

HUMAN RADIATION STUDIES: REMEMBERING THE EARLY YEARS

*Oral History of
Medical Physicist Katherine L. Lathrop
and
Physician Paul V. Harper*



Conducted January 26, 1995

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

MASTER

50-2-23

100-100-100-100

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 As part of this initiative, the Department of Energy undertook an effort to identify and catalog historical documents on radiation experiments that had used human subjects.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 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. □

CONTENTS

	Page
Foreword	iii
Short Biographies	1
Lathrop's Education and Early Career (Manhattan Project, 1945-46)	2
Lathrop's Work at Argonne National Laboratory (1947-54)	7
Lathrop's Work as a Chemist at the Argonne Cancer Research Hospital (Beginning in 1954)	7
Harper's Education and Early Career (1940s to Early '50s)	9
Harper's Thoughts on the Mixture of Medicine and Science (Late '40s and '50s)	14
Lathrop's Early Cancer Therapy Research	16
Harper's Early Determinations of Radiation Doses	17
Development of Iodine-125 Production Methods and the AEC Review Process	22
Discussion of Radiation Research Standards	24
Lathrop and Harper Collaborative Research (1965-67)	29
Thallium Research	36
Antifibrinogen Research	41
Various Radioactive Isotope Research by Lathrop and Harper	46
Argonne Cancer Research Hospital History (Early '70s)	53
Research on Brain Tumor Imaging Agents	54
Collaborative Metabolic Studies	55
Selenium Tumor-Imaging Studies (Early '70s)	57
Other Isotope Research	63
Alpha Emitter Studies Using Radioactive Isotopes	69
Difficulties Involved With Using Human Volunteers	72

DISCLAIMER

The opinions expressed by the interviewees are their 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 interviewees.

ORAL HISTORY OF MEDICAL PHYSICIST KATHERINE L. LATHROP AND PHYSICIAN PAUL V. HARPER

Conducted January 26, 1995, in Chicago, Illinois, by Dr. Darrell Fisher from Pacific Northwest Laboratory and Michael Yuffee from the Department of Energy's Office of Human Radiation Experiments.

Katherine L. Lathrop was selected for the Oral History Project because of her research during the Manhattan Project, her work at Argonne National Laboratory, and her investigation of radionuclides at the Argonne Cancer Research Hospital and the University of Chicago. The oral history covers Ms. Lathrop's research into the biological effects of radiation, her radionuclide and radiopharmaceutical research, and her collaboration with Dr. Paul Harper.

Paul V. Harper was selected for the Oral History Project because of his medical research and collaboration with Katherine Lathrop at the Argonne Cancer Research Hospital and the University of Chicago. This joint oral history examines his research into intraoperative radioisotope therapy, radiopharmaceutical development, and nuclear medicine instrumentation, and his collaboration with Ms. Lathrop. Dr. Harper and Ms. Lathrop have made significant contributions to the development and testing of new radiopharmaceuticals for applications in nuclear medicine. Many of their studies involved human subjects.

Short Biographies

Ms. Lathrop was [REDACTED]. She received her B.S. (Biology 1936), B.S. (Physics 1939), and M.S. (Chemistry 1939) from Oklahoma State University. She is widowed and has five children. Ms. Lathrop began her career as a research assistant at the University of Wyoming (1942-44). Ms. Lathrop joined the Manhattan Project as a junior chemist at the Metallurgical Laboratory, where she worked from 1945 to 1946. From 1947 to 1954, Ms. Lathrop was an associate biochemist at Argonne National Laboratory (ANL), and a chemist at the University of Chicago. In 1954, Ms. Lathrop joined the staff at the Argonne Cancer Research Hospital, first as a research associate, and ultimately as a Professor. Although she has held emeritus status since 1985, she still is active in research today. While serving in her career positions, Ms. Lathrop has had the following assignments:

- 1966 to present—member, Medical Internal Radiation Dose (MIRD) Committee of the Society of Nuclear Medicine
- 1977 to 1984—chair, Medical Internal Radiation Dose Committee
- 1968 to 1984—member, American National Standards Institute Committee N44.3 on Nuclear Medicine
- 1970 to 1975—member, Advisory Panel on Radioactive Pharmaceuticals, The United States Pharmacopeia.

Dr. Harper was [REDACTED]. He received his Ars Baccalaureate (Biology 1939), and M.D. (1941) from Harvard University. He is married and has four children. Dr. Harper began his career as a Research Assistant in the Department of Surgery at the University of Chicago (1942, and 1945-46). From 1946 to 1951, he was a resident, and eventually Chief Resident, in the Department of Surgery. In 1949, Dr. Harper began his teaching career at the Department of Surgery, beginning as an instructor and eventually becoming a Professor in 1960. Dr. Harper attained emeritus status in 1986, but is still active in research today. Concurrently with his formal duties, Dr. Harper also has had the following positions:

- 1954 to present—member, American College of Surgeons
- founding and life member, American Board of Nuclear Medicine
- 1967 to 1969—president, Central Chapter, Society of Nuclear Medicine
- 1969 to 1974—member, Cancer Special Programs Advisory Committee for the Sloan-Kettering Single Instrument Grant
- 1975 to present—member, International Commission on Radiation Units and Measurements

Ms. Lathrop and Dr. Harper have published many times, jointly and separately, on the development of radiopharmaceuticals, surgical radioisotope therapies, and nuclear medicine instrumentation. Additionally, they have researched and published on the biological effects of radiation.

Lathrop's Education and Early Career (Manhattan Project, 1945-46)

FISHER: This is an interview with Dr. Paul V. Harper and Mrs. Katherine Lathrop of the University of Chicago, taking place at the University of Chicago Hospital. My name is Dr. Darrell Fisher; I'm here with Mr. Michael Yuffee to conduct this interview. Katherine, maybe we could start with you and ask you to tell us, in as much detail as you would like, how you became interested in the field of nuclear medicine,¹ how you became affiliated with the University of Chicago, a little about your education, and your professional career.

LATHROP: There was [no field of Nuclear Medicine in which to become interested]. I was there when it started. There was a Society of Nuclear Medicine that had been formed. [Around 1954 to '55, small groups of interested people began meeting in Chicago and on the West Coast.]

HARPER: There were only half-dozen or so [people involved].

LATHROP: It was mainly people using iodine-131² to [treat] thyroid³ disease. [By 1960 the Society of Nuclear Medicine and the *Journal of Nuclear Medicine* were started.]

¹ diagnostic and therapeutic medical techniques using radionuclides

² Radioiodine (¹³¹I) is widely used to diagnose thyroid function and also is a highly effective therapy for hyperthyroidism, Graves' disease, and thyroid cancer.

³ an endocrine gland located at the base of the neck and secreting two hormones that regulate the rates of metabolism, growth, and development

FISHER: You weren't a native of Chicago. You went to school in Oklahoma.
LATHROP: That's right.
FISHER: Would you tell us a little about this?
LATHROP: I was [REDACTED]
FISHER: [REDACTED]
LATHROP: That's right.

(material deleted. Mrs. Lathrop inserts the following for clarity and accuracy:)

My maternal grandparents moved from Iowa to Indian Territory in 1902, when my mother was about ten years old.] My father's family [moved from Texas to Oklahoma Territory a few years earlier. The two territories were combined into the state of Oklahoma in 1907. At one time the two families lived within a few miles, although in separate territories. My parents were married in Lawton, Oklahoma, in 1912. I was there first child.

I was married in Lawton in 1938, while a graduate student at Oklahoma State University. My husband was from New Mexico, where we lived from 1939 until early 1942, when we moved to Laramie, Wyoming. I worked in the poisonous plant laboratory at the University of Wyoming, replacing personnel drafted for military service. My husband taught Chemistry to students enlisted in the military service. Similar programs were available in medical schools leading to an M.D. degree. My husband applied and was admitted as a student at Northwestern University [in Evanston, a northern suburb of Chicago]. We moved to Chicago in 1944.

We thought that we had enough money from the sale of our house and savings. However, living in Chicago cost much more than living in Laramie.

One of my husband's friends told us about [a very secret project, where he had worked before entering medical school, that had jobs for people trained in scientific fields. I applied by mail. A short time later I was asked to appear for a personal interview and was hired the same day.] The person who [interviewed] me thought I would fit in well within the chemistry or the biology sections of the [Manhattan] Project.⁴ He tried calling someone in [the] Chemistry [Division, who was not there. He then reached someone] in [the] Biology [Division], and I went [at once] for an interview.

As I look back [to that day, I feel it was decisive for my subsequent career. Only because of a turn of fate,] I could have gone on in[to] straight chemistry, but [my experience in determining the quantitative localization and biologic effects of fission was valuable preparation for some of the contributions I was able to make to the development of Nuclear Medicine.]

⁴ The U.S. Government's secret project, launched December 28, 1942, by the U.S. Army Corps of Engineers' Manhattan Engineer District, to develop the atomic bomb. Headquartered in Washington, D.C., the Manhattan Project was the Office of Scientific Research and Development Section on Uranium and was codenamed S-1 (Section One of the Office of Scientific Research and Development).

FISHER: Who were the people that interviewed you for these important decision-making opportunities?

LATHROP: *(material deleted. Mrs. Lathrop inserts the following for clarity and accuracy:)*

I don't really remember. Possibly I talked with one or more of these people: Drs. Prosser,⁵ Austin Brues,⁶ Herman Lisco, Kenneth Cole at the biology section. These were top people in directing the research.

Dr. Ray Finkle was head of the group I worked in. Dr. David Anthony was my immediate supervisor until about the time the Manhattan Project became the Argonne National Laboratory.

HARPER: At one point you actually got interviewed by General [Leslie] Groves.⁷

LATHROP: *(material deleted. Mrs. Lathrop inserts the following for clarity and accuracy:)*

I'm not really sure about that. The entire day was rather overwhelming to me. I was definitely interviewed by someone in Army uniform, and one of the office personnel said I was being taken to General Groves's office.

The original project was, as you know, established under the military. Some enlisted people in Army uniform were working along with civilians, in the laboratories, doing the same work. Having grown up next-door to Fort Sill (Oklahoma), where I daily saw, on the streets of Lawton, men of all ranks on uniform, the military was just part of the background, and did not impress me. The same was true for Indians.

FISHER: This was your first introduction to the Metallurgical Laboratory⁸ of the Manhattan Project.

LATHROP: That's right.

FISHER: How long did you work in the Met Lab?

LATHROP: I worked there until it became the Argonne National Laboratory.⁹ And then I worked in the Argonne National Laboratory for a few years.

FISHER: What work did you do in the Met Lab?

LATHROP: Animal distribution studies[: studies on the biological uptake,¹⁰ retention, tissue distribution, and excretion of radioactive materials].

⁵ C. Lad Prosser was well-known in the field of Comparative Physiology. He went on to teach at the University of Illinois.

⁶ a professor at University of Chicago and Senior Biologist, Division of Biological and Medical Research, Argonne National Laboratory

⁷ Groves, of the U.S. Army, assumed command of the Manhattan Engineer District in 1942 and led it to completion of the Manhattan Project in 1945.

⁸ Also known as the Met Lab, the Metallurgical Laboratory was set up at the University of Chicago during World War II to lead the secret research and development of methods for production and chemical separation of plutonium for atomic weapons under the Manhattan Project.

⁹ Argonne National Laboratory outside Chicago, Illinois; operated by the University of Chicago

¹⁰ an excess assimilation of a radioisotope, indicating abnormality

FISHER: On which kinds of materials?

LATHROP: Radium,¹¹ because radium was the radioactive material that there was some information about [its effects] in humans.

FISHER: Okay. Did you do any toxicity studies¹² with any other radioactive materials?

LATHROP: With fission products.¹³

FISHER: Fission products, also?

LATHROP: *(material deleted. Mrs. Lathrop inserts the following for clarity and accuracy:)*

Yes. I learned the first day I came to work in the biology section (site B). It was located on University Avenue, about three blocks south of where we are sitting today, in a building that formerly served as a brewery and another time as a stable, with labs partitioned off with cardboard. Dave Anthony said, "I think it would be best for you to read for a few weeks in order to learn something about the work we are doing."

He took me upstairs to a room, maybe 15 by 30 feet, lined with bookshelves holding about six books. There was a door like those used on the safety deposit room in a bank that, I learned later, was a depository for classified documents from the various sites working on the bomb project. An attendant sat at a desk to check out documents requested from the "vault." She never seemed very busy and I wondered how many trashy novels, or Great Books,¹⁴ she read per month.

