(12)

REPOSITORY PNL
COLLECTION General
BOX No. N/A
FOLDER N/A

717099

Please return to
H D Brewer
Rt 1 Box 3397
Bonita Springs FL
33923

PNL-10226

NUCLEAR ENERGY IN MODERN MEDICINE

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

Date? about 1967?

In 1895 and 1896 Roentgen reported the discovery of X-rays and Henri Becquerel announced the discovery of natural radioactivity in uranium salts. The medical profession was quick to exploit these discoveries in the treatment of disease with the result that within less than a 10 year period ionizing radiation had been produced artificially, observed as a natural phenomenon, had been used in the diagnosis and treatment of disease--and had caused cancer of the skin. From then on until World War II, the principal applications of these radiations outside the laboratory were in the fields of medical diagnosis and therapy, industrial radiography, and the manufacture of luminous dials.

Following the war, those who had been concerned with the various phases of atomic energy came to appreciate the totality of its potential for the good of mankind. They saw it as a source of almost unlimited energy, energy enough to build and operate almost any machine; and subsequently we have learned to use it for space travel, for excavation purposes and for submarine exploration. Concurrent with this expanding recognition, however, there has been a healthy respect for its hazards as a lethal weapon of war and the possibility of harm to people who use it carelessly or unwisely in the laboratory, in industry, or in the practice of medicine.

1107256

During the first 40 years after the discovery of X-rays and radium, atomic energy was used in medical practice for two general purposes. First, there developed very rapidly a widespread use of the penetrating properties of X-rays for diagnostic purposes, whereas gradually, and to a considerably lesser extent, the direct damaging effect on living cells of ionizing radiations from radium and from X-ray machines was taken advantage of in the treatment of cancer. In addition, there were a few applications of ionizing radiations in other fields of medicine, as for example, the treatment of acne vulgaris or the indirect treatment of ringworm of the scalp in children.

In the research laboratory these radiations were used as experimental tools. For example, in the middle 1920s, Hermann Muller exploited X-rays to the great advance of the science of genetics. Hevesy in Denmark did something quite different; he did not utilize the damaging effects of ionizing radiations as Muller was about to do. Hevesy understood that radioactive elements behaved chemically like their non-radioactive counterparts, but in addition he realized they could reveal their presence by the very fact that they were radioactive. Thus, one could use radioisotopes to trace the movement of chemical elements in a living organism. Lead was known to behave in many ways much like calcium in plants and animals and so Hevesy employed a naturally occurring radioactive isotope of lead to study by analogy certain facets of calcium metabolism in plants. He thus

1107257

established in 1923 the basic principles for the use of radioactive elements as tracers in the elucidation of biological processes. Today, of course, with the wide variety of artificially produced radioisotopes available, he would select radioactive calcium-45 or calcium-47 for such a study. Incidentally, both Hevesy and Muller received Nobel Prizes for their work with radiation.

In 1934, Joliot and Curie reported the first successful artificial production of radioactive elements. They bombarded boron and aluminum with the alpha particles from a naturally occurring radioelement, polonium-210, to produce nitrogen-13 and phosphorus-30 respectively; both are radioisotopes having very short half-lives, 11 minutes and 2.5 minutes, respectively, but long enough to be detected conclusively.

Beginning about 1930, Ernest Lawrence began to develop the principle of the cyclotron into a machine that provided a much more powerful and flexible source of high-energy particles than had hitherto been available. Soon there was a cyclotron which produced radioactive isotopes of sodium, iodine, and phosphorus in quantities sufficient for exploring their potential value in medicine as therapeutic agents and as tools for study of life processes; it was fortunate that these radioisotopes had reasonably long half-lives and were important components of tissue cells. And so, in 1936, a medical team at the University of California, Berkeley, under Dr. John Lawrence, Ernest Lawrence's brother, first administered an artificially produced radioactive isotope, phosphorus-32, to a sick human being with the express purpose of treating his disease. This event marked a milestone in the practice of medicine.

1107258

Since then the therapeutic uses of artificially produced radioisotopes have been in the medical spotlight; they have been administered internally, used like X-ray therapy machines as sources of high energy gamma-rays, and as needles much as radium has been used. The preoccupation of the medical profession and the public at large with the urgent need for more effective ways to treat cancer has largely been responsible for this. However, it has turned out that the diagnostic uses of radioisotopes are outstripping the therapeutic uses. At the same time, the unpublicized day-to-day uses of radioactive tracers in fundamental research into the nature and causation of disease have far exceed in variety and in eventual importance the immediate diagnostic and therapeutic applications.

