

## CLINICAL STUDIES

Gould A Andrews

The past year has seen the strengthening of the Medical Division's clinical staff by the addition of a senior permanent staff member, an internist, Beecher W. Sitterson.

The research program consisted in continuation of several of the long-term clinical studies, plus increased activities in the use of total-body irradiation and attempts at bone-marrow transplantation. The latter study was largely stimulated by the basic work of Charles C. Congdon at the Oak Ridge National Laboratory, and much assistance in connection with this problem has also been obtained from Dr. Congdon's associates, T. T. Odell and T. Makinodan. The care of patients has been managed largely by Dr. Sitterson and Robert H. Nightingale, with the help of a considerable number of short-term residents. Diagnostic radiology and radiotherapy have been carried on by Donald B. Darling and Orren W. Hyman. Douglas A. Ross has collaborated closely with the clinical staff in connection with external counting procedures and interpretation of scintiscans. The pathology staff members, C. Harold Steffee and Bill M. Nelson, in addition to routine and research pathology, have participated in active teaching in connection with the clinical rounds. Betty M. Cooper, in addition to performing the techniques involved in anesthesia for a variety of operations and for multiple bone-marrow aspirations, has assisted with electrocardiography and clinical care of pre-operative and postoperative patients.

The outpatient service has continued to increase somewhat in size, and has been largely handled by Etna L. Palmer.

A major contribution to the research program has been the collaboration with practicing physicians in Oak Ridge, including Robert R. Bigelow, William W. Pugh, Dana W. Nance, Paul Spray, Robert P. Ball, Dexter Davis, Raymond Johnson, and C. J. Speas. Assistance and consultation have been provided by Eidsen Smith and Robert Newman of Knoxville. George Minor has come from Charlottesville, Virginia, on several occasions to perform operations and offer consultation.

The nursing staff under Mrs. Adren Sutliff has continued to contribute a major share to the research effort in the collection of data as well as in maintaining routine care.

## STUDIES WITH IODINE-131

## Clinical Staff

Continuation of studies of patients with carcinoma of the thyroid has led to further emphasis on a group of patients who have functioning thyroid

tissue or tumor in the neck after attempted total thyroidectomy for carcinoma. Several more of these patients have been subjected to reoperation with the probe counter in an effort to remove the tissue that concentrates iodine. Correlation of histologic findings with preoperative scintiscan records has shown some interesting results. It appears that when such areas are discovered, even in the region of the thyroid bed, there is a considerable likelihood that they are tumor. A surprising number of areas of residual or recurrent tumor occur in the region of the trachea and larynx where radical neck dissection does not succeed in removing them. Surprisingly enough, some of these are in lymph nodes almost in the midline. There seems to be no clear-cut pattern of uptake and release of the iodine that is sufficiently striking to allow separation of tumor and normal thyroid on the basis of external counting or scintiscan studies. Location of the lesions is, of course, important, since those that occur outside the region of the normal thyroid or thyroglossal duct are almost certainly tumor. It is believed that these studies may eventually lead to some further evaluation of the usefulness of radical neck dissection and total thyroidectomy in treating relatively early, well-differentiated carcinoma of the thyroid without distant metastases.

Preliminary studies in a small number of patients with carcinoma of the thyroid treated by desiccated thyroid or thyroxine have failed to show clear-cut regression of lesions, although maintenance of a relatively static clinical state has been demonstrated.

#### STUDIES WITH THE SCINTISCANNER

##### Clinical Staff

Continued use of the scanner has resulted in some further familiarity with the interpretation of records. Technical defects have been largely eliminated, and more adequate identification of records has been instituted. Cases of carcinoma of the thyroid have been encountered in which the primary lesion in the gland is palpable but not detectable by the scanner, even with the most careful technique. Douglas A. Ross has instituted more careful surveys of the whole body in connection with local-area scanning, and by more adequate coverage of areas of interest some lesions, which were previously overlooked, have been discovered. These have included areas of activity high in the neck and substernally in patients with carcinoma of the thyroid.

#### TOTAL-BODY IRRADIATION AND BONE-MARROW TRANSPLANTATION

##### Clinical Staff

A study of total-body irradiation followed by infusion of freshly aspirated bone marrow is a major project at the Medical Division. The work

is based on studies, in animals, indicating the possibility of transplantation of marrow with resulting greatly improved survival after large doses of radiation. If such a procedure could be worked out for human beings, it would offer a form of treatment for accidental exposure to large doses of radiation. There is also the possibility that it could serve as a form of treatment for certain diseases characterized by abnormality of, or failure of, the bone marrow.

