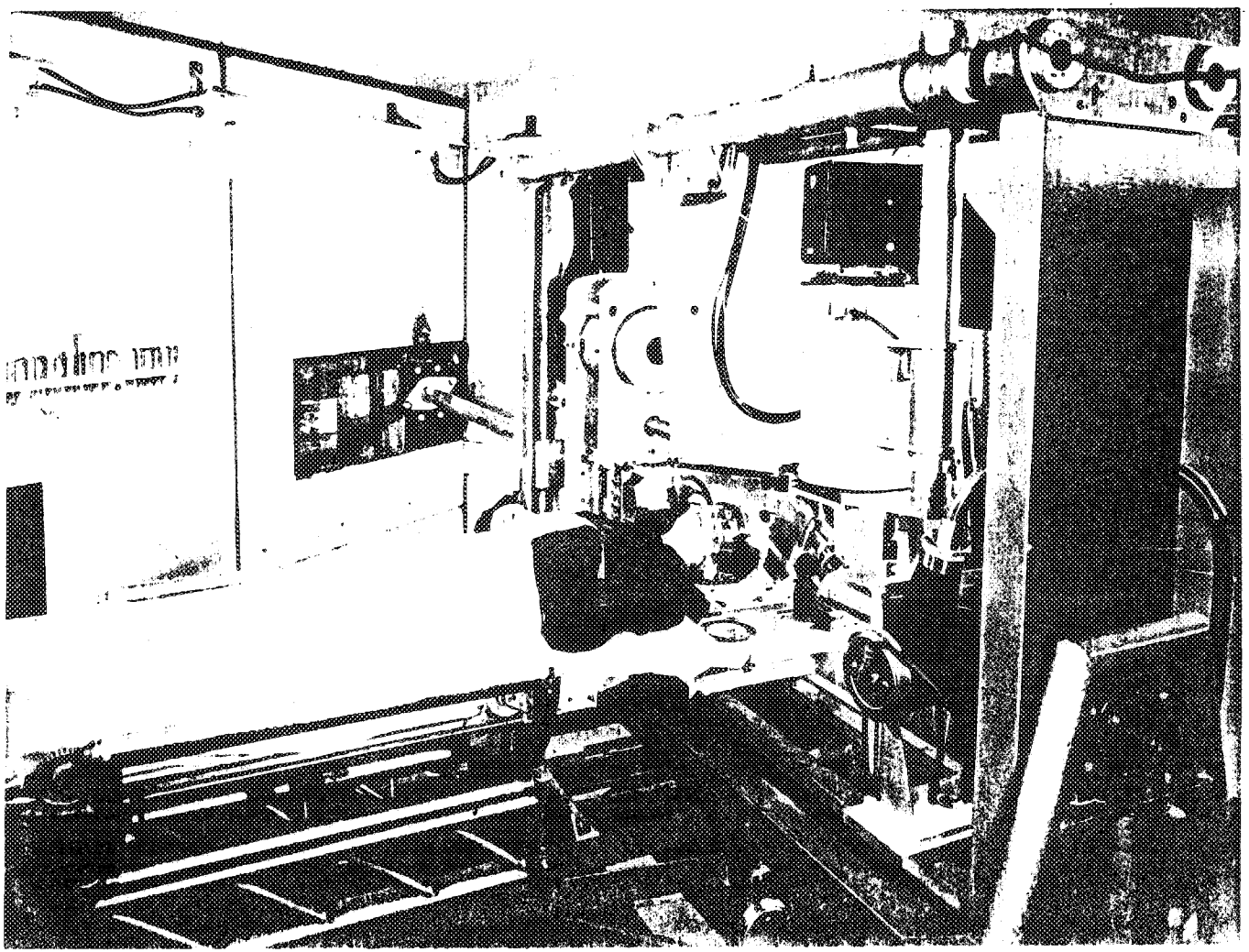
Follow-up studies are being maintained on all patients. Of the smaller series of patients (30 receiving 340 Mev proton particles) irradiated in 1954-55, one is living. In the second series of a total of 134 irradiated with 900 Mev alpha particles, 65 patients are living. All of these patients are being carefully studied at intervals of four to six weeks. Complete endocrine studies are being done on all patients. Results of analysis of this group will be published.

Pituitary Irradiation Studies

Clinical and Metabolic Studies in Patients after Alpha-Particle Irradiation to the Pituitary

The largest group of patients irradiated were those with mammary carcinoma. All of these had progressive metastatic disease and in most instances were in an advanced stage, having been subjected previously to all conventional forms of therapy and in some instances to bilateral adrenalectomies. The total number of patients receiving pituitary irradiation with high energy particles from the 184" cyclotron at the Lawrence Radiation Laboratory of the University of California and the type and distribution of cases are given below:

Diagnosis	No. of Patients Irradiated
Cancer of the breast	118
Diabetes mellitus with retinopathy	23
Acromegaly	12
Chromophobe adenoma	3
Malignant exophthalmus	2
Chronic lymphatic leukemia	1
Acute leukemia	1
Dysgerminoma	1
Cancer of the prostate	1
Cushing's disease	1
Cancer of the adrenals	1



Patient receiving treatment for pituitary ablation in the proton beam of the 184 inch cyclotron.

Selection of patients for irradiation was done after careful clinical and laboratory investigation. All were in a progressive state of disease and were no longer considered responsive to the usual conventional forms of treatment. The patients with diabetes mellitus had progressive retinopathy and in some instances nephropathy. They were typical long-term diabetics with the disease difficult to control. Those with acromegaly were all symptomatic, and five of them had associated diabetes. The majority of these had received one or more courses of conventional 200-kv x-ray therapy.

The early schedule of irradiation was based on experience gained from extensive animal studies. Since the effect of high energy particles in suppressing the function of the human pituitary gland was not known, it was necessary to investigate its effects by starting conversatively with low dosages. These were gradually adjusted towards an optimal level as histologic studies, patient response and sequelae indicated, and, of course, when any significant modifications were made in techniques. On the present schedule, the patients are irradiated three times weekly for two weeks. The highest total amount, 30,000 rad, has been given to patients with advanced metastatic mammary carcinoma. It is believed, however, that complete hypophysectomy can be obtained within the present range of 18,000 to 24,000 rad and possibly less. The patients with diabetes mellitus received from 11,000 to 24,000 rad, and those with acromegaly up to 7,200. These doses were calculated to the center of the pituitary, the average hypophyseal dose integrated over the isodose surfaces being between 55 and 75 per cent of the peak dose at the center of the gland.

Changes in pituitary function were measured before and after irradiation by determination of the urinary excretion of pituitary gonadotropins and by effects on the target end organs, namely, the thyroid, adrenals, and ovaries. The uptake of iodine-131 by the thyroid gland, the protein-bound iodine, the 24-hour excretion of urinary estrogen were considered as important indices of the effects of pituitary irradiation on the target end organs.

Clinical Management

Since there was no morbidity during the course of pituitary irradiation, those patients who were ambulatory could be treated on an outpatient basis and did not require hospitalization. Follow-up studies were done on all patients at intervals of four to six weeks in order to evaluate response to irradiation as manifested by a decrease in pituitary function and to follow the clinical course of their disease.

Mammary Carcinoma. Twenty-four patients of the group of 118 with metastatic carcinoma irradiated with high energy particles are now living. Thirteen of these are living for more than one year following irradiation, the longest now being five years post-irradiation. Ten of these are in an excellent state of remission. The largest and most beneficial response was obtained in the group of patients receiving the highest amounts of irradiation, i.e., 24,000 to 30,000 rad.

Acromegaly. Thirteen patients with acromegaly were exposed to alpha particles in dosages ranging from 4,000 to 7,200 rad. Those receiving the lower amounts of irradiation were ones who had previously received one or more courses of conventional 200-kv X-irradiation. Two of the group who had associated with their disease a diabetes necessitating management with insulin no longer required insulin following irradiation. In all of these patients, subjective symptoms of headache, loss of potency, and ease of fatigability were present and were difficult to evaluate. All but one patient claimed marked relief following irradiation. There was a fall in serum phosphorus in all patients receiving over 5,000 rad.

