Early Experiences in Nuclear Medicine

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From inadvertently damaging an early cyclotron by carrying a pair of pliers into a powerful magnetic field to participation in some of the most exciting phases of modern research, the author has had 20 years of experience, always interesting, often highly rewarding. Among lessons learned is the fact that research needs gifted individuals whose investigative drive is not hampered by a director or committees.

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Your president has asked me to recount for you some of the early experiences in the application of artificial radioactivity to medicine. It seems a long time ago that we started. In fact, it is exactly 20 yr since we first used isotopes in medical research and therapy.

It is a great privilege to be here at the home of the founding group of this new society but, much as I am impressed with your program here this week, I believe we must say that progress in this field has been surprisingly slow. In the early days, men like the distinguished physiologist, A.V. Hill, would visit us and say that the isotope was going to be as important to biology and medicine as the microscope. If the pressure had been there, all of the isotopes could have been available to workers much earlier. The construction of cyclotrons went ahead rapidly, and the means for producing isotopes for medical and biological use were there. Recently I heard that at one of your chapter meetings the program read "Society of Unclear Medicine." Perhaps that explains the slow start. It was a new field of Unclear Medicine. Certainly, it is not unclear now, but Nuclear, and with the activity in the field of nuclear medicine here in the Northwest, we can be sure it is here to stay and is of first importance in medical study, diagnosis and treatment.

THE PERIOD OF SUSPICION

In the early days a Geiger counter was a curiosity and, when giving a talk, one would swallow a little radioiodine or radiosodium or do an experiment with a mouse or a plant to show the tracer technic. For the next 10 yr a speaker could always make an impression with such a demonstration, usually extracting some unsuspecting physician out of the audience to act as the guinea pig. However, little attention was paid to the articles we wrote on the application of artificial radioactivity to biology and medicine, and one was usually pointed out as a "half quack" or long-haired dreamer, either doing things that were unethical or dangerous to the patient or spending time carrying out studies and developing treatments that had no real application in medical research and practice. Then, of course, regardless of how much one leaned over backwards to stay out of the newspapers, the reporters would occasionally break through and a story would come out which would arouse even more suspicion in the medical profession. Tragedies of the radium dial painters were pointed out with the inference that the same factors would apply for artificial radioactivity too. If we were not poisoning the patient with radioactivity, we were doing it with red phosphorus or strontium or whatever chemical was bombarded to produce the isotopic material.

RADIUM TRAGEDIES WERE NOT REPEATED WITH ISOTOPES

In 1935, I made several trips to see Harrison Martland in Newark, New Jersey. He had had extensive experience with the radium dial painters who later developed aplastic anemia, osteonecroses, and osteogenic sarcomata. I soon became convinced that we would not encounter the same complications with artificial radioactivity since we were not dealing with alpha particle emitters or elements which become permanently deposited in bone or other tissues. As a matter of fact, in the 20 yr since we first used artificially produced radioisotopes in humans, we have not run into delayed effects or complications as some of the skeptics predicted we would. Also, fortunately in those early days we could talk over our problems with some very sound men who were either in the laboratory or on the Berkeley campus, men such as Professors G.N. Lewis, Edwin McMillan, Luis Alvarez, Isadore Perlman and many others. Dr. Glenn Seaborg and Dr. Martin Kamen were working right across the bench and would often do the radiochemistry of the solutions we used. We were not too troubled by the accusations directed against us and realized that it was only human for some to regard us as being somewhat odd to want to work with

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these frightening new materials. The field was simply too new and apparently too remote from reality. Of course, there were exceptions, men like my teacher, Harvey Cushing, who told me, "You are pioneering in a very exciting new field, which will have a tremendous impact in medicine. Go to it." Finally, we had the enthusiastic support of Professor Ernest O. Lawrence and his associates, who gladly supplied us with radioactive materials. This pleasant cooperation between physicists and physicians, so important in this field of work, has continued in a unique way through the ensuing years.

HOW TO BECOME UNPOPULAR

Actually, there was another limiting factor. Isotopes were available, but they were not really plentiful, and in many ways they were hard to come by. In the summer of 1935 in the old radiation laboratory where the 37-in. cyclotron was in operation, I had a colony of a thousand or more mice and rats, normal and tumor animals, for studies of the relative effects of the new radiations on tissue as a basis for setting up safety levels for radiation protection. At the same time, my colleague, Dr. Joseph Hamilton, was carrying out his pioneering experiments with radioactive sodium in normal human subjects (*1*). There was great competition for cyclotron time since the physicists and chemists needed bombardments for their experiments too. They were discovering a new radioisotope almost every day and needed cyclotron time for this work. Unlike the present, in those days it was not unusual for the cyclotron to break down, and a day or more would be required for getting it back into operation. Usually this involved the master touch of Ernest Lawrence. On one of these days, after a crew of physicists had worked all night to get it back into operation, I absentmindedly walked by the large cyclotron magnet with a pair of pliers in my laboratory coat pocket. They flew in the Dees, hit the vacuum chamber, and smashed it, and the cyclotron was again out of operation. A conservative statement is that I was not popular for a long time, and now when I am near a large cyclotron a conditioned reflex brings the painful experience to mind. In those early days, running the cyclotron was not like turning on an x-ray tube, as it is today.

Another experience may interest you because it might have had something to do with the good radiation safety record that followed in Berkeley. The cyclotron was running night and day, except for breakdowns, but no one knew anything about the biological effects of the radiation coming from it, especially the neutrons, so we decided to find out.

