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HUMAN RADIATION STUDIES: REMEMBERING THE EARLY YEARS

Oral History of Hematologist
Karl F. Hubner, M.D.

Conducted December 30, 1994

United States Department of Energy
Office of Human Radiation Experiments
September 1995

FOREWORD

In December 1993, U.S. Secretary of Energy Hazel R. O'Leary announced her Openness Initiative. As part of this initiative, the Department of Energy undertook an effort to identify and catalog historical documents on radiation experiments that had used human subjects. The Office of Human Radiation Experiments coordinated the Department's search for records about these experiments. An enormous volume of historical records has been located. Many of these records were disorganized; often poorly cataloged, if at all; and scattered across the country in holding areas, archives, and records centers.

The Department has produced a roadmap to the large universe of pertinent information: *Human Radiation Experiments: The Department of Energy Roadmap to the Story and the Records* (DOE/EH-0445, February 1995). The collected documents are also accessible through the Internet World Wide Web under `http://www.ohre.doe.gov`. The passage of time, the state of existing records, and the fact that some decision-making processes were never documented in written form, caused the Department to consider other means to supplement the documentary record.

In September 1994, the Office of Human Radiation Experiments, in collaboration with Lawrence Berkeley Laboratory, began an oral history project to fulfill this goal. The project involved interviewing researchers and others with firsthand knowledge of either the human radiation experimentation that occurred during the Cold War or the institutional context in which such experimentation took place. The purpose of this project was to enrich the documentary record, provide missing information, and allow the researchers an opportunity to provide their perspective.

Thirty audiotaped interviews were conducted from September 1994 through January 1995. Interviewees were permitted to review the transcripts of their oral histories. Their comments were incorporated into the final version of the transcript if those comments supplemented, clarified, or corrected the contents of the interviews.

The Department of Energy is grateful to the scientists and researchers who agreed to participate in this project, many of whom were pioneers in the development of nuclear medicine. ❑

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DISCLAIMER

The opinions expressed by the interviewee are his own and do not necessarily reflect those of the U.S. Department of Energy. The Department neither endorses nor disagrees with such views. Moreover, the Department of Energy makes no representations as to the accuracy or completeness of the information provided by the interviewee.

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Interview with Karl F. Hubner, M.D.
Setting: December 30, 1994; Knoxville, Tennessee
Interviewers: Marisa Caputo and David Harrell
(DOE Office of Human Radiation Experiments)

ORAL HISTORY OF HEMATOLOGIST KARL FRANZ HUBNER, M.D.

Conducted on December 30, 1994 in at the University of Tennessee (UT) Medical Center in Knoxville, Tennessee, by Marisa Caputo of the U.S. Department of Energy (DOE) and David Harrell of COMPA Industries, on behalf of the DOE's Office of Human Radiation Experiments (OHRE).

Karl Franz Hubner was selected for the Oral History Project because of his participation in the Oak Ridge Institute of Nuclear Studies (ORINS)/Oak Ridge Associated Universities (ORAU) Medical Division cancer therapy research program, involving total-body irradiation. This oral history covers his education and early medical practice in Germany, his participation in the experimental immunology and cancer therapy programs at ORINS/ORAU, and his role in the development of Positron Emission Tomography (PET) and PET scanning agents.

Short Biography

Dr. Hubner was born in Striegau, Germany, on January 20, 1934. He received his M.D. from the University of Heidelberg (Germany) in 1959. From 1960 to 1961, he served his internships: first at the Second General U.S. Army Hospital, then at the 86th Tactical U.S. Air Force Hospital[, both in Germany]. Dr. Hubner began a Residency in Nuclear Medicine at the Oak Ridge Institute of Nuclear Studies (ORINS) in 1962. In 1964 he returned to Germany. There he practiced pediatrics until 1967, when he returned to the United States to serve as a Research Assistant in Experimental Immunology at the Oak Ridge Associated Universities (ORAU) Medical Division. This three-year position gave Dr. Hubner the opportunity to participate in cancer therapy research involving total-body irradiation and bone marrow transplantation.

In 1970 he joined the Clinical Staff of ORAU's Medical and Health Sciences Division, a post he held for 12 years. During his final five years on the staff, Dr. Hubner directed the ORAU Radiation Emergency Assistance Center/Training Site (REAC/TS). Upon leaving in 1982, he served as a consultant to REAC/TS until 1990.

From 1982 to 1984, Dr. Hubner was on the Courtesy Staff of the Medical Department at East Tennessee Baptist Hospital. Since 1984, he has been on the Medical Staff for Diagnostic Radiology and Nuclear Medicine at the University of Tennessee Medical Center, where he continues to be involved with the applications of radiopharmaceuticals.

Education and Early Training (1950s, Early '60s)

CAPUTO: Dr. Hubner, I would like to start off with your educational background.

HUBNER: Do you want me to start at high school?

CAPUTO: Sure, wherever you want to start.

HUBNER: I went to school in a small town, Tauberbischofsheim, which means "the bishop's home on the river Tauber," in Germany. I graduated from high school in 1954. Then I went to the University of Heidelberg straight into [premed and] medical school. In the German system, the last 2 years of

high school are equivalent to the first 2 years of college. The average graduate is 20 years old; by then you are ready to go to the university. You could go into law, medicine, or whatever. I went to medical school and graduated in 1959.

As part of the graduation requirements for medical school, back then, we had to write a thesis. We had a choice between experimental work or some sort of analysis of data. I chose to do a rather lengthy project: two-and-one-half years of experimental work in bone marrow[1] transplantation in animals. I started that in 1957, under the guidance of Dr. Fliedner, who spent quite a few years at the Brookhaven National Laboratory [(Long Island, New York)], working together with people like Dr. [Victor P.] Bond[2] and Dr. [Eugene] Cronkite.[3] At any rate, I was working on the thesis, which involved total-body irradiation of rats and transplantation of bone marrow and spleen[4] cells to save them. This was in the early days of bone marrow transplantation ideas.

Back in Oak Ridge,[5] Dr. Charlie Congdon was one of the first to do bone marrow transplants in mice; and Dr. Stodtmeister, Professor Stodtmeister of the Medicine Clinic in Heidelberg, and his assistant Dr. Fliedner (both hematologists),[6] were very much interested in [developing bone marrow transplantation].

So, with my interest in hematology,[I started my thesis work with Dr. Fliedner and] I became interested in bone marrow transplantation in humans. Dr. Fliedner at the time indicated that there may be something developing in the United States that I might [be interested in]. But first, of course, I had to do my internship, which in Germany is a two-year [program]. I did my internship in the Second General U.S. Army Hospital in Landstuhl, Germany, for 12 months and then rotated into the 86th Tactical Air Force Hospital [for the second year].

CAPUTO: So, was that a U.S. Hospital?

HUBNER: [Yes], United States Army and United States Air Force. I did 12 months' rotating internship at the Army Hospital, which is a big hospital (2,000

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1 the soft, fatty vascular tissue in the cavities of bones; it is a major site of blood-cell production.

2 Victor P. Bond, M.D. (1919–), was a radiation biophysicist with the Naval Radiological Defense Laboratory (1948–55) and Brookhaven National Laboratory (starting 1955). He conducted research on the biological effects of radiation. At Brookhaven, he conducted pioneering research in bone marrow transplants and served as an Associate Laboratory Director.

3 Eugene P. Cronkite, M.D. (born 1914), a physician and hematologist at the Naval Medical Research Institute (1946–54) and Brookhaven National Laboratory (1954–79). He conducted research on control of hemopoiesis in health and disease conditions.

4 an organ, located at the cardiac end of the stomach, that helps form mature lymphocytes, helps destroy worn-out red blood cells, and serves as a reservoir for blood

5 During World War II, the Manhattan Project had built a vast complex of highly classified facilities in and near Oak Ridge, Tennessee, to process uranium for use in atomic bombs. The Atomic Energy Commission took control of these facilities upon its creation and, today, they belong to the Department of Energy.

6 physicians specializing in hematology, the branch of medicine that studies the nature, function, and diseases of the blood and of blood-forming organs

beds), the biggest in Europe. Then I switched over to the Air Force Hospital and did family practice for a year. That was in 1960 and 1961. Then I came to the United States as a [research] fellow to Oak Ridge.

HARRELL: Was nuclear medicine[7] work being done at the Air Force and Army Hospitals?

HUBNER: [Only in a limited way at the Second General U.S. Army Hospital]. I wasn't involved. I was doing my basic medical training, just out of medical school.

HARRELL: With Dr. Fliedner being from Brookhaven, was there other AEC[8] involvement with a lot of European doctors at that time?