Diabetes Mellitus. Twenty-three patients with diabetes mellitus received alpha-particle irradiation in a dose range of 11,000 to 24,000 rad. These patients had marked diabetic retinopathy, and in some instances nephropathy. Twenty-one patients are currently being followed, but it is still too early to determine whether pituitary irradiation will permanently slow down the progression of their ocular disease process. It is anticipated that only partial hypophysectomy will be required in this group of patients.

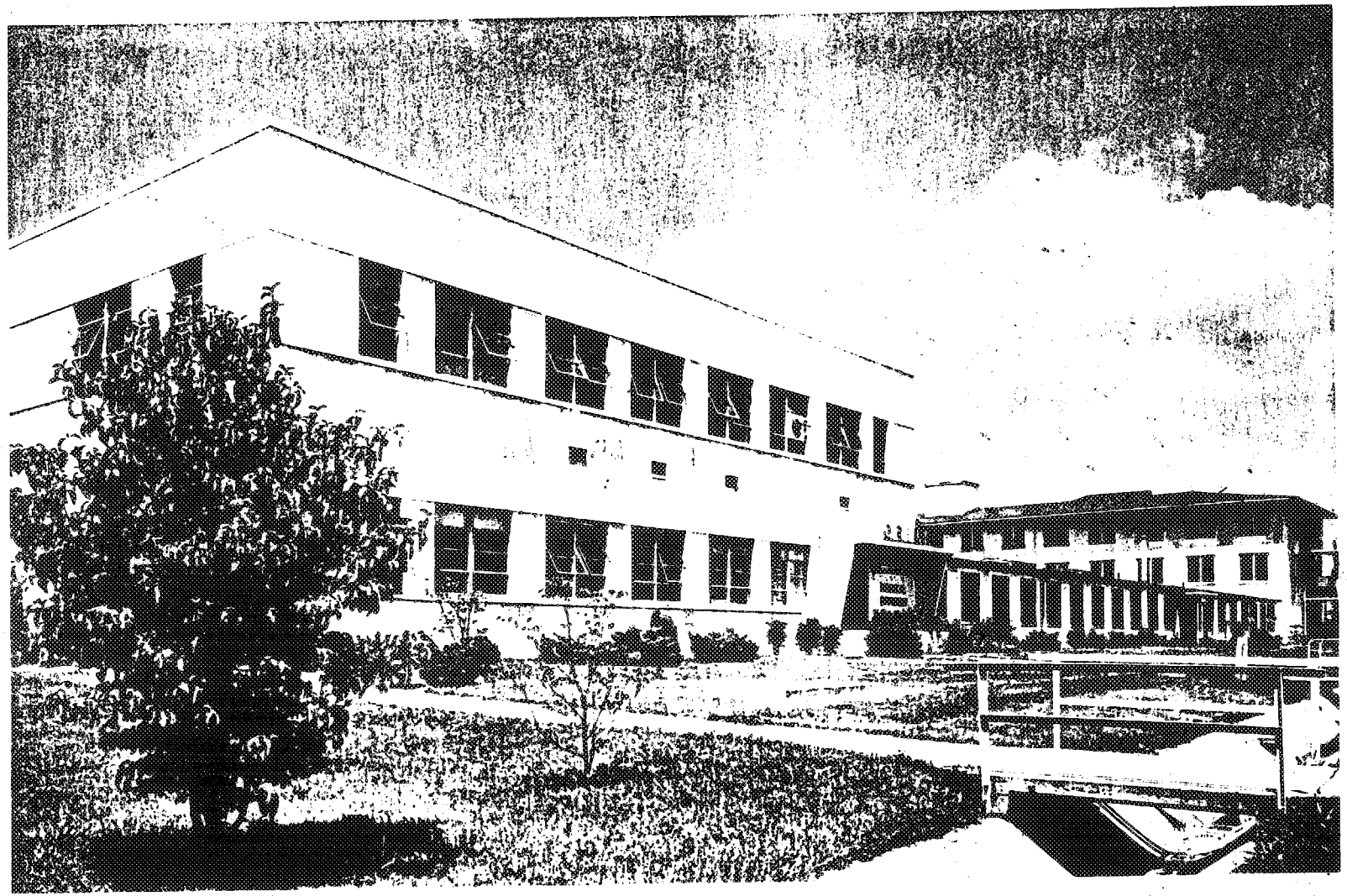
Externally delivered particulate radiation from the 184" cyclotron offers the only non-surgical means for inhibiting or ablating the function of the pituitary and can thus be used to produce metabolic and morphologic changes similar to those observed following surgical hypophysectomy. Its usefulness in the investigation and palliative control of malignant and endocrine diseases mediated through the pituitary potentiates the possibility of more effective approaches to these and other serious disease problems confronting modern medicine.

OAK RIDGE INSTITUTE OF NUCLEAR STUDIES, INC.

Medical Division

Oak Ridge, Tennessee

Marshall H. Brucer, M. D.	Chairman
Gould A. Andrews, M. D.	Associate Chairman
J. Howard Harmon	Sr. Administrative Officer



Oak Ridge Institute of Nuclear Studies, Medical Division
Front view of hospital and laboratory area

OAK RIDGE INSTITUTE OF NUCLEAR STUDIES

Medical Division

The Medical Division was formally organized in January 1949, and the research program initiated shortly thereafter was centered around the nuclear facilities available in Oak Ridge. The construction of a 36-bed hospital, including facilities for fundamental as well as clinical research, has made possible a well rounded program.

The research program of the Medical Division emphasizes three specific areas: preclinical research, clinical research, and training, the latter being integrated within the other two areas.

Preclinical Research

Biochemical research. Interest in rare metals metabolism and pertinent biochemical studies developed progressively out of the original "new isotopes" program; the latter was initiated some eight years ago to evaluate certain rare earth radioisotopes selected for their potential medical usefulness. The rare metals metabolism studies evolved a few years later when the need arose to define the toxic and metabolic effects of carrier, which had become a major influencing factor on internal radioisotopic patterns. The acute hepatic lesion, first observed about three years ago during a course of study in rare metals metabolism, led to a third phase of the preclinical program, namely, studies at the biochemical level. Current efforts in the preclinical program are devoted largely toward biochemical approaches in an effort to characterize numerous influencing factors and the mechanism of acute fatty infiltration that occurs in the liver following intravenous injection of any one of the various rare earths in the cerium group.

During the early phases of the "new isotopes" program, emphasis was almost exclusively placed on radioisotopes for internal therapy, both at the clinical and preclinical levels. The experimental approach was limited for the most part to patterns of distribution using tracer and autoradiographic methods. More recently efforts have been directed toward fundamental studies in an effort to gain more specific information on the potential hazards in the use of isotopes. Some of the more recent accomplishments under this part of the program are: the development and application of a small animal linear scanner for

the rapid screening of various internal gamma emitters, including more recent measurements of calcium-47; the mobilization and distribution of a new colloidal preparation of a well known radioisotope (yttrium-gelatin-phosphate); and, thirdly, the application of paper electrophoresis and of hemodialysis to radiation effects and internal contamination.

This group, in the past, had done a considerable amount of work with gallium-59 and 72 and subsequently with gold-198 and other colloids, out of which developed an extensive preclinical research program in the rare earths, primarily because of initial interests in their application for medical therapy. The rare earth group of elements offers a wide choice of radioisotopes that have desirable characteristics, and are practical to produce. The research staff has continued to focus attention on the rare earth elements and has extended studies to yttrium, lutecium, and holmium in an effort to learn their characteristic behavior in experimental animals with the ultimate objective always being their use in patients. Of the various influencing factors that have been evaluated, the chemical nature of the preparation, the route of administration, and the quantity of carrier have been of major importance. Potential medical use focused greater attention on the effective carrier, which ultimately led to acceptance of a common carrier which will control mobilization of any of the characteristic rare earth radioisotopes.