The books on the shelf were those published about radioactivity since Becquerel's great discovery. The professor who served as advisor for my Master's thesis had given me a copy of Eve Curie's biography of her mother,¹⁵ which I had read several times.

Of course, I knew very little about the various types of radiation, but the work I saw going on around me seemed mostly to involve handling animals. In high school I had chosen Chemistry and Physics for science because I wanted nothing to do with the cats being dissected in Biology. Faced with earning enough money to care for my two children and get my husband through medical school, I quickly decided I could learn to work with animals. I had taken a nonlaboratory Anatomy class in college.

¹¹ a radioactive, luminous white, metallic element that occurs in very small quantities in combination with minerals. Radium emits alpha particles and gamma rays to form radon gas. Radium has been used in luminous surface materials, such as the numbers on watch faces, and used in treating cancer. At that time, no radioisotope had been more thoroughly characterized for its biomedical effects.

¹² research dealing with the effects, antidotes, detection, etc. of poisons.

¹³ products such as the elements strontium and cesium that are formed during the splitting of uranium atoms in a nuclear reactor

¹⁴ In the early 1930s, under president Robert Hutchins and professor Mortimer Adler, the University of Chicago had developed the "Great Books" program, in which undergraduate students studied the approximately 100 books judged to be the most important works of Western civilization. For many years, the program became popular in reading circles across America.

¹⁵ Marie Curie (1867-1934), a physicist and chemist who, with husband Pierre, discovered radium in 1898. Both would die from the radiation exposure they received in the course of their pioneering experiments.

Dave told me we were working on some radioactive explosive material that might win the war for the Allies. He solemnly asked me to tell no one what I was working on, not even my family. I never did until after the bomb was dropped.

FISHER: Well, it was a very tightly kept secret.

LATHROP: Yes, but everybody in the [research] community knew that the project was here. But they didn't know what it was [about].

HARPER: Yes. My father was a trustee of the University [of Chicago] at the time. He mentioned there was something big going on, but he didn't say anything about any of the details. I don't know how much he knew [about the Manhattan Project research].

FISHER: Paul, was your father aware of the work by [Enrico] Fermi?¹⁶

HARPER: I doubt it. He wasn't a scientist.

LATHROP: He was a lawyer.

(laughter)

FISHER: [Did] you have discussions with him about the construction of the [nuclear] reactor [(the first reactor under the west stands of the stadium at the University of Chicago)]?

HARPER: No, he just mentioned in a vague way that there was something big and secret going on. That's all, nothing further.

YUFFEE: Is it your guess, then, that, for the most part, only a handful of university administrat[ors] might have known the real details of what was going on?

HARPER: I have no way of knowing.

FISHER: Anyway, Katherine, at some point, you became more interested in and more active in the biochemistry and medical aspects of radiation, and you didn't stay with the Manhattan Project forever. Of course, it ended at some point. Would you like to tell us how your work evolved from the Manhattan Project into the work of the [Argonne Cancer Research] Hospital?¹⁷

¹⁶ Italian-born physicist under whose leadership Met Lab researchers produced the first sustained nuclear chain reaction in Chicago on December 2, 1942

¹⁷ the Argonne Cancer Research Hospital, one of three clinical facilities created by the Atomic Energy Commission (AEC) in 1948. While the AEC owned the 58-bed Chicago hospital, the University of Chicago medical school administered and staffed the facility. Patients were admitted on a selective basis: physicians chose persons whose condition best suited the hospital's research and treatment applications. The hospital admitted its first patient in January 1953. The AEC terminated its contract with the hospital in 1974.

Lathrop's Work at Argonne National Laboratory (1947-54)

LATHROP: *(material deleted. Mrs. Lathrop inserts the following for clarity and accuracy:)*

After the Manhattan became the Argonne National Laboratory, the biology section continued to function at Site B for several years until new facilities were constructed near Lemont, Illinois. I was assigned to the group doing radium studies. One of the people working with the group was Bill Neal,¹⁸ who had been discharged from active duty with the Navy and was waiting to begin a residency in surgery at the University of Chicago. While at the university he contacted me about a possible job with J. Garrott Allen,¹⁹ a surgeon who also was on the staff of ANL. Bill knew I was dissatisfied with my group leader at Site B.

It was arranged for me to transfer to the hospital, but remain as an ANL personnel. Bill Neal and Paul Harper had a research project in a lab across the hall from me. I became friends with Georgiana, the technician helping them. The four of us often ate lunch together in their lab. I continued to work at the university until physical facilities for the ANL Biology Division were nearing completion. The decision was made that ANL would no longer support personnel offsite. Dr. Allen wanted me to remain with him, but was unable to find salary support. I returned to Site B, where I did perfusion studies with radioactive materials in excised dog organs until the move, around 1950, to the ANL site.

In November of 1952 my fifth child was born. (Incidentally, I am sometimes asked how I felt about working with radioactivity while pregnant. My answer is: I believed I was working in safe conditions. I have two controls [(two children born before their mother's participation in radiation research)], three experimentals [(children born during their mother's participation in radiation research)], and ten grandchildren, all healthy and intelligent.

Lathrop's Work as a Chemist at the Argonne Cancer Research Hospital (Beginning in 1954)

LATHROP: *(material deleted. Mrs. Lathrop inserts the following for clarity and accuracy:)*

I began to find the two-hour drive to and back from ANL with the business of being a long-distance mother and not being able to return home quickly in the event of an emergency, more stressful than I liked. While I was looking for work closer to my home, located two blocks from the University of Chicago campus, Dr. Harper and I happened to meet on the street. He told me that construction of the Argonne Cancer Research Hospital, attached to the other buildings of the medical complex, had just been completed, and he had been given space and funding. He asked if I would be interested. I decided to try it, although the salary was about half of that I was paid at

¹⁸ Bill Neal, M.D., a surgeon, was in residency training together with Paul Harper at the University of Chicago. Neal also worked at the Manhattan Projects Biology Division at Site B, just off-campus at the University of Chicago.

¹⁹ Joseph Garrott Allen, M.D. (born 1912), a professor of Surgery at the University of Chicago, served as a research associate in radiation pathology on the Manhattan Project there.

ANL. We began working together in February 1954. I remember that Julie[, one of my children,] was not quite two years old.

FISHER: In your résumé, it says that, in 1954, you were a biochemist at the University of Chicago.

LATHROP: That was my official title.

HARPER: That's when you were in the Department of Surgery.

LATHROP: That's right. That was the first title I had.

YUFFEE: I have a question in regard to your experience up until that point. I think it's interesting to note that, through trying to research the early days of nuclear science, nuclear medicine, there weren't very many women involved in the research aspects. What was it like being one of a very few number of women involved a male-dominated profession?

LATHROP: Well, as a matter of fact—

HARPER: I didn't think it was male-dominated.

LATHROP: *(material deleted. Mrs. Lathrop inserts the following for clarity and accuracy:)*

I believe Dr. Harper really believes his statement. I think both of us may have come from families where males and females were equally valued. I have read that Paul's grandfather hired female faculty and welcomed female students when he established the University of Chicago in the 1890s. Although I grew limited to being a wife and mother, or an old maid school teacher, my parents treated each other and me as equals, so I never thought of myself as inferior to my male contemporaries. Besides, I always made better grades than the boys. On entering college, I enrolled in the school of Home Economics. I believe this training better prepared me for coping with my subsequent roles of working mother and homemaker. I was led into chemistry through a class in textile chemistry, required of all students in the course I was pursuing. The professor, a woman, was highly impressed with the required notebook I handed in at the end of the semester. She was taking a sabbatical the next year and, since no one in the department wanted or felt qualified to teach textile chemistry, she suggested me. I had a great time with the course, learned to know the chemistry staff, became interested in graduate study in chemistry, and was asked if I would be a graduate teaching assistant while pursuing a master's degree. Again, I had found equal treatment.

YUFFEE: Sure.

LATHROP: But I would say that there were more women there [at ANL in Lemont] than there were when I came over here [to the Cancer Research Hospital, back from ANL, in 1954].

Harper's Education and Early Career (1940s to Early '50s)

FISHER: So that brings us up to 1954. At this point, I would like to turn to Dr. Harper and ask him the same question.

Give us your educational background, what led you into the desire to study medicine at Harvard, what led you into the field of surgery, and how you came back to the University of Chicago and became interested in radioactive materials in medicine. Paul?

HARPER: Yes.

FISHER: Go ahead and say anything you would like to about this early part of your life history. Your birthplace was Chicago, I believe.

HARPER: That's right. Michael Reese Hospital [on July 27, 1915].

LATHROP: Why not Lying-In[, the University of Chicago's obstetrics hospital]?

HARPER: There wasn't any [Lying-In Hospital]. That wasn't built until 1927.

LATHROP: I didn't realize that.

HARPER: I think. Well, I grew up in Chicago.

YUFFEE: On the south side?

HARPER: No, on the north side.

YUFFEE: The north side.

HARPER: Suburbs, and moved around a bit. My father took a flyer [(looked for a career opportunity)] in the coke and iron business, so we were in St. Louis for a while, but he gave that up after a year or so and came back, became a lawyer in one of the big firms—a lawyer, anyway.

Then I went away to school in New England. Didn't do anything spectacular there.

FISHER: But this was at Harvard; right?

HARPER: No, I hadn't got to Harvard yet.

FISHER: Hadn't got to Harvard yet? Okay.

HARPER: I ended up in Milton [Academy in Milton, Massachusetts, near Boston], after several places, and Milton is sort of a prep school for Harvard, so I got into Harvard, and survived there.

I had sort of wide interests. I majored in what was called Biochemical Sciences, where anything in Physics, Chemistry, Biology, Botany, Mathematics counted as part of your major field. There was actually one course in Biochemistry by an old gentleman that was hypnotized [(fascinated)] with blood chemistry and respiration.

Then I got admitted to Harvard Medical School and didn't do anything very distinguished there. Actually, when I was in college, I did a project—senior project—with George Wald,²⁰ who later—

FISHER: How do you spell that?

HARPER: W-A-L-D. He later was one of the Nobel people [(Nobel laureates)]—on visual science. He was the guy that did the major work on visual purple. Then I worked at the Harvard Fatigue Lab on the visual threshold experiment apparatus that I built, and finally got published under somebody else's name[, a common practice when you're just a college student].

In medical school, nothing much happened. I came here for summer quarter as a surgical extern and, when I got through, surgery seemed like something that appealed [to me], and I don't know why, particularly; I liked doing things with my hands.

I went through the surgical residency back in the good old days when beds were four dollars a day. Everybody paid their bills.

(laughter)

FISHER: Maybe they could afford to pay their bills.

HARPER: They *had* to, *then*. The emergency room consisted of one little room on the fourth floor.

Blood transfusions were handled in a different way. You'd cross-matched the donors ahead of time and had them waiting in the emergency room, and then, if the patient needed blood, you dropped out of the operation, went down, and drew the blood and brought it back upstairs. Quite different.

FISHER: Interesting.

HARPER: That situation evolved some. There was an icebox that people would draw blood and keep it in. Blood donors who were menstruating women were sought after because their blood settled out very rapidly. You could draw the plasma²¹ off and use that.

By the end of my internship, the [Second World] War was going on, and I got involved with a group that wanted to be one of these [military] unit hospitals. I got started off down in Texas at an Air Force station hospital, and then, gradually, the people that had recruited us got shipped elsewhere.

We got shipped all over the world. I ended up in a clearing company, first in Alabama, and then, France.

FISHER: And you were married at this time.

HARPER: Yeah, I got married the last year of medical school.

²⁰ Wald (born 1906), a biochemist at Harvard University, received the Nobel Prize in Physiology in 1967.

²¹ the fluid part of blood, as distinguished from the cellular components

FISHER: Did your family accompany you on these assignments?

HARPER: Not to Europe. But they were in Texas and in Alabama.

Then I got back here after the war, and resumed a surgical residency, which involved spending a year in the laboratory, to start with. The idea was—this is an old-fashioned idea—you got your fingers wet in the laboratory and got a project going. Then, you could keep it going on the side during the rest of your residency.

LATHROP: Maybe we should tell them about the philosophy of the University of Chicago?

HARPER: What was that?

LATHROP: Well, that you—everybody was supposed to do some research.