HUBNER: I think the University of Freiburg in Germany may have had some collaborative common interest in hematology. Dr. [Ludwig] Heilmeyer, a very famous hematologist, and Dr. Hoffman in nuclear medicine, in the early days and at Freiburg, had relationships with the United States.

HARRELL: But were there other members of your program at school who were involved?

HUBNER: Who went to the United States?

HARRELL: Or who were doing AEC work, was there any—

HUBNER: I don't know of anybody.

HARRELL: No?

CAPUTO: I was just curious about the availability of radioisotopes in Germany during the 1960s and where they came from. You don't know?

HUBNER: I think it may have come from England.

CAPUTO: Okay.

HUBNER: I think most of what we had in Europe back then, was essentially radioactive iodine. I remember in the basement of the radiation therapy unit, which was a betatron,[9] there was an early diagnostic imaging program being developed. This was in 1956, '57, and we started to develop these dot counters[10] and rectilinear scanners.[11] This was in the earlier days of nuclear medicine.

HARRELL: You worked on that, too?

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7 diagnostic and therapeutic medical techniques using radionuclides or radioisotopes

8 the U.S. Atomic Energy Commission, predecessor agency to the U.S. Department of Energy and Nuclear Regulatory Commission (NRC); established January 1, 1947

9 an accelerator in which electrons are accelerated to high energies by an electric field

10 a device that recorded ink dots corresponding to radiation counts to form an image when a detector scanned across a patient

11 scanners that moved across the patient, shifted a short distance longitudinally, and then rescanned the patient, to form a whole-organ or whole-body count image

HUBNER: I was peripherally involved. I saw those people everyday. So I knew about it, and Dr. Scheer, who was in charge of that program. He's passed away, unfortunately, prematurely.

Research in Bone Marrow Transplants (Early '60s)

CAPUTO: How was your thesis? You did the rats and bone transplants. How successful were you in achieving—

HUBNER: We could clearly demonstrate that we could rescue these animals—not all of them, but we could save a fraction of them by giving bone marrow transplants.

HARRELL: At that time, were there bone marrow transplants being done on humans in Seattle [at the Fred Hutchinson Cancer Research Center]?

HUBNER: No, not yet. No, much later. In the '70s, late '60s.

HARRELL: Really?

HUBNER: Yes.

CAPUTO: Okay, so then you decided to go to—

HUBNER: The bone marrow transplantation really started to pick up around 1965 to '66.

CAPUTO: So you decided to go to Oak Ridge because of—

HUBNER: Well, because there was some indication that they are going to do bone marrow transplants.

CAPUTO: How did you have that indication?

HUBNER: What happened in Oak Ridge that sort of pushed the issue, was the so-called Y-12[12] radiation accident. Dr. Lushbaugh[13] may have talked about that. In June of 1959, eight men accidentally were exposed to neutrons in this criticality accident,[14] when they put enriched uranium into this 55-gallon drum. It reached a critical geometry and soon we had this small nuclear excursion.[15] [At] any rate, they got exposed to a range of doses from 28 rads[16] up to 365 rads. Those people were admitted to the

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[12] a large facility constructed at Oak Ridge during the Manhattan Project to separate out uranium-238 from natural uranium hexafluoride and thereby enrich the uranium in uranium-235

[13] Dr. Clarence C. Lushbaugh, M.D., Ph.D.—Staff member of the Biomedical Research Group at Los Alamos National Laboratory from 1949 to 1963. Chief Scientist of the Medical and Health Sciences Division at Oak Ridge National Laboratory, 1963 to 1975, and Chairman of the Medical and Health Sciences Division at Oak Ridge, 1975 to 1984. For the transcript of the interview with Lushbaugh, see DOE/EH-0453, *Human Radiation Studies: Remembering the Early Years; Oral History of Pathologist Clarence Lushbaugh, M.D.* (April 1995).

[14] an event in which a fissionable material unexpectedly undergoes a chain reaction

[15] an unexpected rapid increase in fission rate, resulting in a nuclear chain reaction

[16] a measure of the absorbed dose to tissue from exposure to radiation

Medical Division of the Oak Ridge Institute of Nuclear Studies [(ORINS)][17] in Oak Ridge.

That hospital actually was opened in 1950, '51. Dr. [Marshall] Brucer was the first chairman, and they developed nuclear medicine. Eventually they had a patient research unit; I think it started with 35 beds and it was then scaled down to 28 and 25 beds.[18] There was this so-called expertise in treating radiation injury. Nobody had confronted the situation up to that point. Nobody [had experienced this type of accidental radiation exposure], aside from the atomic bomb in 1945; that's a different issue. Dealing with fissionable material, you take the risk of having accidents.

So, the question is: How do you save somebody's life who has been accidentally exposed [to potentially lethal doses]? The answer is: The best thing you could offer is a compatible bone marrow transplant. So, in the late '50s, I think the Y-12 accident really pushed the need for bone marrow transplantation.

At the same time, the treatment of leukemia[19] was a very unsuccessful effort, and we treated children and lost most of them. Translating accidental radiation exposure and rescue with bone marrow into medical applications in leukemia, aplastic anemias,[20] and so forth—it's a logical step.

So, the Biology Division of Dr. [Arthur C.] Upton and Dr. Congdon, they started to grind out the basic approach to bone marrow transplantation in animals after total-body irradiation. It was all there in Oak Ridge: the basic biology, radiation biology, and hematology, in this small clinical unit. So, that's why I went to Oak Ridge to get involved in bone marrow transplants. My appointment in Oak Ridge was limited. I got there in 1962, for one year, but then it was extended.

I finally went back [to Germany], and my goal was to do pediatrics. So I went back to Germany in 1964, and did my residency in pediatrics at the University of Tübingen.

Now what happened in Oak Ridge, to get back to 1962 and '63, and early '64, [was] they didn't do any bone marrow grafts. They weren't ready.

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[17] established in 1946 by the Manhattan Engineer District and operated under a Manhattan Project (and later Atomic Energy Commission) contract. ORINS was responsible for training physicians and researchers in the safe handling of radioisotopes and in the development of isotope applications in medicine. In addition, ORINS was responsible for selecting both students and established scientists for fellowships and other temporary research assignments. Today, the educational and training functions of ORINS are carried out by its successor, Oak Ridge Institute for Science and Education (ORISE).

[18] The ORINS Medical Division Facility was one of three AEC-supported hospitals. It had approximately 30 beds for people with cancer.

[19] any of several cancers of the bone marrow characterized by an abnormal increase of white blood cells in the tissues, resulting in anemia, increased susceptibility to infection, and impaired blood clotting

[20] severe anemias due to destruction or depressed functioning of the bone marrow, usually resulting from bone cancer, radiation, or the toxic effects of drugs or chemicals

HARRELL: Had they done some previously on animals?

HUBNER: Animals, yes. But this went on outside the Medical Division. It was in the Biology Division of the Y-12 plant, the weapons plant at Oak Ridge. There was a huge basic biology program directed by Dr. Alexander Hollaender. He did the basic radiation biology; huge program, one million mice in one building. I guess [the] AEC put a lot of money into its facilities and programs.

HARRELL: Was the clinic feeding off of their data and their research?

HUBNER: No, not really; not really. There was some collaboration, and some of the scientists who started at the Y-12 Biology Division in the Medical Division developed and started a basic research program: like Dr. [Nazareth] Gengozian and Dr. Urso, who was one of his associates. Later on, I worked with Dr. Gengozian for two-and-a-half years in his lab. That was in the late '60s, early '70s.

Anyway, there was no bone marrow transplant during my first stay in Oak Ridge. What I did was learn nuclear medicine, which was [being] very strongly developed in Oak Ridge. I did a quasi-residency in nuclear medicine, and took care of cancer patients.

Development of Nuclear Medicine at Oak Ridge

HARRELL: What kinds of things were you learning in nuclear medicine? Did they have a set curriculum that you would go through?

HUBNER: Well, back then there was no formal training at all. You see, one of the missions of the Oak Ridge Institute of Nuclear Studies was to train people in the applications and the use of radionuclides in industry; agriculture and research; and chemistry. Nobody had that experience. It just became available in 1948 and 1949 when President Eisenhower suggested this peaceful ("Atoms for Peace") program.

They had people in Oak Ridge from all over the world, from all over the country, going to Oak Ridge to the Institute of Nuclear Studies. And they had these courses that trained thousands of people in the use of radionuclides. As far as medicine and nuclear medicine goes, there was this strong relationship to Harvard Medical School. They sent their third-year Radiology residents to Oak Ridge for half a year to learn the basics of nuclear medicine. So, they took the basic introductory course at ORINS, and they learned to do the liver scans and brain scans [and other] nuclear studies.

