

OAK RIDGE
INSTITUTE of NUCLEAR STUDIES

MASTER

Medical Division

Midyear Report

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CLINICAL STUDIES

Gould A. Andrews

During the past year the clinical program has been characterized by further emphasis on studies of total-body irradiation and attempts at bone-marrow transplantation. The unexpected responsibilities associated with caring for the men exposed to radiation in the Y-12 accident constituted a major activity during the year. The study of the accident victims was of interest in relation to the program already under way, because it offered a unique opportunity to correlate the changes in the normal persons subjected to accidental radiation with the changes observed in patients with various diseases treated by total-body irradiation.

During the year Dr. Frank Comas rejoined our staff. He has been developing an active program in radiation therapy and a research program related to biological mechanisms in radiation effect. Dr. C. Harold Steffee left our staff to work full time at the Oak Ridge Hospital. He is, however, continuing to take an active part in the training program. He serves in laboratory activities involving the Oak Ridge Hospital and cooperates with Dr. Nelson in various problems of mutual interest to pathologists.

During the year the Medical Division has had the generous cooperation of a considerable number of physicians in Oak Ridge. Among these are Dr. Robert R. Bigelow, Dr. Robert P. Ball, Dr. William W. Pugh, Jr., Dr. Dana W. Nance, Dr. Henry B. Ruley, Dr. C. J. Speas, Dr. Raymond A. Johnson, Dr. Dexter Davis, Dr. Avery King, and Dr. Paul Spray. We have also had assistance from Dr. Robert Newman and Dr. Eidson Smith of Knoxville. Dr. George Minor of Charlottesville, Virginia, has come several times for special thoracic operations and we have benefited from visits from a large number of clinical consultants. During the first part of the year, a major share of the clinical load was carried by Dr. Ryosaku Tanida, and during the later part of the year, Dr. Felix Pircher carried these responsibilities. Dr. Akira Tsuya and Dr. Yoichiro Umegaki, working chiefly with Dr. Brucer on problems related to scanning and isotope measurements, also participated actively in clinical rounds. In December, Dr. Jose B. Briones joined our group as postresident in radiology on a one-year

appointment in conjunction with the Oak Ridge Hospital.

The permanent clinical staff (medical and nursing), the short-term residents, postresidents, and visitors from abroad are listed in the section on staff at the end of this report. The projects described in the clinical section represent the combined work of this group.

IODINE-131 STUDIES

Clinical Staff

Carcinoma of the Thyroid

There has been a further extension of our series of cases of patients, with well-differentiated carcinoma of the thyroid, who have areas of iodine-concentrating tissue in the neck after presumed total thyroidectomy. Repeated surgical procedures have been done in some of these patients with the probe counter used for locating the functioning tissue. In the majority of cases it has been found difficult or impossible to remove the last remnant of functioning tissue. Histologic studies have been of great interest, but often puzzling, because it is difficult to differentiate normal thyroid from tumor in some instances. In general, this study seems to indicate that radical neck dissection for carcinoma of the thyroid is not a very satisfactory procedure. The areas of remaining tumor are often in the region of the thyroid bed or closely associated with the larynx and trachea; because they are in these locations they are not necessarily more adequately resected by radical neck dissection than by more conservative surgery.

Other cases of carcinoma of the thyroid not falling into the foregoing group have been investigated, with special emphasis on scintiscans at various intervals after test doses, in an effort to show the iodine-131 turnover rate of tumor tissue. Studies of surgical specimens with autoradiography and assay have helped correlate histologic type with iodine metabolism. The use of larger test doses of iodine-131 than were formerly used have made it possible to reveal poorly functioning metastases by external measurements. New observations have been made on areas of iodine-131 concentration on nonthyroidal tissue.

We have followed a small number of patients who have been given large doses of thyroxin for carcinoma of the thyroid. The lesions have shown lack of progression but have not shown regression.