Prior to World War II only a few biomedical scientists were privileged to have radioisotopes, those who were fortunate enough to be associated with universities at which there were high energy accelerators. They were able to secure only small quantities because only very limited amounts of cyclotron time could be made available by the physicists to produce isotopes for their medical colleagues.

With the close of World War II and the ready availability of large quantities of neutrons in our nuclear reactors, the stage was set for the production and full exploitation of radioisotopes in medicine, biology, agriculture and industry.

1107259

On August 2, 1946, the first shipment of radioisotopes was dispatched from Oak Ridge, Tennessee. This signaled the present era of freely available, artificially produced radioisotopes at reasonable cost to all persons who could demonstrate that they could use these new tools safely. By August 1, 1966, there had been 205,793 shipments of radioisotopes by the Oak Ridge National Laboratory, amounting to almost 5½ million curies of radioactivity. Although ORNL is our primary Laboratory for this function, additional quantities (about 2½ million curies of mainly cobalt-60) have been furnished directly to customers by the Brookhaven National Laboratory, Mallinckrodt Laboratory, Savannah River Project and Idaho Operations.

Today just about every medical specialty has found a use for radioisotopes. The internists are using phosphorus-32 and other radioisotopes to treat a variety of blood diseases such as polycythemia rubra vera, and certain of the leukemias. They use radioactive iodine and radiotechnetium to diagnose various thyroid conditions and to treat hyperthyroidism and appropriate cases of thyroid cancer. They use iodine-131 to destroy the thyroid gland in order to control selected cases of intractable angina pectoris and chronic heart failure. Radioiodinated human serum albumen is finding daily use in blood volume and cardiac output studies. Radioactive iron, iron-59, is used to measure the rate of red blood cell formation while chromium-51 is used to tag red blood cells for measuring the red cell mass. A very simple diagnostic test for pernicious anemia consists of administering by mouth vitamin B-12 labeled with radiocobalt and subsequently checking for radioactivity in the

1107260

urine; if the "intrinsic factor" is lacking, comparatively little of the labeled B-12 is absorbed systemically. Excretion of the iodine-labeled dye, Rose Bengal-I-131, appears to be many times more sensitive as a test for liver function than many of the older tests.

The neurosurgeons have found radioactive iodine, radioarsenic, and more recently radiotechnetium important aids in the diagnosis and localization of brain tumors. They are also using radioisotopes to study the dynamics of the cerebrospinal fluid.

In ophthalmology radiostrontium applicators have proved valuable in treating benign growths on the sclera and phosphorus-32 has been found helpful in some clinics for localizing and diagnosing tumors within the bulb of the eye itself.

Plastic surgeons may use radioisotopes of sodium or chlorine to determine the adequacy of blood supply in pedicle skin grafts.

Radioiodine and radiomercury are used successfully for a variety of kidney function tests; radioselenium has been proposed as a diagnostic tool for cancer of the pancreas.

Technetium-99m has in recent years proved a most versatile tool. It is used for the diagnosis of thyroid disease, liver disease, brain disease and kidney disease, depending on its physical and chemical state. Technetium-99m is obtained from a "radioisotope cow." The "cow" consists of a tube of ion exchange resin upon which has been deposited molybdenum-99 with its 43 day half-life. As the molybdenum-99 decays technitium-99m is formed and can readily be "milked" off

1107261

by an appropriate chemical process whenever there is need for the isotope. Other "cows" have been developed to provide iodine-132, strontium-87m, indium-113m, yttrium-90, etc.

In experimental surgical studies, aimed at controlling certain cases of disseminated cancer, malignant diabetes mellitus, or Cushing's syndrome, implantation of radioactive pellets of ceramic yttrium-90 in the pituitary gland has been used by some as a substitute for surgical hypophysectomy. At the Lawrence Radiation Laboratory, Berkeley, a proton beam from the large cyclotron has been able to accomplish the same result without surgery of any kind.

This by no means exhausts the uses to which radioisotopes have been put in the practice of medicine, but I trust you now have some idea of their versatility. At the recent annual meeting of the Society for Nuclear Medicine, the program ranged from papers on how to use whole body counters for diagnostic studies so as to minimize the radiation exposure to the patient, to the use of a compound containing mercury-197 for scintiencephaloscanning for the detection of non-neoplastic intracranial disease. You will note that nuclear medicine has already developed a jargon of its own.

