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Remarks by

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at the dedication of the

Biomedical Cyclotron

University of California at Los Angeles

Los Angeles, California

June 30, 1971

THE BIOMEDICAL CYCLOTRON

When Chancellor Young invited me to be one of the speakers at the dedication of your biomedical cyclotron I was quite pleased–pleased because of the role I know this new facility will play and pleased to be, in a sense, returning home. Returning to the place of one's undergraduate years is said to induce a state of introspective nostalgia, but that is not my reaction. Haines Hall, the focus of so many of my days as a chemistry student is now a hall devoted to anthropology and sociology, housing a museum of archaeology and the Harry Welcome Collection of Ethnic Art. But I do wonder whether the special aroma of a chemistry building doesn't still emerge now and then. I must look into that.

Rather than nostalgia, I think my reaction is one of pride– quiet pride–in this institution where teachers and professors provided me with a mature outlook on life and shaped my somewhat amorphous ambition to be a chemist. They also instilled the principles of scientific inquiry which have never left me. The University continues to do this although the styles are different and the tools for teaching–witness this specialized cyclotron–are beyond anything I could have imagined 40 years ago. I feel I have reason to be proud of my University.

At this point I must also confess to another feeling which I can only describe as one of anticipation and excitement– perhaps combined with something akin to a "primordial urge" to return to the lab. For when Dr. George V. Taplin and Dr. O.R. Lunt described to me their plans for using this cyclotron, I recalled my early days working with the 37-inch cyclotron at Berkeley to produce radioisotopes for medical uses and I felt the need to become involved, in some way, with your fine new facility.

Of course, the cyclotron and its biomedical applications have come a long way since those early days, even prior to my own work with Jack Livingood, when Bob Stone and Joe Hamilton used some sodium-24 made by Ernest Lawrence with his 27-inch cyclotron to perform what is believed to be the first experiment in which a cyclotron induced radioisotope was employed in man. That was back in 1936. And as some of you will recall, in the ensuing years a great many radioisotopes for biological and medical uses were made via cyclotron bombardment. Notable among these were: carbon-14, phosphorus-32, iron-59 and iron-55, cobalt-60 and cobalt-57, zinc-65, technicium-99m, iodine-131 and cesium-137.

All these valuable medical isotopes were produced in a relatively few years in the late thirties and early forties. With the forties, of course, came the development of the reactor with its seemingly unlimited flux of neutrons. By comparison with a cyclotron, a reactor could produce massive amounts of radioactive isotopes, many of them new and often in a pure or easily purified form. Because of this,

cyclotrons began to be developed in directions dictated by high energy physics, but Paul Aebersold saw to it that a specially designed cyclotron at Oak Ridge was reserved for radioisotope production.

It is altogether clear that the Oak Ridge cyclotron helped remind investigators that there was more than one way to produce curie amounts of radioisotopes. There is no question that it irradiated many a special target over the years. Meanwhile, the desirability of reducing the radiation dose to the patient was becoming increasingly obvious and besides, most of the potentially useful radioisotopes had already come under study. It was natural, therefore, that radioisotopes with relatively short lives, i.e., a few minutes to a few hours, should suggest themselves. Even more to the point, radioisotopes of carbon, nitrogen, oxygen fluorine, chlorine, elements that had been passed over because they had to be cyclotron-produced, had these properties. But most important of all, these elements make up the bulk of the chemicals comprising living tissues and the possibilities for diagnostic procedures and biochemical tests in patients stretches the imagination if ways are found to make proper use of these low atomic number radioactive isotopes before they decay.

This possibility was before Dr. Michael Ter-Pogossian at the Washington School of Medicine in St. Louis while he was designing and practically hand-building a cyclotron small enough to fit into a hospital complex and yet consistent with the flexibility required for biological experiments. His faultless demonstration in 1965 that oxygen-15, despite its 2.05 minute half-life, could be used for lung function studies in man served to refocus attention on this short-lived low atomic number radioisotope. At the annual meetings of the Society of Nuclear Medicine for 1965 and 1966 such isotopes were subjects of speculative discussion by small groups of seasoned investigators, that special sort of discussion that precedes making a major commitment.

The commercial cyclotron designers/builders both here and abroad, sensing the possibility of a market, began offering designs for a compact cyclotron based on related instruments at St. Louis, Buffalo, and London. The Commission decided that the time was ripe for exploring the potential usefulness of a cyclotron designed to yield short-lived isotopes suitable for diagnostic procedures and investigation of chemical biodynamics of man. To this end, therefore, three cyclotrons were funded at laboratories having the requisite research teams, access to suitable clinical material, and a sober willingness to make this investigation the hub of their research efforts for at least five or more years. So there is one in the Laboratory of the Sloan-Kettering Institute for Cancer Research, one at the Argonne Cancer Research Hospital of the University of Chicago, and this is the third. I congratulate the Administration, the faculty and all the research teams who will use this facility. The spirit of collaboration and cooperation which surrounds this project promises that we shall see decisive, original research flowing from this laboratory to the end that UCLA's reputation as a leader in Nuclear Medicine will become even greater.