HARPER: Well, but the philosophy was that it was a full-time organization. You practiced on a salary, and you—it was a group practice. For a long time, it was very unpopular with the surrounding physicians, because it was “corporate medicine,” which was anathema in those days.

FISHER: But not only was it “corporate medicine,” but there was a strong research component.

HARPER: Oh, yeah. And they didn’t pay you much. They would give you a bed, and they gave you food, and the chief resident got 200 dollars a month and made money on it [(covered his other living expenses with a few dollars to spare)].

(laughter)

HARPER: I worked in the laboratory on various odd things that drew Dr. [Lester] Dragstedt’s²² interest, which involved a lot of dog surgery.

FISHER: It was in his lab that you became interested in radioactive tracers.²³

HARPER: That was after I got—I think—yeah, it was after I was in my clinical residency.

Katherine mentioned Bill Neal, who got sick of counting rat bones for alpha particles²⁴ over at Site B and came over and was going through the same residency that I was. We worked together a fair amount.

He had the experience over at Site B of radioactivity, and I had some physics background that I picked up in college.

²² Lester Dragstedt, M.D., chairman of the Department of Surgery, University of Chicago. A physiologist by training, his main contributions were in gastric physiology. Dragstedt developed the procedure of vagotomy, cutting the vegus nerve for acid peptic ulcer. The procedure became obsolete after the introduction of Tagamet™ by SmithKline Beecham.

²³ radioactive tags on biomolecules, used to study a biological, chemical, or physical system

²⁴ positively charged particles, each consisting of two protons and two neutrons, emitted in radioactive decay or nuclear fission; an alpha particle is the nucleus of a helium atom.

I took a course in—I don't know what kind of physics it was—atomic physics—Bainbridge and Street²⁵ [(then the leading researchers in atomic physics)]. Bainbridge is the mass-spectrometer²⁶ man, and that was interesting. So I knew a little bit about this sort of thing, and I learned more by osmosis [(just by paying attention)].

LATHROP: When did Dwight Clark²⁷ start working with ¹³¹I [(iodine-131)]?

HARPER: That was a separate enterprise. My first clinical year [of medical school] was with Dwight Clark. [During medical school,] we were with one surgeon for a year, then another surgeon for a year, and so forth. That has changed, too, of course.

Dwight Clark had spent two years down at Oak Ridge²⁸ during the war and he came back all hot [(excited)] about ¹³¹I [for therapy of] carcinoma²⁹ of thyroid and thyroid disease.

FISHER: He had been training at the Oak Ridge Institute of Nuclear Studies, ORINS.³⁰

HARPER: I don't know what he had been doing. He had been down at Oak Ridge, operating with isotopes in a big way. He managed to collect a huge stable of patients with carcinoma of the thyroid from all around the Midwest and the rest of the country, and, ultimately, when he died of hepatitis, and I inherited his stable [of patients] for a while.

So I had all these patients with carcinoma of the thyroid that we treated with radioiodine, and also the patients with hyperthyroidism.³¹ That was a clinical operation.

In the laboratory—in Dr. Dragstedt's laboratory, I had become interested in lipid [(fatty substances)] problems because of the type of experiment Dr. Dragstedt was doing with depancreatized³² dogs, about fatty livers and this sort of thing.

²⁵ Bainbridge and Street were two professors at Harvard who taught courses in physics in the 1930s.

²⁶ a device that uses deflection of ions in an electromagnetic field as a basis for identifying the elements (or elemental components) present in a substance

²⁷ Dr. Dwight Clark, M.D., started nuclear medicine at the University of Chicago. Clark, a surgeon, was accidentally infected with hepatitis during an operation and died (during the 1950s).

²⁸ 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 assumed control of these facilities upon its creation and, today, they belong to the Department of Energy.

²⁹ a malignant tumor composed of epithelial tissue—the tissue layer covering body surfaces or lining the internal surfaces of body cavities, tubes, and hollow organs

³⁰ 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).

³¹ overactivity of the thyroid gland, resulting in basal metabolic rate and other physiological problems

³² having undergone the removal of the pancreas

Our first experiment along those lines was looking at the turnover³³ of a phospholipid³⁴ labeled³⁵ [with] ³²P [(phosphorus-32)]. That didn't seem to lead very far. Then, Bill Neal suggested using carbon-14.³⁶ So we discovered that acetate³⁷ is a general precursor for all sorts of things in the body. So we got some barium carbonate from Oak Ridge and manufactured our own acetate and injected it into dogs and drew [their] blood and looked at the metabolites.³⁸

One of the big experiments we did was to take repeated substantial liver biopsies from a dog who had been injected with acetate. Then we fractionated³⁹ the lipids—[separating them into] free cholesterol, bound cholesterol, phospholipids, free fatty acids—the best we could with ordinary, unsophisticated clinical laboratory methods. These residues that we ended up with, we oxidized and collected the CO [(carbon monoxide)] in little planchettes⁴⁰ and counted them in a flow counter, a Geiger counter⁴¹ we made ourselves, and ended up publishing it in the first issue of *Metabolism*. That was really pretty unsophisticated.

Some biochemist repeated these experiments later, and, when he was halfway through, he discovered what we had published and abandoned it. We scooped him [(did the research first)].

(laughter)

FISHER: Oh, that's interesting.

YUFFEE: I wanted to backtrack one question that I was interested in. I noted in one of the biographical sketches that was sent to us that your grandfather[, William Rainey Harper,] founded the University of Chicago.

HARPER: With Mr. Rockefeller's help.⁴²

YUFFEE: Right. And I was curious as to why you chose to go away to school—to Harvard.

HARPER: I've always sort of retreated from that situation [(my grandfather's involvement with the University of Chicago)]. I don't read his biographies and that sort of thing.

³³ clearance from the body and replacement by new intakes of the same materials

³⁴ composed of phosphoric esters, present in living cells

³⁵ incorporated with a radioactive isotope to make it traceable

³⁶ a radioactive isotope of carbon having a half-life of about 5,730 years; widely used in the dating of organic materials; also called *radiocarbon*

³⁷ a salt or ester of acetic acid

³⁸ a product of the chemical processes that take place in the body

³⁹ separated or divided into component parts

⁴⁰ small, flat dishes or plates used to support samples for determination of radioactivity; the samples usually are evaporated on the planchettes.

⁴¹ an instrument for detecting ionizing radiation and measuring dose rate

⁴² William Rainey Harper dreamed of establishing a world-class research university in the Midwest. John D. Rockefeller endowed the project with the money needed to build the campus and make the university operational. The University of Chicago opened its doors in 1892; Harper served as its first president.

YUFFEE: And so did you sort of feel like you were eventually going to come back here?

HARPER: No.

FISHER: So that was a—

HARPER: Just did.

YUFFEE: Not a conscious thought.

HARPER: That's sort of the way I drifted into medicine, because it was an easy transition from what I had been exposed to in college and that sort of thing.

Harper's Thoughts on the Mixture of Medicine and Science (Late '40s and '50s)

FISHER: You've always been a scientist, as well as a physician, Dr. Harper.

HARPER: Yes, that's correct.

FISHER: What did you find more interesting, the science and the research or treating patients? Or did you enjoy a healthy mixture of these activities?

HARPER: That's a good way of phrasing it.

FISHER: When Dwight Clark came back from Oak Ridge and you worked with him on the iodine-131 thyroid therapy—

HARPER: Yes.

FISHER: —was there concern for the irradiation of children or infants in utero?⁴³

HARPER: Dr. Dragstedt was interested in this. He treated some dogs with healthy doses of radioactivity, pregnant dogs, and the baby dogs turned out to be classical cretins.⁴⁴ He had their skeletons around, looking cretinous, in a glass case in the corridor outside his office for a long time, so that— actually, it was through Dr. Dragstedt that I got interested in radiation therapy.

He had a patient with carcinoma of the pancreas⁴⁵ that was inoperable, and we [surgically] exposed it [(the pancreas)] and planted radium needles in it. There were strings on the ends of the radium needles, brought out through a drain. After the appropriate time, we pulled them out, all but one, and we had to go back [in] after that [to find the missing radium needle].

FISHER: The suture broke or something.

HARPER: Yeah. So the conclusion from that was, there must be a better way, and I was directed to find a better way. That's when I developed the tub-

⁴³ in the uterus; before being born

⁴⁴ a condition characterized by stunted growth, deformity, and mental retardation

⁴⁵ a large, elongated gland behind the stomach. Its secretions are concerned in digestion.

ing—plastic tubing that you could sew in, following the radium rules, and then you could “afterload”⁴⁶ it.

FISHER: That was an early application of a new technology called “afterloading.”

HARPER: Yes. I hadn’t heard of afterloading before that. I don’t know if it’s the first instance of it or not.

FISHER: This tube wrapped around the pancreas?

HARPER: Yeah.

FISHER: As close as you could get it, I guess.

HARPER: No, you—the tubing was PE-10 polyethylene tubing, very fine, like a suture. It had a piece of wire with the end tapered off, so I could thread the tubing onto it and sew it around. So it went around and around, with about a centimeter spacing, and then back and forth through the middle, using the approximately correct distribution. You probably saw pictures of them in the prints [that were published in our paper].⁴⁷

FISHER: Yes, I’ve read that paper.⁴⁸

HARPER: And then filled it with mercury and radiographed⁴⁹ it to get some idea of the volume so we could calculate how much iodine to put in. We ignored the beta radiation⁵⁰ from the iodine, and we calculated the dose on the basis of the gamma radiation.⁵¹

Getting it in was rather tricky, because you didn’t want ends loaded with radioactivity sticking out on the skin. That happened to us once, and we got a nice beta burn like that on the abdominal wall. It healed up all right.

FISHER: Was there—were all your subjects of these early investigations people with disease?

HARPER: Oh, yeah. I mean, for therapy. Of course.

FISHER: And was there a reasonable expectation that these new attempts would be better therapies than anything else previously?

⁴⁶ introduce the radioactive component after the receiving assembly is in place around the organ to be treated

⁴⁷ In the early 1950s, an established cancer treatment was adapted for use at the Argonne Cancer Research Hospital in patients with carcinoma of the pancreas. This procedure was used to treat carcinoma of the pancreas in seven patients, ranging in age from 42 to 66 years. The calculated total radiation dose to the tumors ranged from 5,000 to 9,200 rads. This method of treatment provided palliative (relief, not cure) benefit for four patients and appeared to extend the survival of one patient. For more details, see UC-32, “Treatment of Pancreatic Cancer Using Implanted Iodine-131,” in *Human Radiation Experiments Associated with the U.S. Department of Energy and Its Predecessors* (213 pages), DOE/EH-0491, July 1995.

⁴⁸ P.V. Harper and K.A. Lathrop. “Isotope Therapy for Intra-Abdominal Tumors.” *Semiannual Reports to the U.S. Atomic Energy Commission*. Vol. 1, Part 2, 1954. Chicago: Argonne Cancer Research Hospital, pp. 54–61. The University of Chicago, Office of Legal Counsel, Semiannual Reports of the Argonne Cancer Research Hospital.

⁴⁹ photographed by means of autoradiography, a technique whereby photographic film is placed over thinly sliced tissue to record, in image form, the radiation tracks from the tissue that pass through the film’s emulsion

⁵⁰ release of electrons or positrons during radioactive decay

⁵¹ a highly penetrating photon of high frequency, usually 10^{19} Hz or more, emitted by an atomic nucleus

HARPER: Well, there was no alternative therapy [at the time].

FISHER: There was nothing else other than that available?

HARPER: I mean, with carcinoma of the pancreas, it was pretty-well shown that surgical excision [(cutting out)] didn't get you very far.

FISHER: Because you couldn't get all the tumor.

HARPER: That's right.

FISHER: And you still needed to leave some pancreas in the patient.

HARPER: No. You don't need to worry about that. It had to be treated. No, the tricky part of that was getting 100 millicuries of ¹³¹I into a couple of tenths of a milliliter.⁵²

FISHER: Of tube.

HARPER: Well, in a centrifuge tube.⁵³ And then, we sucked it in, stood back at the other end of the tube that was full of mercury, and sucked out the mercury.

FISHER: I see. Ah, yes.

HARPER: And then the activity got sucked in, precipitated⁵⁴ the iodine with a carrier as potassium iodide (KI),⁵⁵ silver iodide, and then dissolved it in saturated KI. That way, we could get the activity on a very small volume, suck it into the tube.

Where were we?

Lathrop's Early Cancer Therapy Research

FISHER: Katherine, were you involved in this early study?