HARRELL: All types of equipment?

HUBNER: Oh, yes. Some of this equipment was homemade, prototypic-type equipment, until then, finally, there was commercial equipment. The Ohio dual-head rectilinear scanner was one of the first ones into Oak Ridge.

Then in the '70s, the gamma camera[21] became commercially available. So anyway, in the '50s and '60s nuclear medicine evolved slowly. In the '70s and early '60s there was no formal training program [in nuclear medicine].

All these early nuclear medicine people, Dr. Henry Wagner, they came to Oak Ridge. That's where it was done. They went and took it back to Harvard, [The] Johns Hopkins [University in Baltimore], [University of Alabama at] Birmingham (Dr. Tauxe), etc. For many years, annual symposia on nuclear medicine were held in Oak Ridge. Everybody came back to Oak Ridge. Some people call [Oak Ridge] "the cradle of nuclear medicine." And certainly, Dr. Marshall Brucer was one of [the pioneers of nuclear medicine].

HARRELL: So that was a productive and busy time?

HUBNER: Yes, everybody felt good and it was wonderful. There were no limitations. Funding was a lot easier to get in those days.

CAPUTO: Who did you work with during the 1962, '64 time period?

HUBNER: The chief of medicine of the clinic was Dr. Beecher Sitterson. Dr. Gould Andrews was the chairman of the Medical Division. Dr. [Ralph] Kniseley[22] was the associate chairman. Shortly after, I think it was after I came, we were joined by Dr. [Helen] Vodopick[23] and [her husband,] Dr. [Francis] Goswitz, who came as hematologists from Salt Lake City. They, together with a fellow named David White, did the hematology work at the Institute and assisted in testing radiopharmaceuticals[24] being developed at the Medical Division. Dr. [G.] Kyker, who just died last week, was director of the chemistry program. Shortly after he started, he was joined by Dr. Ray Hayes, who later on actually built up the radiopharmaceutical development program.

HARRELL: During that period in '62 and '63, they were doing ingestion studies with various nuclides. Dr. [George] Leroy[25] did one with lanthanum and [S.R.] Bernard with iodine-131. Were there other studies in that vein?

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[21] a large, flat circular crystal of thallium-activated sodium iodide, backed with photomultiplier tubes arranged in honeycomb geometry, for obtaining an image of gamma emitting pharmaceutical in the patient; developed originally by Hal Anger at the University of California at Berkeley

[22] formerly a pathologist at Lovelace Clinic (Lovelace Inhalation Toxicology Research Institute) in Albuquerque

[23] For the transcript of the December 28, 1994 interview with Vodopick, see DOE/EH-0482, *Human Radiation Studies: Remembering the Early Years; Oral History of Oncologist Helen Vodopick, M.D.* (August 1995).

[24] radioactive drugs approved for human use

[25] formerly dean of the University of Chicago medical school. During the days of the Met Lab he researched the metabolism of radionuclides by man. At Argonne Cancer Research Hospital during the 1950s and '60s he researched lipid chemistry to understand the role of cholesterol in atherosclerosis. In 1951 he served as biomedical director of the AEC's Operation Greenhouse series of atomic-bomb tests. Several of the publications he coauthored can be found in the University of Chicago section of DOE/EH-0491, *Human Radiation Experiments Associated with the U.S. Department of Energy and Its Predecessors* (213 pages), July 1995.

HUBNER: Oh yes, there were thorough genetic studies. A lot of thorough genetic studies. Dr. Bateaux did a lot of iron turnover[26] studies.

HARRELL: With iron-59?

HUBNER: Iron-59 kinetic studies,[27] and vitamin B_{12}, and cobalt studies. The Schillings test, and these things, were used quite heavily, like you would expect in hematology. *Now,* the iron kinetics are only done in special studies. We don't do them here. We send our patients to Nashville and other places, like [the University of Utah in] Salt Lake City.

HARRELL: Were all these studies related to cancer therapy or were they general educational studies?

HUBNER: They were not only related to cancer. Some of these things are basic hematology. You see, one has to distinguish between three different types of research. One is a clinical investigation for the purpose of developing a new diagnostic agent which may benefit the patient down the road, or develop[ing] a new therapeutic application which may benefit the patient down the road. Even the patient who's getting the experimental treatment [as a participant in] a stage 1[28] or stage 2[29] study, might [benefit from it]. That's one thing.

If you do basic research just to find out how a certain tracer[30] behaves in vivo [(inside the body)], its kinetics, how it is excreted—just for the sake of science—that is of no obvious benefit to the patient. But it might add to some more basic biochemical questions down the road that might help us to develop something that is of benefit.

But if we use a patient just for this basic research, that's a different issue. You really have to determine the risks involved, very precisely, to make sure you don't do any harm.

The doses they used are in the same range as being used today in accepted FDA [(Food and Drug Administration)]-approved tests. I don't think there was recklessness, in terms of the doses. That's the nice thing about radionuclides: You don't need a big dose to trace the radioactive material. That's what Dr. [George von] Hevesy[31] did when he went and studied, in London, I believe. He had the sneaking suspicion that the kitchen was recycling the food for tomorrow and the next day's meal. So he put some radium on his plate when he was finished, and then he proved the next day—the radium was all over the place [because Hevesy's leftovers had been mixed back in with the kitchen supply]. For the tracer studies you can really use a tracer [(a small amount)].

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[26] clearance from the body and replacement by new intakes of the same materials

[27] studies of the rates of metabolism of elements or compounds and their metabolic pathways

[28] phase one—a dose escalation study to determine maximum tolerable amount

[29] phase two—an efficacy study at the level of maximum tolerance

[30] a radioactive tag on biomolecules, used to study a biological, chemical, or physical system

[31] George Charles von Hevesy (1885–1966), Hungarian-born chemist who won the 1943 Nobel Prize in Chemistry for his discovery of hafnium and his work on the use of isotopes as tracer elements

HARRELL: The human subjects for those studies during the '60s; were they using the patients who were in the Medical Division?

HUBNER: Yes.

HARRELL: About how many studies would they do in a year?

HUBNER: Do you have copies of the annual reports?

CAPUTO: Sure. Yes we do.

HUBNER: All of the numbers are in there. There weren't many patients, the numbers are very small.

Experiment Protocols and Consent (Mid '60s)

CAPUTO: Were you ever involved—I realize you were still in your residency—but do you know how an experiment would be approved during that time period? Who would make the decisions and would propose experiments, how the actual decisionmaking process occurred?

HUBNER: The mechanism was something like—this was before human use committees were in place anywhere.

CAPUTO: Right, before.

HUBNER: The first stipulation of protecting experimental subjects officially was announced in 1948 in Nuremberg[, Germany]. Then in 1964 [the Accord of] Helsinki, and in 1966 the American Medical Association suggested to develop institutional review boards.[32] So in March of 1966, Oak Ridge Associated Universities Medical Division instituted an institutional review board called the Committee on Human Studies of ORINS and the National Laboratory. Up to that point, and this was 1966, they used a sort-of consent form; they had a general agreement when the patient signed it. You have the copies in the [hearings of the U.S. Congressional Committee].[33]

CAPUTO: Right, I've seen them.

HUBNER: There were some general consent forms that had to be signed when the patient was first admitted, and then more-specific consent forms developed, as the program developed, that were signed and kept with the patient records in addition to the global consent form that anybody signs—even coming to this hospital you sign a consent form.

Now the mechanism of developing the project was, there were lots of clinical conferences. Clinical conferences were typically every Wednes-

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[32] In 1966, the National Institutes of Health (NIH) made recommendations to the Surgeon General's Office for the creation of what are now known as Institutional Review Boards (IRBs). IRBs review and approve medical research involving humans.

[33] U.S. Congress. House. Committee on Science and Technology. Subcommittee on Investigations and Oversight. *Hearings on Human Total Body Irradiation (TBI) Program at Oak Ridge.* 97th Cong. 1st sess., September 23, 1981. No. 63.

day morning—went on for several hours. That was the place to make suggestions, to come up with ideas; and then they would be discussed.

A protocol could be developed and discussed extensively, then it would be approved and done. But the decision to develop, let's say, radiopharmaceuticals and put them in a patient, and [to determine] a dose and so forth, was a great, lengthy process. There was radiation dosimetry,[34] [and the] radioisotope committee needed to look at the dose problem before it could be considered as part of the clinical protocol. Then it was by consensus, more or less, that something was implemented.

CAPUTO: So there was no AEC involvement, it was purely—internal?