Neck Background

Rates of iodine accumulation by the thyroid gland are most informative if they are measured early, shortly after the dose has been administered, and it is precisely at such times that the high nonthyroid neck background is a most troublesome stumbling block. A search is continuing for a practical method that will get around this difficulty, and thus enhance the value of thyroid-uptake measurements. In addition, the experiments may well provide useful information on thyroid physiology, and on the gland's response to some of the newer drugs (e.g., perchlorates) that show promise for the chemical control of thyroid dysfunction.

SCINTISCANNING

Clinical Staff

Dot Factor

Studies by Dr. Pircher, using a thyroid phantom, indicate the importance of the "dot factor" (or counts per print). Scans made with a low dot factor may be misleading and may suggest uneven deposition when there is no real unevenness.

Thyroid Remnants

In the program on treatment of residual thyroid remnants in the neck after total thyroidectomy for carcinoma, greater effort is being exerted in correlating the scintiscans before operation with the findings at surgery and the pathology studies on the removed tissue. At the time of surgery a drawing is made showing the location of each thyroid remnant found, and each remnant is given an identifying number. Each remnant removed is assayed for radioactivity and examined histologically. The data obtained are correlated with previous scintiscans. It is hoped this effort will provide a basis for more skillful interpretation of scintiscans and some evaluation of distinguishing characteristics (between normal and malignant thyroid tissue) that might be detected by scintiscans.

Scanning the Liver

Studies by Dr. Tanida, using a liver phantom, have indicated the limitations of scanning in showing small lesions of the liver. It was very difficult to determine lesions smaller than 3 cm in diameter. The location within the liver is important in determining whether or not the lesion can be located.

TOTAL-BODY IRRADIATION

Clinical Staff

Leukemia

Studies of total-body irradiation followed by attempted marrow transplantation in leukemia have diverged in two directions. First of all, it seems clear that in some patients with acute leukemia a remission occurs that is probably not caused by the marrow infusion but is a result of the radiation itself. This is cause for renewed interest in the subject of the effect of irradiation alone on acute leukemia. This is important as a possible palliative therapeutic means, and it is also important because there is danger that remissions due to irradiation alone will be misinterpreted as evidence of success of marrow transplantation. To prove the latter, more specific information is necessary than simply that there is development of a remission. There are scattered previous references in the literature to success with total-body irradiation in acute leukemia, although in general it has been thought to be a worthless therapeutic procedure. It appears now that with large doses of radiation it may be possible to produce remissions in some patients. We are attempting to determine which types of patient this applies to. It appears that it is applicable in the primitive-cell leukemias in children, and that it is much less likely to succeed in the subacute leukemias in older age groups. There is no doubt that the leukemic cells are exceedingly radiosensitive, and that rapid tissue breakdown occurs after total-body irradiation in acute leukemia. Of greater concern are the problems relating to regenerative phenomena, and why these occur in certain patients and not in others.

The attempts to transplant bone marrow seem, up to the present, to be unsuccessful, or at best to have shown only a transient and dubious graft in one case in our series. Radiation doses up to 800 r were reached (in one case), higher than we had given previously. Attention has been focused on several factors that may have to do with the success of the marrow transplantation.

Y-12 Plant Accident Patients

During six weeks in June and July, the major portion of the time and effort of the clinical staff was directed toward the treatment and study of patients exposed to an excessive amount of radiation in the Y-12 plant accident of June 16, 1958. Five patients were admitted at 1:00 AM on June 17, and three patients who received much smaller doses of radiation were admitted on June 18. The admission of these patients posed a bed-space problem, which was solved by discharging some patients from the hospital earlier than would have been done otherwise and

postponing the scheduled admissions of other patients. The five patients admitted originally were kept in the hospital for 44 days. The three patients receiving the lower doses were discharged after nine days because there was very little evidence of radiation effect during this period of observation. All the patients have been followed on an outpatient basis since their discharge from the hospital. Rather detailed clinical, hematological, and biochemical observations and studies were obtained on the patients.