LATHROP: Yes.

FISHER: Can you give some of your perspectives on this early work in cancer therapy?

HARPER: We made a model of the implanted tubing. We made some attempt to measure the radiation dose inside it.

LATHROP: Yes, and I spent hours at the microscope, taking readings of density across the film that had been exposed to that.

HARPER: Oh, that was something—

LATHROP: It was part of this, I thought, in the beginning.

HARPER: That was part of the yttrium pellets.

⁵² A milliliter is one-thousandth of a liter; about three-hundredths of a fluid ounce.

⁵³ the polyethylene tubing used in Dr. Harper's experiment

⁵⁴ the act of separating a substance in solid form from a solution

⁵⁵ a white, crystalline, water-soluble powder used chiefly in the manufacture of photographic emulsions, as a laboratory reagent, in biological staining, and to treat thyroid conditions

- LATHROP:** I thought it started with the iodine, but maybe not.
- HARPER:** Maybe it did.
- LATHROP:** Anyway, it was all the same sort of technique. It was very tedious work, getting information for what the radiation dose was.
- FISHER:** How did you calculate the dose from that unusual iodine distribution around the pancreas?
- HARPER:** Katherine did it.

Harper's Early Determinations of Radiation Doses

- FISHER:** Did you do that work?
- HARPER:** Yeah. That was easy. You used the radium tables and scaled the numbers down from eight rads per hour to whatever it is, three-tenths of a rad⁵⁶ for the gamma [from iodine-131].
- FISHER:** By radium tables, you're probably referring to the Paterson-Parker tables?⁵⁷
- HARPER:** Yeah, that's what we used, not the Quimby.⁵⁸
- FISHER:** It's interesting to me that you began working with gold-198 around the same period of time.
- HARPER:** Well, that was fashionable, and—
- FISHER:** Yttrium-90 pellets.
- HARPER:** Yes.
- FISHER:** Which was fairly unusual for that era.
- HARPER:** Yeah. We started that work, I think. No, that was—Dr. [Austin] Brues was doing something out at Argonne with animals and radioactive pellets.
- LATHROP:** You would have to look back through the ANL reports, I guess, to see. I don't remember that.
- HARPER:** Anyway, that was a bright idea that occurred to us, that if you planted beta sources in a tissue, it would produce a necrotic⁵⁹ lesion.⁶⁰

⁵⁶ a measure of the absorbed dose to tissue from exposure to radiation

⁵⁷ The Paterson-Parker system is a series of tables for radium dosimetry; see "A Dosage System for Gamma Ray Therapy," Part I (R. Paterson) and Part II (H.M. Parker) in *British Journal of Radiology*, vol. 7, 592-632, 1934.

⁵⁸ At the Neurological Institute in New York, Edith Quimby was working with G. Failla to develop ways to determine dose estimates from total-body and interstitial irradiation.

⁵⁹ dead portion of animal tissue

⁶⁰ any localized areas of diseased or injured tissue or of abnormal structural change

You didn't have to worry about the radiation dose, because you couldn't kill anything twice. [(Necrotic tissue is already dead.)] The [radiation was attenuated] so you ended up with a very sharp border of the lesion.

FISHER: Were these pellets retrieved or left in place?

HARPER: Oh, left in place.

FISHER: Allowed to decay out?

HARPER: Yes. We started off with the neurosurgeons on this. They exposed the pituitary⁶¹ through a frontal flap.⁶² The idea was that, if you see what you're doing, you can put the [pellets] in just right.

It turned out that that's a mistaken notion. Once you put a pellet in, you can't see it anymore, and to place the pellets under vision turned out to be a disaster.

Then we thought of doing it transsphenoidally,⁶³ and developed instruments to go in through the nose, through the sphenoid sinus⁶⁴ into the pituitary fossa.⁶⁵ This worked fairly well, except that it was difficult, again, to get [the pellets] placed correctly.

FISHER: Exactly where you wanted them.

HARPER: Although it was done under x-ray control. That worked moderately well. We got a few good results, but we did get some patients where the ocular motor nerves⁶⁶ got damaged, because they're lying in the cavernous sinus, right next to the pituitary [gland].

FISHER: Did that discourage further work in this area?

HARPER: No, we switched to a strontium-90 source on the tip of a needle, [which we developed]. We put that in [transsphenoidally], one applicator on each side. [The source] contained, nominally, about 100 millicuries of strontium-90 [each]. Constructing those, I developed a wrinkle in my thumbnail. It grew out after a while.

FISHER: That leads me to the question of radiation protection of yourself and coworkers. You worked with a lot of radioactive sources. And you also worked under conditions with x-ray fluoroscopy,⁶⁷ I would assume.

⁶¹ the small gland attached to the base of the brain, constituting the master endocrine gland affecting all hormonal functions of the body

⁶² a surgical procedure exposing brain tissue via the skull covering the frontal lobe

⁶³ across the sphenoid sinus

⁶⁴ one of the sinus cavities or chambers

⁶⁵ tissue region containing the pituitary gland

⁶⁶ nerves controlling eye movement

⁶⁷ the use of a fluoroscope (a tube or box fitted with a screen coated with a fluorescent substance, used for viewing deep body structures by means of x-ray or other radiation)

HARPER: The fluoroscopy [doses] were trivial, because we could step back from the fluoroscoping. It was one of these little C-arm things [(a swing-arm with two articulated hinges, like a dentist's lamp)].

FISHER: But the beta sources were hazardous.

HARPER: We worked with them under water whenever possible and in little shielded containers. A few millimeters of lead is sufficient for that. It stopped everything but the bremsstrahlung.⁶⁸

FISHER: Did you keep track of your radiation exposures during this time?

HARPER: I didn't. I'm sure the radiation protection people did, the film badge⁶⁹ people did. I just couldn't worry about it too much.

FISHER: Katherine?

LATHROP: I never worked where we didn't wear film badges.

HARPER: No, the only objective effect I ever got was [radiation damage to] my thumbnail. You were asking about children with ¹³¹I.

FISHER: Yes, we did really—

HARPER: You saw the blurb that Alex Gottschalk⁷⁰ wrote, where he mentioned the great discovery that Dr. Gottschalk and Dr. Dwight Clark made with babies.

FISHER: Yes. It's on the first page.

HARPER: How to tell the cretins from mongols [(mongoloids)]⁷¹: a millicurie dose of ¹³¹I, [and surveying the baby's thyroid with a Geiger counter]. That was pretty horrendous.

Actually, one of the things that stimulated me to look into the nuclear medicine applications was the discovery somewhat later—when they developed crude scanning instruments—that a thyroid scan with ¹³¹I caused a good many rads, which seemed out of line [(doses too high for acceptable patient diagnostics)].

Dwight Clark had tumbled to the fact that most of his children [patients] with carcinoma of the thyroid had had previous radiation for [shrinking] tonsils or adenoids or [thymus].

FISHER: Were these x rays or radium [(the radiation source)]?

HARPER: Those were x rays.

FISHER: X rays?

⁶⁸ radiation, especially braking radiation, gamma rays, or x rays, emitted by decelerating charged particles
⁶⁹ a dosimeter worn routinely to measure accumulated personal exposure to radiation on photographic film

⁷⁰ Alexander Gottschalk, M.D. (born 1935), previously a research associate at Donner Laboratory, UC Berkeley; professor of Radiology and chief of nuclear medicine, University of Chicago Hospitals and Yale Medical School; conducted research in isotope development

⁷¹ victims of Down's syndrome, a genetic disorder associated with the presence of an extra chromosome 21, characterized by mental retardation, weak muscle tone, and epicanthic folds at the eyelids

HARPER: Yes. I think something like 12 out of the first 13 juvenile cases [of thyroid carcinomas] had had previous radiation.

FISHER: Was that Dr. Clark [who made the discovery]?

HARPER: Dwight Clark, yes.

FISHER: Okay.

HARPER: So he pushed that, and somebody in Buffalo[, New York] did a prospective study on this. I've forgotten his name. It showed that people that have radiation to the neck region got lots more thyroid lumps, and some of them have gotten thyroid malignancies [(cancers)] some years later. We didn't do that.

Anyway, the only disaster that happened to me in that situation was a lady with carcinoma of the thyroid that we were treating with radioiodine, and she got hypothyroid.⁷² That's normal.

And then, she stopped having periods [(menstruating)], which was normal with hypothyroidism. Then she turned out to be pregnant, and the baby was definitely damaged. That was the only disastrous experience I had with the radioiodine.

FISHER: Did that lead to any changes in practice? What was the ultimate benefit of these observations?

HARPER: Well, you worry more about dealing with pregnant people because, once it [(harm)] has happened to *you*[r patient], that's how medical prejudices get formed; [they are] not [made] on a rational basis. [But] because of the bad things that happen to you, you swear [it] will never happen again.

FISHER: How did that change your procedures in the future or in that time?

HARPER: We worried more about pregnancy [in patients], *of course*.

FISHER: Was there ever a study done on the uptake of iodine in the thyroid of unborn children?

HARPER: I'm not sure how you would go about doing that.

FISHER: Well, for example, if a woman was diagnosed using iodine-131 during a period of pregnancy, was there any evidence of children being born without thyroid function?

HARPER: Dr. Dragstedt's dogs are the only thing I was aware of.

FISHER: Okay.

HARPER: We had some episodes with people lactating and iodine comes out in the milk.

⁷² deficiency in thyroid secretions, resulting in goiter, myxedema (thickening of the skin, blunting of the senses and intellect, and labored speech), and, in children, cretinism (stunted growth, deformity, and mental retardation)

Anyway, as I said, I was horrified at the cost of a thyroid scan in terms of rad[iation dose], and started looking around at other alternative possibilities. And there, sitting in the isotope table was ^{125}I , and everybody ignored it because of the long half-life [(60 days)].

But a few quick calculations showed that the total energy dissipation⁷³ was about the same as with ^{131}I .

FISHER: I knew it was close to that.

HARPER: Yeah. So that, in theory, you should be able to get by with a lower radiation dose, because of the biological dissipation of the isotope. We pushed that [idea] for a while before we discovered that ^{131}I betas and ^{125}I Auger electrons were bad things.

FISHER: You were one of the first to use iodine-125 in the clinic.

HARPER: Yes.

FISHER: And, in fact, the—

HARPER: We didn't [actually] use it for anything but experimental purposes. We didn't really use it in the clinic; we used it for human studies. There's a difference.

FISHER: Okay. And can you amplify on that just a little bit more?

HARPER: We thought, here we have a wonderful isotope that we can study for a long time, and the radiation dose is considerably lower than with ^{131}I ; and we ought to be able to do something with it. So we tried doing some things with it.

FISHER: In a typical experiment, how did this take place? Did you choose normal subjects for these studies?

HARPER: Volunteers.

FISHER: Volunteers?

HARPER: [We] showed them what we were doing.

FISHER: Were they paid?

HARPER: Usually not.

FISHER: How do you recruit such volunteers?

HARPER: Friends and acquaintances, usually.

LATHROP: Ourselves.

HARPER: *(smiling)* Captive personalities are much easier to manage.

FISHER: So were you ever the subject of your own ^{125}I thyroid experiment?

HARPER: I'm sure I was. I don't remember.

⁷³ release of radiation during radioactive decay

LATHROP: We both were.

FISHER: Katherine, you, too?

LATHROP: *(nodding)*

FISHER: The nod probably doesn't record.

(laughter)

LATHROP: *(smiling)* Yes, sir.

FISHER: For the benefit of the transcriber, that was a "yes."

Development of Iodine-125 Production Methods and the AEC Review Process

LATHROP: Our principal contribution concerning ^{125}I was that we developed the production method.

FISHER: Which is still used today, I understand. It's the same chemical principle.

HARPER: Yeah, that's right.

FISHER: The same radiation principle, using xenon-124.⁷⁴

HARPER: Yeah, that was sort of interesting. We just froze the xenon into a capsule, a zirconium capsule, which Argonne Laboratory insisted on making, because it was going into their reactor.

We were able to get about ten grams of xenon in by freezing it, then sealed it up with a copper O-ring, sealed and bombarded it in the reactor, then brought it back and froze it again and, then, let it warm up slowly while the xenon came off into a tank and the iodine stayed behind on the walls of the vessel, [which] we then washed out, and it was heavily loaded [(irradiated)] with cesium-137 from a different reaction, so we had to pour it through [an acid-phase Dowex-50 column].⁷⁵

FISHER: Clean it up?