SALUTARY ACCIDENT

Paul Aebersold, then a graduate student and now head of the Isotopes Division of the AEC, obtained a Victoreen ionization chamber, and I borrowed some rats from Professor Herbert Evans, a microscope and some blood counting pipettes. Paul rigged up a small chamber, a cylinder within which we placed one of the rats. There was little room for the Victoreen chamber and the rat near the Dees, so the animal was enclosed in a small space. Of course we did not want it to get loose and scare our physicist colleagues.

Everything was set, and the beam was directed against the beryllium target to produce the neutrons. Incidentally, the quality and energy of these neutrons and gamma rays were like those produced by the first atomic bomb, and in a study made in 1935 and published in 1936 these hematological and biological findings were described and predicted in detail (*2*). After the beam had been on for three minutes, we asked the crew to turn it off since we did not then have any idea of how much radiation would constitute a lethal dose, and we wanted to look at the rat to be sure that this new form of radiation had not killed the animal instantaneously. On crawling into the space where the rat was domiciled in his brass cylinder, we were alarmed to find the animal dead.

Everyone crowded around, and from this time to the present there has been a great respect for the new radiations of the atomic age and their lethality. Perhaps it is safe now—20 yr later—to admit that when the histologic sections of the rat came through a few days later, we found that the rat died not of radiation but suffocation!

The dramatic effect of finding the rat dead was not wasted, since a healthy fear was instilled which served to save the early workers from damage, especially radiation cataracts. This, together with the fact that there were always a few medical men around looking for a chance to do an experiment, is probably responsible for the outstanding radiation health record of these early workers with cyclotrons in Berkeley.

Another experience I remember occurred in 1936. That was the first time a patient had ever received an artificially produced radioactive isotope in therapy. Radiophosphorus was given to a patient with chronic lymphatic leukemia. A short time later a patient with polycythemia vera was treated with ^{32}P for the first time, and today at 74 she is living and well. We are now all familiar with the many therapeutic applications of isotopes, but taking the first step into therapy of human patients was an awesome experience.

NEW TOOLS APPLIED

In the 20 yr we have had artificial radioactivity, I do not think any of us have fully appreciated how radioactive isotopes give us a tremendous tool for determining body composition. Ordinarily in medicine we study what we hope are representative samples, from which we then draw conclusions about total body composition. For example, we might take a sample of blood and measure its electrolyte, red cell, fat or water content, but usually we fail to remember that in taking a sample and measuring the amount of a certain material in it, we are not actually quantitating the total amount of that material in the body. Here is one place where isotopes have proved of great value—in determining the total blood volume, total electrolytes, total body water, total body fat and other substances.

DISTILLATION OF EXPERIENCE

I would like to make a few remarks on the philosophy of research, since Dr. Seeds says I am supposed to do this. During the 20 yr that I have been associated with medical research and directing a research laboratory, I have learned two or three lessons I would like to mention.

First, in medical research, the bottleneck is not lack of equipment or plant, but personnel. Every once in a while a person comes along who makes a real contribution and pushes the whole field forward. Although I do not want to embarrass him, I think there is a good example of one of these men here tonight. Radioactive iron was available from the very early days, when it was being made in the Berkeley cyclotron and shipped to several groups in the country. In recent years Dr. Huff and associates have revolutionized the methodology of using tracer iron in medical investigation (*5–7*). Now everyone talks in terms of iron turnovers and dynamics. In fact, the concept of the dynamics of iron turnover and this work with radioiron have influenced the whole course of tracer work with many other isotopes. Over the years, as the quality of our laboratories and equipment have shown such great improvement, I have learned more and more that our real bottleneck continues to be the shortage of gifted research personnel, and the rare individuals who really push the scientific frontier forward.

The second lesson I had reaffirmed, which is partly related to the first, is that the future of medical research and therapy is increasingly tied up with the basic sciences, physics, chemistry and mathematics, and medical education must be adjusted to these needs. We are lagging behind several countries in this respect, particularly Sweden and England,[1] where it has long been recognized that the basic sciences are an important part of the training of the physician and medical research worker. It is time for us to establish in our medical schools professors of chemistry and biophysics with rank equal to the clinical professors and to see that these natural sciences become an integral part of the medical curriculum.

[1]At the Atoms for Peace Conference in Geneva, through association with Russian investigators, I learned that the highest paid workers in their economy are scientists. Their salaries are higher than those heading the factories and the collective farms and second only to the politicians.

FREEDOM AND ITS REWARDS

The third point I want to make is that it is dangerous for an individual or a university to exert strong control over the direction of research activity. Freedom of the individual is a strong tradition in this country, and in no place is individual freedom more important than in research. It was not so long ago that it was suggested at a meeting of a research committee that no research project be submitted in application for support outside that university unless the committee agreed it would be worthwhile and approved the proposal. Fortunately, this proposal was defeated since the committee as a whole finally saw that it would take the heart out of any university to put this power into the hands of a committee. One large commercial company considers it worthwhile if one percent of its research activity pays dividends. One cannot predict whether a piece of research is going to produce important results or not. Accidental by-products of research sometimes are important. There have been many examples of this in the past.

In conclusion, I believe that we are now entering a new era, one of Nuclear Medicine and not Unclear Medicine. Your society and your many contributions in the field constitute the best evidence for this.

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