HUBNER: Internal—yes, because the AEC knew exactly what was going on because there were annual reports, progress reports, and budget requests. Each budget request needed to be accompanied with a progress report: what have you done, what were the results, and so forth.

CAPUTO: Did the AEC provide feedback?

HUBNER: Oh yes, sure. They discontinued certain projects, suggested to do other things. But they—I'm sure they knew exactly what was going on [at] Headquarters; they knew in Oak Ridge, and in Washington.

HARRELL: During that time, in the early '60s, they were using the METBI[35] facility quite a bit. Was there cancer therapy?

HUBNER: Yes, quite a bit. They used maybe a total of 150 to 200 patients over the years.

HARRELL: They were also using chemotherapy?

HUBNER: Yes.

Bone Marrow Transplants at Oak Ridge (Late '50s and Early '70s)

HARRELL: How was the development of bone marrow transplantation being talked about at that time? Was that something on the horizon that they were hoping to do?

HUBNER: This was during the time when I was in Europe doing my pediatric training.

HARRELL: When you were there earlier, was that talked about as something they were going to do?

HUBNER: Yes, but there wasn't a single patient they were trying while I was there. I think the first ones they did were in the late '50s. There were [11 patients with leukemia, who were treated with radiation and bone marrow

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[34] the process or method of measuring or calculating the dose of ionizing radiation, or energy absorbed per unit mass, using data from bioassay and other radiation measurements

[35] Medium-Exposure-Rate Total Body Irradiator

infusion in 1957, 1958, and 1959. That was before I came to Oak Ridge. The results of those early marrow transplants were published in *ACTA Haematologica* in 1961].

HARRELL: I thought there were four bone marrow transplantations.

HUBNER: Yes, that was in 1970, '71, '72, '73. That was different. But that was a more modern approach to bone marrow grafting. That was after we had learned about the HLA[36] antigens and matching histocompatibility[37] of mixed lymphocyte[38] cultures. Those things were not there in 1965. There was no white blood cell testing or match. Someone took a sibling, or a mother or father, as the donor. The only thing we could match, or they could match for, was the blood type. But there was no lymphocyte typing or HLA typing and no mixed lymphocyte culture. That was available in [the late '60s].

CAPUTO: So when you were in West Germany in 1965, they did do some transplantation?

HUBNER: In Oak Ridge? [I do not think so.]

CAPUTO: Do you know who was involved with the bone transplantation in the 1965 time period?

HUBNER: Dr. Andrews was chairman. Dr. Sitterson was the clinical chief or chief of clinical services, and Dr. White was in [outpatient] hematology. Then of course [there were] Dr. Vodopick and Dr. Goswitz.

CAPUTO: Do you know how successful they were?

HUBNER: They were not very successful at all. So they stopped doing it.[39]

HARRELL: Was this similiar to other programs that were going on throughout the country at the time?

HUBNER: There may have been some attempts at other places—rudimentary. I don't think anybody had a big program. A lot of the problems with these earlier attempts in bone marrow grafting was, typically, a patient would be treated as best as they could with chemotherapy—maybe some radiation therapy—until all of the means were exhausted. And at that point, when you had a very sick patient, who was immunosuppressed and defenseless as far as infection goes—at that point they attempted bone marrow grafts. That was not the best way to do it.

Today we bring [in] patients in good shape and do the bone marrow grafts on patients in excellent condition; not handicapped by infections

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[36] human leukocyte antigen: any of a complex of genetically determined antigens, occurring on the surface of almost every human cell, by which one person's cells can be distinguished from another's and histocompatibility established

[37] the condition of being similar antigenic types such that cells or tissues transplanted from a donor to a recipient are not rejected

[38] a type of white blood cell important in the production of antibodies

[39] See "Bone Marrow Treatment of Leukemia" in the Vodopick transcript (DOE/EH-0482).

and other things. But back in those days, to justify an experimental approach like that, you had to exhaust the conventional wisdom and procedures and then reach that desperate situation, and then say, "Let's try it." So there were just 20, or 22, or 23 cases tried.

When I came back in 1967, '68, they didn't do any bone marrow grafts. By that time, Dr. Gengozian had developed the immunological[40] basis for bone marrow grafting as we do it today. The HLA typing became available. Dr. Gengozian and Dr. [Gayle] Littlefield—especially Dr. Littlefield, who's still at ORAU—developed and set up the mixed lymphocyte culture so that we could type and select the proper donor.

HARRELL: This preceeded the attempts at immunotherapy[41] that went on later with Dwayne Sexton?[42]

HUBNER: No, that was after [Dwayne Sexton].

HARRELL: But the bone marrow transplantation preceded that?

HUBNER: [There were] two attempts [to develop a bone marrow transplantation program] at the Oak Ridge Institute of Nuclear Studies or Medical Division with bone marrow. One was in [1957 to '59,] the earlier phases. They did some total-body irradiation, very modest doses, and injected bone marrow cells from a sibling or relative.

Total-Body Irradiation

HARRELL: They were using METBI in that program?

HUBNER: [No, they were using a teletherapy[43] cobalt-60 source in the '50s]. METBI, if I'm not mistaken, opened up for business during 1965. LETBI[44] was built in 1969.

HARRELL: I thought it was built in 1967.

HUBNER: Okay, okay. Then the second phase of bone marrow grafting was in the '70s. So they did, or we did, one graft [each] in 1970, '71, '72, '73 and no more afterwards. So there were four bone marrow grafts done, with appropriate modern-type testing of compatibility and whole-body irradiation as the primary immunosuppressive means.

Actually, the total-body irradiation has two objectives. One is to kill all the leukemic cells that might still be around. The philosophy was to bring the patient into remission when the tumor burden or the load of

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[40] pertaining to immunology, the branch of science dealing with the components of the immune system, immunity from disease, the immune response, and immunologic techniques of analysis

[41] use of tumor-specific antibodies as carrier for a toxic agent for cancer therapy

[42] the first patient to be treated at ORINS with immunotherapy. See "Introduction of Immunotherapy" in Vodopick.

[43] radiation treatment in which the radiation source is located outside the body and rotated around a central axis (the tumor being treated)

[44] Low-Exposure-Rate Total Body Irradiator. Clarence Lushbaugh directed the LETBI facility.

leukemic cells is as low as possible. Then, if you come in with a large dose of radiation exposure, hopefully you can kill the last leukemic cell. So you have a clean starting point, and then you give the bone marrow and hope there is adequate immunosuppression to assure a take to supply the patient with the blood elements needed.

So the protocol for those four patients at Oak Ridge was 500 Roentgen (R)[45] whole-body exposure. They had a high dose rate, and concomitant immunosuppression with antithymocyte globulin (horse antihuman or goat antihuman thymocyte globulin) to augment the immunosuppression, followed by the bone marrow graft. Actually, the sequence is: you give 7 days of immunoglobulin, followed by the total-body irradiation at the end, followed by the bone marrow graft within a few hours after the total-body irradiation. So we used 500 Roentgen, the high dose rate of approximately 45 to 50 R per minute.

Today, in 1994, the doses are 1,000 to 1,200 R given in fractions over a few days. But the total dose is 1,000 or 1,200. The reason we used 500 in Oak Ridge is that Dr. Gengozian had shown that a radiation dose delivered at a high dose rate is more immunosuppressive than a larger dose given at a lesser dose rate. That was shown in animals; there was no doubt about it. It turns out that, shortly after we started talking about 50 rads per minute of exposure, the [group at M.D. Anderson Hospital at the University of Houston] upped their dose, too. They went higher, up to 26 R per minute. So you get the same immunosuppressive effect with a higher dose rate, but a lesser [total] dose. Then you put the patient at a lesser risk, because we know that with the properly [matched] bone marrow you can save anybody who's basically healthy—with a matched bone marrow graft. We know we can save somebody with 500 or even 750 rads. With today's sophisticated techniques of isolation, laminar air flow units, antibiotics, sterility, we can save [patients] with a matched bone marrow donor. We can save somebody after these high doses.

HARRELL: Was this using the CARL[46] facility for these doses?

HUBNER: Yes.

HARRELL: Was some of the research that indicated that higher dose rates would be effective [based on] on the METBI experience?

HUBNER: No, that was, [I believe, a cobalt-60 source].

HARRELL: Animal research?

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[45] a unit of radiation dosage equal to the amount of ionizing radiation required to produce one electrostatic unit of charge of either sign per cubic centimeter of air; named for Wilhelm Konrad Roentgen, 1845–1923, German physicist, who discovered x rays in 1895 and received the Nobel Prize in Physics. The Roentgen was

HUBNER: Animal research, and I forgot what Dr. Gengozian used. There were two teletherapy machines there. One was a cobalt-60 and the other was a cesium-137 machine. They could both be used to deliver high dose rates to a cage of animals. For those experiments, METBI doesn't make much sense because the dose rate is 15 [R per hour].

