George Von Hevesy Memorial Lecture*
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"Some Early and Recent Experiences in Nuclear Medicine"

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Mr. Chairman, Madame Hevesy, members, and guests:

It is a great honor to be present at this International Meeting, and a special pleasure to be here in the city of Athens and the native country of my distinguished and long-time friend, your late President, Professor Basil Malamos. I was shocked to hear of his passing just before leaving California, and I have so many pleasant memories of visits with him at meetings, in my own Laboratory, and in Athens. Just last October I spent a lovely Sunday afternoon with Professor and Mrs. Malamos in their home in Athens. It is also a great honor to be invited to give the Von Hevesy Memorial Lecture, especially since he was an old friend whom I respected so much. My country is largely the product of transplanted citizens from other countries. All of us are much indebted to Greece which led and laid the foundation for freedom and democracy. Also, my country has benefited greatly from confreres from other countries who accomplished so much in the field of atomic energy. The names are too numerous to mention all, but a few whom I knew or know are: Bohr, Fermi, Hevesy, the Curie-Joliots, Hahn, Bothe, Cockroft, Oliphant, Gentner, Teller, Wigner, and many others.

Professor Hevesy visited and worked in our Laboratory and gave us seminars many times. In 1947 he autographed my copy of his book with Paneth. During one summer he spent nearly three months with us, and it was stimulating to all of us to absorb his knowledge, humor, and excitement. All of us knew his first use of the radioactive tracer technique in 1913 using Radium D in solubility studies in chemistry (1), and in 1923 in plant tracer studies (2). This was long before the discovery of artificial radioactivity, and the subsequent production of radioisotopes in large quantities by cyclotrons, and

later by reactors. Professor Hevesy's first experiments with artificial radioactivity in biology were carried out with isotopes produced from a radium-beryllium source, but the amounts of radioactive material available to him were very small. Nevertheless, by means of a single mouse or rat study, he would achieve a remarkable understanding of previously-unknown biological and biochemical processes.

I recall an interesting experience in 1935 when the young physicists around the 39-inch cyclotron in Berkeley had noticed that after the cyclotron had been operating and was turned off, the Geiger counters would continue to click. Soon in the public press, an announcement was made that Joliot and Curie had discovered artificial radioactivity. In Berkeley it was immediately realized that this delayed Geiger counter clicking meant that artificial radioactivity had been induced. Immediately large amounts of many radioactive elements were produced in the cyclotron, including P-32 and Na-23, and also many new ones such as I-131, C-11, C-14, and many others. Quantities of radioactive isotopes were made available to investigators who wanted them, including Professor Hevesy.

In the 1930's, radioisotopes were still so precious that it is interesting to quote from a letter Professor Hevesy wrote to my brother, Ernest Lawrence, in January 1938:

> "That was a nice Christmas present you sent me. Accept my most heartiest thanks. A trace of phosphorus penetrated the envelope -- it was only a trace, but this induced us to dissolve your letter and to recover the trace of phosphorus it contained. The preparation is very active and entirely sufficient for all investigations we intend to carry out about milk formation. When historians describe your life history, I hope they won't omit this incident showing how precious your letters were."

On one of Professor Hevesy's last visits to our Laboratory, my long-time colleague and a good friend of Professor Hevesy, Professor

Hardin Jones, arranged a video tape recording by Professor Hevesy for our students and staff. Here is a short section of this tape to show you now, not only for the benefit of those of you who never knew him, but also for the enjoyment of those of us who did know him. (NOTE: It was not possible to present the tape because the video equipment was not available. However, in this short excerpt Professor Hevesy talked about his work with Paneth in the first preparation of Radium "D", and the problems involved in working with very tiny amounts of very short-lived elements. He then related an anecdote about [redacted] who had carried a tube of radium chloride in his waistcoat from London to Paris, and on arriving home had noted an erythema on his arm. The observation of the effects of radium on tissue led to its use in treating uterine cancer, and the excerpt concludes with Professor Hevesy's quotation of Madame Curie that, "nothing gave me greater pleasure in connection with the discovery of radium than medical application -- relieving suffering.")

I could go on talking of Professor Hevesy's work! In short, he created the tracer concept, established the classical principles of its use, and then made the pioneering applications of the techniques -- first with natural radioisotopes, secondly with stable isotopes, and finally with artificial radioisotopes.

Now, briefly I want to discuss a few examples of our early and later work with radioactive isotopes, and some of the new penetrating particulate radiations. My work has always been, and continues to be in the direction of medical research, diagnosis, and therapy, using radioactive tracers to elucidate metabolic processes in normal and abnormal states in animals and man. In the time available to me I can only briefly go over some of these past and current studies.

Some of the isotopes I have worked with in such investigations are phosphorus-32, iron-59, hydrogen-3, carbon-11, argon, krypton, xenon, nitrogen, neon, carbon-14, and many others. Always, however, I was constantly looking for applications of isotopic research which pointed to possible therapeutic applications. So, even though my chief work has been in research and diagnosis (basic and applied research cannot always be distinguished from one another), I was always looking for therapeutic applications and the relief of human suffering. Such an atitude or such a viewpoint is very common among investigators, whether they be physicians, physicists (such as Professor Hevesy), chemists, or others. However, my enthusiasm has always been in basic research to learn more about metabolic processes, and that is the history of the work in the Donner Laboratory, and also the Lawrence Berkeley Laboratory. Basic research must always be emphasized, always looking, too, for knowledge gained which would be useful in diagnosis and treatment.