It is interesting to observe how the modes of production of radioisotopes have shifted during the years. First there was the radium-beryllium produced, water moderated, neutron source; then the successively higher energy particles as cyclotron technology evolved; the reactors with their intense neutron flux and range of neutron energies; and now the small cyclotron designed to yield short-lived radioisotopes for special purposes.

What are some of these short-lived radioisotopes? What are some of those that will be produced in the cyclotron we are dedicating today and how will they be used?

A most important one certainly will be carbon-11 with a half-life of 20.3 minutes. Carbon-11, on being formed by the $^{10}B(d,n)^{11}C$ reaction is "boiled off" the target as a mixture of carbon monoxide and carbon dioxide. On inhalation, the carbon monoxide is rapidly and tightly bound to hemoglobin and thus becomes a label for the carrier red cells. It may be used for scanning the placenta and determining the location of placental attachment for diagnosis of tubal, cervical, and abdominal pregnancies.

Carbon dioxide labelled with carbon-11 may be especially useful in respiratory investigations related to pulmonary diseases, including pulmonary embolism and congenital defects of the heart.

Through the use of carbon-11, many compounds, especially the simple metabolic building blocks, may be labelled rapidly enough to be useful for studies of carbon absorption, transport via the plasma compartment, distribution into other compartments and finally excretion. The dynamics of transport and metabolism of toxic substances such as carbon tetrachloride might be studied. Similarly, amino acids, cholesterol, benzoic acid, DDT, etc., randomly or specifically labeled, might be traced in normal people. An amino acid such as methionine might be doubly labelled with sulfur-37 or sulfur-38 and carbon-11 for study of the reasons why and how it tends to localize in pancreatic and hepatic tissues.

There are no limits to what could be selected for study if methods for rapid separation of the isotope and synthesis of it into a reasonably pure known compound were available. It will be of more than passing interest to observe the competition between stable carbon-13 and radioactive carbon-11 in such investigations. Each has quite different but very useful properties for metabolic and diagnostic studies, particularly as carbon-11 does not necessarily require destructive sampling.

Another valuable radioisotope that your cyclotron will produce is nitrogen-13 with a half-life of about 10 minutes.

Nitrogen-13 could be used much like carbon-11 or carbon-13 for transport, compartment, and metabolic studies. Its special significance would be related to nitrogen incorporated organically in the amino, amide, heterocyclic nitrogen, quarternary ammonium, and other chemical forms. If biologic enzymes are used it is conceivable that nitrogen-13 labelled purine and pyrimidine could be synthesized and converted into RNA-DNA. This work

would require extremely fast organ iemistry–perhaps on the order of that which we do in identifying the new heavy elements.

Nitrogen-13 as nitrogen gas, ^{13}NN, can be used for studying the dynamics of the respiratory system. Nitrogen dioxide labelled with nitrogen-13 may also be used, and in addition may be developed, for estimation of cerebral blood flow using external counting.

The Biomedical Cyclotron will produce fluorine-18, with a half-life of 110 minutes, which is becoming increasingly valuable for early detection of bone tumors. It deposits on the apatite crystal components of bone and in areas of bone tumor; where the metabolic activity is increased compared to normal bone, fluorine-18 is found in increased amounts. That which is not deposited is rapidly cleared from the body water with the result that good contrast is achieved. This isotope has proved useful for demonstrating benign tumors, fractures and both osteoblastic and osteoclastic bone diseases. Fluorine-18 being a halogen can substitute under special conditions for chlorine, bromine or iodine and so label a compound. It may, however, confer properties which may make it "unrecognizable" or toxic to living tissues.

Perhaps one of the most important medical isotopes this cyclotron will be making is iodine-123, an isotope with a half-life of 13.3 hours. The short half-life of this isotope, compared to the half-lives of other readily available iodine isotopes, makes it the iodine isotope of choice for an increasing number of diagnostic procedures; further, the energies of the photons emitted are ideal for scanning purposes.

It is expected, therefore, that many of the diagnostic tests based on use of iodine-131 in various forms and compounds will be reevaluated with iodine-123. The dose commitment to the patient from the test will be much smaller and tests can be repeated if necessary after much shorter waiting periods. If iodine-123 works out as expected, perhaps iodine-131 will in large part be reserved for therapy and those circumstances where the radiopharmaceutical must be shipped fair distances or where transportation is uncertain. With its 13.3 hours half-life, there is time to transport iodine-123 for local use or, if it is needed farther away, to ship it by air.