Before moving on to other ways in which atomic energy activities are modifying medical research, I would like to say a few words about possible future applications of radioactive tracer studies in intermediary metabolism and the promise they hold for the future. Based on the Hevesy theorem that a radioactive element differs from its stable

1107262

sisters only in its radiative emission of particles, there now exists a large body of information on biochemical transformations, metabolic cycles, drug metabolism, etc., which is fundamental to modern biochemistry. (We trust that the Hevesy theorem is true--a great deal depends on it.) In the simplest tracer study one introduces a drug or compound, labeled with a radioactive isotope, into the body and then follows its subsequent course. If it is catabolized by the body, one can determine with the aid of chemical separations the routes by which it was broken down and also discover the pathways of excretion of the fragments. The reverse can also be carried out. For instance, radioactive sodium acetate can be fed and after a time it will be found that complex compounds such as fat acids, cholesterol, and certain of the sex hormones have been built up within the body using the acetyl group as one of the building blocks. By such techniques the whole field of intermediary metabolism is moving forward with tremendous strides. As these studies have grown more sophisticated, the use of electronic data processing techniques has become more and more essential to their success.

Whereas few basic science departments in medical schools were using radioactive isotopes for research in 1950, it is now rare to find a department which does not have at least one detector system for radioisotopes. A department that does not use radioisotopes in some way or other probably is carrying on very little research.

Metabolic tracer techniques are equally important to the clinician because he must take care of a greater frequency of "diseases of maturity." Now that the infectious diseases have been brought under control, the

1107263

mean life span has lengthened and with this come a variety of disturbances of metabolism that bulk large in our efforts to control hardening of the arteries, hypertension, and perhaps even neuropsychiatric disorders. Many laboratories today are well along in such studies using radioactive isotopes incorporated into organic compounds. As the metabolic defects are pinpointed, there is reason to hope that diagnostic tests will be devised, using related techniques, which will permit earlier recognition and correction of the defects before irreparable damage has occurred.

The use of iodine-131 alone or in labeled compounds to detect aberrations of thyroid gland activity is commonplace. In the future, carbon-14 and tritium (hydrogen-3) are the isotopes most likely to be useful. Unfortunately, their beta radiations are of relatively low energy and consequently are not as readily detected as the gamma-rays from iodine-131. Furthermore, for such studies and tests to be undertaken safely in relatively normal people, the amount of these isotopes introduced into the body for any one study will have to be strictly limited. This means that the conventional, low sensitivity methods of counting are being superseded in medical research by much more sensitive methods such as were developed by Dr. W. F. Libby a decade ago for detecting traces of radiocarbon.

Activation analysis has proved helpful to scientists interested in precise measurements of very small quantities of certain elements. Material for analysis is placed in a nuclear reactor and bombarded with neutrons so as to cause the element of interest to become radioactive

1107264

in a highly specific and identifiable way. Unfortunately, many other elements also present in any sample become radioactive as well, so only those which give rise to a radioisotope with especially distinctive characteristics can be measured in this way. On the other hand, appropriately timed, conventional chemistry has proved of great help by separating out many elements with competing radiation spectra. In this way, the hours of computer time required for gamma-ray spectral analysis are greatly reduced. What would really move this technique forward would be the development of inexpensive, relatively high intensity sources of monoenergetic protons or neutrons. In this way, the emission from unwanted radioisotopes induced in the sample could be reduced to a mere trace. In time it is certain that many elements will be effectively measured by this technique.

Meanwhile our detection techniques are being significantly improved. Multi-dimensional gamma-spectroscopy, developed within the past three years, has increased the sensitivity by one to two orders of magnitude for gamma-emitting isotopes. The lithium-drifted silicon detector will be a very major stride forward when it is perfected.

These things which we have been talking about up to now constitute some of the more readily identifiable contributions of the atomic age to medicine and medical research. But there are also a number of indirect contributions resulting from the demand for more and more precise information about radiation effects on biological systems.

1107265

Take the problem of whole-body radiation injury such as was incurred by thousands of Japanese at Hiroshima and Nagasaki. One of the most important effects of a single large exposure of the whole body to atomic radiation is prompt, but temporary, suppression of proliferation of cells in the bone marrow and lymphoid tissue. The body for a matter of days is incapable of forming new blood cells and this response has proved to be an excellent one for finding methods of ameliorating radiation effects when the treatment is instituted prior to exposure. In rats, the amino acid cysteine given a few minutes before exposure can reduce the effect by about a half. Chemicals which injure the bone marrow, if given 7 to 10 days previously so that the exposure occurs just when the marrow is beginning to recover its function, have a similar sparing effect. Irradiation at a time when the animal's tissues are temporarily deprived of an adequate oxygen supply permits increased chances of recovery. Bone marrow transplants administered after a large exposure have also been effective in promoting recovery and it was largely the stimulus of this work on marrow transplantation which led to a renewed interest in and some success with human organ transplantation. All these observations add to the general store of knowledge about the factors which control the formation of blood cells. Each successful procedure for promoting prompt recovery of the marrow will some day be of value in controlling the anemias encountered in ordinary medical practice. For example, some of the same scientists, who have worked on this radiation problem, have separated from blood

1107266

and urine a hormone-like material called "erythropoietin" which can stimulate the formation of red blood cells.