HARRELL: 1.5.

HUBNER: 1.5 R per minute [for METBI] and for LETBI, it was 1.5 R per hour, a factor of 60. So METBI would not be a good machine to use to get high dose rates. But if you have a radiation therapy [machine] (teletherapy that we use in oncology[47] today), if you put that cage close up, you can have a very high dose rate.

HARRELL: At what time were these experiments done indicating that the higher dose rates were effective?

HUBNER: Well I guess it was in 1966 and '70 that—there are some papers that were published.

HARRELL: At the same time, you were going to higher doses for bone marrow transplants and—

HUBNER: Higher dose *rate,* [not higher doses].

HARRELL: LETBI was going to lower doses at the same time?

HUBNER: Yes.

HARRELL: Was that because you were treating different cancers with the two methods?

HUBNER: Yes, the high dose rate was considered to be necessary for preparing someone for a bone marrow graft—that's one issue—in the process also killing the last leukemic cells. But the lower dose rate was an attempt to treat slower, less aggressive processes like lymphoma,[48] chronic lymphocytic leukemia,[49] and polycythemia vera.[50] They're not as aggressive as acute lymphoblastic leukemia.[51] They're chronic blood diseases, proliferative diseases, that can be treated with a less aggressive form of radiation therapy that does not put [the patient] in jeopardy, as far as infection is concerned. Excessive suppression of the bone marrow, that's the idea to give as much as needed to keep the chronic lymphocytic leukemia in control, but give as little as you can [get by with], in order to save the bone marrow. That's the philosophy behind it: low dose rate

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[47] the branch of medical science dealing with tumors, including the origin, development, diagnosis, and treatment of cancer

[48] a tumor arising from any of the cellular elements of lymph nodes

[49] an accumulation of immunologically incompetent lymphocytes in the circulatory system, leads to enlarged spleen, fatigue, increased susceptibility to infections, and conversion to high-grade lymphoma

[50] a disease characterized by overproduction of red blood cells

[51] comprises 90 percent of childhood leukemia, but is uncommon in adults, manifested by elevated white blood cell counts and blasts in circulation; causes fatigue, bone pain, bleeding, and easy bruising

that doesn't cause any side effects. If you go to a higher dose, you get nausea, etc. So that was the philosophy.

HARRELL: Were there animal experiments that used low dose rates that demonstrated this?

HUBNER: Yes.

HARRELL: The effectiveness of this therapy?

CAPUTO: Any potential effectiveness?

HUBNER: Yes. I don't know of any animal model for chronic lymphocytic leukemia. I think dogs may have it, but I know that they didn't do any dog [leukemia] experiments [in Oak Ridge]. You really have to ask someone else. I don't think there is a rat model for chronic lymphocytic leukemia. But I don't think anybody did therapeutic experiments with animal disease models [at ORINS or ORAU].

HARRELL: So they built the new LETBI facility just on the theory that this would be more effective?

HUBNER: Yes. I think so.

HARRELL: The CARL facility was already built for other uses?

CAPUTO: That was the University of Tennessee facility.

HUBNER: Yes. That was AEC. That was in '65 and later in the '60s with ERDA.[52]

CAPUTO: Right. The CARL facility was built for agricultural and animal studies.

HUBNER: Yes. They had one facility, I guess it still exists, with six huge cobalt sources. Originally each was 75 curies of cobalt. The room was large enough to bring large animals in for radiation exposure experiments.

CAPUTO: Why do you think, in the 1970 bone marrow transplant effort, that it was not successful—or do you think it was successful in some terms?

HUBNER: After the '70s?

CAPUTO: Right, in the '70s, the ones at Oak Ridge?

HUBNER: Well, we had success in those four transplants. I didn't say we were never successful. One of them survived [for] a year. He died from a heart attack and he was still free of leukemia.

CAPUTO: Okay.

HUBNER: A local man from Knoxville was a successful transplant. Another one was successful, in the sense of sustaining that woman's life between six and nine months, pretty much disease-free. These were early successes. Two of the patients developed a reaction called *graft-versus-host reac-*

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[52] The U.S. Energy Research and Development Administration succeeded the AEC in the early '70s, and in turn was replaced by the DOE in 1977.

tion.[53] Which is the same problem today if you don't have the perfect match; you run the risk of killing a patient with graft-versus-host reaction. That's even true today. This is just the basic biologic consequence if you don't have a good match. The lymphocytes of a donor can easily attack the recipient, or kill, and this is classical graft-versus-host disease. So no, we were very happy about what we achieved.

HARRELL: Was there hope of setting up a successful long-term transplantation program?

HUBNER: Have you been to the Medical Division?

HARRELL: We haven't visited that facility.

HUBNER: One of the criticisms of the past of this medical division was [that] it was disconnected, isolated—it was not associated with a major medical facility. It did not have patients, didn't have the resources to maintain—it was very expensive to do this kind of clinical research. So, that was one reason it was eventually closed down. As clinical investigations were concerned, it was not [the] only one that was shut down; [the] Brookhaven [research hospital] was shut down, Argonne [Cancer Research Hospital in Chicago],[54] Navy Hospital in California.

CAPUTO: So it was part of a national—

HUBNER: Oak Ridge was one of the last ones to be shut down. *Now,* in the state of Tennessee, there is not a single medical center with a clinical investigative unit. There is no way to do clinical investigations like they did then. There was a place and role for these laboratories in Brookhaven and Argonne and Oak Ridge and Los Alamos to develop nuclear applications in biology and medicine.

HARRELL: Were there any institutions that were using what you learned in your bone marrow transplantations to develop their own program?

HUBNER: Surely, they read our paper and they knew what we were doing—and Dr. Mortimer Bortin, I guess he's now in Seattle [at the Fred Hutchinson Cancer Research Center]. We adopted Dr. [E.] Donnall Thomas's[55] method of procuring the bone marrow. We used his method of preparing bone marrow exactly the way he did it. As a matter of fact, he came to visit and told us how to do it. We were happy to see that the Nobel Prize for bone marrow grafts involving total-body irradiation, finally [was given to Thomas]. It was two or three years ago.

HARRELL: You were all very happy to—

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[53] graft-versus-host disease—rejection response to bone marrow transplantation; also may involve skin rash, liver and intestinal tract complications

[54] The hospital admitted its first patient in January 1953. The AEC terminated its contract with the hospital in 1974.

[55] Dr. E. Donnall Thomas was awarded the Nobel Prize in medicine for his pioneering work in bone marrow transplantation in 1990.

HUBNER: Sure, because we were part of that development. Nobody had the solution, but we tried and we were very happy for [E.] Donnall Thomas to get the Nobel Prize for bone marrow transplantation.

HARRELL: When you went back to Germany to work on pediatrics, were you working on pediatric cancer therapy?

HUBNER: Yes. Leukemia and immune deficiency syndromes. We had also ideas about bone marrow, and we did bone marrow grafts in Germany. It was not very successful; that was in 1966, '67. A young patient, named Romanoff, had immune deficiency syndrome. One aspect about these experimental investigational approaches to blood diseases or leukemia or immune deficiencies is the problem of the danger of infections: how do you isolate the patient?

The patient we had was isolated in a bubble-like sphere. You know David, the bubble boy [in Houston]? We had a smaller bubble for our immune-deficient child in Germany. In Oak Ridge, for the bone marrow transplantations, they had built a very fine, up-to-date, cutting-edge, isolation facility called the Laminar Air Flow Unit, where the patients were kept under practically sterile conditions. The food was sterilized—everything that went in, and there was constant filtration of the air to keep the air clean, to prevent the patient from getting infections.

Because, following the total-body irradiation, you get this severe depression of the bone marrow which lasts for about three to four weeks before you can see quick recovery. So you have to protect the patient from infections. That was well-done in Oak Ridge, and it was a shame that this facility was taken out. The costs, [according to] Dr. Baylisch, the microbiologist on the team, to keep the patient in a sterile environment back in 1970, was $10,000 a month.

HARRELL: Is that high by today's standard?

HUBNER: Sky-high, just to keep the environment clean.

CAPUTO: How long would they normally be in that room?

HUBNER: Well, fifty, sixty days. So there was every effort made to make this clinical experiment safe, safe as possible.

HARRELL: That money just came out of the overall budget?

HUBNER: It was budget. By today's standards, talking about health costs and research money, it couldn't be done.