I remember in the mid-thirties when I began attending radiological meetings, how impressed and concerned I was in meeting scientists and radiologists who had evidence of radiation damage, such as the loss of fingers or a hand from over-exposure to radium and x rays. Therefore, in our early isotopic studies in 1935, we felt it very important that workers around cyclotrons not be damaged, such as many of the early pioneer users of radium and roengten rays, and became concerned with the unknown biological effects of fast neutrons which were irradiating workers around the cyclotrons. Paul Aebersold and I teamed up to carry out studies on the unknown effects of neutron radiation.

Figure 1 is a Wilson Cloud Chamber photograph of neutron and

gamma radiations coming from the 39-inch cyclotron. It reveals the striking differences in the dense ionization tracks produced by protons (induced by neutron bombardment) and the fine tracks in the background which represent the electron ionization from the associated gamma rays. Nothing was known about the biological effects of neutrons. We initiated experiments in which mice, rats, and tumors in mice were exposed to neutrons. The biological effects of neutrons were compared to those resulting from equal doses of roentgen rays (3,4). A small chamber containing a single rat or mouse was placed near the Beryllium target which was being bombarded with deuterons (called deutons in those days). The ionization was measured with a Victoreen condenser r-meter. A system was devised to provide air to the animals during exposure. Crawling back between the Dees of the magnet, after having exposed the rat for a few minutes, we found to our surprise that the first irradiated rat had expired. We did not know the cause, but had to assume it was from neutron radiation. However, one of the air hoses had become disconnected. All of us were concerned and impressed about the lethal effects of neutron rays from small doses. The physicists from there on were extremely careful about such exposure. Shielding was increased. Only later did Aebersold and I discover that the rat had died of suffocation and not of radiation exposure! We did not advertise the mishap. The incident led to a continuous respect for neutron radiation exposure, and probably accounted for the good record we have had in Berkeley in avoiding radiation damage, including no cataracts from neutron exposure.

The results of these studies demonstrated that on normal mice and on neoplastic cells, the relative biological effect (RBE) for

neutrons compared to x rays, was high in all cases. We immediately set the so-called safe allowable exposure to one-tenth that permitted for Roentgen-ray workers; this was useful in setting up the standards of radiation safety during reactor development during World War II, and in radiation protection programs ever since.

One other interesting finding came from this early work. The RBE for normal mice was four, and for tumor tissue it was five (5). At that time we did not know of the so-called oxygen enhancement ratio; that is the enhancement of the biological effect of roentgen rays or gamma rays when cells were exposed in an atmosphere of oxygen as compared to exposure in air or nitrogen. The neoplastic cells (carcinoma of the breast in mice) were exposed in vitro and thereafter transplanted, so these cells were relatively hypoxic. In any event, these early studies suggested greater sensitivity of neoplastic cells to neutron radiation and led us to enlist the interest of Dr. Robert Stone in a trial of neutron rays in the therapy of patients with advanced incurable cancer (6,7).

Our first radioisotope work was with P-32 (8,9,10), Na-23 (11), and I-131 (12), but we soon extended these studies to many other elements such as C-11 (13), C-14 (14), Fe-49 (15), tritiated water (16), and many other isotopes which were being newly produced by the cyclotrons. I have selected a few examples of some of this work. It is necessary to skim over much of it, but I will make some points about each investigation. I have always been fortunate in working closely with physicists, engineers, chemists, mathematicians, and physicians, often individually, and often as a member of a team. It is not possible to mention all of these colleagues, many of whom I still work with. They include many graduate students, post-doctoral

fellows, and others now distributed throughout the world. Examples are Paul Aebersold, Joseph Hamilton, Hardin Jones, Cornelius Tobias, Hal Anger, Rex Huff, Nathaniel Berlin, H.S. Winchell, Donald Van Dyke, Joseph Garcia, Claude Chong, Thomas Budinger, William Siri (who wrote one of the early reference books on isotopes in biology and medicine (17)), James McRae, and many others. In addition, of course, are many other colleagues: Ernest Lawrence, Edwin McMillan, William Libby, Martin Kamen (a young chemist who was generous in helping me).

First, a few remarks on blood volume. We all remember the first study of the blood volume in rabbits by Professor Hevesy using P-32-labeled red cells (18). Isotopes now are widely used throughout the world for the measurement of blood volume, which is so important in the diagnosis and therapy of so many conditions. In one piece of work, for example, we clarified the blood volume situation in a group of patients with various forms of polycythemia (19), and in other conditions (20,21). But, time permits me to mention only a few of the studies in polycythemia.

When patients are referred with polycythemia, our diagnostic work-up includes studies of the blood volume and of the arterial oxygen saturation, in addition to the routine clinical work-up (22). An interesting point is that in the late thirties, I was very suspicious of the diagnosis of polycythemia in many patients referred to us with high red cell counts. Blood volume studies showed that although some patients had high hematocrits, their plasma volumes were low. About one out of four patients referred to us today with polycythemia has this picture. We named this syndrome the polycythemia of stress (23). It is not really a disease, and such patients should not be

treated with radioactive phosphorus. Often these patients have very interesting histories from the standpoint of mental or physical stress, and when these are removed, they show improvement by a return to normal blood volume values.