Forty years ago the problem of the hazards of radioactive materials, which may be ingested and eventually deposited in various tissues of the body, was dramatized by the tragedy of the women radium dial painters of New Jersey who died of radiation-induced aplastic anemia. Now, as a result of that experience, elaborate and expensive precautions in the atomic energy industry are taken against this type of hazard. Nevertheless, the internally deposited radioactive isotope is a constant threat. Plutonium, used in making atomic weapons; thorium, which will be used some day in atomic reactors; and radioactive strontium, which, as fallout from nuclear weapons testing, has been the source of so much worry; All resemble radium in that they tend to localize in bone, and thus they have presented us with a common challenge. Two lines of investigation are being pursued. One is by use of chelating agents to redirect the radioelement to the kidneys, and thus permit its excretion before it can be deposited in the bone. We have already made progress along this line with respect to wounds contaminated with plutonium. Our other response has been to learn more and more about the physiology and biochemistry of bone. The result is a major increase in our knowledge of the mechanisms by which bone minerals are deposited and removed, a process which is continually going on throughout our lives. But whether we ever come up with a method for removing radiostrontium from bone without at the same time taking out the calcium remains to be seen.

1107267

Meanwhile, what we are learning about bone formation will certainly lead to a better understanding of many bone diseases.

Another aspect of this internal emitter problem lies in trying to estimate how much of a given radioisotope is present in the body and, equally important, how much is deposited in bone. Two approaches are available: One, to be discussed later, is whole body counting of the gamma-radiation; the other is to calculate on the basis of excretion rates how much ought to be present. In the later case mathematical models play an extremely important role.

Shortening of the life span is one of the long-term effects of total body irradiation. It is non-specific in the sense that no single cause of death seems to be responsible for life shortening. So far as can be determined, this life shortening parallels the natural aging processes and it follows that what we learn about radiation-induced aging should apply to natural aging. In this way, radiation may help us to answer the baffling question: "What precisely is aging?" Or the very practical question: "Irrespective of chronological considerations, how old is Doctor Bruner?" Perhaps, we can look forward to the day when retirement will be based on something more meaningful than an arbitrary number of years after births. These observations, like the genetic studies to be mentioned in a moment, involve data on many thousands of individuals. To cope with them without modern data processing equipment would be an almost hopeless task.

The Atomic Energy Commission spends each year several millions of dollars of its research funds on cancer research; that is, for

1107268

researches into the cause, diagnosis and treatment of cancer, making use of the unique tools and by-products of atomic energy activities--radioisotopes, high-energy accelerators, betatrons, cyclotrons, and even nuclear reactors.

The Oak Ridge Institute of Nuclear Studies played a major role in developing the use of cobalt-60 and cesium-137 in teletherapy devices as a substitute or supplement to high voltage X-ray machines. Those who use these teletherapy machines claim excellent therapeutic results, and certainly they have a very high operational reliability.

Radiocesium, like radiostrontium, is one of the longer-lived byproducts of fission in atomic reactors, and hence there is potentially an almost limitless supply of the material.

The Argonne Cancer Research Hospital at the University of Chicago, School of Medicine, is exploring a variety of modalities for treating cancer. These include a 60 Mev flying-spot linear accelerator and a 3,000 curie high specific activity cobalt-60 rotational teletherapy device.

At many laboratories, especially the Argonne Cancer Research Hospital, Brookhaven National Laboratory, and the University of Rochester, we are sponsoring efforts designed to learn how to concentrate radioelements more effectively in tumor tissue; that is, to secure selective localization. Two approaches are being used: One method attempts to develop antibodies against cancer cells (or their matrix) similar to the natural antibodies that we produce against bacteria. If this can be accomplished, it may then be possible to incorporate radioisotopes

1107269

in the antibodies in amounts sufficient to destroy the cancer cells to which they become attached. Another method of approach is to search for special affinities that cancer cells may have for certain radioactive elements or chemical compounds; these would then be taken up and concentrated by the cells, and so lead to their death. This, of course, is simply an extension of the principle employed in the use of radioactive iodine to treat hyperthyroidism; although no other tissue may show a high specificity such as the thyroid for iodine, even a 10-fold concentration might prove useful.