PET Scanning and Imaging

HARRELL: So when did you get into tomography[56] and imaging?

HUBNER: Oh, that was—I had also learned nuclear medicine in Oak Ridge.

HARRELL: Was that in '62 when you first—

HUBNER: Yes, right: that's when I—

HARRELL: —learned about that?

HUBNER: Yes, and I got back into it with Dr. Hayes when he and Dr. Washburn proposed to use positron[57] emitting and radionuclides and radiotracers for the detection of cancer. See that's the way I got into what I'm doing today—is pediatric, pediatric oncology; leukemias, other cancers. And now I have got into how to detect cancers [and methods to] measure the response to treatment. So with positron tomography, as proposed in the mid-70s by Michael Phelps at [the] UCLA[58] group and Hayes and Washburn in Oak Ridge, they proposed to use carbon-11–labeled radiotracers, amino acids[59] in particular, as tumor-imaging agents. And the reason they used carbon-11 is because that was the only thing you could make at the 86-inch cyclotron at Oak Ridge at the Y-12 plant. They developed the synthesis methods to tag amino acids with carbon-11, and I did the clinical part of it with positron tomography. We finally got a grant from DOE. Actually we had a grant from NIH[60] to buy a positron tomograph.

CAPUTO: What year was this?

HUBNER: It was 1977. Then the grant was $240,000, and we were $40,000 short. And DOE chipped in $40,000 so we could pay for the machine. These machines today cost [between 1 and 2 million dollars].

HARRELL: That machine was given to what organization?

HUBNER: That was given to the Medical and Health Sciences Division of ORAU. By that time it [(ORINS)] had become ORAU. So that was the first, actually it was the second, commercially available PET[61] scanner. We were supposed to get [the] first one, but our site wasn't ready. So the first one went to UCLA.

HARRELL: Did ORINS assist in developing the prototypes of that machine?

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[56] high-resolution imaging by rotating a fine x-ray beam around a patient and using computer analysis to reconstruct the image

[57] a particle with the mass of the electron but with a positive electric charge

[58] University of California at Los Angeles

[59] any of a class of organic compounds that are the building blocks from which proteins are constructed

[60] National Institutes of Health (Bethesda, Maryland)

[61] positron emission tomography—the process of producing a PET scan, a medical image obtained by examination with a PET scanner, a device that produces computerized three-dimensional images of biochemical activity in the brain or other organ through use of radioactive tracers that emit positrons and twin 0.511 MeV gamma rays

HUBNER: No. That was developed at the Mallinckrodt Institute in St. Louis and then taken over by EG&G ORTEC in Oak Ridge (a company that makes a lot of different radiation detectors). A core group of people who were associated with the development of positron cameras bought out that part of EG&G ORTEC and established an independent company here, between Oak Ridge and Knoxville on Pellissippi Parkway (CTI, Computer Technology and Imaging). They are now, together with [the German industrial giant] Siemens, building cyclotrons[62] and SPECT cameras.[63]

HARRELL: What kind of machine would they use for gallium tracer work?

HUBNER: For gallium, we used a whole-body rectilinear scanner, which was originally developed by Ohio Nuclear. It was a dual-head detector, with one detector on top of the patient and one below the bed. The detectors would move across the whole patient and scan the whole patient. That's what we used for gallium. Today nobody's using rectilinear scanners anymore. Today we use whole-body gamma cameras. Gallium is still used; and that was—I should [have] mentioned gallium was one of the radionuclides, tracers, with gallium citrate, developed at Oak Ridge—that was one of the early good successes.

HARRELL: That was developed right near the end of the Medical Division program—early '70s?

HUBNER: Late '60s early '70s, you're right. There was this multi-institutional, collaborative study with the Oak Ridge [National] Laboratory [(ORNL)].[64] Ray Hayes would distribute the gallium that was produced at X-10 [(an early name for ORNL)] and ship it to these different collaborating sites, for the purpose of getting a large number of patient studies with gallium-68 citrate, to get a statistically significant number in a short time to promote the tracer. Now it's [in use], worldwide. We do gallium scans every day here [at the University of Tennessee Medical Center].

Immunology Research at Oak Ridge (Late '60s)

HARRELL: So when you first returned to Oak Ridge from Germany [in 1967], what kind of work did you start out doing?

HUBNER: That first time, I spent two and one-half years, I believe, in Dr. Gengozian's laboratory. I did basic immunology.

HARRELL: Were you assisting with immunotherapy research?

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[62] an accelerator in which particles move in spiral paths in a constant magnetic field

[63] single-photon-emission computed tomography, a device that looks at 2-D (and 3-D) distributions of photon emitters in the body

[64] For a history of ORNL, see *ORAU From the Beginning,* written by William G. Pollard with Gould A. Andrews, Marshall Brucer, et al., and published by Oak Ridge Associated Universities, Oak Ridge, Tennessee, 1980.

HUBNER: Not with immunotherapy, no.

HARRELL: He was doing that at the same time?

HUBNER: He never did immunotherapy. His interest was primarily: number one, immunosuppression, amino therapy, immunosuppression for preparation for bone marrow grafting. He was basically interested in the mechanisms of immunosuppression, basic science. The other thing he was interested in was the biological and cytological[65] basis for chimerism.[66]

He developed this marmoset[67] colony, and these marmosets, 85 percent of the time have twins which are chimeras. That is, each twin has hematopoietic[68] cells from the other, a brother. Since they are chimeras, you can transplant bone marrow between those two very easily, 85 percent of the time. So, part of his research was focused on trying to break this chimerism to get an understanding of how to establish tolerance. Dr. Gengozian wanted to disturb this tolerant state to better understand how to establish tolerance, to make somebody accept somebody else's bone marrow. Those are [some of] the things that Gengozian was working on.

HARRELL: He was trying to develop a technique to make somebody who wouldn't ordinarily accept material from the donor—

HUBNER: You want to understand how can you disturb this tolerance. If you understand that, you may be able to find a way to establish tolerance. Dr. Gengozian is still here. He has an appointment here at this hospital in pediatrics, and he's head of the bone marrow transplant program at the Thompson Cancer Survival Center in Knoxville.

HARRELL: So who did the work leading to the injection of the irradiated cancer cells?

HUBNER: That was the Sexton case?

CAPUTO: Right.

HUBNER: That was—who was in that, Charlie Congdon? They said that, I think, [on] the front page of the paper on this; in the hearings.

CAPUTO: Right, it's a whole list of researchers involved.

HARRELL: When did you work with Dr. Lushbaugh? Or did you work with him?

HUBNER: He was the chairman [of the Medical and Health Sciences Division at Oak Ridge for nine years].

HARRELL: Did you assist him in his research?

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[65] related to cytology, the study of the microscopic appearance of cells, especially for the diagnosis of abnormalities and malignancies

[66] the presence in an individual organism of cell populations derived from a different zygote, as in twins

[67] a squirrel-sized South and Central American monkey having soft fur and a long, nonprehensile tail

[68] relating to the formation of blood

HUBNER: He was chairman, became chairman in 1975. I was assistant chairman, became director of REAC/TS[69] in 1976. And so, between 1975 and 1984, he was my boss.

HARRELL: Did you ever do work with the NASA data?[70]

HUBNER: No.

HARRELL: That was before your time?

HUBNER: That went on while I was doing—let's see. Most of that went on when I was doing immunology with Gengozian. I was doing basic immunology when the Sexton case was an issue with LETBI, and NASA of course, in the late '60s.

HARRELL: Then after the immunology where did you focus your attention?

Return to Clinical Service (1971)

HUBNER: Well in 1971, I went into the clinical services again.

HARRELL: Were you treating patients?

HUBNER: Yes. But the clinical program was soon phased out over the years. I think it was done in 1972 to cut down [on expenses]. Finally, it was shut down in 1975. So, after the last bone marrow graft in 1973, things sort of slowed down as far as hematology is concerned and therapeutic investigations. So, finally it was closed down in 1975.

And so here we were: we got this big grant, we've got [this] big PET machine, we had the positron tomography program going, and everything shuts down. No patients, no beds. So that was poor planning. We had to hustle to get patients to try these amino acids for diagnostic purposes.

CAPUTO: Where did you get them from?

HUBNER: We got them from Knoxville. I established a very nice collaborative relationship with Dr. Buonocore at UT Hospital, with Dr. Krauss, a medical oncologist, and with Dr. Solomon, who is primarily practicing at the Baptist Hospital down the street. I got them interested in sending us patients for diagnostic investigations. That's the way we sort of limped along with the program.