Figure 2 illustrates the importance of red cell volume in the diagnosis of polycythemia. The blood volume in "cc of RBC per kilo body weight" is plotted as a function of the hematocrit, with the normal values indicated by an elipse in the lower left corner. Unfortunately one cannot rely solely on the hematocrit or on the red blood cell count in the diagnosis of any kind of polycythemia -- one is often surprised when one measures the red cell volume and the plasma volume. Here we see the scatter of points and note that some patients with a high hematocrit also have a low plasma volume and actually a normal red cell mass (polycythemia of stress)*, and vice versa. This is also true of people and animals who go from low altitude to high altitude -- they initially develop a polycythemia of stress, but later, of course, a real polycythemia. However, in polycythemia vera, there is a real excess of red cell mass and a normal, decreased, or increased plasma volume, but a normal oxygen saturation. In secondary polycythemia, the red cell mass is increased, but there is a decreased oxygen saturation (24,25). In the polycythemia of high altitude, which develops after long stays at altitude or in the inhabitants of high altitude areas, the red cell mass, of course, is increased proportionately to the altitude (26). We also observed this in animals living in the low pressure chamber, simulating high altitude (27).

Iron-59, as you all know, is an extremely valuable isotope in

* We described the syndrome shortly thereafter (23).

research and diagnosis. Although we had available iron-55 made in the cyclotron, it was our feeling that in view of the scarcity of this material, it was important that iron isotopes be made available immediately to those already working on the metabolism of iron. Among these was Dr. George Whipple at the University of Rochester, and we shipped these isotopes to him very early. Among younger workers with him were Dr. Paul Hahn and later Dr. Joseph Ross and others. On our own campus was Dr. David Greenberg who did promising work with radioactive iron with the assistance of my friend and his graduate student, now Professor Mario Austoni of Padua.

Our first work with iron was in 1947 with Fe-59 in animal and clinical studies (15). Figure 3 shows, as far as I know, the first clinical kinetic study ever carried out with a radioactive isotope.* The plasma disappearance rate of iron in five normal subjects is compared with the rates in five patients with polycythemia vera. By the determination of this rate, and the eight-to-ten day appearance of the labeled iron in new red cells, it was possible to calculate the rate of red cell production and destruction in normal and abnormal states. Rex Huff, one of my post-doctoral fellows, was the leader in this work. He was one of the most able, imaginative, and talented among the many young investigators and physicians who have worked with me over the period of years.

Not many years ago while I was attending a meeting at the Atomic Energy Center in Hanford, Washington, I found Professor Hevesy there, and he told me of his interesting studies of iron metabolism in fish

* Until iron-59 became available, we did not want to use the long-lived isotope of iron in humans, because of its slow rate of excretion, and the long half-life of iron-55.

(28). There seemed to be no subject he did not touch, and this reminds me of his work on the radiosensitivity of hemoglobin formation (29). This in turn reminds me of the work in radiation and red cell formation by my colleagues Huff and Hennessey, both post-doctoral fellows working with me. Many of you will remember their pioneering work on the radiosensitivity of red cell production (30).

Then there was our work in South America in the 1950's on three expeditions to the high Andes (26,31,32) where acclimitization from sea level to altitudes of 18,000 feet, and the reverse, were studied, using iron-59 and tritiated water as well as the usual standard techniques. We found that long before there were cellular changes detectable in the bone marrow, there were remarkable changes in plasma iron turnover and iron kinetics.* We worked and lived at altitudes from 15,000 to 20,000 feet, studying iron metabolism and body water in subjects living at these very high altitudes. Tritiated water was used for the determination of body water and lean body mass (34). In our study, after measuring their iron turnover, we took subjects from sea level to the laboratory of Dr. Alberto Hurtado at 15,000 feet as fast as possible. There the iron turnovers were repeated within a few hours after leaving sea level. Figure 4a shows the rapid response to the change in oxygen tension in the atmosphere. The bone marrow punctures before going up and coming back showed no detectable changes. However, the change in iron metabolism was very rapid. When one reversed this study, moving people from high altitude to sea level (see Figure 4b), the iron turnover returned rapidly to normal. Later it was demonstrated that these changes were related to erythropoietin (35,36).

*Another of my long-time colleagues, Dr. Thomas Hayes, has been and continues a pioneer in studies with the electron microscope and the scanning electron microscope (33). All of us have been constantly aware of the importance of relating cells or organ function to morphology

Early in my work with colleagues Hardin Jones and Cornelius Tobias, the radioactive gases argon, krypton, neon, and xenon were used in gas exchange studies (37), and also carbon-11-labeled carbon monoxide (13). In the case of the latter, this was the first human use of a positron emitting isotope. The first use of a radioisotope of carbon in biology was by Dr. Samuel Rubin, a pioneer in the study of photosynthesis (38). When we first used carbon-11, our concern was with the basic question of limiting factors in gas exchange, and also the possible conversion of CO to CO_2 by the human body. The inert gas studies showed that their rate of exchange in tissue was a function of circulation, and not of diffusion rates. The pioneer in this work was my long-time colleague, Professor Hardin Jones, Assistant Director of the Donner Laboratory.

Our first studies with C-11 were carried out in the mid-1940's (13). We wanted to find out if the human body could oxidize CO to CO_2. In this study radioactive CO was inhaled (labeled with C-11 made by bombarding neutrons on boron in the sixty-inch cyclotron). Thereafter the output of radioactive CO_2 in the expired air was measured. Because of the twenty-one minute half-life of the carbon-11, this work had to be carried out in a very short period of time. The amounts of CO burned and CO lost were practically zero in all of the experiments. Since then Berlin and co-workers, in studies utilizing the long-lived isotope carbon-14, have shown that oxidization of CO to CO_2 cannot be occurring in significant amounts because the production rate of CO in the body is within three percent of bilirubin turnover (39).