Cancer is the most dramatic, and for the individual, the most definitive consequence of over-exposure to radiation. It may occur in the form of leukemia, as has occurred among a number of the survivors of the atomic weapon in Japan; it may occur as bone cancer, as happened to a number of radium dial workers many years after exposure; or it may occur as cancer of the skin, as happened to a number of pioneer radiologists. Consequently, a major part of our work in radiobiology uses cancer-induction as its end point, or uses experimental cancer and cultures of cancer cells as the biological system under study. All of these studies are contributing to a better understanding of cancer and will make their unique contribution in varying degree to the eventual solution of the cancer problem.

While we are on the subject of cancer, recent developments in zonal centrifuge technology at Oak Ridge National Laboratory have been of special interest to the National Cancer Institute and virologists in general.

1107270

A modified version of the classified gas centrifuge development program has made it possible to produce centrifuge heads capable of quantitatively separating particles as small as viruses from their biological matrices; for example, virus-like particles can be separated from the serum of human leukemia patients.

The genetic effects of radiation are another of our concerns. We have a very broad research program in this field, both within our special major laboratories and projects, and generally at universities, medical schools, colleges of agriculture and agricultural experiment stations.

Dr. William Russell's studies at Oak Ridge have now involved hundreds of thousands of mice in demonstrating conclusively that the rate at which exposure occurs makes a very real difference in the amount of genetic damage incurred from a given dose of radiation. This observation is of great importance to those concerned with formulating radiation protection guides. We may also point to the genetic research conducted at the Atomic Bomb Casualty Commission in Japan as constituting the first truly large scale human genetics study ever undertaken, and it has provided a base line for all future studies of human genetics. It was not possible, as it turned out, to define precisely the genetic effect of the atomic bomb radiations on the populations of the two cities. The effect was too small. Nevertheless, what was learned from this undertaking is already leading to improved methods of approaching that most difficult of all areas of genetic research--human genetics. The heightened interest in genetics brought about by atomic

1107271

energy activities has resulted in new knowledge relevant to the so-called constitutional diseases and leukemias, and especially the role which chromosome abnormalities may play in the latter condition.

In closing, I would like to make a plea for more widespread understanding of radiation effects in man on the part of the public--and particularly with respect to the long-term or delayed effects.

A few years ago, only a relatively few persons, radiologists and a small number of physicists, were in a position to be injured by radiation. But now the rapidly-growing atomic energy industry has swelled that number to many thousands. Although remarkably few radiation injuries have been recorded to date, despite this expansion and the huge quantities of radioactivity being handled, it has become essential that every physician and medical student become conversant with the biological effects of ionizing radiation and with the diagnosis and treatment of all the various manifestations of radiation injury. This, of course, puts another strain on the already over-burdened medical school curriculum.

It is important for the physician to be able to recognize and give appropriate treatment for radiation injury when it occurs, but it is equally important that he be able to reassure a patient that his symptoms are not due to radiation if indeed no over-exposure has occurred. There is a quite natural tendency today for a person to attribute almost any illness to his prior or present occupation. Similarly, if he lives in the neighborhood of an atomic energy plant or a reactor, he may attribute any illness to be the result of radiation

1107272

presumably emanating from the plant. The physician must be prepared to give his patient sound guidance in such cases, and to determine for him whether or not his illness is at all likely to be a manifestation of radiation injury. We have had everything from German measles to a simple exfoliative dermatitis brought to our attention as supposed manifestations of radiation injury.

The opposite may occur, however: At Lockport, New York, in 1960, nine civilian employees working on radar transmitting units at a military installation were unwittingly exposed to ionizing radiation. Two were seriously injured. They had symptoms that evening, and one was seen by his physician who, unaware of possible occupational radiation exposure and because of a swelling of the parotid gland, diagnosed mumps. I cite this incident only to point out that our profession must become more aware of radiation as a possible cause of acute illness for, the patient probably will not direct the doctor's attention to possible radiation exposure.

To sum up the impact of nuclear energy thus far on Medical Research: It has been tremendous, perhaps comparable to the impact of the light microscope. It promises to become even greater with time, but it also has brought heavy responsibilities along with it for those concerned with guarding a nation's health.

1107273