The quantity of carrier necessary to control internal localization resulted in levels which produced possible pharmacological effects. This eventually led to focusing attention on a toxicity program which in turn revealed that an acute biochemical lesion in the liver of rats could be detected, and this currently led to a major facet in a preclinical program.

Considerable attention has been focused on metabolic studies of the rare earths, including the effect on certain enzymes, indicating an apparent inverse relationship of fatty infiltration and choline oxidase in the liver of cerium-treated rats. This acute fatty infiltration that occurred following the administration of cerium was the first observation relating rare earth elements to specific metabolic reaction. This finding prompted the group to launch an intensive study to determine the biochemical significance of the rare earth group. Only the lower rare earths (the cerium group) cause this typical metabolic disturbance, and it occurs only in certain species with the female the more susceptible. More recently the mechanism of this metabolic disturbance has been the major experimental objective. Synthesis, oxidation, and mobilization of fat are all considered to have a part in the resulting pattern. Tracer studies of specific fractions and constituents of lipid are now being undertaken. Significant contributions to the program derive from collaborations at regional universities through life scientists who affiliate as temporary research participants.

Medical physics. Since the inception of the ORINS medical program, there has been a continuing interest in both the development and improvement of equipment for using and detecting the radioisotopes of medical value. One of the more significant and earlier accomplishments of this group was the development and design of the first cobalt and cesium teletherapy units including the adoption of the standard source container. These pioneer studies in teletherapy led to further refinements and ultimate widespread use of such devices now found in many large hospitals throughout the country and used for the treatment of patients on a routine basis.

With the increasing use of iodine-131 in medical practice, accurate scanning of the thyroid for uptake measurement became a real problem. Recognizing the dilemma the clinician was falling into, the ORINS group undertook a thyroid uptake calibration study. A mock iodine source (barium and cesium) which simulated the properties of iodine-131 was prepared and placed in twenty manikins that were constructed to resemble the head and neck of a human patient. These manikins were distributed on a rotational basis to many clinics throughout the United States. This study had a far-reaching effect on the techniques employed by the various groups and called attention to the marked variations obtained between laboratories.

Attention was then focused on improving and standardizing scanning techniques, which ultimately led to more accurate delineation of the distribution of gamma-emitting radioisotopes in several organs. Much of the investigation goes into the improvement of "area scanning" with continued efforts toward proper interpretation of recorded scans. In collaboration with a research group from the Thermonuclear Division of the Oak Ridge National Laboratory, improved focusing collimators, new mechanisms for the recording process, and other electronic improvements are being developed. Clinical scintiscan records are correlated with data on surgical specimens studied by assay and autoradiographic techniques.

The newly built linear scanner had demonstrated its usefulness in many clinical problems. It shows patterns of distribution of the total dose of a radioisotope at various intervals following administration, yielding a "profile" of the concentration of radioactivity along the long axis of the whole body. Semiquantitative results are obtained.

By studying the same patient with both area and linear scanning techniques, and eventually with a whole body counter, physicians will be able to localize and measure isotopes from outside the body with a precision never before available.

Clinical Research

Originally it was intended that the major emphasis in clinical research would be focused on the use of short-lived isotopes in the treatment of cancer and related diseases. Since then, the clinical program has changed and broadened to include many facets. One of the early objectives was the use of high energy gamma sources for external therapy. The first cobalt-60 unit designed for patient therapy was installed at this center in 1951 with subsequent developments leading to the design of a source capsule which has had universal acceptance. While the chief emphasis has been on the development of teletherapy equipment, a contribution has also been made in clinical use, based on experience with patients at the Medical Division. An additional accomplishment was the design and fabrication of radiation sources, particularly of cobalt-60, to be implanted for the treatment of localized malignancies.

The most recent distinguishing feature of this program has been expansion in the work on the effects of radiation in humans. The staff has carried out a number of studies of total body irradiation followed by attempts at bone marrow grafts in acute leukemic patients and others. Recognizing the potentialities in whole body irradiation as a tool in treating certain patients, the ORINS group designed and recently completed construction of a total body irradiation facility. This addition to the medical building contains eight 500-curie cesium sources located in positions to make possible a dose rate of 300 r per hour delivered uniformly to the whole body of an adult patient.

The availability of this facility has enabled this group to broaden its work on the effects of both total body and local port irradiation. Selected patients with various types of leukemia, lymphoma, polycythemia, and widespread cancer will be treated. Various clinical problems related to bone marrow grafts will be studied.

Fundamental data are being collected on the hematology of radiation. Research efforts also are being directed toward immunological studies which appear to be a critical factor in the marrow graft problem on patients who have received total body irradiation.

Biochemical characterization of irradiation effects and homologous bone marrow disease is a crucial problem. Extensive studies using amino acid analysis techniques and other specialized biochemical approaches have already yielded useful information.

This group continues to emphasize certain long-range programs involving diagnostic and therapeutic uses of internally administered radioisotopes. These investigations have been organized about the use of: radioactive colloids, especially in carcinoma of the ovary; isotopes of gallium, phosphorus, and calcium in bone tumors; and radioiodine in thyroid lesions, especially carcinoma. Some of the newer phases of these activities include iodine uptake by malignant thyroid tissue using the short half-life isotope, iodine-132; autoradiographic studies of concentrations of various radioisotopes in metastatic malignant tissue in the liver; and the distributions of calcium-47 in patients with bone tumors.

THE RADIOLOGICAL LABORATORY

University of California School of Medicine

San Francisco, California

Robert S. Stone, M. D.	Director
Gail D. Adams, Ph.D.	Associate Director

THE RADIOLOGICAL LABORATORY

University of California School of Medicine

The Radiological Laboratory was established in 1949 to investigate methods for improving the radiation treatment of cancer, with special reference to the usefulness of a 70-Mev synchrotron as a source of x-rays and electrons.

The Laboratory is the lineal descendant of a project to study the effects of whole body x-irradiation of humans, started in 1942. The patients treated then are seen only very occasionally. Later, the effect of phosphorus-32 and, later still, of iodine-131 as total body irradiators were studied by hematological methods. To that early activity, research in thyroid physiology using iodine-131 was added in 1945. The iodine studies have slowly been absorbed into service functions or other research programs, with the exception that a follow-up study of radioiodine-treated cases is still aided by Laboratory personnel.

In 1949, the U. S. Atomic Energy Commission entered the field of cancer research, particularly with reference to the effects of radiation. At that time one field not being cultivated elsewhere in the world was that concerned with x-rays and electrons with energies above 31 Mev. This Laboratory was established to study clinical effects of 70-Mev radiations and the related physical and biological problems. It was established within the medical school and adjacent to the hospital so that advantage might be taken of the academic surroundings, as well as the patient material available at a large medical center.

This program at the School of Medicine includes three major areas of endeavor: clinical research, physics section, and biological research.

Clinical Research

This group is concerned with patient treatment and assumes responsibility for the selection, study, therapy, observation, and follow-up of the patients.

In the selection of candidates for treatment with this previously untried energy of 70 million volts, patients have been utilized whose cancers were of such a type or at such a stage of growth that the chance of surviving five years would have been less than 50 per cent with any standard therapy. In addition, patients were selected to take advantage of the unique physical characteristics of the radiation from the synchrotron--for example, patients whose lesions had to be treated through several centimeters of normal tissue; obese patients in whom the radiation must penetrate to relatively great depths before the region is reached in which maximum absorption is desired; patients with lesions in places where either bone or air is interposed between the surface and the tumor (e.g., lung, pharynx).