Figure 5 illustrates a radioactive xenon study, it being a rather crude radioautograph I made of a section of rat that had been

breathing radioactive xenon. On the left one can see a black dot, indicating high uptake due to fat in the spinal cord. I was stimulated to do this work by my colleague Hardin Jones, who while breathing eighty percent xenon and twenty percent oxygen, had become drowsy. The solubilities of various inert gases in fat and water were also measured, using a counter that "looked" at the fat phase and the water phase, by Loomis et al (40). Xenon had a very high fat-to-water solubility ratio. With the aid of the engineering skill of Cornelius Tobias, we then set up a small unit into which we could place mice and administer xenon to them (80% xenon and 20% oxygen). Xenon was found to be a narcotic. Since that time it has been used as an anesthetic in surgery on humans (41,42). However, xenon is too costly to be practical. Radon, because of its even higher fat-to-water solubility ratio, would be an even better anesthetic, but it again is not practical because of the high radiation dosage.

I must not forget to mention the work of my long-time colleague Hal Anger, who continues actively in the Laboratory, and who has spoken before your Society. I will now show some slides on studies using his camera and his tomographic scanner (43). Bone scanning recently seems to have been improved with the use of one of the new technetium-labeled compounds, ^{99m}Tc-EHDP (diphosphonate), which gives great detail in tomographic bone scans. This work was carried out by my colleague Dr. James McRae (44). In one patient who had crush fractures of L3 and L5, increased uptakes at these sites were apparent at the five-inch level on the posterior tomoscan and at the six-inch level on the anterior tomoscan. The ribs and apophyseal joints were also unusually well seen at various tomographic levels.

My colleague, Van Dyke, has used iron-52 to study marrow distri-

bution and fluorine-18 to study hematological and other disorders (45). Figure 6 is an iron-52 picture of a patient with typical polycythemia vera whom I had been seeing yearly for twenty-three years; a marked extension of the marrow is observed with nearly complete absence of red cell production in the long bones, all of the red cells produced in the spleen. This scan was done in 1968, and in 1970 the patient continued to do well, even though she had a moderately enlarged spleen and all of her red cells were being made in her spleen.

Figure 7, an iron-52 scan of another patient with polycythemia vera, shows a hot spot down in the lower part of the femur. We thought he might have an erythroid cell tumor, and a needle biopsy of the lesion revealed that there were about 100% nucleated red cells in the specimen. The area was subsequently treated with radiation (dose about 1,500 r); the polycythemia was not cured, but he continues to do well.

Time is passing and I must close on a subject all of us are interested in -- the relief of human suffering, i.e. therapy. Tracer or metabolic research has always been my chief interest, but I have always looked for therapeutic uses of the findings of this research. First I would like to mention the work with radiophosphorus and radioiodine (46). Figure 8 is one of the first radioiodine uptake studies, by Hamilton, in 1936. The radioiodine, prepared by bombarding tellurium with deuterons from the thirty-nine inch cyclotron consisted mainly of iodine-131, but also contained small amounts of iodine-126. After oral administration, the radioactivity in the thyroid gland was counted by a Geiger counter tube placed directly over the thyroid in this little patient with myxedema, in this pioneering photograph.

It is interesting that until the scintillation counter came along in the 1950's, permitting one to use a few microcuries of I-131, instead of 100 microcuries, we would not study normal human beings with radioisotopes of iodine because of the excessive radiation dosage to the gland. Dr. S. C. Curran of the University of Glasgow, who had introduced the first simple form of the modern scintillation counter in 1944 (47), was working in our Laboratory during this period and stimulated among us much interest in this field. The well-type scintillation counter, developed by my colleague Hal Anger, was used for the first time in our Laboratory in 1950 for in vitro counting of blood samples or other material (48). An early scintillation counter head was also used for the first time for in vivo counting clinically, it being possible to position the counter head over various areas of the body to detect radioactivity in an organ (48). Iron-59 was the first isotope used in this work led by my associate Rex Huff (15). The first instrument designed for isotope scanning was the dot scanner, which employed a single scintillation counter and was developed in 1950, independently, by Cassen at the University of California at Los Angeles (49), and Mayneord et al at the Royal Cancer Hospital in London (50). Shortly thereafter, in 1952, the first multiple scintillation counter, whole-body in vivo scanner was developed by Anger at Donner Laboratory (51). During the past twenty years, very sophisticated isotope cameras and scanners have been developed, including the tomographic scanner already mentioned (43), and these instruments play an important role in medical diagnostic studies today.

Figure 9 shows the fall in basal metabolic rate in studies of the first three patients to be treated with radioactive iodine by

Joseph Hamilton. Figure 10 is an early whole-body scan of one of our patients with multiple metastases from thyroid cancer. He was treated successfully with iodine-131. He died fifteen years after treatment at the age of eighty-three years, of normal aging. The uptake in the metastatic lesions was 200 times that in any other tissue, and he was cured of his metastatic thyroid cancer.

We have been using P-32 to treat patients with chronic leukemia and polycythemia vera since 1939 (52), based on our earlier experiments in normal animals and leukemic animals using P-32 (10). It is in this work we found that leukemic tissues and bone marrow had high uptake of P-32, and Figure 11 is an example of the clinical course of one of our early patients treated thirty years ago. We treated him with P-32 periodically over a number of years. This figure summarizes the course from 1943 to 1963; ten more years of observation have been added and he continues well. Thirty years after his first treatment with P-32 he had a normal red cell count, hematocrit, and platelet count, and he was asymptomatic. These values continue in the normal range, and he continues to be asymptomatic at the age of seventy-nine.