There is no question about the utility of iodine-123. The question is whether enough can be produced in the present target-cyclotron configuration and then rapidly extracted for conversion into pharmaceutically suitable forms. If this alone can be accomplished, AEC's investment of men, machines, and time shall have been a major success.

One special use of radioiodine should be noted, namely, the technique of immunoassay. It is used for detecting very small amounts of biochemicals, e.g., hormones circulating in the blood. For example the immunoassay of insulin is a critical test in the differential diagnosis of diabetes mellitus. The procedure w. seemingly complex is quite reliable. Briefly, the antigen component is iodinated and the difference between the amounts bound and not bound to antibody are related to the amount of circulating non-iodinated antigen in the body.

Recently it has been found that an animal tumor secretes or generates an antigen which may be detected and measured by means of this radio-immunoassay technique. This finding will cause others to ask whether tumor cells in their patients or experimental animal may not also be giving rise to antigens.

In addition to those important radioisotopes I have just reviewed, it is expected that the cyclotron will be called upon to produce many other medically useful isotopes, covering a large spectrum of the periodic table.

With all these radioisotopes as potential products of this cyclotron and with all their potential benefits to the medical profession and to mankind I think you can recognize why I share your great enthusiasm for this facility.

By way of concluding I want to speak briefly of, and give credit to, two men who have been guiding forces behind the creation of this biomedical cyclotron. They are Dr. Benedict Cassen and Dr. Stafford L. Warren.

Dr. Cassen has been one of those quiet scientists–original thinkers, competent workers, first-class team men–who do not have a taste for public appearance, announcement of discovery, etc.

Dr. Cassen was among the pioneers in the development of the scintillation crystal plus photomultiplier system which now is standard for X- and gamma-ray detection. Cassen helped develop the concept of organic liquids and crystals as scintillators–the anthracene crystal specifically–and calcium tungstate as an inorganic crystal. Calcium tungstate has everything going for it except the crystal could not be made larger than a few millimeters on a side. Meanwhile the Harshaw Chemical Company learned how to grow and "can" large crystals of thallium-activated sodium iodine, so Dr. Cassen used this scintillator to devise the linear scintillation scanner which today is the basic instrument for all scanning of radioisotopes in man. His instrument has been modified, inverted, improved, and computerized with print-out in technicolor, but basically it is unchanged. For these accomplishments, Benedict Cassen was recently honored by being made a recipient of this University's Distinguished Scientist Award.

Dr. Cassen also devised a clever method for separating the phagocytic granulocytes of the blood from the lymphocytes. He added an iron-containing particulate to the plasma which the phagocytes ingested. They were now heavier than the lymphocytes and a little judicious centrifugation gave him pure cultures of lymphocytes. Later he worked out independently of Dr. Norman Anderson of Oak Ridge a system for centrifugal gradient separation of lymphocytes.

He has been a moving force b[illegible] l the preliminary studies and engineering of the cyclotron. His contributions to the ultimate successes of this machine are numerous, varied, and significant. But the men using it will probably not recognize their debt. This will not disturb Dr. Cassen for he is a generous man and a quiet scholar.

Let me now turn to Staff Warren. As Director of the MED Project at the University of Rochester during World War II, Professor Stafford Warren's title changed to Colonel Stafford Warren. But military protocol sat lightly on his shoulders. There are stories about how he got the best out of the mixtures of civilians and military personnel under his command, and how he got his way with General Groves, an accomplishment which set the patterns for the superior radiological and occupational safety and health measures of which the AEC is justly proud. Considering the absolute time pressures to develop the nuclear weapons and the monumental problems that burst forth from day to day, it is almost unbelievable that Stafford Warren could have imposed the cautionary restraints that from this vantage point we now see were so absolutely necessary.

Meanwhile the MED Project at the University of Rochester was producing toxicological data of critical importance for the safe handling of uranium and its salts and of other elements such as beryllium, radium and polonium required for the project. In addition the project developed the first really organized long-term experiments on the relative effects of graded doses of X-radiation in several species of mammals. The data, later published in six volumes of the National Nuclear Energy Series, would be landmarks under any conditions, but at that time they were indispensable for the MED project.

Dr. Warren's next contribution was recorded in the second volume of the AEC history, "Atomic Shield," as follows: "The interim committee, consisting of the leaders of biomedical projects in the major laboratories and private institutions, assembled in Washington on January 23, 1947, under the direction of Dr. Stafford L. Warren, who as a colonel had directed the Manhattan District program. The committee found the results of wartime research impressive, particularly from pilot studies of the biological effects of radiation, the physical measurement of radiation of various types, and the development of protective measures. But existing projects had scarcely begun to provide the biological data needed to protect workers and the public in peacetime research and technology.