In the Medical Division the chief effort has been on a clinical level and the patients treated have had acute leukemia. After preliminary studies of marrow aspiration and infusion, a technique for handling the marrow was established, involving simple aspiration of the posterior ilium of adult donors given a general anesthetic and compatible according to the major red-cell groups. The marrow aspirate is diluted with a medium containing citrate and electrolytes placed in a polyethylene transfusion bag, and is administered intravenously with minimal handling. A small group of patients has been given radiation plus marrow, and in two with acute leukemia a temporary remission in the disease has apparently been produced.

This study involves the cooperation of almost the entire personnel of the Medical Division. Marshall Brucer and Douglas A. Ross have worked out a special irradiation setup, and they have measured the radiation distribution, with the help of L. C. Chiang, J. Fujita, and others. Surface dosimetry measurements have been provided by Raymond L. Hayes with the help of Washington Butler. The radiation has been administered by Donald B. Darling and O. W. Hyman, Jr., along with Dr. Ross and members of the clinical staff. For each patient treated, four marrow donors have been used; the multiple anesthetics needed have been given by Betty M. Cooper. The study has put a special burden on Martha Clevenger and Barbara Unger in the hematology laboratory because of the large number of special laboratory determinations. Electrophoretic studies have been done on the serum by Granvil C. Kyker and Martha Stewart. Special red-cell subtyping studies designed to demonstrate the success or failure of the transplantation are being conducted by C. Harold Steffee and Joe Gray. Studies on nitrogen balance and free amino nitrogen of the serum have involved the efforts of Arthur L. Kretchmar, B. L. Byrd, the nursing staff, and the Oak Ridge Hospital dietary staff. The patients have presented special clinical problems for Drs. Andrews, Sitterson, Nightingale, and the resident staff, as well as nursing problems for Mrs. Adren Sutliff and her staff.

#### RADIOACTIVE COLLOIDS AND RARE-EARTH ELEMENTS

##### . Clinical Staff

Studies have continued on the intracavitary use of radioactive colloids. A group of patients with carcinoma of the ovary has been treated by vigorous surgery and intraperitoneal radioactive gold. This form of treatment appears to be of value for patients with papillary and pseudomucin-forming tumors that do not readily spread outside the peritoneal cavity. Tumors of this sort may

appear more hopeless than they actually are because of the massive involvement and widespread peritoneal dissemination. Such patients are frequently denied the benefit of adequate palliative surgery because the initial laparotomy showed an apparent hopelessness of the lesion. It has proved worth while to perform repeated operations, sometimes as many as five or six in one patient, in an effort to resect the tumor. In many of these patients, radioactive gold has been administered immediately after the operation, within a few hours. No difficulty with the healing of the wound has been encountered. The gold is injected by way of polyethylene tubes inserted at the time of surgery. It is difficult to evaluate the benefit of the gold, as compared with the benefit from the vigorous surgical therapy. In some patients, the presence of raw surfaces from which tumor has been removed without adequate surrounding normal tissue has been considered an indication for the gold treatment. Untoward effects of the radioisotope treatment have not been important, although there may be some contribution to the formation of adhesions. In general, these patients have had relatively few adhesions, considering the extent of their disease and the multiple operations. A similar program has been followed with a small number of patients having tumors of this type arising in the appendix or colon.

Continued use of yttrium-90 has yielded some beneficial results in the control of pleural effusions. Doses used have been in the neighborhood of 20 millicuries, with 50 mg or less of stable carrier. Relatively little use has been made of lutecium-177, but it is anticipated that further studies will be made of this radioisotope. A few patients have been given nitrogen mustard intrapleurally on one side, and a radioactive colloid has been given on the other side in an effort to determine the comparative histologic effect of these two forms of symptomatic treatment for effusions caused by malignant neoplasms.

#### STUDIES ON LIVER DISTRIBUTION OF RADIOACTIVE ISOTOPES

##### Clinical Staff

A few studies have been conducted on various radioisotopes that may be of some use in delineating liver metastases. These have included radioactive rose bengal (I-131), radioactive gold, yttrium, and lutecium, and iodine-labeled albumin. The Medical Division has been interested in trying to collect autoradiographic data from operative or autopsy specimens showing the distribution of radioisotopes in lesions as compared with normal liver. It appears that all the radioactive colloids and rose bengal are almost completely absent from metastatic tumors in the liver. Reports in the literature about the localization of iodine-131-labeled albumin in liver metastases are rather confusing. Within a very limited experience, there is little evidence of any significant concentration of the isotope in the lesions.

Plans are under way to undertake phantom studies on the scintiscanner in relation to detection of liver lesions.