Figure 12 shows the survival curve for our large series of patients with polycythemia vera, and is compared to a matched population of the same age and sex. For this group of patients with polycythemia vera who were treated with P-32, the median survival was about fourteen and one-half years, twice that previously reported. At present there has been demonstrated no other way of treating this disease which brings the survival up to that for the matched population. The survival for patients treated with P-32 is about the same

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FIGURE CAPTIONS

Figure 1. Photograph of ionization tracks produced by neutrons and gamma rays in a Wilson Cloud Chamber filled with hydrogen (taken with the cloud chamber at a distance of 20 feet from the Beryllium target of the cyclotron). The very dense long tracks represent recoil protons which are the result of the collisions of neutrons with hydrogen nuclei. The finer lines in the background represent the ionization produced by gamma rays, the result of secondary electron emission.

Figure 2. Total red cell volume plotted as a function of hematocrit with the normal area indicated by an ellipse in the lower left corner of the graph. This shows the great variation in red cell mass for a given hematocrit and emphasizes the importance of red cell volume in establishing the diagnosis of polycythemia.

Figure 3. Plasma iron disappearance curves after injection of iron-59. Note the more rapid iron turnover rates of the five patients with polycythemia vera (right) compared to the five normal men (left).

Figure 4. Plasma iron-59 clearance rates in a group of medical students with sea-level habitat (4A) and a group of miners acclimatized to 14,900 feet (4B). Compare the dashed lines with the solid lines: note the rapid increase in clearance rate after ascent to 14,900 feet in 4A, and the decrease in rate after descent to sea level in 4B.

Figure 5. Radioactive xenon study -- a rather crude radioautograph of a cross section of a rat that had been breathing radioactive xenon. Note uptake of xenon in spinal cord (black dot, center left); in mesenteric fat (center); and trapping of xenon in hair (upper left), this occurring because the rat was quickly frozen solid by being dropped into liquid hydrogen.

Figure 6. Iron-52 scan of a patient with typical polycythemia vera taken in 1968, twenty years after diagnosis and first treatment of this disorder. Note the marked extension of the marrow, with nearly complete absence of red-cell production in the long bones and all of the red cells being produced in the spleen.

Figure 7. Iron scan of patient with polycythemia vera which revealed a hot spot in the lower part of the femur. An erythroid cell tumor was suspected, and a needle biopsy of the tumor revealed the presence of about 100% nucleated red cells.

Figure 8. One of the first radioiodine uptake studies in progress. After oral administration, the radioactivity in the thryoid gland was counted by a Geiger counter tube placed directly over the thyorid.

Figure 9. Fall in basal metabolic rate of the first three patients Dr. Joseph Hamilton treated for hyperthyroidism with iodine-131.

Figure 10. An early whole-body scan of a patient with multiple metas-

Figure 14. Change in plasma growth hormone level in 159 patients with acromegaly who have been re-evaluated one or more years after completion of heavy-particle pituitary irradiation. Growth normone determinations by radioimmunoassay were made both prior to and from one to eight years after therapy in 144 patients (note open-dot line), the N's at the tope of the graph indicating the number of individuals used in calculating the median for each time interval. Fifteen patients did not have pre-treatment growth hormone determinations by this metnod (treated prior to October 1961), but their growth-hormone levels determined four to twelve years after treatment (note solid-dot line) are consistent with those of the remaining group.

Figure 15. Photographs of a patient with acromegaly taken in 1960 before treatment (left) and five years later (right). He continues in satisfactory remission, it now being thirteen years since heavy-particle therapy.

Figure 16. Survival curves calculated in December 1969, December 1971, and August 1973, compared to the expected survival for age-and-sex matched general population (dotted line) and diabetic population (dashed line). As the follow-up period increases, the median survival increases (from ten years in 1969 to thirteen years in 1973), and it approaches the curve for the diabetic population.

Figure 17. Adrenal scintiphotos made on the sixth day after administration of ^{131}I-19-iodocholesterol. The upper view is of normal adrenal glands; the lower view is of adrenal glands in a patient with bilateral adrenal hyperplasia (Cushing's disease).

Figure 18. Photographs of a patient with Cushing's disease taken in 1966 before treatment (left) and three years later (right). The patient continues in satisfactory remission, it now being seven years since heavy-particle therapy.

Table 1. This table summarizes the 272 patients with pituitary tumors treated with heavy particles.

as that for treated diabetic patients or patients treated for pernicious anemia (53,54). For many years there has been concern about the possible induction of leukemia by P-32, and in 1969 we summarized our thirty years of experience which indicated the unlikeliness of such an effect (53). I have recently learned that the Polycythemia Vera Study Group (PVSG), under the Direction of Dr. Louis Wasserman, has eleven cases of polycythemia vera treated only with phlebotomy who have developed acute leukemia. In addition, they have twenty-one cases of acute leukemia that have developed in chemotherapy-treated cases. In the PVSG cases per se (a total of about 350 cases randomized) they have two cases of acute leukemia that have developed since the project got underway in 1966, and both patients had been treated with Leukeran.* Thus, it seems probable that in those patients with polycythemia vera who develop acute leukemia, it is a phase in the natural course of the condition in this group.