HARPER: Clean it up. And that worked fine. We encountered some people in a European expedition—I think it was at Badgastein⁷⁶—that did some experiments with the ^{125}I in rats.

They gave ^{131}I , a couple of hundred microcuries, to rats and completely wiped out their thyroids; histologically,⁷⁷ we couldn't see any thyroid tissue. ^{125}I , same dose, the thyroid looked beat up a little bit, but it was still

⁷⁴ a noble gas; symbol Xe

⁷⁵ Dowex-50 column—a column of glass filled with Dowex-50 ion-exchange resin beads for separating chemicals

⁷⁶ a resort city in Austria known for its thermal spas

⁷⁷ in terms of the structure of tissue

distinguishable as thyroid tissue. [With the ^{125}I , most of the radiation dose from the low-energy electrons was dissipated in a cellular colloid.⁷⁸]

FISHER: You published your work on production and use of iodine-125 in 1961. Looks like it was in *ACRH* [(*Argonne Cancer Research Hospital*)], volume 12.

HARPER: It got into the *Journal of Nuclear Medicine* eventually.

LATHROP: Reports of the work that was done at the Argonne Cancer Research Hospital. Our work would usually go into [the *ACRH* reports] before we published in the open literature.

FISHER: Was this an annual report of the hospital?

HARPER: Semiannual.

FISHER: Semiannual report, *ACRH*?

HARPER: Yeah.

FISHER: And so that would appear as a work sponsored by the Atomic Energy Commission.⁷⁹

HARPER: Right, definitely.

FISHER: Was there—

HARPER: I mean, Argonne Cancer [Research] Hospital was a[n AEC] Laboratory.

FISHER: Right. Was there support by the Atomic Energy Commission for these kinds of projects? Were you totally independent from Washington?

HARPER: Almost totally.

FISHER: Was there review?

HARPER: A one-paragraph write-up of what we were going to do, or what we had been doing. I forget the name of it [(the form)].

LATHROP: I don't remember, either.

HARPER: Nobody argued with us.

LATHROP: Essentially, they gave us money and told us to do something with it, which we did.

HARPER: Yes. It was permanent, free funding. It was great. It was that period [when] we made most of our [scientific] progress.

(laughter)

FISHER: You know, for us younger investigators, we don't have that luxury.

HARPER: I know you don't. We were spoiled.

⁷⁸ the region immediately surrounding a deposition site

⁷⁹ the AEC, predecessor agency to the U.S. Department of Energy and Nuclear Regulatory Commission (NRC); established January 1, 1947

FISHER: It's very difficult to get funding in basic nuclear medicine research anymore.

Discussion of Radiation Research Standards

YUFFEE: Was there any form of human-use committee at the time?

HARPER: There was one physicist, Professor Lester Skaggs,⁸⁰ who went over whatever you were planning to do and said it was okay or it wasn't.

FISHER: On what basis would he make that kind of a decision?

HARPER: His own feelings. He was a senior physicist.

LATHROP: You know, Dr. Skaggs is still living. You might want to interview him.

FISHER: Well, it's interesting that he would make these professional judgments.

HARPER: Well, he was stuck—somebody assigned him the responsibility.

FISHER: Who did he work for? Argonne Cancer Hospital?

HARPER: Yes. He was the chief physicist in the Therapy Section of Radiology.

FISHER: I see.

HARPER: Therapy was in Radiology at that time.

FISHER: These questions are of interest now to the President's Advisory Committee on Human Radiation Experimentation.

HARPER: Yes, I'm sure.

FISHER: So you'll understand why we—

HARPER: Well, there wasn't any FDA [(Food and Drug Administration)]; there wasn't any IRB [(Institutional Review Board)].⁸¹ There were just people like this. There were some radiation protection people that occasionally goofed and tracked stuff all over the hospital themselves. It was early in the game.

YUFFEE: Do you remember when Dr. Skaggs started reviewing human use?

HARPER: He was the first one that was around.

YUFFEE: Was this right at the beginning, when Argonne Cancer Research Hospital first opened?

HARPER: Yes, he must have been, because I'm sure he was there then. He recruited [D.B.] Charleston and crew.

⁸⁰ Lester Skaggs, Ph.D., professor of Medical Physics at the University of Chicago 1953–76; emeritus professor, known for his work on high-energy and neutron therapy of cancer and associated dosimetry

⁸¹ In 1966, the National Institutes of Health 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.

- FISHER:** Were these decisions based on amounts [of radiation] that were not considered harmful?
- HARPER:** Most of what we were doing was therapy-oriented, so we were dealing with large amounts.
- FISHER:** Of activity in here?
- HARPER:** Yeah, this wasn't nuclear medicine territory.
- FISHER:** It was—
- LATHROP:** It wasn't until we started working with technetium-99M [$^{99\text{M}}\text{Tc}$] that things—that our orientation [shifted] towards diagnosis.
- FISHER:** Okay. That's interesting, too. I think that—
- HARPER:** Well, I mean, the ^{125}I was the—
- FISHER:** —was diagnostic.
- HARPER:** Diagnostic. But technetium turned out to be better [for diagnostic purposes], for many reasons.
- FISHER:** Let me ask a few more questions about some of the experimental research in normal subjects.
- HARPER:** [In many cases, we were the subjects.]
- FISHER:** Can you recall different examples of experiments that were conducted in this way outside the clinic, you might say?
- HARPER:** Outside the clinic?
- FISHER:** Not involving cancer patients.
- HARPER:** For instance, the technetium sulfur colloid⁸² [research] for liver and spleen⁸³ scanning. I was one of the early subjects, and Dr. Gottschalk was terrified [to tell me that] he found a big hole in my liver. It turned out that one of the [photomultiplier tubes] in the camera was out.
- (laughter)*
- FISHER:** That would have been of concern, wouldn't it, to find a metastasis⁸⁴ in your liver?
- HARPER:** Then there was the one before we had the camera, we had to do scanning. When you breathe, your liver moves up and down, and the scanner moves back and forth, and you end up with [scaloped] lines along the edges. We had a bright idea for this. We would temporarily anesthetize the phrenic

⁸² a suspension of a solid in a liquid, where the solid does not dissolve

⁸³ 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

⁸⁴ a tumor growing from the spread of disease-producing organisms or of malignant or cancerous cells to other parts of the body by way of the blood or lymphatic vessels or membranous surfaces; or, the condition so produced

nerve⁸⁵ so the diaphragm on the right side wouldn't move. That worked. We abandoned that when we found one of our technicians trying to explain to one of the radiology residents how to inject the phrenic nerve.

It was interesting. We could make the liver hold still on the right side, but the left lobe moved more to compensate.

The spleen was really jagged in these studies. That's the sort of thing that we tried to do. There were some other things that we got involved with in connection with the therapy—brachytherapy.⁸⁶

We had the bright idea that, if you used a low-energy emitter like cesium-131, then the radiation outside the region that you're trying to treat will be reduced, so we looked at that, and palladium-103.

FISHER: Cesium-131 because of its low-energy photons.⁸⁷

HARPER: Yeah. We never treated anybody with cesium-131, but we used palladium-103 in people who had advanced tumors that needed therapy.

FISHER: Had palladium-103 been used before?

HARPER: I don't think so.

LATHROP: The production of palladium-103 was done in two ways. With the Oak Ridge National Laboratory cyclotron.⁸⁸

HARPER: It was also done in the MTR reactor⁸⁹ out in Idaho. That had a lot of carrier palladium with it, and the procedure we called "tattooing the tumor" with palladium black.

Then we tried to get rid of some carrier palladium. We irradiated rhodium targets in the big cyclotron at Oak Ridge, and that was quite an adventure, too. We had to develop equipment for getting the palladium out of the rhodium target. I don't know if that ever got written up in detail.

FISHER: You know, one of the other interesting things that you've done is, you've used beta radiation as a technique for pain relief.

HARPER: Oh, that. Well, that was the same needle that we were using to destroy the pituitary.⁹⁰

FISHER: Was it? Was that yttrium-90?

HARPER: No, that was strontium-90.

FISHER: Strontium-90?

⁸⁵ a nerve serving the diaphragm and used for breathing

⁸⁶ placement of sealed radiation sources into cavities of the body for treatment of cancer, such as uterine cancer; these sealed sources are later removed when treatment is completed.

⁸⁷ same as "gamma rays"

⁸⁸ an accelerator in which particles move in spiral paths in a constant magnetic field

⁸⁹ a test reactor facility near Arco, Idaho, at the Idaho National Engineering Laboratory

⁹⁰ the small gland attached to the base of the brain, constituting the master endocrine gland affecting all hormonal functions of the body

HARPER: Yeah. The strontium needles, you could stick those in percutaneously,⁹¹ [under x-ray control], and lay it against the spinothalamic tract or the anterolateral⁹² portion of the spinal cord.

FISHER: These were only used in terminally ill cancer patients?

HARPER: The alternative was cordotomy.⁹³

FISHER: Right.

HARPER: And cordotomy in patients of that sort had a substantial mortality. This approach was abandoned because the lesions that were produced [by radiation] tended to grow a little bit and cause trouble.

FISHER: Paralysis?

HARPER: Yes. Neurologic⁹⁴ defects. So what the neurosurgeons ended up doing was using the same approach, anatomically, but using electrical lesions, which were more localized and didn't grow. That worked better.

FISHER: You mentioned that these experiments were conducted before there was an FDA [(Food and Drug Administration)] that regulated radioactive materials.

HARPER: Well, yes. The Atomic Energy Commission had responsibility for radioactive pharmaceuticals.⁹⁵

FISHER: What level of oversight was there at the Federal level at this time?

HARPER: Dr. Skaggs.

FISHER: Dr. Skaggs at the hospital?

HARPER: Yes.

FISHER: And really nothing else in Washington[, D.C.]

HARPER: We wrote up what we did and sent it in.

FISHER: Was there feedback and response?

HARPER: None.

FISHER: Oversight, review?

HARPER: None [that we were aware of].

FISHER: To what would you attribute that? Just lack of experience in radiopharmaceuticals?

HARPER: [The use of radiopharmaceuticals] was just growing. Take the kids that Dwight Clark treated [with iodine-131, to see if they were cretins or

⁹¹ through the skin

⁹² lateral nerve pathways from the spinal chord

⁹³ surgical cutting of nerves

⁹⁴ relating to the nervous system

⁹⁵ drugs approved for human use

Down's syndrome victims]. That's one end of the scale. Gradually, regulation grew.

FISHER: Was the University of Chicago considered a training ground for other physicians?

HARPER: Of course.

FISHER: Or did you work quite independently?

HARPER: What do you mean?

FISHER: Did you have a lot of interactions with other physicians and teach these techniques that they then took to their [practices]?

HARPER: Not particularly. I mean, we published, and if people were interested, they followed [the procedures].

LATHROP: Well, we always went to the Society of Nuclear Medicine meetings.

HARPER: Yes, but actually, a lot of [the technology] went to Europe. The Europeans were much less inhibited about plunging into new things than the people in this country.

FISHER: How well were these techniques received by your peers?

HARPER: They sent us patients.

FISHER: They sent you patients? And, in general, how successful was radionuclide⁹⁶ therapy in, let's say, the 1950s to the early 1960s?

HARPER: The radiologists,⁹⁷ the therapeutic radiologists,⁹⁸ were much more interested in doing things with their machines.

FISHER: "Machines," meaning x-ray machines?

HARPER: Yes. And if I wanted to fool around with isotope therapy, [that was my privilege], but I always tried to involve them [(the radiologists)], because it was therapy. They gave up on me and let me do what I wanted, pretty much. I would explain what I was doing [and they would say,] "Fine."

YUFFEE: In regard to when you treated patients—and listening to this, being a lay person, the terminology often goes over my head.

HARPER: Yes.

YUFFEE: So the idea of informing them as to what you were doing, must have been a difficult task.

⁹⁶ atomic species in which the atoms all have the same atomic number but different mass numbers according to the number of neutrons in the nucleus

⁹⁷ physicians who diagnose disease, broken bones, and other physical conditions, using x rays or other imaging techniques

⁹⁸ physicians who treat medical conditions, using x rays or other forms of radiation

HARPER: No. You would tell them what you wanted to do; no big deal. I mean, if the patient got cancer, you're going to try to treat it. There isn't any alternative.

YUFFEE: Mm-hmm. Did you explain that?