Patients having cancer were first treated with 70-Mev x-rays from the synchrotron during July, 1956. Up to the end of December, 1959, 129 patients had been treated, most of whom had advanced disease, and the mortality, as expected, has been high. The 54 living patients are being followed at frequent intervals. The aim is to follow every patient through his entire remaining life. A study of the records shows that in some patients the cancer did not disappear even in the most heavily treated regions. It should be stated that there is no special anti-cancer activity in 70-Mev x-rays. There are, however, definite advantages in using them that will be mentioned.

The advantages of using 70-Mev x-rays in the treatment of cancer result from the pattern of absorption of energy from these rays. The following are situations in which this advantage can be utilized:

(1) It is easier to deliver any desired dose to a deep-seated lesion.

(2) The 95 per cent dose level for 70-Mev x-rays extends 8 centimeters, from the 6- to 14-centimeter depth.

(3) Stout patients can be treated as adequately as thin ones.

(4) When it is necessary to avoid certain surface areas such as previously irradiated skin, it is easy to treat through wide or thick parts of the body where the skin had not been previously irradiated.

(5) Simple one- or two-field techniques can be used on 95 per cent of the patients.

(6) The use of single fields makes it easier to avoid vital tissues in many instances.

(7) The use of simple techniques makes possible greater accuracy of aiming at and encompassing the tumor than is possible with many other techniques.

Because of the above advantages, it is obvious that the greatest usefulness will be found in the thicker parts of the body. The useful dose region is not reached until 6 centimeters have been penetrated and that the next 8 centimeters are quite evenly and equally irradiated; this allows one to treat "through" the good side of an involved area such as the neck, sparing much of it, and thoroughly irradiating the involved side by the use of a one-field technique.

The uniformity of the irradiation of a given volume of tissue deep in the body makes this quality of radiation of special advantage in the treatment of extensive disease in the pelvis and chest. Patients with the following types of cancer are therefore considered to be the ones that can profit most by the use of this machine:

(1) Late Stage II and Stage III cancer of the uterine cervix;

(2) Cancer of the uterine corpus, pre- or post-operative;

(3) Invasive cancer of the bladder;

(4) Cancer of the lung or bronchus, when inoperable;

(5) Advanced cancer of the paranasal sinuses.

Disadvantages in the use of the synchrotron are:

(1) The synchrotron is large (weight, 17 tons). Its position and angulation are controlled by a semi-automatic device, and any desired setting can be reproduced; however, because of its weight, changes in position are relatively slow. A large room is required for the synchrotron, with some special requirements for shielding.

(2) The synchrotron is electrically more complicated to operate and to service than conventional equipment. Thus, the operating crew must be more highly trained than the nurse-technician employed in conventional radiation therapy.

(3) Temporarily, the time required to change fields is greater than desirable; this condition will soon be rectified.

Physics Section

The Physics Section is (1) charged with the responsibility for the development, operation, and maintenance of the 70-Mev synchrotron, (2) involved with treatment planning and related aspects of the patient treatment program, and (3) concerned with various aspects of dosimetry, primarily of x-rays from 100 kvp to 70 Mev.

The synchrotron arrived in San Francisco on August 29, 1951. The installation and initial operation period culminated July 1, 1952, with the acceptance of the device from the manufacturer. During the four-year interim period between its acceptance and the instituting of treatments, the synchrotron was converted to a clinical machine, that is, to a condition permitting known radiation doses to be delivered accurately, reproducibly, and reliably. Included in this period were engineering revision of several functioning parts of the synchrotron, development of means to control and measure the radiation it generates, and some preliminary tests on biological systems of the relative effectiveness of this radiation.

The x-rays generated by the synchrotron did not have a uniform intensity at all points of a field of useful size. This situation was rectified, however, by the introduction of specially shaped absorbers. An electro-mechanical system was designed and incorporated which forcibly maintains proper alignment of the shaped absorber with the x-ray beam.

Biology Section

The experimental work of the Biology Section has centered on a number of problems that are associated with the practice of radiology and that lend themselves to laboratory experimentation. Some of these studies bear directly on the practice or theory of the x-ray treatment of cancer, and, in addition, retrospective statistical studies have been made of cancer cases in the General Tumor Registry of the Medical Center. Other studies, to be mentioned briefly, relate to the hazards of x-ray exposure.

When describing the x-ray treatment of cancer, it is necessary to specify, among other things, the quality of x-rays used and how the treatments were distributed in time. The following experimental studies relate to these two considerations.

Relative Biological Effectiveness.

The extensive introduction of supervoltage and megavoltage beams during the past 10 years has raised questions concerning their relative biological effectiveness (RBE). The data in the literature prior to 1950 indicated that the reported differences in RBE were small enough to have resulted from imperfections in dosimetry and experimental design, yet were large enough to be of potential clinical importance. A program was therefore decided on in which biological methods for RBE determinations would be reviewed and a standard set selected in which dosimetric methods would be made to conform to the recommendations of the International Commission on Radiological Units, and in which the informal collaboration of other clinical laboratories would be sought in order to make possible significant interlaboratory comparisons.

The results obtained from this study indicate that there is no significant difference in the mode of action of the various super- and megavoltage beams. From this, it follows that the action of such beams in the patient will be alike when similar doses, distributed within the patient in the same way, are administered.

Several conclusions may be drawn from the results of this program:

(1) An important factor limiting the accuracy of most RBE determinations is the physical measurement of the absorbed dose. For a variety of reasons, this has been poorly done in the past.

(2) For the clinical spectrum comprising 1 to 70 Mvp x-rays and gamma-rays, the values of the RBE cluster in the range 0.80-0.90 (relative to approximately 200-kvp x-rays, HVL 0.5-1.5 mm Cu).

(3) The value of the RBE is not especially sensitive to the biological endpoint used for its determination, at least on the basis of recent studies.

Studies in progress, which it is expected will continue over a period of years, deal with the nature of the survival curve in cancer of the breast and of the cervix after surgery and/or radiological treatment. One result indicated by the data thus far available for cancer of the breast is that radiological treatment does not have a measurable life-shortening effect analogous to that reported for animals subjected to whole body exposure.

Other kinds of studies that have been carried out or are in progress relate to the chemical protection problem and to late effects and genetic effects. The latter two have a bearing on the general theory of the hazards of medical and industrial exposure.

Chemical Protection and Treatment.

In this kind of investigation, one is seeking agents that can modify radiation effects, either at the time of exposure or afterwards. More recent work has indicated the role of certain physiological factors in determining the action of cysteine, and has demonstrated this agent to be active under anerobic conditions. Current studies with animals include a test of the influence of continuous estrogen treatment on late radiation effects.

Late Effects.

In collaboration with the Cancer Research Institute at this Medical Center, the late effects of whole and partial body exposure to x-rays in small laboratory animals are under study. Such late effects include a change in the cancer incidence rate of the exposed animals. One facet of the general problem that is of special interest to this program is the factor of age at the time of exposure.

THE UNIVERSITY OF ROCHESTER

Atomic Energy Project

Rochester, New York

Henry A. Blair, Ph.D.	Director
William F. Bale, Ph.D.	Chief, Radiology and Biophysics Division (Cancer Program)

THE UNIVERSITY OF ROCHESTER

Atomic Energy Project

Cancer research in the Atomic Energy Project laboratories at the University of Rochester has been carried out on a rather modest scale. The group here has been interested primarily in a study concerned with tissue specific antibodies as possible therapeutic agents in the treatment of cancer. Though the work to date has been conducted at a very fundamental level, it is hoped that sufficient progress can and will be made during the coming years to make possible progress toward the treatment of human tumors.