Dr. Hamilton and I reported the treatment of polycythemia vera and of thyroid disease at the American Society

* Information from the Polycythemia Vera Study Group, November 1973, to be published by Wasserman, Berlin, and Kaplan.

of Clinical Investigation meeting in Atlantic City in 1942 (55). Our paper was followed by a paper by Dr. Hertz on his treatment of hyperthyroidism with radioiodine (56).

Finally, a brief discussion of work which has taken much of my time during the past twenty years -- the use of high-energy, heavy particles in therapy in association particularly with my long-time colleague Cornelius Tobias. It is a return to my first work on radiation protection carried out in 1935 on the biological effects of neutron rays, which produced dense ionization and the greater RBE (3,4).

Figure 13 illustrates the depth-dose distribution of several types of radiation in a tissue-like "phantom". The heavier, higher energy particles are seen to have greater depth dose with less scatter, and also there is the Bragg peak effect (the very large dose produced at the end of their track in tissue) (57).

During the past fifteen years we have treated 208 patients with acromegaly (58), using the plateau method for most, the Bragg peak in five cases where tumors were very large, and a combination of the plateau and the Bragg peak in three cases. The patient lies on a treatment table with diagnostic x-ray units located AP and laterally, and with the aid of cross hairs one can accurately place the beam over the sella turcica. The head is then held firmly in place by means of a plastic mask fitted to each patient individually, thus insuring accurate beam placement throughout the procedure. During treatment there is continuous rotation of the head and body, resulting in a cone of radiation centering on the sella turcica.

Figure 14 shows the changes in radioimmunoassay growth-hormone levels following heavy-particle therapy in patients with acromegaly

(59). Accompanying the fall in growth hormone there is dramatic improvement in the signs and symptoms of this disorder. Significant metabolic improvement is usually seen when the growth-hormone level has dropped to 10 mμg/ml or less, a level attained by fifty percent of the patients within one year; growth-hormone values were eventually within normal limits (≤ 5 mμg/ml) in ninety-five percent of the patients.

Photographs of a physician whom we treated in 1960 are shown in Figure 15. He has had a satisfactory response to therapy; his growth-hormone level is normal and his disease is now inactive. Replacement therapy was started with thyroid in 1965, with testosterone in 1969, and with cortisone in 1971. He continues well and active in the practice of medicine, it now being thirteen years since therapy.

Although some degree of hypopoituitarism has occurred in about one-third of the patients as a result of achieving adequate control of their disease, this develops slowly in most patients. Cortisone replacement therapy has been required in a third of these patients, with such therapy being initiated usually between two and four years after completion of heavy-particle therapy (range, one to twelve years). It is reasonable to expect that along with the improvement observed in the metabolic picture, there will also be an extension of comfortable and chronological life in these patients to normal or nearly normal for their age group, and for a group of people with similar incidence of vascular disease or other independent disease processes. It is of interest to note that twenty-three of these patients were referred to us and treated by us after failure of satisfactory results after procedures such as transfrontal hypophysectomy, transsphenoidal hypophysectomy, or cryohypophysectomy. Also, many

of the patients were referred to us for treatment because they were poor surgical risks. So, as a group, they were not a favorable one for the achievement of a normal life expectancy. Also, when treated by us, their acromegaly was on the average of eight years duration. Only fourteen of the 208 patients treated during the past fifteen years have died. Five patients died of cardiovascular complications, this being the most frequently observed cause of death, and we are waiting for the confirmation of cardiovascular causes as the cause of death in a sixth patient. The remaining eight died of varying causes. One took his own life seven months after treatment before the maximum effect of therapy was achieved. One died of an accidental overdose of barbituates five years after treatment. One died four years after treatment from acute myelogenous leukemia. Another died four years after treatment from systemic toxemia, the organism being identified as histoplasma capsulotum. One died two months after treatment from complications of a bleeding ulcer. One died eleven years after completion of therapy from a meningioma (the tumor was lying superficially and could have been surgically removed, but the patient and his wife refused treatment). The meningioma was in an area of the brain estimated to have received 300 rads, and it seems unlikely that a cause-effect relationship between therapy and tumor was present. One died from an acute vascular collapse during surgery (a spinothalamic cordotomy was being performed to relieve intractable pain resulting from an osteogenic sarcoma arising from the lower lumbar vertebrae). Another died twelve hours after a transfrontal craniotomy. This patient had undergone one transfrontal craniotomy with optic chiasm decompression and removal of a cystic tumor seven months prior to heavy-particle irradiation (administered

because growth-hormone levels remained in the presurgery range of 14 to 18 mμg/ml). The growth-hormone level still did not fall satisfactorily, and when we last saw the patient in March 1971 (3 years after treatment), it was elevated to 40 mμg/ml. We later learned that early in June 1971 the patient had complained of visual loss and that subsequent studies had revealed a left temporal field defect and pneumoencephalographic evidence of recurrent suprasellar extension of the pituitary tumor. The second transfrontal craniotomy, therefore, was performed in June 1971, and the patient died twelve hours postoperatively from a lacerated carotid artery.

Figure 16 compares survival for our series of patients, and it is noted that as the follow-up period increases, the median survival increases (from ten years in December 1969 to thirteen years in July 1973), and approaches that for a treated diabetic population. The curve for the expected survival in an age-and-sex matched U.S. population is also shown. These results show that good control of acromegaly can be achieved by this safe method (even in this group of high-risk patients) with a low incidence of side effects.