Of the five patients who received the higher dosage, four had nausea and vomiting beginning about two hours after the accident. The fifth patient had no vomiting and only slight nausea of brief duration on the second day. In those in whom it occurred, the vomiting was not severe and subsided after two days, except for one patient who continued to have isolated episodes of vomiting through the fourth day.

Loss of hair from the scalp started in all five patients on the 17th day. The hair loss became great enough to be obvious on casual inspection in only two. In these two, the greatest loss occurred in the occipital region. The loss of hair persisted in these two until the end of the hospital stay, after which there was a gradual and progressive regrowth to normal proportions.

During the period of greatest blood-platelet depression, one patient developed a patch of petechiae on the abdomen and experienced slight bleeding of gums on brushing the teeth on the 25th day. Another patient had slight bleeding of the gums on brushing the teeth on the 26th and 27th days, but had no petechiae. A third patient developed petechiae over the body beginning on the 25th day, but had no evidence of bleeding.

The fact that the patients did not have any traumatic lesions or radiation damage to the skin helped to eliminate factors that might otherwise have influenced the hematological picture and provided an unusual opportunity to observe the effects of radiation on bone marrow and peripheral blood. The lymphocytes showed a striking fall within three days to levels of less than one-third the initial count. They tended to remain low, with some fluctuations, for about five weeks, after which there was a slow and gradual return to normal levels. Shortly after irradiation, abnormal monocytic forms were seen, as well as degenerating cells. A few days later, giant granulocytes were prominent.

The initial blood studies showed the patients to have white-blood-cell counts in the high-normal range. By the sixth day the total white cells were low-normal, where they remained with some variation until about the 20th day. About a week later the lowest levels were reached, some of which were about 1000 per cm. During the next month there was a slowly progressive rise to approximately normal levels.

The blood-platelet count showed a suggestion of an initial rise followed by a return to approximately normal levels, where they remained until about 16 days after the radiation. Then they began to fall strikingly, with the minimal values reached in about 25 days. All five patients had blood-platelet counts below 40,000 per cu mm at some point, and in two patients the blood platelet count fell to exceedingly low levels. The counts remained at their low levels for a few days and then increased rather rapidly. Normal levels had been attained again six weeks after the irradiation.

Red cell values showed considerable variation from patient to patient. In two patients a definite anemia developed, with the lowest values occurring about 36 days after the radiation exposure.

The reticulocyte count showed a tendency to fall during the first eight days, but reticulocytes were never totally absent in any case. Between the 13th and 25th days there was an abortive rise, and then a distinct rise after the 30th day. The highest reticulocyte count occurred around the 45th day.

Serial bone marrow studies showed a tendency toward progressive decrease in cellularity. In the early stages there was a relatively greater drop in red-cell precursors, so that on the 5th day a relative granulocyte predominance was present, with the red-cell precursors being less than one-fifth of the nucleated elements. Three to five days after the irradiation, giant neutrophil forms were prominent. A pronounced decrease in megakaryocytes occurred, becoming most severe 24 days after the irradiation. This was preceded by the presence of many degenerating megakaryocyte forms. At the point of greatest marrow depression, 33 days after the accident, there was a pronounced increase in unidentifiable mononuclear cells, and plasma cells were prominent in certain cellular areas of the marrow samples. After the period of greatest hypocellularity, there was rather rapid regeneration to normal or increased cellularity by the 54th day.

No serious infections occurred in any of the patients. There were several episodes of minor infections such as furuncles, upper respiratory infection, acute pharyngitis, and acute tonsillitis. The only elevations in temperature occurred in two patients, at the time of acute pharyngitis on one and acute tonsillitis in the other. Both of these patients were treated with tetracycline for 10 days. Otherwise there was no use of antibiotics.

The results of biochemical studies are reported elsewhere.

During the early part of the treatment, the use of bone-marrow infusions in the five patients receiving the larger doses was considered; however, it was decided not to use this measure unless the subsequent condition of the patient became precarious. Donors were obtained for

each patient for this purpose as well as for fresh whole-blood transfusions in the event they might be needed.