HARPER: Of course.

YUFFEE: And you would explain the idea of, say, using the strontium needle?

HARPER: Sure.

YUFFEE: And what it meant?

HARPER: Of course.

Lathrop and Harper Collaborative Research (1965-67)

FISHER: Probably the contribution to science that both you and Katherine will be remembered for [is the] development of technetium-99m pertechnetate.⁹⁹

HARPER: Right.

FISHER: —as a diagnostic agent in nuclear medicine. And now there are something like 35,000 separate procedures [every day in the United States].

HARPER: I know. We never patented it.

(laughter)

FISHER: Mallinckrodt¹⁰⁰ appreciates that.

HARPER: I went to a big meeting in Rome[, Italy] just when I was all [excited] about ¹²⁵I and talked about ¹²⁵I, presented a paper and sat next to Jim Richards from Brookhaven¹⁰¹ on the plane. He tried to sell me on this wonderful stuff that they had developed at Brookhaven.

FISHER: Which was what? What stuff?

HARPER: Technetium-99m, what else? I didn't hear a word he said. A couple of years later, two things happened: one of our friends was interested in a short-lived isotope for looking at things going through the heart; and Dr. Sorensen was interested in liver metabolism.¹⁰²

FISHER: Which Sorensen was this?

HARPER: Leif.

FISHER: Leif Sorensen.

⁹⁹ pertechnetate—the chemical form TcO₄

¹⁰⁰ Mallinckrodt is a St. Louis-based pharmaceutical company that sells or distributes technetium-99m generators to nuclear medicine clinics.

¹⁰¹ Brookhaven National Laboratory, Upton, NY

¹⁰² the rate at which chemical processes take place in the liver

HARPER: Leif Sorensen.¹⁰³ He was interested in—what is it called?

FISHER: Well, in the write-up here, it says, “xanthine oxidase.”¹⁰⁴

HARPER: Yes, that’s it. I’m trying to—I’m old enough now so I go blank on things occasionally. Pardon me.

Molybdenum is the cofactor¹⁰⁵ for xanthine oxidase in the liver. So he wanted to use radioactive molybdenum [as a tracer for stable molybdenum].

Katherine set him up with the people at Argonne to make some radioactive molybdenum for him to study. He studied it and was concerned about the technetium daughter,¹⁰⁶ [which] was sort of a nuisance.

He actually [obtained] a blood disappearance curve of technetium, and [determined that] the molybdenum localized in the liver and decayed to technetium, which stayed in the liver.

So he had a project for looking at the—imaging the liver with technetium as the daughter of the molybdenum that was [localized] in the liver. This [research] didn’t appeal to me very much, because there’s a lot of high-energy gamma from the molybdenum that [obscured the image]. I asked Sorensen [whether,] if he was [not] interested in the technetium itself, could we work on it? He said, “Sure, go ahead,” and we were off and running.

FISHER: Now, that leads me to a next question. What happened to the work under [Jim] Richards at Brookhaven?

LATHROP: He made the generators. [(molybdenum-99/technetium-99m generators)]

HARPER: Yeah. He was the supplier of generators for years.

FISHER: So he built your generators and you applied them in the clinic [(Argonne Research Hospital?)].

HARPER: That’s right.

LATHROP: They had a whole group that was working on making generators. Remember, down at Oak Ridge one time, we spent half the night talking with two people [from the group]. I forget their names.

HARPER: Yes.

LATHROP: And we were told to be quiet after a while.

(laughter)

LATHROP: Well, that was because—

¹⁰³ Leif Sorensen (born 1928), a professor of medicine at the University of Chicago, is a Danish physician and specialist in gout, purine metabolism, and aging of the immune system.

¹⁰⁴ a liver metabolite, without which children express unusual behavior

¹⁰⁵ an essential contributor in metabolism

¹⁰⁶ an isotope formed by radioactive decay of another isotope

HARPER: —that's because we had a bottle of whisky.

LATHROP: That was because of the cardboard walls in the hotel. [(People in the next room would be disturbed.)] But, anyway, they had a whole collection of generators.

HARPER: Yeah, iodine-132, and there were a variety of other things that they developed. But the technetium was the one that flew [(was successful)].

FISHER: It sure was.

HARPER: Unfortunately, the technetium that came off the generator was slightly contaminated with iodine and with various other things.

Mrs. Lathrop dug out some literature from Russia in *The Proceedings of the Peaceful Uses of Atomic Energy*, [that explained] separating technetium and molybdenum using methyl-ethyl-ketone [(MEK, an industrial cleaning solvent)] extraction from sodium hydroxide.

So, after that, we just bombarded the molybdenum oxide in the local reactor, and it dissolved in [sodium hydroxide] which reacted with [molybdenum oxide.]

FISHER: Was that the Argonne reactor?

HARPER: Yes, CO-5 reactor. We even constructed a big, fancy apparatus to do it remotely, more or less.

FISHER: That's amazing.

HARPER: We supplied the clinic with technetium [as pertechnetate for thyroid studies] and started looking at the other applications of technetium. We knew it stayed in the liver when it arrived on the scene from molybdenum in the liver, so we thought there must be some way of making it stick in the liver.

We found a preparation, technetium thiocyanate, [that] was soluble in fat. And so we were injecting it mixed with fat emulsion. It all ended up in the liver, and that was a temporary solution. The actual solution which we ended up with, [was developed by] Jim Richards [at Brookhaven.]

We told him we would like to have technetium in a colloidal form that would [localize] in the RE [reticuloendothelial]¹⁰⁷ system.

FISHER: For liver scans, for example?

HARPER: Yeah, for liver scans, [spleen, and] bone marrow.¹⁰⁸

LATHROP: Both he and Hal Atkins¹⁰⁹ came to visit us, and we were discussing all these things. I said I tried using sulfur colloid, but I couldn't get any

¹⁰⁷ a family of cells that function in the immune system's defense against foreign bodies

¹⁰⁸ the soft, fatty, vascular tissue in the cavities of bones; it is a major site of blood-cell production.

¹⁰⁹ Harold L. Atkins, M.D. (born 1926), a physician in nuclear medicine at the State University of New York, Stony Brook. Atkins collaborated in radiation research with the medical department at Brookhaven National Laboratory.

kind of sulfur to precipitate [with hydrogen sulfide], but I couldn't get any precipitate that I could recover.

So they went back home. It was less than a week when they called us and said that they had used this same method; they had added gelatin to the preparation [to make the process work].

HARPER: Yes, as a protective colloid.

LATHROP: You know. And they had been able to [produce] something that they thought could be used.

HARPER: We put it in a mouse, and it stayed in his liver, and, I think, a few days later, we [tried it in a human subject]. It stayed in his liver. The alternative was gold-198 [colloid]. So, [we had developed a method with technetium that vastly reduced] the radiation dose.

LATHROP: There had been a horrible episode [elsewhere], where someone had given ^{198}Au [(gold-198)].

HARPER: [In error.] Millicuries instead of microcuries.

HARPER: We got the patient, eventually. I think he or she didn't survive. Anyway, we were [particularly concerned] about this. The procedure was to bubble hydrogen sulfide through IN (normal) [(pH-neutral)] HCl [(hydrochloric acid)] containing the pertechnetate and [gelatin]. It formed a colloid with the gelatin, [carrying the technetium], which was then diluted so that the acid concentration wasn't too high to give intravenously.

FISHER: Katherine, did you do these preparations?

HARPER: We all did them.

FISHER: You all worked together on this?

HARPER: Yeah. I mean, from now on, we're a team. So the way I phrased it was: I provided the ingenuity and Katherine provided the scholarship.

FISHER: Well, you've been collaborating [together] now for more than 40 years.

HARPER: That's right.

FISHER: This sulfur colloid—was it first tested in a patient, or an animal?

LATHROP: We always tested them in mice [before human testing].

HARPER: For the first six months, we didn't dare give it to people without trying it on a mouse first. After a while, we got some faith in ourselves and didn't bother with the mice anymore.

FISHER: When you found good localization, then it was used diagnostically?

HARPER: Right.

FISHER: And by that time, the rectilinear scanners¹¹⁰ or the imaging cameras were sufficiently developed. You could get a pretty good image?

HARPER: Yes. [The cameras came later.]

FISHER: Okay. Now, tell us more about your human studies with technetium-99m.

HARPER: Our first experience with it, we put it in a mouse, and it ended up in his stomach, his bladder, and his thyroid and salivary glands. We said, "My God, what's it doing in the thyroid?"

Then we discovered that the people at NIH¹¹¹ had been using technetium-99m pertechnetate as a tracer for the thyroid. It's similar to perchlorate and iodide and thiocyanate. It has the same characteristics. They had been using it for physiologic¹¹² studies. We went off pursuing the thyroid.

LATHROP: We also had a reference from someone up at Battelle Northwest,¹¹³ I think, who said that it did not localize in the thyroid.

HARPER: I don't remember that.

LATHROP: Yes.

HARPER: Anyway, we had an eager-beaver surgical resident working with us at that time who did a lot of study; this was George Andros.¹¹⁴

FISHER: You know, technetium-99m was a contaminant in the plutonium fuel cycle.

LATHROP: Yes.

HARPER: Of course. Anything long-lived [(with a long radiation half-life)] is.

FISHER: That was a particularly nasty one, because it followed uranium through the gaseous diffusion. Technetium-99 built up in uranium fuels after each recycling of the material; so the concentration grew and grew.

HARPER: I was not aware of that.

FISHER: So there was some concern about technetium-99 exposures of workers. Perhaps that's the reason why some studies were done [on the subject].

LATHROP: I think that's probably it.

HARPER: That could have been.

¹¹⁰ 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

¹¹¹ the National Institutes of Health (Bethesda, Maryland)

¹¹² relating to the functions and activities of living organisms and their parts

¹¹³ Battelle Memorial Institute, headquartered in Columbus, Ohio, operates the Pacific Northwest Laboratory for the U.S. Department of Energy in Richland, Washington.

¹¹⁴ George J. Andros, M.D. (born 1916), an obstetrician and gynecologist and a professor at Jefferson Medical College, Philadelphia, Pennsylvania

LATHROP: But somehow or other, they missed the fact that it [(technetium-99)] was localizing in the thyroid.

FISHER: In the thyroid.

HARPER: Well, technetium-99 would be—there might be enough carrier present to suppress the thyroid localization. I don't know. That [study is going to be done] on people.

FISHER: There were a number of experimental studies conducted on technetium in various forms from that point on.

HARPER: That would also be in Katherine's—

LATHROP: I don't think we gave you—did we give them a report of the Oak Ridge—the paper that was given at the Oak Ridge symposium [at Knoxville]?

HARPER: I don't know.

LATHROP: We had—this was back in 1965, I think—

HARPER: Yeah, I think you did. It was—

HARPER: And there is a picture in there that shows the number of organs that were visualized with technetium.

HARPER: Yeah, that looks like it, something that was about that size.

FISHER: What—for the benefit of the transcriber, we're looking at chapter 18, on "Pharmacodynamics of Some Technetium-99m Preparations" by Paul Harper, Katherine Lathrop, and Alexander Gottschalk, spelled G-O-T-T-S-C-H-A-L-K, in the proceedings of the—this is probably the first?

LATHROP: This was the first symposium of the sort. They had—

FISHER: Oak Ridge Institute of Nuclear Studies.

HARPER: Well, I think we presented at in Badgastein[, Austria] before that, in Europe, and maybe even in Athens[, Greece].

LATHROP: Yes, but I understood him to be referring to the publication.

HARPER: Oh, yes.

FISHER: This one is in a publication called *Radioactive Pharmaceuticals*, available as CONF651111, April 1966, edited by Andrews, Kniseley, and Wagner. [I am referring to] Henry Wagner and [former ORINS director] Gould Andrews, of course, early pioneers in nuclear medicine.

HARPER: Right.

FISHER: And [Ralph M.] Kniseley¹¹⁵ had an interest in both nuclear medicine and therapy. Those are all names that come to mind [when thinking of that field]. You worked with some good people during these years.

¹¹⁵ A medical doctor, formerly a pathologist at Lovelace Clinic in Albuquerque, Kniseley left Lovelace for Oak Ridge, where he served as associate director of the Medical Division.