We have also treated twenty-nine patients with Cushing's disease, using heavy-particle pituitary therapy to control adrenal hypersecretion (60). Following treatment there is usually a reversal of abnormal metabolic signs and a fall to normal of steroid excretion with disappearance of exaggerated steroid response to metyrapone. Adrenal scans using ^{131}I-19-iodinated cholesterol have provided a valuable diagnostic tool in Cushing's disease, and all of this work was made possible by availability of the first labeled cholesterol (provided by Counsell, Beierwaltes, and associates (61)). The top view in Figure 17 is of normal adrenal glands; the lower is of

those in a patient with Cushing's disease (bilateral adrenal hyperplasia). Even though metabolic studies on patients with Cushing's disease rule out adrenal adenoma, carcinoma, or tumor elsewhere secreting ACTH, we now routinely do adrenal scans to be sure we are dealing with bilateral hyperplastic adrenal glands.

Photographs of a patient with Cushing's disease who had a satisfactory response to heavy-particle therapy are shown in Figure 18. He had undergone a subtotal adrenalectomy in 1958, and then when symptoms of Cushing's disease continued, had undergone excision of the adrenal remnant in 1964. Cortisone replacement was initiated, but discontinued after a short period. In December 1965, symptoms of Cushing's disease recurred, and the patient was referred to us. We treated him in January 1966 (11,000 rads/12 days). Subsequently his symptoms disappeared, and the laboratory values reverted to normal. The picture on the left was taken before treatment, and the one on the right, three years after treatment. He remains in full remission, it now being seven and one-half years since therapy (cortisone replacement was started in 1969).

Of the twenty patients for whom we have follow-up information one year or more after treatment, partial or complete remissions occurred in all but one case. Further analysis of these patients indicated that a higher percentage of lasting results were observed in the group of patients treated with higher doses. Among the seven patients who were treated in the lower-dose range (6,000 to 10,000 rads/11 days), remissions were observed in six. The other patient, who had previously undergone unilateral adrenalectomy, did not return for follow-up evaluation, but studies elsewhere demonstrated failure to respond. Without consultation with us, he subsequently

had total adrenalectomy there, nine months after treatment by us (if a longer waiting period had been allowed, this might not have been necessary). Two patients had only transient remissions and later relapsed and underwent total adrenalectomies at seven months and thirty-eight months respectively. One patient in this group [redacted] who had been in clinical remission for 6.5 years, died from acute pneumonia and internal hydrocephalus (she had suffered severe meningo-encephalitis at the age of eleven years with resultant blindness and mental retardation, and had postencephalitic chronic brain syndrome in addition to the pituitary adenoma).

All thirteen patients who were treated in the higher dose range (11,000 to 15,000 rads/11 days) have had partial or complete remissions, and only two subsequently relapsed. One of these two had a partial remission within three months, but when she continued with only partial remission seven months after heavy-particle therapy she was started on Eliptin (aminoglutethimide). Although she then showed apparent improvement in some respects, much of her symptomatology remained; seven months later (fourteen months after heavy-particle therapy), the plasma steroid level was again elevated and it was decided that total adrenalectomy should be carried out. This was done in June 1972, and the pathology report revealed bilateral adrenal hyperplasia rather than nodular change in the adrenals. The other patient [redacted] died eleven months after treatment, presumably from a cardiovascular or cerebrovascular accident (no autopsy performed). This fifty-four-year old woman had a fifteen-year history of adult-onset diabetes (controlled with twenty units of insulin) and a ten-year history of hypertension with reportedly three previous myocardial infarctions (not documented). Eight months after heavy-particle therapy she was in partial remission. Clinically she had improved

longer required insulin, and her hypertension had settled at a respectable level without therapy. However, while hospitalized at another medical center for re-evaluation of her pituitary adrenal status, she suffered a cerebrovascular accident (the tests indicated she was still in a hypercorticoid state, but because of the stress from the CVA these results could not be adequately interpreted). About one month after discharge she became markedly hypertensive, and after several weeks of poorly controlled hypertension she went into congestive heart failure and required digitalization and treatment with diuretics to which she responded (we were told that during this period her diabetes remained well controlled). Several weeks later (11 months after heavy-particle therapy), the patient died suddenly at home, presumably from a cardiovascular accident.

The response rate in these twenty patients for whom we have one or more years of follow-up information, appears to be significantly better than that obtained in patients treated with conventional radation (a recent paper reported twenty percent of the patients cured with such radiation therapy (62). In addition, this form of treatment is a direct approach to the pathological secretion of ACTH, and has the additional advantage of preventing the subsequent development of pituitary tumors in the rare patient who may have to have adrenalectomy later. None of the patients with Cushing's disease whom we have treated initially with heavy particles to the pituitary developed pigmentation or evidence of pituitary tumor following therapy.

Eight other patients had previously been treated elsewhere for Cushing's disease by bilateral adrenalectomy and then, after developing Nelson's syndrome, were referred to us for heavy-particle treatment to the pituitary gland. Six of the eight patients had en-

larged sellas, these having developed following bilateral adrenalectomy elsewhere. One of these six underwent removal of a suprasellar extension before heavy-particle treatment, and another (not included in this table) underwent surgical hypophysectomy and was then referred for post-operative heavy-particle treatment. We have observed stabilization or decrease in pigmentation in all these patients, and a fall in serum ACTH.