After discharge from the hospital, and during observation as outpatients, the most prominent and uniformly present symptom was weakness, especially in the upper legs. This was reported a few days after discharge from the hospital and persisted in varying degrees of severity in the different patients for several weeks. After six weeks of convalescence and progressive increase in physical activity at home, the patients returned to work. In one patient in the lower-dose group, the weakness in the legs became so severe that he was absent from work because of it. There was gradual improvement and he returned to work in about two weeks; however, the symptoms again became severe and another period of absence from work occurred because of them. Thereafter his course has been one of slowly progressive improvement.

Other symptoms have consisted primarily of various manifestations of nervousness, restlessness, and inability to sleep well.

BIOLOGICAL CHANGES THAT FOLLOW TOTAL-BODY IRRADIATION

Clinical Staff

A continuing study of the metabolic effects of total-body irradiation in man is being made. In the normal men accidentally exposed to neutron and gamma irradiation, a great many routine biochemical procedures were performed. Of particular interest among these is a detailed study of creatine and creatinine excretion. Mr. Billy Eyrd has spent several months studying and carefully standardizing a method for the measurement of creatine and creatinine that was described in the literature in 1954. The data on these normal men have been checked several times, and it is evident that total-body irradiation at levels up to about 300 r does not alter creatine or creatinine excretion. The amino acid nitrogen that is measurable with the ninhydrin manometric technique has been determined in these patients and shows no consistent changes. The chromatographic analysis, which will give detailed information about the excretion of individual amino acids, is currently being performed. The data available are very preliminary but suggest that taurine excretion is increased and that beta aminoisobutyric acid is excreted in increased amounts in irradiated subjects. The increased excretion in taurine is not so clear-cut as that in beta aminoisobutyric acid. This latter amino acid arises from the breakdown of desoxynucleic acid and might be an indication of cell-nucleus breakdown. There is some suggestion that the levels of excretion of this amino acid are correlated sufficiently well with dose of radiation to be a useful in vivo dosimeter. Present

evidence also suggests that a change in serine excretion follows total-body irradiation.

BONE-MARROW AUTOTRANSPLANTATION AFTER NITROGEN MUSTARD

Clinical Staff

An effort is under way to make use of an autograft of bone marrow in conjunction with large doses of nitrogen mustard. This project is related to the total-body irradiation experiment in acute leukemia, and the same method of obtaining and infusing marrow is used. A group of patients (selected because their neoplastic disease has progressed beyond conventional therapeutic measures and because there is a lack of demonstrable metastases to bone) are being given large doses of nitrogen mustard intravenously. The dose rate is 1 mg/kg body weight, all given within a period of 5 to 10 minutes. The procedure, including general anesthesia and aspiration of bone marrow, is conducted in the same way as with the bone-marrow donors for the acute-leukemia program. The diluted bone marrow, in its plastic bag, is stored for 4 to 6 hours at icebox temperature, subsequently warmed to approximately body temperature, and infused intravenously. Control members of this series have been selected from a table of random numbers, and the decision to include a patient in the series is made independently of a knowledge of whether the subject will fall in the bone-marrow or control group. No conclusions with regard to bone-marrow transplantation can be drawn at this time. Two patients have responded encouragingly, with marked regression of lesions, to this large dose of mustard.

CONTINUING PROGRAMS

Clinical Staff

Certain long-range programs have continued to occupy a part of the clinical activity of the Medical Division. Some of these are carried on chiefly for purposes of teaching the resident staff and offering a variety of clinical experience to the permanent staff. Certain of these projects have specific research value; others do not.

Study of thyroid disease, in addition to the specific projects mentioned, includes a long-range investigation of carcinoma of the thyroid. Some patients with hyperthyroidism and cardiac or pulmonary insufficiency are also treated with iodine-131. There is a continuing interest in early and late histologic effects of iodine-131 on thyroid tissue, and additions to this group of specimens have been made during

the year.