- HARPER:** We didn't work with them. We were all working in parallel in different places.
- LATHROP:** Well, that shows the number of [human] organs that we had visualized in a fairly short time [using ^{99m}Tc].
- HARPER:** The one thing that we missed was the bone [visualization] agents.
- FISHER:** Who came along later and developed the bone—the diphosphonates?¹¹⁶
- LATHROP:** Oh, that was [Gopal] Subramanian.¹¹⁷
- HARPER:** Katherine's special friend.
- LATHROP:** That was Subramanian.
- FISHER:** That was a clever idea, to attach technetium to a bone substrate.¹¹⁸ Did you do additional ^{32}P —phosphorus-32 studies?
- HARPER:** The only ^{32}P studies we did were the original one with lipids when I was a resident. The only other use we made of it was as pyrophosphate¹¹⁹ pellets that we used as flux¹²⁰ monitors when we were irradiating things in the reactor.
- FISHER:** Why has it not been used more therapeutically?
- HARPER:** I haven't the slightest idea.
- LATHROP:** I assayed¹²¹ tissues that were sent to me when I was still at the Manhattan Project¹²² from children who were being treated for leukemia. ¹²³They were autopsy samples; they [the researchers] were using it that far back.
- FISHER:** ^{32}P in the treatment of leukemia?
- LATHROP:** Yes. And then the—
- FISHER:** Who was using it at that time?
- LATHROP:** Pediatricians here at the hospital.
- FISHER:** At the Argonne Cancer—
- LATHROP:** No, here at the University of Chicago.
- FISHER:** At the University of Chicago.

¹¹⁶ having two phosphonates

¹¹⁷ Gopal Subramanian, Ph.D., a nuclear medicine scientist known for having developed the bone imaging agent. Subramanian is now at Upstate Medical Center in Syracuse, New York.

¹¹⁸ an essential nutritional component

¹¹⁹ a bone-seeking agent for nuclear medicine imaging

¹²⁰ a quantity expressing the strength of a field of force in a given area

¹²¹ determined the amount of material present in tissue, urine, or feces by any trial measurement

¹²² the U.S. Government's secret project, launched December 28, 1942 by the U.S. Army Corps of Engineers' Manhattan Engineer District, to develop the atomic bomb.

¹²³ 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

- LATHROP:** This predated the Argonne Cancer Research Hospital.
- FISHER:** Oh, I see.
- LATHROP:** This was while it was still the Manhattan Project. They sent me tissue [from] autopsies.
- HARPER:** Well, was Dr. Jacalin doing it, or—
- LATHROP:** No. It was a woman pediatrician[, Mila Pierce.]
- HARPER:** Okay.
- FISHER:** During the Manhattan Project, using ^{32}P in the treatment of childhood leukemia?
- LATHROP:** Yes.
- FISHER:** That's interesting.
- HARPER:** I don't know where they got the ^{32}P .
- LATHROP:** Well, I'm not sure where they got the ^{32}P , either, but they were sending them [the tissue samples] to me to assay so they would know what the localization was and, maybe, something about the radiation dose.
- FISHER:** And how did you do those assays?
- LATHROP:** It was a beta assay [(an assay to determine the amount of ^{32}P present in the tissue sample)].
- FISHER:** Using what kind of samples? Blood samples?
- LATHROP:** No, they were tissue samples.
- FISHER:** Tissue samples? From autopsies?
- LATHROP:** Well, there was probably blood, too, but there were other tissues, various [internal] organs.

Thallium Research

- FISHER:** One of the interesting things that I came across was your use of thallium-199 as a heart-scanning agent.
- (laughter)*
- HARPER:** That's an interesting story.
- FISHER:** Now, you didn't have positron¹²⁴ detectors at that time, did you?
- HARPER:** No.
- FISHER:** Thallium-201, I'm thinking of.

¹²⁴ a particle with the mass of the electron but with a positive electric charge; the detectors measured the accompanying 0.511-Mev gamma rays emitted during positron decay.

HARPER: Yes. The "eye people" called me up one day and said, could I make them some radioactive potassium, because they had been reading. [The ophthalmologists] were interested in thallium localization, because thallium apparently localizes in pigmented tissues in the eye; it localizes differently in the eyes of white rabbits and black rabbits.

They wanted to use radioactive potassium, because the potassium and thallium ions behave somewhat similarly, and they wanted to use potassium to trace thallium.

We said, "My God, if you're going to trace thallium with potassium, you can certainly trace potassium with thallium." So we were off and running with thallium. We made some thallium on our little cyclotron by bombarding mercury. It was a horrible mix, and that's where the thallium-199 came in.

LATHROP: We couldn't make the [thallium]-201 in our cyclotron.

HARPER: We didn't have a big enough cyclotron. So we went ahead and tried it [(thallium-199)] on a couple of people. One of them was Mrs. Lathrop, and one of them was a gentleman that had a melanoma [(skin cancer)]. We said, "Aha, melanoma! This should tie in with the eye people, a pigmented lesion. It should pick up the thallium."

FISHER: Thallium has a half-life of seven hours. That would seem to be quite suitable.

HARPER: Well, it was a mixture—I mean, if you bombard mercury, you can see what you could get.

FISHER: Sure.

HARPER: So we tried it and what did we get? A good picture of the heart. So that's what we presented to the Society for Nuclear Medicine, [and] that stimulated the people at Brookhaven to make thallium-201.

LATHROP: *(to Harper)* What we got [when you tried it on me,] was a great, big hot [radioactive] spot. You decided that my clothes were contaminated. Remember?

HARPER: No.

LATHROP: Well, you did.

(laughter)

LATHROP: So I had to start peeling them off [(my clothes)].

FISHER: What activity levels were used for these initial studies with thallium-199? For example, Katherine, you say you were a subject of one of these early experiments. How much [radio]activity would you permit going into your blood veins for this early study?

HARPER: A [few] millicuries.

- LATHROP:** Well, you know, it's not a matter, exactly, of how much activity. It also is what the quality¹²⁵ of the activity is, average—
- HARPER:** How much do you need?
- LATHROP:** Yeah, that's right, too.
- FISHER:** Thallium-199 has several higher-energy photons.
- LATHROP:** But we had already—we must have done some animal experiments.
- HARPER:** I don't remember what we did.
- FISHER:** It sounds like you were the subject of an experiment on several occasions.
- LATHROP:** Yes.
- HARPER:** We both were.
- FISHER:** Was this accepted practice, still, in that particular era?
- HARPER:** Still is.
- FISHER:** *Still is?*
- HARPER:** You don't give anything to a patient that you haven't tried on yourself, [that] sort of idea.
- LATHROP:** That's right. I would tell the people that I had asked to volunteer that I wouldn't ask them to do anything I wouldn't do to myself. And one day, one of the people I was working with said he really appreciated that. That was the reason that he decided that he would volunteer for the studies that we were doing.
- FISHER:** Incidentally, this was really quite recently, in 1970, when you worked on thallium-199. I say "recently," because this is not too far back in my own memory.
- HARPER:** That's right. Well, we didn't advocate thallium-199 as an [imaging] agent. It was a study showing that thallium did localize in the heart as we thought it was going to. I mean, the agents that were used before were cesium and rubidium and potassium, and the thallium fit in there [(that category)] because it behaved in a somewhat similar manner metabolically.
- FISHER:** Of course, now, thallium-201 is a widely used cardiac imaging agent.
- HARPER:** Of course. We're still doing dosimetry¹²⁶ on it.
- LATHROP:** We discovered [something] with the thallium. I was a subject and Paul was a subject, and my scan had a lesion, and his didn't. That puzzled him for a while, until we found out that I actually did have a lesion, which had subsequently gone away.

¹²⁵ dose quality—the linear energy transfer and relative specific ionization, energy distribution in tissue, the exposure rate, etc., that influenced the biological effectiveness of the radiation

¹²⁶ 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

- FISHER:** When you make thallium in the cyclotron, you make a mixture of thallium isotopes? [Did] you get thallium-201 or thallium-202?
- HARPER:** We did a thallium-202 study. We bombarded mercury and let the short-lived thing [nuclides] decay out until there was only the thallium-202 left, and then we were able to do a long-term biodistribution study using whole-body imaging system, and that's on its way to the MIRD Committee¹²⁷ at the moment, I think[, but] that was some years ago.
- FISHER:** About what year was the thallium-202 study?
- LATHROP:** Well, that was after it had become used widely in clinical practice.
- FISHER:** Thallium-202 is a positron emitter with some photons—
- HARPER:** [No, it decays by electron capture as listed in Lederer.] We were looking at photons.
- LATHROP:** We wanted to be able to follow the thallium for a long period of time.
- HARPER:** We did it in a whole-body counter¹²⁸ that was [modified] to image [high-energy photons].
- FISHER:** Who were the subjects of this study?
- HARPER:** One subject.
- FISHER:** Dr. Harper?
- LATHROP:** No.
- HARPER:** No, this was one of our technologists; he was captive personnel. He knew what was going on. His family [complained] when he kept his excreta in the icebox [(refrigerator)] at home.
(laughter)
- LATHROP:** Because we had followed him for six or eight weeks.
- YUFFEE:** That's fair [to complain under those circumstances].
- HARPER:** Well, this is just to check on the whole-body counter, because we didn't really trust that. So we collected excreta and added them up to look at the disappearance [of radioactivity].
- FISHER:** We see in the published literature many references to the whole-body counter.
- HARPER:** Yes.
- FISHER:** Sometimes it's not clear where the whole-body counter is. Is this Argonne?

¹²⁷ Medical Internal Radiation Dose Committee of The Society of Nuclear Medicine

¹²⁸ an apparatus that measures radionuclides in man using shielded detectors and multichannel energy analyzers. The sensitivity and non-invasive nature of this instrument permitted studies at levels 10 to 100 times below established limits of exposure. It opened an entire area of clinical diagnosis and the development of new diagnostic methods.

HARPER: It's the one here.

FISHER: It's the one here at the hospital?

HARPER: Yes.

FISHER: You have your own [counter] here in the Argonne Cancer Hospital?

LATHROP: We did.

HARPER: We did. It broke and it has been [dismantled]. Its use has been discontinued.

FISHER: But the hospital had its own whole-body counter for many years.

HARPER: Yes.

FISHER: Do you remember how long that operated?

HARPER: Maybe 20 years.

LATHROP: It died when we were doing the OIH¹²⁹ study. The first study we did with it, was [with selenomethionine.]

HARPER: Yeah. Mrs. Lathrop followed a [patient] for three years who had an ordinary diagnostic dose of selenomethionine. That's the number-one MIRD dose estimate.

LATHROP: There's the selenomethionine dose estimate report I think that I put into that packet.

FISHER: Yes.

LATHROP: Well, that was our first study, but the reason the whole-body counter was constructed was to do potassium studies.

HARPER: Most of our progress was made back before the regulators [(institutional review boards, or IRBs)]¹³⁰ got into the act.

FISHER: You know, I'm envious because—

HARPER: You should be.

FISHER: —in today's science, it's not only difficult to discover things because you've made so many fantastic discoveries already, but it's also hard—

HARPER: Well, it was an open [research] field. Nobody had done the legwork. We lucked out.

FISHER: It's hard to get [research] funding, and I think you and many others who did the work during this particular era, 1940 through 1980, were able to discover so many new and exciting things.

¹²⁹ orthoiodohippurate, used for imaging the kidneys, labeled with iodine-131

¹³⁰ In 1966, the National Institutes of Health 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.

When you make thallium by cyclotron, do you also end up with some long-lived thallium-204 contaminant?

HARPER: [In the present commercial system, thallium-203 is bombarded with high-energy protons, producing a (p-3n) reaction,¹³¹ giving lead-201. Contaminating lead-202 decays rapidly to thallium-202, which is removed on a column. The longer-lived lead-201, then decays to thallium-201 and is removed from the column, leaving the contaminating lead-203.]

FISHER: You worked originally with mercury as a source for thallium, didn't you?

HARPER: Yes, we did. That's because—that was the only way we could do it.

FISHER: Okay. But now, is it made—

HARPER: Yeah. You bombard the thallium-203, and it makes lead-203, lead-202, [and] lead-201. Now, what do you do? This is short-lived [(half-life: 8.4 hours)]. Okay. So you let these decay out and it leaves you with lead-201, and then you milk it off the thallium-201.

FISHER: I see. That's interesting. So you have a tradeoff between yield and purity.

HARPER: Sure.

FISHER: Have you been able to register any patents?

HARPER: We haven't attempted to.

FISHER: Haven't attempted?

HARPER: It's just too much hassle.