Human cancer is not susceptible to cure by any known treatment, surgery, radiation, or chemotherapy once distinct metastatic spread has occurred from the region where the neoplastic growth originated. The usefulness of radiation therapy of cancer would be substantially extended if a technique were to become available for injecting a radioactive isotope intravenously in such a form that it would localize preferentially in a malignant growth and selectively radiate it wherever in the body the neoplasm might be. A program of investigation in this laboratory of the possibility of producing antibodies with a preferential tendency for localizing in cancer tissue, and the possible use of such antibodies, coupled with a radioactive isotope for localizing therapeutic amounts of radioactivity in cancer, has been under way since 1952. As a part of this program, an extensive study of methods of producing, purifying, and labeling with iodine-131 (I^{131}) antibodies with selective tendencies for localizing preferentially in particular normal organs of experimental animals was carried out, as well as a study of the immunological and *in vivo* localization characteristics of antibodies made to several transplantable rat and mouse tumors. In particular, antibodies to the transplantable rat Murphy-Sturm lymphosarcoma were intensively investigated, and it turned out to be possible to make and label with I^{131} antibodies that, after intravenous injection, would lead to many times higher levels of radioactivity in these tumors than to any normal organ or tissue of these tumor-bearing rats.

It would appear that a variety of malignant tumors share in common an antigen that seems to result from a host reaction to the invading neoplasm rather than from the primary neoplastic nature of the tumor cell itself. This antigen is, or is closely

related to, fibrin. Apparently the invading neoplastic growth produces some stimulus, perhaps an inflammatory reaction or blood vessel injury, that leads to the conversion of circulating blood fibrinogen to fibrin and its deposition in the tumor. Experimentally it has been found that I^{131}-labeled antibody to fibrin injected into animals bearing some types of tumors also localizes with high selectivity in these tumors and remains bound there for periods of several days.

In an experimental radiation therapy study highly radioactive antibody to rat fibrin has been prepared and injected intravenously into rats bearing the Murphy-Sturm lymphosarcoma. Rapid and permanent regression of tumors has been induced by radiation doses of approximately 1,000 rad per day delivered to tumors by this means during a time when control tumors on untreated rats continued progressive growth. The treated animals continued in good health and to gain weight during and after the period of tumor regression.

In collaboration with the Medical Division, studies have been carried out on the localization in spontaneous tumors of dogs of intravenously injected I^{131}-labeled antibody to dog fibrin. In about 25 per cent of the injected dogs (5 to 18) tumor biopsy or removal three days after intravenous injection of I^{131}-labeled antibody showed I^{131} concentrations in the range of 8-14 per cent of the injected dose in amounts of tumor tissue equal to 1 per cent of the animals' weight.

These studies are expected to continue on a rather broad basis aimed at achieving immunological techniques useful in the treatment of disseminated human cancer. It is also anticipated that studies will extend to experimental therapy of other rodent tumors, as well as in spontaneous tumors occurring in dogs. The total research effort, it goes without saying, is to continue to extend these experiments with the hope of one day making possible therapeutic trials in human cancer patients.

OFF-SITE PROGRAM

In addition to the aforementioned cancer research programs, a limited number of individual projects are currently being supported in various medical schools, hospitals, and research institutions throughout the United States. This off-site program is limited intentionally to the support of unique uses and applications of radioisotopes in pursuing cancer problems both at the basic and clinical levels. For purposes of administration the off-site cancer program is divided into four significant areas which may be grouped in the following manner:

Carcinogenesis.

The Atomic Energy Commission's concern and responsibility in this area has prompted support of programs directed toward the potential carcinogenic activity of certain radioisotopes. With the rather widespread use of iodine-131 in clinical practice, the Commission is alerted to the possibility of a therapeutic dose producing abnormal changes in the thyroid following an interval of several years. Long-term studies are being pursued relative to I^{131} treatment of hyperthyroid patients as well as euthyroid patients with cardiac difficulties. Though no incidence of cancer has appeared in any of these patients so studied, the follow-up will be continued indefinitely.

There continues to be moderate interest and activity in radiation carcinogenesis, and the following summaries represent the type of research supported by the Atomic Energy Commission. Each summary has been prepared by the investigator responsible for the research being pursued.

Contractor : Albert Einstein Medical Center

Contract No. : AT(30-1)1727

Title : Enzymatic and Biochemical Studies of Epidermis Which Has Been Irradiated with Beta Particles

Investigator : Charles Weiss, M. D.

Scope of Work:

About 5 days after a single dose of 3,000 rep beta radiation guinea pig epidermis shows an increase in its acid-soluble constituents and a decrease in nucleic acids. These changes are accompanied by increases in nuclease activity (RNase and DNase). Future experiments are designed to confirm the observation that these increases are due to solubilization or release of the enzymes following irradiation. By chromatographic analysis, an attempt will be made to determine whether low molecular weight derivatives of nucleic acids accumulate in irradiated epidermis. A determination of the activities of several additional hydrolases (proteinase, acid and alkaline phosphatases and phosphodiesterase) one to 60 days after irradiation will, it is suspected, demonstrate an interrelationship between the observed biochemical changes and altered enzymatic activities. Our recent observation of a large (2.5 cm) fibrosarcoma in one of 4 animals, two years after irradiation, has encouraged us to include more animals in a long-term project.

Contractor : Beth Israel Hospital

Contract No. : AT(30-1)916

Title : The Long-Term Effects of I^{131} on the Thyroid Gland

Investigator : H. L. Blumgart, M. D.

Scope of Work:

Continuing observations on the long-term toxic effects of I^{131} in man are being carried out. The therapeutic effectiveness of I^{131} of intractable congestive failure due to various types of heart disease is being evaluated. The mechanism of the improvement associated with the induction of I^{131} hypothyroidism is under active investigation.

Contractor : University of California

Contract No. : AT(11-1)-34

Title : Studies on the Induction of Thyroid Cancer by Irradiation

Investigator : I. L. Chaikoff

Scope of Work:

The first part of this project deals with the induction of malignant tumors in the thyroid gland of rats by single and repeated injections of I^{131}. We are attempting to learn just how I^{131} administrations induce tumor formation, and what factors accelerate and diminish the incidence of thyroid tumor formation under these conditions.

The second phase has to do with the nature of the metabolic blocks induced by irradiation. We are attempting to localize the enzymatic site or sites where irradiation interferes with carbohydrate utilization and lipogenesis in tissues. In this study we are making use of C^{14}-labeled hexoses and intermediates. Individual enzyme systems are also being investigated. By detecting which of the enzyme systems is vulnerable to irradiation, we hope to devise means of circumventing damaged enzyme systems and so restore to the irradiated animal a normal capacity for metabolizing glucose.

Contractor : Harvard University

Contract No. : AT(30-1)609

Title : Radiation Effects on the Lung

Investigator : Shields Warren, M. D.

Scope of Work:

Epidermoid carcinomas have been produced by the use of implanted sources of cobalt-60 in the lungs of mice. The dose levels required are high, often in the range of several hundred thousand roentgen in the regions in which tumors develop. Tumors have not been successfully produced with beads incorporating strontium-90. The dose levels required for production of epidermoid carcinoma of the bronchus and the relative susceptibility to carcinogenesis of other irradiated tissues are being studied. The work is being done on mice and will be extended to rats and other rodents. One of the difficulties of the experiment has been the high mortality of the locally irradiated animals from leukemia, radiation pneumonitis and esophageal lesions.

Contractor : Health Research, Inc., Roswell Park Memorial Institute

Contract No. : AT(30-1)2463

Title : Research in Radiation Neoplasia

Investigator : Jacob Furth, M. D.

Scope of Work:

Continuation of the study of radiation-induced, hormone-producing neoplasms of mice; their induction mechanisms, functional capacity, and character with special reference to hormone dependency.

Enhancement and control of tumor induction by ionizing radiation by procedures applied before and after radiation. Character of pituitary tumors induced by head radiation in rats. Verification of the finding that the thyroid induction has a high neutron RBE and finding out whether iodine concentration in the thyroid is accountable for this high neutron RBE (in cooperation with Dr. H. J. Curtis of Brookhaven). Character and control of mammary tumors induced in rats by whole body radiation (in cooperation with Bond, Cronkite and Shellabarger at Brookhaven).