Hematologic disorders have occupied much of the attention of the staff. Therapy with potassium-32 is used as previously for certain cases of polycythemia and chronic leukemia. Splenectomies are done in a few cases and the excised spleens assayed for chromium-51 or iron-59 in an effort to make a correlation with external counting measurements. Quite a number of patients with leukemia are followed in preparation for, or follow-up from, total-body irradiation treatment. We continue to see patients who present diagnostic problems in hematology, on referral from physicians in surrounding areas. Much of the hematology is done on an outpatient basis. The outpatient program is showing a gradual shift in emphasis from the blood diseases to follow-up studies on patients treated with iodine-131 and patients having intracavitary administration of colloids. About 30 outpatients are being seen each month.

Interest in carcinoma of the ovary continues. This study ties in with the investigation of intracavitary colloid therapy. Efforts to compare yttrium-90 and lutecium-177 with gold-198 for this purpose have not progressed very far; it has been difficult to find suitable cases and to establish criteria for evaluation. It is clear that yttrium-90 can be effective for this application, but its merits relative to gold-198 are not established. A vigorous surgical approach to palliation of certain patients with carcinoma of the ovary has been continued, and the results appear favorable. Some patients with this disease fit into the study of large doses of nitrogen mustard and this treatment has yielded pronounced transient benefit in some patients.

We have measured the concentration of phosphorus-32 in tumors biopsied or removed at operation. Simultaneous blood samples are obtained as a basis for comparison. This group of operative specimens supplements a series of autopsy studies already made.

Resection of pulmonary metastases has been carried out in a few selected patients. The results of this program appear to warrant continuation of it, with efforts to clarify criteria for selection of cases.

RADIOTHERAPY

F. Comas

A newly installed cobalt-60 teletherapy machine was readied for use in radiation therapy. This is a rotational unit provided with two sources of about 600 curies each of cobalt-60, located 180° apart, in an open ring arrangement. The center of rotation is located midway between the sources, and at 60 cm from them. At this point the dose ray from each source ranges from 27 to 32 r per minute, according to the field size. In certain instances (in using parallel opposing fields,

360° rotation) both sources can be in the "on" position at the same time, doubling the dose rate. The net effect is that of having a hectocurie unit, with its small size and mobility, with an output corresponding to that of a kilocurie machine.

Whether the patient is treated with stationary fields or by arc or circular rotation, the tissue doses are calculated by making use of the tumor to air ratios. With this method, attention is focused mainly on tissue doses, rather than skin dose, which in cobalt teletherapy is of little significance. To obtain tumor to air ratios a simple experimental setup was used. It consisted of a Lucite water phantom in which a Victoreon 25 r-meter was submerged. The r-meter was fastened to the frame of the machine and the phantom was laid over the treatment table. By moving the phantom laterally, the water thickness between source and probe was reduced at 1-cm intervals, and the ratios between dose rate in air at the center of rotation and dose inside the water phantom were plotted. Measurements were made for several field sizes. Our data agree within 3 per cent with one set of published values.

The treatment table is of aluminum alloy in order to minimize the attenuation of the cobalt-60 beam when it points upward. To determine the degree of attenuation, a Victoreon r-meter was placed at the center of rotation of the machine, 8 and 10 cm above the surface of the table, and measurements were taken with the cobalt beam traversing the table at different angles. The maximum attenuation amounted to about 15 per cent at 30° from the horizontal. At 90° it was about 8 per cent, small variations being due to the area of the field. On the average, the intensity of the beam at the center of rotation is reduced 8 per cent when the machine is moving through a 180° arc under the table. For 360° the over-all reduction is taken as 4 per cent.

Twenty-two patients with several types of malignancy have so far been treated.

AUTORADIOGRAPHY

William D. Gibbs

The response of a large number of commercially available X-ray films to sulfur-35 and chromium-51 has been determined. In conjunction with data previously obtained from phosphorus-32, iodine-131, and mercury-203, it seems that the range of linearity for any type of film decreases as the beta energy becomes lower. Analysis of all data is not complete as yet.