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[69] Radiation Emergency Assistance Center/Training Site of the Medical and Health Sciences Division, Oak Ridge; maintains a registry for radiation accidents and a center for training people to learn how to respond quickly and treat people who may have been exposed to high levels of radiation

[70] NASA sought to determine whether astronauts would be protected from the radiation flux in the Van Allen belts and from radiation in space in the event of a highly energetic stellar event (such as a supernova). Such exposures, NASA calculated, would amount to about 1.5 Roentgens (R) per hour. Some LETBI patients would receive similar rates of exposure for days at a time, as astronauts might. Accordingly, NASA paid ORINS to report on the effects of such exposure on patients in order to develop techniques that could be used to diagnose whether an astronaut was developing radiation sickness. The funding led to charges that NASA was dictating the exposure rates that the LETBI staff administered to patients. See "NASA Support for LETBI Research" in the Vodopick transcript (DOE/EH-0482, August 1995), and "NASA-Sponsored Studies" and "Questioning the Propriety of NASA-Funded Studies" in the Lushbaugh transcript (DOE/EH-0453, April 1995).

HARRELL: So you still kept a small program going?

HUBNER: Yes. We had patients [come to Oak Ridge], did the scans, and sent them back here. We started the clinical applications of PET in 1977, on an outpatient basis (an arrangement primarily with UT hospital). I did this until 1984. What happened in the meantime? Dr. Buonocore, chairman of the department, is my boss here now. He left UT Hospital in 1979 and took a job at the Cleveland Clinic.

Early in 1984, he asked me whether I would be interested in going to Knoxville, and he would come here and restart the radiology program, and whether I would be interested in [taking a position in] positron tomography and nuclear medicine. I said, "Yes." So, that's when I started here. We started and renewed the nuclear medicine program here and then in 1986, '87, we developed plans for the PET center. The PET center finally opened in January of 1988.

HARRELL: What happened to the equipment that was at ORAU?

HUBNER: You want to buy it?

HARRELL: It's just sitting idle?

HUBNER: It's sitting idle. It's going to be mothballed.

CAPUTO: Is it outdated, at this point?

HUBNER: Yes it is, but I think it could be used for some experimental work. They offered it to the vet[erinary] school across the street, but they don't have the money to even move it.

Closing of ORAU Medical Division's Clinical Program (Mid '70s)

HARRELL: So when they closed it down in '74 or '75—

HUBNER: The clinical inpatient facilities.

HARRELL: —what were the main programs that were going on? Was there more LETBI work being done?

HUBNER: In 1975, when the clinical part was done, they tried to maintain basic radiopharmaceutical development. Dr. Fred Snyder, a biochemist, still has a research program in lipid[71] chemistry. Lipid chemistry was developed as a program, early on in the early days of ORINS, when certain lipid changes in the bone marrow were observed after radiation exposure. That's how Dr. Snyder, as a lipid chemist, came into the institution; and he's still there.

So, after the inpatient activities stopped, there was a program in radiopharmaceuticals (Dr. Hayes), that continued the lipid chemistry;

[71] compounds consisting of fat, waxes, or similar substances, that are one of the chief structural components of the living cell

and Dr. Gayle Littlefield, a cytogeneticist,[72] continued her program. But there was change in direction of the whole division. In 1976, [ERDA] decided to establish this Radiation Emergency Assistance Center and Training Site in Oak Ridge—critical ward in the hospital, next to the emergency room. That started up the REAC/TS program, the training and the assistance program. I [was Director of REAC/TS] for a few years, and then Bob Riggs took over. I think it's a worldwide, well-known facility, program. That's about what's left of the [Medical] Division.

HARRELL: If the reports in 1974 hadn't come out, if they hadn't done that review that finally led the closing of the Medical Division, how do you think it would have continued? What programs do you think were successful there that would have continued, and what ones would not have?

HUBNER: I think radiopharmaceuticals definitely could have continued if it had been possible to organize a collaborative program between the Oak Ridge National Laboratory (for radiopharmaceutical development), ORAU, and UT hospital. There were attempts in the past, several times, to pull things together—never were successful.

HARRELL: Would the bone marrow transplant program [have] continued, or would they have developed new therapy?

HUBNER: No, I don't think so. I think [ERDA] back then decided that it was just not feasible to support programs that provide free treatment. That's what they actually did. That treatment was free, chemotherapy, all of the... For instance, they had the one project on ovarian cancer, and they had a very nice operating room there; they did hysterectomies and cancer surgery and a lot of thyroid surgery. That was all [done] there for free. That couldn't be done today; no way.

Preparation of Protocols for Human Use Committees and the FDA (1970s)

CAPUTO: Going back, did you ever have to present a protocol to the [ORNL] Human Use Committee?

HUBNER: Yes, I have had an opportunity to do that several times.

CAPUTO: Can you describe the process and how that worked?

HUBNER: The proposals that I submitted to the Human Use Committee, were all on positron-emitting radiopharmaceuticals for diagnostic purposes. These proposals were developed in collaboration with the chemists, because you need, for the FDA [(Food and Drug Administration)].

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[72] a practitioner of cytogenetics, the branch of biology linking the study of genetic inheritance with the study of cell structure; Dr. Littlefield specializes in correlating radiation exposure with cytogenetic changes in the chromosomes of peripheral blood lymphocytes.

Eventually, since we had to apply for IND investigations[73] into a new drug complication, you need to provide very precise information on how you make it, what materials go into the product, where you buy your gas containers, and all the chemicals, and so forth. I couldn't do that. So Dr. Washburn and Ray Hayes prepared the chemistry statement on the product that eventually goes into the patients.

CAPUTO: So this is [in the] 1970s?

HUBNER: Yes.

CAPUTO: Okay.

HUBNER: So, in essence, it meant to write an IND application for the FDA chemistry part. The second part is, you have to work out the dosimetry: what radiation dose is the patient going to get from this radiotracer? What is the dose to the eyes, to the gonads, to the bone marrow, to the whole body? All of this dosimetry has to be worked out. Now there's good expertise to do that in Oak Ridge. There's the Medical Internal Dosimetry Center, which is used [by most researchers] in the United States; that's in Oak Ridge. So we had that expertise to do the radiation dosimetry.

Then we had to write a research proposal, assuming that the [chemical] compound is going to be a very good compound for brain tumors, to detect brain tumors. If there is no prior knowledge about this compound, having a higher affinity for brain tumors, you have to provide that information, at least to indicate that there is good reason to believe that this is going to happen.

HARRELL: Animal experiments?

HUBNER: Right. So you need—the other thing you need is a lot of toxicity information. The compound should not be toxic; [it] should be chemically inert. Also, it should not cause any pharmarcological effects. All of that goes into writing a proposal. Then you have to [write the] research protocol, and submit this proposal to the radiation safety or radioisotope committee to review the dosimetry.

Then it goes in front of the institutional review board (IRB). The review boards usually have—well, every member gets a proposal, at least two weeks before the meeting. Usually two experts on the institutional review board do an in-depth review of this proposal and come up with the recommendation. Then it's presented to the IRB board, discussed and approved, or disapproved or postponed; because you have to submit it with the proper consent forms that go along with it.

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[73] Investigational New Drug application to the Food and Drug Administration. An IND approval is required before a new drug or radiopharmaceutical can be administered to human patients.

So you do this for each compound and for any new applications if you want a product, let's say EDTA,[74] for renal[75] studies, you may have to go back to the board and submit that [again because you are going to] use this compound for something else. You don't go through all the toxicity anymore, but you have to justify the use for that particular purpose.

Research on New Imaging Compounds

HARRELL: Do you do research anymore?

HUBNER: Yes. What happened to me when I came here—I had to write all of the INDs for the compounds we're using now in PET: 2-deoxyglucose, palmitate, ^{13}N ammonia, the amino acids. So I had to write all of these and go through the same processes and stuff in 1984. So I did a lot of writing proposals.

HARRELL: So was PET still fairly new then, when you started out here?

HUBNER: Well, I'm very happy, very proud to say, that this is the first clinical PET center in the United States. That's acknowledged. We are the first who did it clinically. Since the radiotracers are all FDA-approved, we do need consent forms [for each study], although the applications in 80 percent of everything we do are strictly clinical. The doctor calls up and asks for PET scans. We're not beating the drums and asking for patients. We have come to a point where the surgeons and the oncologists *ask* us for PETs.

HARRELL: Your radiopharmaceuticals are fairly tried and you've been using them for quite a while?

HUBNER: Yes. (*knocks on the table*) We haven't had a single untoward effect or reaction to any of the products. But the quality control is very strict. If there's the least bit of doubt about the product, we don't give it to a patient: we cancel everything.