Contractor : Massachusetts General Hospital

Contract No. : AT(30-1)667

Title : The Biologic Effects of Radiation on Thyroid Tissue

Investigators: Oliver Cope, M. D. and J. B. Stanbury, M. D.

Scope of Work:

This is a long-term study of the biologic effects of I^{130} and I^{131} irradiation on the thyroid, both of patients and experimental animals. The follow-up of patients covers a period of 18 years. Thus far these isotopes appear not to have been responsible for the development of either thyroid cancer or leukemia. The goitre of one patient 17 years post therapy with recurrent hyperthyroidism has been studied in detail. Histologic observations in this patient as in others have revealed that follicle cell abnormalities constitute the major changes in the thyroid resulting from this form of irradiation. Perhaps some of these cell changes may represent a pre-malignant phase or a carcinoma-in-situ phase. A program has been under way to investigate the function of the ultramicroscopic structures of the thyroid cell in order to define more precisely these cellular changes.

Diagnosis and Localization.

A considerable amount of effort under this category has been directed over the past few years toward the delineation of intracranial lesions. The unique application of a positron-emitting isotope has proven to be not only a reliable but also a rapid and relatively inexpensive procedure for localizing brain tumors. The following summaries represent the Commission's effort in this area of cancer research:

Contractor : Baltimore City Hospitals

Contract No. : AT(30-1)2182

Title : The Use of Positron Emitting Isotopes in the Localization of Intracranial Lesions

Investigator : J. D. McQueen, M. D.

Scope of Work:

The localization of labeled tumor specific antibodies, chloroarsenic phthalocyanine and tris-theophylline arsenic in human brain tumor transplants will be studied. The tumors used will be glioblastomas and the technique that of Toolan. Minced tumor will be quickly transplanted subcutaneously to cortisone-treated hamsters. Regional scintillation counting will be carried out two weeks after transplantation. One group of these tumors will be transplanted at this time into the cerebra of similarly treated monkeys. Regional counting will be repeated and the crania scanned approximately one week later. Investigation will be directed to the labeling of other appropriate compounds with positron-emitting isotopes.

Contractor	:	Health Research, Inc., Roswell Park Memorial Institute
Contract No.	:	AT(30-1)2455
Title	:	Tumor Localization with Radioisotopes
Investigator	:	Merrill A. Bender, M. D.

Scope of Work:

Radioisotope scanning has been successfully used for the detection of brain, liver and thyroid tumors. It is our intent to continue our research in this field in two major areas that relate to this problem; i.e., instrumentation and the development of improved localizing agents. Contemplated improvements in instrumentation are concerned primarily with the reduction of the time necessary to perform the scan so that slow dynamic processes may be visualized and a larger number of patients may be accommodated. An "autofluoroscope" has been designed which will incorporate the advantages of the most advanced scanning systems available today and will include a detector that has high efficiency, good resolution and depth response, as well as a high-contrast data presentation system that can readily resolve small differences in radioisotope content between the target and non-target tissues. It is estimated that this instrument will reduce scanning time by a factor of 40.

We will continue our research in the field of tumor specific agents. By taking advantage of the metabolic, functional or immunologic differences between various tissues and tumors, it should be possible to extend scanning techniques to cover many clinical situations where x-ray diagnosis is difficult; i.e., the pancreas.

Contractor : Massachusetts General Hospital

Contract No. : AT(30-1)1242

Title : External Localization of Brain Tumors Employing Positron Emitting Isotopes

Investigator : W. H. Sweet, M. D. and G. L. Brownell

Scope of Work:

The object of this project is to investigate the application of positron-emitting isotopes with automatic scanning for the detection and localization of intracranial space-taking lesions. The investigations cover biological studies of isotope concentration and distribution, theoretical and experimental studies of scanning devices, and physical studies of new isotopes of potential interest.

Contractor : Massachusetts General Hospital

Contract No. : AT(30-1)1962

Title : Positron Scanning in Organs Other than Brain

Investigator : Gordon L. Brownell

Scope of Work:

This project is concerned with external localization of radioisotopes in organs other than the brain by means of positron scanning. Organs of primary interest are the liver and pancreas. Among the various positron-emitting isotopes that have been studied are copper-64 and zinc-62. Various compounds of these isotopes are being studied.

A scanning device has been constructed for this project. It scans in the horizontal plane and is of sufficient size to produce scans over a large portion of the body. The scanner may be used for both positron detection and for focusing collimation.

Therapy.

The clinical evaluation of various high energy sources has been a major undertaking from a therapeutic standpoint. Through support of various programs, the Commission has made an effort to determine the relative efficacy of cobalt-60, cesium-137, as well as high energy electrons from the linear accelerator. In addition, limited studies have been supported involving unique applications of isotopes at the clinical level. The following summaries are examples of the research oriented toward the use of radioisotopes at the clinical level.

Contractor : Cedars of Lebanon Hospital

Contract No. : AT(04-3)-57

Title : To Investigate, Develop, and Evaluate Radioisotopes for Teletherapy

Investigator : Henry L. Jaffe, M. D.

Scope of Work:

The development of new sources of gamma radiation by the Atomic Energy Commission has permitted the exploitation of therapy techniques which were formerly impractical.

In October of 1954 a ceiling-suspended, cobalt-60 teletherapy machine was installed in a newly constructed therapy room with adequate shielding for protection of patients and personnel. The cobalt-60 source in the machine contained 1,066 curies. A remote controlled, motor-driven chair and table were installed. An image-intensifying type of fluoroscope, together with a 125-KV x-ray unit, was installed on a newly designed overhead mounting system in connection with a closed-system television circuit. This permits the fluoroscopic image of the tumor site to be transmitted to a television screen in the control booth. The operator is therefore able to adjust the patient's

position in relation to the cobalt beam by remote control devices. This arrangement insures the fact that the treatment beam is centered on the diseased area at all times.

A phantom of each patient is made of plastic material. This permits physical measurements under treatment conditions for more accurate direct dosage measurement in the tumor site.

A second method of measuring the distribution of ionizing radiation after moving field cobalt teletherapy has been developed. This consists of x-ray film isodose plotting with the use of a densitometer, digitizer, and automatic scintiscanner.

761 patients with various types of malignant disease have been treated up to August 31, 1959. The evaluation of this therapy was reported at a symposium on cobalt-60 teletherapy held at the Oak Ridge Institute of Nuclear Studies on July 20, 1956. A comparison between stationary cobalt-60 therapy results and rotation therapy results, both from the clinical and physical standpoint, was presented. This was published by the U. S. Atomic Energy Commission under the title, "Roentgens, Rads and Riddles." Four additional publications have appeared in the literature dealing with this work.

Contractor : Columbia University

Contract No. : AT(30-1)2086

Title : Impregnation of Rubber Balloons with Radioactive Isotopes

Investigator : Hans H. Zinsser, M. D.

Scope of Work:

Rubber balloon catheters have successfully been impregnated with silver-111 and, within the limits of solubility of silver metal in body fluids, the silver has been retained, resulting in an elastic, deformable, beta-emitting source. Efforts to impregnate rubber with other potentially useful ions have thus far been unsuccessful, but work will be continued with electrodeposition. The subsequent covering of the impregnated catheter with an additional latex layer may produce more useful intracavitary radiation instruments. Calibration of dosage has been carried out with an ionization chamber designed by the staff of Dr. Failla.

To further reduce leaching of metals, a secondary layer of rubber can be deposited over the silver impregnated layer without serious loss of output.

Animal experiments to date have shown massive destruction of bladder mucosa at unexpectedly low dosages, which has forced re-examination of basic assumptions and more precise scanning procedures.

Contractor : Health Research, Inc., Roswell Park Memorial Institute

Contract No. : AT(30-1)2651

Title : The Localization of Physiologically Active Amounts of Radioactivity in Human Tumors by Means of Radioactive Antibodies

Investigator : David Pressman, M. D.