"In addition to the existing projects, Warren recommended much more research on radiation effects and the exact toxicity of substances commonly used in atomic energy activities, the mode of entry of such substances into the human body, and the types of biological changes produced. He also saw the need for an intensive study of the hazards in production operations and development of new preventative measures."

And thus the AEC's Division of Biology and Medicine was conceived.

When Dr. Warren [illegible]ved to UCLA to build the School of Medicine, he took with him a number of MED and University of Rochester staff members. He housed them in temporary wood buildings near the site planned for the School of Medicine. Soon they were carrying on the kinds of work they had been doing at Rochester and indeed were branching out to include the investigation of radiological hazards to civilian populations. Being a member of the inner councils of the MED project and subsequently a consultant to the AEC, he was in a position to anticipate the radiological health problems that should be considered when reactors are sited in the public domain and he built up that part of his staff accordingly. Later (1949-1950) when President Truman decided that weapons tests would be conducted in the continental United States, Dr. Warren's staff was in a position to plan and conduct a comprehensive radiological monitoring/surveillance program with respect to the fallout from fission devices exploded just above the ground. From a distance of nearly 20 years it is possible to be critical of things which the UCLA team did or did not do. But it may be recalled that they fielded a team on short notice that worked with rather primitive radiologic instruments and performed on a scale that no one else had conceived of before. In those days nuclear weapons tests were novel events.

The special contribution of the UCLA field teams under Stafford Warren was the attention paid to environmental contamination by fission products, their disappearance by decay, and the progression of the radioactive isotopes into the soil, plants, and/or animals. And beyond that they maintained surveillance in areas affected by the weapons tests and heavy fallout for the purpose of determining the recovery, succession and repopulation of plant and animal life in those areas. It is not out of order to say that the UCLA teams set the patterns of environmental radiological surveillance which subsequent investigators have expanded and attempted to quantify. The UCLA team and Stafford Warren have continued their environmental and ecological researches at the test site. Now that atmospheric testing has been eliminated from the U.S. program, their interests have shifted to long- term study of recovery of desert biomes contaminated by radioactive isotopes and a well-controlled study of the effects of low- level effects of gamma radiation on the ecological relationships of an otherwise undisturbed desert community.

It is fair to say that Stafford Warren had, or rather has, a sure instinct for "knowing what was needed to be done in order to make atomic energy acceptable to the public." Another example of this prescience was his persuading a young marine bilogist, Dr. Lauren Donaldson, to begin researches on the effects of irradiation and waste heat on fish and marine animals. These studies began in 1943 at the Applied Fisheries Laboratory of the University of Washington, Seattle, well before the first power reactor was on the drawing boards. The expertise developed at this center proved invaluable for the radiological safety activity at the July 1, 1946 Operation Crossroads at Bikini Atoll. It was Lauren Donaldson and his students who invented and carried out the radiobiological studies on the marine life

that permitted use of that part of Pacific Ocean for a number of years. In fact, the staff of the Laboratory of Radiation Biology, founded in 1958 on the campus of the University of Washington with Lauren Donaldson as its director, continues surveillance of the marine life at intervals of two to three years.

In December 1962 President Kennedy asked Dr. Warren to come to Washington to be his special assistant for developing improved communication between the sciences, education and the public; and President Johnson reappointed him. He selected the area of mental health and mental retardation for demonstration of what might be accomplished and how to go about it and it is probable that a good part of the presently more enlightened attitude toward mental retardation can be traced to his personal persuasiveness.

On returning to UCLA in the summer of 1965 he began an active research-consultant schedule. One very interesting observation is his identification of a transmissible agent found in arthritic c kens that will induce arthritis upon innoculation into chicks.

He is also a man who acts positively with respect to his convictions. Since he feels strongly about air pollution he has equipped his car to run on propane.

It has been a pleasure for me to be here today to recognize the contributions of such men as Staff Warren, Ben Cassen, Michael Ter-Pogossian, Ray Lunt, George Taplin and all of you who have given so much to the important field of nuclear medicine and to the realization of the biomedical facility which will mean so much to your University and the medical community. What will be accomplished by that cyclotron will be a lasting tribute to your talents and dedication. Some will believe that such a machine will only be creating radioisotopes but its ultimate products will be new knowledge of biological systems, the alleviation of suffering, the conquest of disease and the saving of human lives. These are the true measure of what we have dedicated today and it is something in which you can all take great pride.