HARRELL: Are there new ones being developed all the time?

HUBNER: Yes. Right now we are developing oxygen-15–labeled butanol, an alcohol for blood–brain profusion studies.

HARRELL: You do that work here?

HUBNER: Yes. We are in [the] process of implementing the method. We are tagging L-dopa[76] for Parkinson's disease.[77] We are in the process of labeling phenylalanine, a natural amino acid, with fluorine-18 to work together with the folks in Brookhaven for the [boron] neutron capture

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[74] ethylene diaminetetraacetic acid, a chelating agent for ^{99m}Tc used in renal function studies in the nuclear medicine clinic

[75] relating to the kidneys or the surrounding regions

[76] a chemical converted in the brain to dopamine: used in synthetic form to treat Parkinson's disease

[77] a neurologic disease believed to be caused by deterioration of the brain cells that produce dopamine, occurring primarily after the age of 60, and characterized by tremors (especially of the fingers and hands), muscle rigidity, and a shuffling gait

therapy[78] of brain tumors.[79] Those are two proposals I have to write, the L-dopa and the phenylalanine.

HARRELL: So, it's still a pretty dynamic field?

HUBNER: Yes.

HARRELL: Your work hasn't changed all that much from the last days at ORAU to here?

HUBNER: No, that's right. As far as radiopharmaceuticals and imaging is concerned, this is just a continuation.

HARRELL: Except for who's paying for it?

CAPUTO: You originally went to Oak Ridge for bone marrow transplants and now you're more into imaging—

HUBNER: Imaging and diagnosis.

CAPUTO: Do you know how that change occurred, or why, or did your interest just change?

HUBNER: Well, as I said, I was coming from pediatrics, pediatric hematology, and that sort of got me into, got me interested in, detection of soft tissue tumors and how do you do that with x rays and with radiotracers. I had no idea 20 years ago that is where I'd end up.

CAPUTO: You thought you'd be doing bone transplants?

HUBNER: I thought I was going to be a hematologist, oncologist in pediatrics—like what they do at St. Jude's [Hospital in Knoxville], but I branched out into the imaging part.

CAPUTO: Have you accepted ever self-administered radioisotopes?

HUBNER: To, me?

CAPUTO: Yes.

HUBNER: That's a no-no.

(*laughter*)

CAPUTO: That's a no-no?

HUBNER: Some of our colleagues do that or have done that.

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[78] Brain tumor patients were injected with a discrete amount of boron that was intended to deposit in the tumor. The tumor was then bombarded with a beam of neutrons that was directed to the boron in the hope of destroying the tumor.

[79] From 1951 to 1961, Brookhaven conducted boron neutron capture therapy (BNCT) on 45 patients. All were suffering from aggressive and otherwise untreatable types of brain tumors; all had received conventional radiation treatments. The therapy was unsuccessful. Patients so-treated generally lived only as long as patients with the same types of brain tumor who were treated with conventional radiation therapies. However, advances in technology that deliver higher concentrations of boron to tumor tissues for potentially improved therapy have brought about the return of boron neutron capture therapy. As a result, Brookhaven is currently involved in BNCT research and clinical trials.

CAPUTO: Right. Do they currently do that?

HUBNER: You'll have to ask them.

CAPUTO: *(to Harrell)* Do you have more questions?

HUBNER: We have very strict rules here. For instance, if we wanted to use any of these compounds for normal controls, we have a department rule that a resident or any employee of the department cannot volunteer to be a normal control for any of our work. It has to be outside the institution or at least outside the department.

CAPUTO: Okay.

HUBNER: That's a conflict-of-interest situation.

HARRELL: Is that because these drugs are expensive? Are they're being developed by the companies?

HUBNER: No, no. [It's because] if I[, a physician in a position to hire and fire, were to] ask a resident to volunteer to do a stress test back there with carbon-11–labeled acetate,[80] he may want to do it to please me.

CAPUTO: Do you think that there is anything that we missed that we should have talked about, but we haven't, especially about that early period when you first hit Oak Ridge?

HUBNER: Well, the big issue is for the DOE right now, is to find out if there were any of these early tracer studies, or total-body irradiation studies, which were done in an irresponsible way; unjustifiably poor science, or poor research. Those questions—how good was the science, how safe was it, how safely was it done—those questions should be presented to the program directors [from] back in those days. The biomedical program directors at AEC and ERDA, the original officers, and the department chairman.

HARRELL: I'm going to be speaking to Dr. Totter.[81]

HUBNER: Oh yes, John Totter, yes, yes.

HARRELL: Did you have any dealings with him?

HUBNER: No.

HARRELL: He was just much higher up?

HUBNER: He was way up, in Washington and then in Oak Ridge.[82] But I think in his late days, after he had retired, he had sort of a small office in Oak

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[80] a salt or ester of acetic acid

[81] Totter headed the AEC's Division of Biology and Medicine from 1967 to 1972. For the transcript of the January 23, 1995 interview with Totter, see DOE/EH-0481, *Human Radiation Studies: Remembering the Early Years; Oral History of Biochemist John Randolph Totter, Ph.D.* (September 1995).

[82] From 1972 to 1974, Totter served as Associate Director of Biomedical and Environmental Science at ORNL.

Ridge in the Medical Division. I don't know what he did; maybe some late-night reading.

Public Perceptions of Radiation Research

CAPUTO: Right now, the general public, when they hear the term "human radiation experimentation," generally people think, "Oh, that sounds so horrible!" So what would you like the public to understand about human radiation experimentation, if you can make them understand?

HUBNER: Well, number one is: [ranked] after surgery, radiation therapy is a very effective way to treat cancer. So [radiation therapy is] not going to go away. [We need radiation therapy]. We're just going to try to make it safer, to deliver the radiation in a more focused way in order to avoid damage to the surrounding healthy tissue. I think the whole-body radiation protocols for bone marrow transplantation—those protocols are safe, and one issue you didn't talk about with leukemic children is the whole-brain irradiation that's still [the] accepted standard of care in treating acute lymphoplastic leukemia.

HARRELL: Very high levels?

HUBNER: Yes. Even though we do know that there's the danger of [brain] damage. The least of it being, maybe—well, we know that if children under the age of four with acute leukemia get whole-brain irradiation, they end up having mental problems, behavioral problems, intellectual deficits, and so forth. That's part of the price you pay to survive. You question how can we justify additional radiation experiments. I don't think anybody is—well, I guess we do new things like the proton[83] therapy that was discussed last night on PBS [(Public Broadcasting Service)] at great length.

CAPUTO: I know they're doing immunotherapy with labeled isotopes.

HUBNER: Yes. [Edward B.] Silberstein[84] at [the Uiversity of] Cincinnati [Medical Center]. That is something we are not into here at this hospital. We don't use monoclonal antibodies[85] for diagnostic purposes, because we have PET. We're very content and successful with fluoro-2-deoxyglucose in oncology. So we don't use monoclonal antibodies. But it's going to be better, safer, in the future. But there are risks involved in anything like monoclonal antibodies—they're still not where we would like for them to be. But the idea for using it for therapeutic purposes is intriguing.

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[83] an elementary particle in the nucleus of all atoms, carrying a positive charge

[84] Edward B. Silberstein, M.D., a nuclear medicine physician with research interests in isotope applications for cancer therapy and paliation of bone pain from cancer metastases

[85] antibodies produced by a laboratory cell clone to achieve greater abundance and uniformity than provided by a natural collection of polyclonal antibodies. Studies are currently ongoing to test the anticancer effectiveness of monoclonal antibodies labeled with iodine-131 at several medical centers in the United States; inital results have been very positive.

CAPUTO: This human radiation experimentation has received a lot of public attention this past year. There was a Presidential Executive Order, ordering all of the departments and agencies of the Federal Government to open up their records. The Presidential Advisory Committee [on Human Radiation Experiments] was established. What do you think about all this activity this past year?

HUBNER: Well I think it's perfectly in order. The only thing I was sort of astonished about was the very sudden request by [Energy] Secretary [Hazel] O'Leary. The [DOE] regional offices, and the institutions involved, all of a sudden were confronted with a request to immediately have all of those records in order and available for inspection. You know, these cases, some of them have been shut down. You are talking about 15 or 20 years of inactivity, documents in boxes and file cabinets in warehouses, and the staffs of these institutions whittled, [and] the budgets down. Secretary O'Leary maybe could have eased into this to be better prepared. Because to me, nobody looked good in the public eye. The institutions look bad, and even DOE looks bad.

CAPUTO: Thank you very much for your time today.

HUBNER: You are welcome.

CAPUTO: I appreciate it very much. ❑