Scope of Work:

The prime objective is to determine whether anti-tumor antibody prepared against a human tumor actually localizes in the tumor. For this, a double labeled control technique using radioactive labels has been developed. We plan to inject anti-tumor serum labeled with one radioisotope and control serum labeled with another. The preparations are injected simultaneously and any preferential uptake in the tumor of the anti-tumor preparation indicates the preferential uptake of anti-tumor antibodies. Immediate research is concerned with means for preparing suitably purified tumor localizing antibodies.

Animals bearing transplanted and chemically induced tumors are being used for the preliminary investigations.

Contractor : University of Illinois College of Medicine

Contract No. : AT(11-1)-67

Title : Intragastric Irradiation in Man with Beta Rays of Ruthenium-Rhodium 106

Investigator : Armand Littman, M. D.

Scope of Work:

Three patients have been given a total of nine treatments. The first patient, with duodenal ulcer, was given one treatment which was terminated because of air leakage to the degree that further therapy was not considered advisable. One patient with gastrojejunal ulcer was given four daily doses of 150 rep at a rate of 8.5 rep per minute for 18 minutes. The total dose was 600 rep. Moderate diffuse anatomic changes resulted and minimal reduction in gastric acid response to Histalog was achieved during a ten-week period of observation after therapy.

A patient with inoperable, large fungating, friable carcinoma of the gastric cardia was similarly treated with a total of 600 rep. Diffuse coagulation necrosis was observed in post therapy biopsy specimens, without a slough, necrosis or ulceration. The size of the tumor was not changed during a ten-week observation period. In the last two cases there was no air leakage, and in all the treatments were well tolerated without sequelae. Additional cases are being treated with larger doses.

Contractor : Massachusetts General Hospital

Contract No. : AT(30-1)1093

Title : The Use of Thermal and Epithermal Neutrons in the Treatment of Neoplasms

Investigator : William H. Sweet, M. D.

Scope of Work:

We are now: 1) seeking to prepare less toxic compounds of boron which concentrate well in tumor for long periods; 2) studying the precise localization of these compounds with boron-10 radioautographs; 3) preparing the portal of the Massachusetts Institute of Technology reactor for use in the neutron radiation of patients at open operation.

Contractor : University of Michigan

Contract No. : AT(11-1)245

Title : Clinical Evaluation of Cesium-137 Teletherapy

Investigators: F. J. Hodges, M. D. and Isadore Lampe, M. D.

Scope of Work:

Comparative clinical evaluation of teletherapy units housing isotope sources in the treatment of malignant disease is being carried out. The isotope sources are cobalt-60 and cesium-137. A cobalt-60 source housed in a Theratron has been under study since February 1955 both from physical and clinical radiotherapeutic standpoints with periodic modification to improve its clinical utility. An automatic isodose plotting device was developed and isodose curves for fixed beam and rotational beam techniques for numerous field sizes were made and are on file. An original technical system of tumor localization and beam direction has been developed for treatment with fixed and rotational techniques by the Theratron. For the special case of irradiation of the head and neck, a unique headholder has been developed based on the principles used in orthodentic radiography permitting exact duplication of head position daily during the weeks of radiotherapy.

A second Theratron was modified to house a cesium-137 source and to overcome the handicaps of large source size and low radiation output. Only fixed beam techniques are possible; a source-skin distance of 50 centimeters is used and secondary fixed brass diaphragms determine field size. The cesium is in clinical use at present with the objective of evaluating the potential position of this radiation in clinical radiotherapy in relation to cobalt-60 radiation.

Contractor : University of Oregon Medical School

Contract No. : AT(45-1)581

Title : Studies of Hemic Effects of Radioisotopes, X-Rays, and Adrenocortical Hormones in Man

Investigator : Edwin E. Osgood, M. D.

Scope of Work:

The major new project planned is a study of the growth rate of all the different types of hemic cells in our long term cultures combining the quantitative determination of tritiated thymidine incorporation in DNA, radioautographs of such tritiated cells growing in situ, determination of the number of alpha cells (capable of starting colonies) and the number of n cells (which differentiate and die) by comparison of the radioautographic multiplication rate with the actual number of new cells present in cultures. Mitotic indices with the aceto-carmine stain can be obtained on the same material.

Efforts will be made to clone the different types of hemic cells which are now in mixed cultures.

The data on water, nitrogen, and electrolytes of human leukemic leukocytes will be statistically analyzed and reported.

We will continue the studies on the life span of leukocytes and erythrocytes, alkaline phosphatase in myeloproliferative disorders, and the various abnormalities of hemostasis and blood coagulation occurring in patients with diseases of the blood-forming organs.

Long term comparative studies of the action of phosphorus-32 and chemotherapeutic agents in the leukemias and lymphomas will be continued.

Contractor : Stanford University

Contract No. : AT(04-3)-21

Title : Mark IV Electron Beam Clinical Project

Investigator : Henry S. Kaplan, M. D.

Scope of Work:

An investigation is being made of the physical and clinical problems associated with the therapeutic use of a beam of electrons with energies between 10 and 60 Mev. The electron beam is produced in a microwave linear accelerator. The physical problems concern techniques for producing an optimal dose distribution within the patient, and for measuring the dose to the patient with adequate precision.

Electrons have a limited range in tissue which can be adjusted by varying the energy of the beam. As a result, tumors close to a body surface can be adequately treated with a single field, while sparing the underlying tissue. Tumors of the head and neck region have been found most suitable for this type of treatment.

In addition, several patients have been treated with cross-firing electron beams. With this technique, high doses are produced in the center of the treatment area, with a rapidly decreasing dose in the surrounding tissue. Selected tumors of the head and thorax have been treated with this technique.

Since May, 1958, 35 patients have received 38 courses of therapy using electron beams with energies varying from 10 to 40 Mev. The clinical results have borne out the theoretical advantages of electron beam therapy in treating relatively superficial lesions.

Contractor : University of Texas, M. D. Anderson Hospital and Tumor Institute

Contract No. : AT(40-1)2028

Title : Physical and Radiobiological Investigations with 22 Mevp X-Rays and Electrons as Compared with Cobalt-60 Gamma Rays and 200 Kvp X-Rays

Investigator : Robert J. Shalek

Scope of Work:

This investigation is concerned with the quantitative estimation of the relative biological effectiveness of 22 Mevp x-rays and cobalt-60 gamma rays compared with 200 Kvp x-rays. Experiments have been designed to provide uniform radiation dose throughout the test medium, which to date has included yeast LD_{50}, mice LD_{50}, and rat LD_{50}. Experiments are in progress on iron-59 uptake in rats and are soon to be initiated on LD_{50} in chicken eggs; it is anticipated that these experiments will be completed in the proposed period.

Dosimetry is presently based on calibrated ionization chambers and confirmed with chemical dosimeter determinations. Further studies on an absorbed dose calorimeter and on a comparison between this calorimeter and the chemical dosimeter over a wide energy range are planned.

Contractor : University of Texas, Southwestern Medical School

Contract No. : AT(40-1)2582

Title : Changes in Radiation Quality with Depth, Measured by a Biological System

Investigator : F. J. Bonte, M. D.

Scope of Work:

The contractor will undertake studies, utilizing ionizing radiation, to explore the use of tissue culture systems for evaluating biological effectiveness of radiations of various types at depths within tissues. The work will proceed initially with use of 250 Kvp x-rays and cobalt-60 gamma rays. Tissue culture cells will be irradiated in plastic test tubes within a phantom system. Cell viability and survival values will be obtained utilizing criteria of Puck et al.; individual as well as masses of cells will be studied and evaluated grossly and microscopically, and individual cells will be examined for effects, including formation of giant cells, and cell counts will be made by more than one individual to enhance statistical quality.