One patient with Nelson's syndrome had an invasive pituitary tumor and died four years after treatment, following difficult surgery to relieve a large suprasellar extension. This patient had shown dramatic loss of pigmentation following therapy. Her plasma ACTH levels were markedly elevated prior to treatment (bioassay ACTH determination was 100 mu/100 ml); subsequent ACTH determinations were by radioimmunoassay method, and the plasma level of 1,000 pg/ml at seven months following treatment had fallen to 600 pg/ml at twenty months. However, the ACTH level again increased, and it was markedly elevated (greater than 2,500 pg/ml) just prior to her transfrontal cranial surgery. Postmortem examination revealed a malignant pituitary adenoma which had extended superiorly to involve the optic chiasm, left optic nerve and tract, and inferior portion of the internal capsule. The intrasellar portion of the pituitary adenoma showed radiation fibrosis, but there were areas of well-preserved tumor tissue invading bone laterally. The tumor had the appearance of the chromophobe tumors which are often associated with patients with Cushing's disease treated with bilateral adrenalectomy (except for pleomorphism of some of the cells), and no distant metastases were found. This case points out the tendency to invasiveness and malignancy of these tumors, and emphasizes the need for aggressive

management of these patients (62-65). It also supports our previous statement that in patients with Cushing's disease (when ecoptic-ACTH-producing tumors and adrenal adenomas or adrenal carcinomas can be ruled out), the initial therapy should be directed to the pituitary and not to the adrenals. Currently the experts feel that Cushing's disease is usually due to hyperactivity of the hypothalamic-pituitary-adrenal axis, and at present the pituitary should be the target for its treatment. When a sufficient radiation dose is delivered to the pituitary, then a much higher percentage of patients with Cushing's disease will respond to pituitary therapy. In summary, because of the demonstrated efficacy, the capability of administering higher doses with heavy particles, and the role of pituitary irradiation in the prevention of later development of post-adrenalectomy hyperpigmentation, heavy particles are an effective treatment for Cushing's disease.

Table 1 summarizes our experiences with heavy particles in treating patients with pituitary disorders. Since 1958 we have treated 272 such patients; ninety-five of them have now been followed from five to fifteen years, and ninety-seven percent of this group are still living and doing well.

These studies of heavy particles continue in our Laboratory. Because of the valuable properties of heavy particles in therapy, other important applications of this form of energy must be further investigated. We believe that the treatment of certain types of malignant tumors might be improved if it were possible to administer an adequate dose of densely-ionizing radiation to the tumor. For many years studies of the effects of extremely dense ionization on normal and neoplastic cells, first with neutrons (4,5), then with

charged particles (66), and most recently with penetrating beams of such atoms as argon, neon, oxygen, and carbon (67,68) have been carried out. As the so-called LET* goes up to the range of 60 to 100 KeV/micron, the oxygen effect nearly disappears. My associates Tobias et al are now carrying out radiobiological studies using a very high energy carbon, oxygen, or nitrogen beam (250 MeV per nucleon) from the Bevatron (67,68,70). Currently plans are underway so that the Bevatron can be used in conjunction with the Super-HILAC, the latter acting as an injector of heavy particles at low energy for acceleration in the Bevatron to energies greater than 400 MeV per nucleon. This combination, called the Bevalac, will make other heavier, higher energy particles such as neon (400 MeV per nucleon) available for radiobiological studies and therapeutic uses in certain cases of incurable cancer. In this Laboratory, Budinger and Tobias have exposed themselves and other subjects to low doses of heavy particles into their retinae and have experienced light flashes (69). Such flashes have also been experienced by the astronauts themselves in space, presumably due to heavy-particle irradiation in cosmic rays. The heavy-particle exposure to astronauts on really long-term missions in space could be a serious health hazard, and there is need for much more study of the biological effects of various heavy particles in relation to space travel.

There is a reduction of oxygen dependence when high-energy heavy particles are used, and if it were possible to deliver dense ionization with an LET of around 50 to 100 KeV per micron to deeply-lying tumors, the oxygen effect would be markedly decreased. It is known that some neoplastic cells are anoxic or hypoxic, and such particles

* Indicates the density of ionization per unit path in tissue.

could be particularly advantageous in treating these neoplastic cells because of the important characteristics of densely-ionizing radiation effects on tissue. Also, the finite range of the particulate beams could be of special value in the treatment of patients with circumscribed tumors that lie closely adjacent to sensitive structures such as the spinal cord, intestines, and so forth. Finally, there are other qualities such as lack of recovery of cell growth after very dense ionization as compared to low-LET ionization.

Groups using cyclotrons at Harvard University (71), the University of Uppsala (72), the Joint Institute for Nuclear Research in Dubna, and the Institute of Theoretical and Experimental Physics in Moscow (73,74), and in Leningrad, are now also using heavy particles in therapy. However, today there are accelerators in many centers throughout the world which are capable of producing protons and alpha particles with sufficient energy to be used therapeutically. Hopefully, more groups will initiate such programs.

In conclusion, returning to the future use of isotopes, I want to mention some recent work of my colleague Thomas Budinger and associates: the successful imaging of radionuclides in animals using a liquid xenon multi-wired chamber operated in the proportional mode. Dr. Budinger, who is with us here at this meeting, and Luis Alvarez and associates at Berkeley (75), have been able to image thyroids of 250 gram rats, as well as liver and kidneys using a parallel hole collimator. This new imaging device has an efficiency slightly greater than the NaI scintillation camera, but a resolution three or four times finer.

Instrumentation has moved ahead of metabolic knowledge. We need, for example, more selectively localizing compounds, especially for

use in the early diagnosis of cancer, and many other pathological states. Tracer research in biology, animals, and man, and alertness to therapeutic uses, are certain to lead to exciting new methods in the diagnosis and treatment of the many unsolved problems in medicine.

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