## HEMATOLOGIC DISORDERS

### Clinical Staff

Continued study of a group of patients with leukemia and polycythemia has led to additional clinical experiences of interest, particularly in connection with the development of late complications of polycythemia. The clinical staff has a particular interest in following the bone-marrow pattern in patients with polycythemia late in the course of the disease. Cooperative studies with T. T. Odell of the Biology Division of the Oak Ridge National Laboratory have been undertaken in two patients. These are studies on platelet survival with sulphur-35.

The use of radioactive gold in a small series of patients with chronic granulocytic leukemia has been continued, but new patients are not being added to this series, since the results do not seem to warrant its expanded use.

Previous studies of multiple myeloma were not continued during 1957.

## RADIOISOTOPE DISTRIBUTION IN BONE TUMORS

### Clinical Staff

A group of patients with carcinoma of the breast and bone metastases has been studied, most of them without the use of radioisotopes. Stable chemical measurements relative to calcium and phosphorus metabolism have been done, and it is anticipated that radioisotope studies will be used in patients in this group. Interest is centered on efforts to select the proper hormone therapy for these patients.

The evaluation of the distribution of phosphorus-32 has continued. This work was reported in last year's midyear report. Since that report, the series has been expanded somewhat. Autoradiographic data indicate the complexity of the distribution of phosphorus-32, and the difficulty of expressing in any simple way this distribution. In general, the data on localization in bone metastases from breast tumors and in other types of bone lesions do not indicate that phosphorus-32 will be a useful isotope for irradiating such lesions. Certain concepts of isotope distribution and methods of expressing the distribution have been developed from this study.

## PATHOLOGY

C. Harold Steffee, B. M. Nelson, and William D. Jones

Collaborative efforts involving the pathology laboratory in studies of rare earths and in the attempt to follow the survival of transfused human bone-marrow cells are outlined in other sections of this report.

A major achievement of the past year has been the planning and presentation of the first week of the seminar for pathologists on the diagnostic uses of radioactive isotopes. This seminar is cosponsored by the American Society of Clinical Pathologists and is conducted as two one-week sessions separated by a period of three months. The first week consisted of a five-day program lasting until 10:00 or 11:00 PM each night. The second week will be similar, but will involve sessions on Saturday as well. The seminar has included lectures, demonstrations, laboratory work, and animal experiments, and has involved the cooperation of the entire senior staff of the Medical Division. The seminar seems to have been well received by the participants and additional seminars are planned for the future, since there were many more applicants than could be accommodated in this first session.

Elsewhere in this report is a summary of the technical aspects of the autoradiography program during the past year. In addition to these features, it should be noted that an analytical report is being written for each gross and microscopic autoradiogram prepared on human tissue. For surgical specimens, the autoradiographic report is subsequently added to the clinical chart. For autopsy material, the report of autoradiograms now forms an integral part of the autopsy protocol. This procedure is an endeavor to make the pathology records as complete as possible.

Also during the past year, approval has been obtained from the American Medical Association and the American Board of Pathology for a one-year residency program in experimental pathology. This program is planned generally to accommodate short-term residents who will be here for a period of three to four months. During 1957, one such resident was assigned to the division. The four-month program includes participation in the clinical care of patients and diagnostic studies using isotopic procedures, and the clinical experience is supplemented with animal experimentation. With more publicity, more residents are expected to apply for appointment to this program.

#### AUTORADIOGRAPHY

C. Harold Steffee, William D. Gibbs, and Robert L. Burton

During 1957, 900 autoradiograms were prepared for the clinical and research staffs. This number does not include the autoradiograms made by the autoradiography group in its own research efforts, nor does it include autoradiograms made for the participants in the pathology training seminar—these amounted to an additional 400 preparations.

The response of sixteen commercially available X-ray films to phosphorus-32, iodine-131, and mercury-203 has been determined. Only four of these films exhibit a linear response to densities greater than 1.5, and these are films that are extremely insensitive. In general, all films have

a linear response, over a greater range of density, to isotopes of high-energy emitters than to those of low-energy emitters; the reason for this is not entirely clear. This study will be extended to include data on response to sulfur-35 and chromium-51.

Extensive testing of the freeze-dry apparatus designed by the Medical Division staff and built by the ORINS shops has shown the need for some minor modifications, which are now being made. During testing, specimens of good quality were obtained and microscopic autoradiograms were made showing details of phosphorus-32 distribution that had not previously been demonstrated.

Preliminary work on a technique for simultaneous determination of the distribution of two isotopes in the same specimen has been completed. It seems likely that it will be possible to differentiate between sulfur-35 and calcium-45 in the same specimen by means of a two-film technique, and further work on details of the technique is being carried out.

A review of the literature was undertaken to bring the existing punch-card file on autoradiographic publications up to date through 1956.

The staff again lectured to six basic radioisotope-techniques courses at the ORINS Special Training Division.