Correlation will be made between percent survival and effective radiation beam quality, and values will be obtained for each absorbed dose and for each exposure dose for each radiation source. Relative biological effectiveness will be determined for each depth dose, and RBE will be plotted as function of depth for each source. Effective depth dose curves will be produced, and the curves will include effects of both biological and physical factors which cause variation in dose or effective dose with depth. Included in this work will be evaluation of dosimetry methods and apparatus for dose measurement, and in the phantom studies with cells the effective energy of each radiation beam at each depth will be measured and/or determined. Spectral distribution studies will be made where appropriate.

Contractor : Washington University

Contract No. : AT(11-1)782

Title : Radiosensitivity of Tissues and Oxygen Tension

Investigator : Michel Ter-Pogossian

Scope of Work:

It is proposed to continue the investigation undertaken in an attempt to determine oxygen tensions in malignant neoplasms by means of radioactive oxygen-15. The first phase of the study, which has now been completed, consisted in developing and calibrating an oxygen-15 generating system and in performing some pilot experiments. The proposed second phase of this investigation shall consist in using the oxygen-15 in determining the oxygen-15 tensions in malignant neoplasms, when the tumor-bearing subject is exposed to various partial pressures of oxygen. An attempt will be made to correlate the results of the study with the radiation sensitivity of the tumors used.

Other Cancer Research.

In addition to the aforementioned programs, the following summaries cover research which, though basic to the cancer problem, is indirectly related to potential therapy.

Contractor : Catholic University of America

Contract No. : AT(30-1)2457

Title : The Effect of Ultrasound on the Permeability of Ascites Tumors to Labeled Chemotherapeutic Drugs and Radioactive Isotopes

Investigator : Dale C. Braungart

Scope of Work:

Prior investigation has revealed that the permeability of living cell membranes can be altered by treatment with specific frequencies of ultrasonic waves. Living cells have been induced to take up abnormally large amounts of several isotopes by this treatment *in vitro*.

It is proposed to investigate the effect of ultrasound on the permeability of ascites tumors *in vivo* to several labeled chemotherapeutic drugs and to radioisotopes in the hope that they will be more selectively permeable to these compounds than the surrounding tissues.

Contractor : University of Colorado Medical Center

Contract No. : AT(11-1)394

Title : A Study of the Combined Action of Certain Chemical Inhibitors of Metabolism with X-Radiation and Other Ionizing Radiations on the Growth of Certain Malignant Tumors

Investigators: R. W. Whitehead, M. D. and David Gould, M. D.

Scope of Work:

This laboratory has been using radiation protective agents in tissue culture as a method of characterizing the nature of the cellular replication lesion caused by irradiation. Enzymatic (in vitro) studies and experiments with animals have been carried out to clarify associated problems. Using single cell plating techniques, 2-aminoethylisothiuronium bromide HBr (AET) and several of its derivatives have been shown to behave differently than in the intact animal. Albumin bound guanidino ethyl disulphide (GED) may be of value as a long acting radiation protective. By the use of S^{35}-labeled GED, it has been found that its binding to protein involves disulphide linkages. The effect of GED and of mercapto ethyl guanidine (MEG) on the ribonuclease and deoxyribonuclease activity of irradiated cells has been studied.

The effect of radiation and of certain protective agents on myosin adenosinetriphosphatase has been studied. The results suggest that AET's ability to separate the protein from nucleic acid may be as important a factor in its protective action as its ability to protect sulphydryl groups.

Work is still in progress on a sensitive assay of all sulphydryl components per cell. This information will be of value in analyzing the contribution of various cell components to radiation damage and protection. Some correlation has been found to exist between brain serotonin levels, electroencephalographic changes and the behavior of rats given massive doses of x-irradiation. Related problems are to be studied. Work is to begin on a survey of 30 compounds for radiation protection, and several restoration experiments are planned using tissue culture cells. Immunological studies are concerned with obtaining profiles of nucleoproteins from cancerous and non-cancerous urine using DEAE cellulose chromatography.

Contractor : University of Illinois

Contract No. : AT(11-1)314

Title : Synthesis of Boron Compounds

Investigator : H. R. Snyder

Scope of Work:

The ultimate purpose of this project is to find a means of building up in or on a growing tumor a concentration of an organic compound containing boron-10, such that the tumor may be destroyed by irradiation with slow neutrons. The immediate purpose is to synthesize compounds containing systems of unusual stability to hydrolytic removal of boron for study of their toxicity and differential adsorption on or concentration in mouse brain tumors, and to develop the chemistry of such systems so that they can be incorporated into more complex molecules. Of particular interest at the present writing are derivatives of boronophthalide (the inner ester of 2-hydroxymethylbenzene-1-boronic acid), which is extremely stable to hydrolytic deboronation. It is converted to the 5-nitro derivative by cold nitric acid, and the amine is available by reduction of the nitro compound. Reactions of the amine and its diazonium salt are being investigated. Also under investigation are substituted phenylalanines carrying a boronic acid substituent in the aromatic ring, and derivatives of these substances.

Contractor : Meharry Medical College

Contract No. : AT(40-1)1993

Title : Effect of X and Beta Irradiation on Free Growth and Spread of Tumor Cells

Investigator : Horace Goldie, M. D.

Scope of Work:

The problem of inhibiting tumor cell spread into tissues from the body fluids (coelomic metastases from intracavitary effusions, metastatic emboli from the blood stream) is approached in our research by attempts to prevent implantation of free-growing, intracavitary tumor cells before and after their infiltration into serous lining and of metastatic emboli before and after they are arrested in organs. Using "ascites tumors" of the mouse as experimental tool, we have found that pretreatment of peritoneal cavity with radioactive yttrium, phosphate or chromic phosphate induced resistance to tumor cell implantation from the fluid and unfavorable conditions for accumulation of serous effusions. Recently, it was found that analogous procedure may prevent spread of tumor cells from anatomically sharply delimitated areas. The possibility to supplement surgical treatment of primary tumor and to achieve "radioprevention" of tumor cell spread by pretreatment with certain radioisotopes of areas threatened by invasion is being further explored. Moreover, regression of early implants was achieved by combined external (x-ray) and internal (same radioisotopes) irradiation. Small doses of each irradiation given alone inhibited growth and implantation of tumor cells only temporarily and moderately but their appropriate combination resulted in a highly potentiated effect.

Contractor : University of Michigan

Contract No. : AT(11-1)-70

Title : Immunological Study of Tumors

Investigator : W. J. Nungester, M. D.

Scope of Work:

During the past year a search for an antigen peculiar to the lymphoblastoma 6C3HED tumor has been continued. After many attempts, a fraction of homogenized solid tumor has been obtained which contains a lipid, protein and possibly some carbohydrate. This fraction rises to the surface in a sucrose suspending solution on centrifugation. It does not migrate at a pH of 4.2 or 8.4 in an electric field. It blocks the protecting power of antitumor sera. This "antigen" is being studied for its ability to stimulate antibody formation in rabbits and to induce active immunity in mice (C3H).

The ability of 3 strains of rabbits to produce antitumor (Ehrlich) sera has been continued. Using in vitro protection tests, differences in titers of sera from the several strains of rabbits were noted. Also differences in titer of the sera of the several strains of rabbits were noted which could be related to the stage of immunization. There were two periods of immunization when the antitumor properties of the sera were highest. The stability on storage of sera collected early was less than that collected later in the immunization program suggesting a different type of antibody.

Our previous finding that niacin increased the localization of iodine-131 tagged immune globulin in Ehrlich tumors has been confirmed. This was true whether the niacin-globulin mixture was administered at 6, 12, or 24-hour intervals, although 12 hours appeared to be optimum. The data were calculated three ways: "raw data" was expressed as the per cent of injected radioactivity in each tissue examined. The data were also expressed as tissue-blood ratios. Both these methods gave similar results. By considering the estimated blood volumes of the tumors and of liver, kidney, and spleen as normal tissues, it was shown that 4-6 times as much globulin-iodine-131 localized in tumors than in normal tissues.