LATHROP: The University [of Chicago] was not really receptive to it until just recently. Now, they are urging people to [file invention reports].

HARPER: Somebody patented the technetium process, the methyl-ethyl-ketone extraction.

LATHROP: That was [the chemical firm] Union Carbide [Corporation].

HARPER: Union Carbide did. And we were advised that it was just a patent to discourage other people; it wasn't a real patent, [but] a ghost patent of some sort.

Antifibrinogen Research

FISHER: I'm interested in work you did in 1966, or maybe a little earlier than that.

HARPER: I know what that was.

FISHER: On the use of antifibrinogen¹³²—

¹³¹ proton bombardment of a thallium target, yielding a subsequent emission of three neutrons

¹³² antibody-recognizing receptor sites on fibrinogen molecules

HARPER: Oh, that.

FISHER: —labeled with iodine-131 for cancer therapy.

HARPER: That's—you're familiar with the [William F.] Bale¹³³ and [Irving] Spar¹³⁴ operation?

FISHER: Bale was at Rochester.¹³⁵

HARPER: Yeah, the whole operation is there. And so was Spar. He ended up as Dean [of Graduate Studies and Financial Aid].

FISHER: Can you tell us more about this history?

HARPER: The idea was that when clots formed, the fibrinogen was carried down [as fibrin. Labeled antifibrinogen would then be carried down to the fibrin of the clot.]

Then, if you discourage fibrinolysis¹³⁶ by giving [amino caproic acid]—the localization shows up better. [Bale and Spar] even thought that it might be possible to get up to therapeutic levels.

They had to have special ¹³¹I made at Oak Ridge, because there are some inert iodines made by the usual reaction that reduces the specific activity.¹³⁷ I don't remember exactly how they did it, but they got the special run of high-specific-activity ¹³¹I.

They labeled the antifibrinogen, and then [to purify it,] they absorbed this out onto a fibrin column, and then eluted¹³⁸ it. They had a [stricter] IRB in Rochester, so they couldn't [carry out patient] studies, and we could.

So that's how the collaboration developed. We did a number of studies. We even did a therapeutic one.

FISHER: Can you describe the subjects of these studies?

HARPER: We were trying to look at localization in people with advanced malignancy.

FISHER: Okay. So your subjects were cancer patients?

HARPER: Yes. They were not treatable otherwise; and there *was* a possibility of treating them.

We did one experiment in a lady that had advanced ovarian carcinoma. We gave [her] antifibrinogen, and then, after it had localized, we wiped

¹³³ a biophysicist at the University of Rochester

¹³⁴ Irving Spar (born 1926), an immunologist, was a professor of Radiation Biology and Biophysics, School of Medicine and Dentistry, University of Rochester. He conducted early research on cancer therapy and antibodies labeled with iodine-131.

¹³⁵ the University of Rochester (Rochester, New York)

¹³⁶ breakdown of blood clot fibrin

¹³⁷ the concentration of radioactive material (units=activity/gram)

¹³⁸ drew off in solution

out the [remaining] circulating antifibrinogen by giving [anti-rabbit goat] gamma globulin.¹³⁹ There was no problem.

It gave us [improved image] quality because it wiped out the circulating activity, which all went into the liver and metabolized and the iodine was excreted.

FISHER: What were some of the cancer types that this [therapy] was conceived for?

HARPER: Anything. Anything that's outgrowing its blood supply and producing incipient¹⁴⁰ necrosis, [and then] laying down the fibrin.

FISHER: What would be some good examples of that?

HARPER: Any tumor.

FISHER: Any solid tumor.

HARPER: Yes. We presented this at a meeting in Germany, and the Germans leaped onto it; somebody in Berlin, in East Germany, did 50, 60 patients. It [(the therapy)] seems to work best in sarcomas.¹⁴¹

FISHER: Was this work discontinued after some time, for any reason?

HARPER: Well, we got tired of it. [We] got interested in other things.

LATHROP: Well, didn't it [(the fibrinogen therapy)] work sometimes better than it did other times?

HARPER: Yeah. It wasn't 100 percent.

FISHER: Were you able to achieve high enough amounts—administered amounts for therapeutic efficacy—or were you limited in some way?

HARPER: Well, we thought—no, we weren't limited in any way, it was just a matter of how much activity—

FISHER: —you could get?

HARPER: Yes. The people at Rochester made the material and shipped it to us in dry ice [(frozen carbon dioxide)], so it's really an offshoot of their study.

FISHER: So you were only limited by the amount of labeled antifibrinogen that you could obtain.

HARPER: That's right. I mean, you can give hundreds of millicuries of ¹³¹I without it doing any very serious damage if you don't worry about regulations.

FISHER: Katherine, were you involved in the dosimetry of any of those patients?

LATHROP: Of the antifibrinogen patients?

FISHER: Yes.

¹³⁹ the fraction of blood serum that contains most of the antibodies protecting the organism from infectious diseases

¹⁴⁰ in the beginning stages

¹⁴¹ malignant tumors that arise from bone-forming cells and chiefly affect the ends of long bones

LATHROP: No.

HARPER: We weren't particularly worrying about dosimetry. We were just looking at what actually [happened].

FISHER: Localization and—

LATHROP: Now, whether—what was his name—Spar?

HARPER: Who—Irv Spar?

LATHROP: Irv Spar, yes. He may have done something on that. I don't know. Do you?

HARPER: I don't remember.

FISHER: This is interesting because, you know, now, with the advent of—

HARPER: Yes. Well, I think this is the first [clinical monoclonal antibody¹⁴² studies] that I'm aware of.

FISHER: Now, with the advent of highly specialized [antibodies]—

HARPER: No, the pathologists, [at our institution], were doing things with antibodies in rats, curing tumors in rats, but I don't think they ever got to the point of using it clinically.

FISHER: Clinically. With highly specific monoclonal antibodies, iodine-131, high-dose iodine-131 therapy is becoming more and more successful.

HARPER: People are getting more and more enthusiastic about it, but that doesn't always follow.

FISHER: The physicians are really doing quite well, now, with high-dose iodine-131 antibodies in conjunction with bone-marrow transplantation and—

HARPER: Oh, I see.

FISHER: . . . [and with] chemotherapeutic¹⁴³ agents, all in combination to form a very potent attack [on malignancy].

HARPER: Sounds like it's almost worse than the disease.

FISHER: It's a heavy dose for a disease that won't be [effectively] treated any other way, I guess.

HARPER: Right.

FISHER: But the pioneering efforts here, I'm sure, were very, very important in—

HARPER: Have you ever seen them referenced? I have them.

¹⁴² 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; initial results have been very positive.

¹⁴³ involving the treatment of disease by means of toxic chemicals that kill cells or inhibit their ability to grow and multiply

FISHER: Yes.

HARPER: Okay.

FISHER: I have that in this package.

HARPER: Good.

FISHER: Which was really, [it] really caught my attention.

HARPER: Okay. Well, that's your special interest, [or] one of your special interests.

FISHER: And so I was interested in asking about any follow-up [therapy].

YUFFEE: It's on that [subject that] I did have one quick question. You mentioned that part of the origination of your collaboration at Rochester was that you didn't have a strict IRB and they did [have a strict IRB].

HARPER: Yes.

YUFFEE: Was that the basis of other collaborations?

HARPER: No.

YUFFEE: Just in that one instance?

HARPER: Just that one instance; it must have originated in a conversation at a meeting.

YUFFEE: And that sort of goes to the heart of what you were saying [about] the advent of more and more regulation getting in the way [of research].

HARPER: More and more regulations makes it tougher and tougher [to get work done].

FISHER: During this period, Dr. Harper, did you continue to practice surgery?

HARPER: Oh, yes. I ran a service, you know, from the "reactor to the grave."¹⁴⁴
(laughter)

FISHER: That's a quotation that could live on. What were your main interests?

HARPER: General surgery.

FISHER: General surgery? Do you still do that, or are you retired?

HARPER: No, no. I haven't done it [(surgery)] for 10 or 15 years.

YUFFEE: This might be a good time, Darrell, to go through some of the [other] experiments we [need to discuss].

¹⁴⁴ from the procurement of a radioisotope from the reactor to follow-up on patients until they died; a facetious variation on "from cradle to grave"

Various Radioactive Isotope Research by Lathrop and Harper

FISHER: I was still interested in just a couple of things before we move into that. You remember the work at Oak Ridge on gallium-67 and gallium-72?

HARPER: Yes. They made a mistake and did a study on a patient with cancer, and they used gallium-67 because it was carrier-free¹⁴⁵—and they wanted a point with that in their curve—and [happily] it localized in the tumor, so they were off and running [(using gallium-67)].

FISHER: Tell us more about this.

HARPER: So everybody started using gallium for localizing tumors.

FISHER: Did you work with gallium-67?

HARPER: We made gallium-67. It was one of the first things we did when we got the cyclotron. Apparently, we ended it [(meaning the work with gallium)]. That is, after zinc. We were bombarding zinc, in the tank, as an internal target, and it's supposed to be very bad for cyclotrons to have zinc bombarded in the vacuum.

But we got away with it; the cyclotron was sufficiently overdesigned so it didn't hurt.

FISHER: What were some of the [diagnostic or therapeutic] applications that you tested for gallium-67?

HARPER: We didn't do anything with it [in] particular.

FISHER: You made some [(gallium-67)].

HARPER: We made it and gave it to the clinicians to work with.

LATHROP: We didn't do any experimental work in humans [with gallium-67, but] we did experimental animal work.

HARPER: Oh, that's right, you were working on the placenta and the placental transfer and that sort of thing.

FISHER: The article by Gottschalk mentions use of gallium-68 EDTA.¹⁴⁶

HARPER: Yeah, that was off a generator.

FISHER: And that it had potential applications for brain imaging.

HARPER: Well, that's another whole business. We went to a meeting of the Society in Montreal, [Quebec, in Canada] and Gottschalk and Anger¹⁴⁷—this is when Gottschalk was working with Anger in [the University of Cali-

¹⁴⁵ the radioactive isotope in pure form, without an added amount of stable isotope of the same element

¹⁴⁶ ethylene diaminetetraacetic acid, a common chelating agent and food preservative

¹⁴⁷ Hal Anger at UC Berkeley developed the gamma camera—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.

fornia at] Berkeley, and they had an exhibit on [the use of] gallium-68 localization in brain tumors.

They pointed out that it was an extracellular fluid labeled [with] gallium EDTA [(that they used)]. So the lights came on [(we suddenly realized how gallium could be best used) and we thought to ourselves,] "My God, that's how pertechnetate behaves [as an extracellular] fluid [label]!" So we came back [to our lab] and immediately started doing brain [scans, which] worked spectacularly.

LATHROP: We had a brain scanning instrument that was made here at the Argonne Cancer Research Hospital.

HARPER: It was designed around iodine-131 [but it worked well with ^{99m}Tc pertechnetate].

LATHROP: And it had just become operational.

HARPER: So we got lots and lots of brain scans.

FISHER: Did you ever work on any chromium-51 or iron-59 blood studies here at the hospital?

HARPER: *We* never did. The hematologists with the whole-body counter did[, however].

FISHER: There was quite a bit of that kind of work that went on at Argonne Cancer Hospital.

HARPER: Yes. We had nothing to do with it.

FISHER: Back in 19—

HARPER: You were asking about the whole-body counter at one point. The group—Leroy's group—George Leroy¹⁴⁸ and Carol Newton were doing—

LATHROP: —fission products.

HARPER: —fission product studies. Heating the fission products to see how long it took them to go through [(i.e., how long they were retained in the body prior to excretion)] at modest [activity] levels.

LATHROP: The whole-body counter—that was the original purpose of the whole-body counter: potassium studies. And then they used it [(the counter)] for fission product studies. And then—

FISHER: These fission product studies—what was the purpose of those studies, to investigate the metabolism of fission products?

¹⁴⁸ Leroy had been 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 *Human Radiation Experiments Associated with the U.S. Department of Energy and Its Predecessors* (213 pages), DOE/EH-0491, July 1995.

- HARPER:** Yes, how bad is it to heat fission products; how fast do you eliminate them; that sort of thing.
- LATHROP:** It was not our project.
- FISHER:** Who were the investigators again?
- HARPER:** George Leroy and—
- FISHER:** How do you spell that?
- HARPER:** L-E-R-O-Y. He's dead.
- FISHER:** George Leroy.
- HARPER:** And Carol Newton.
- FISHER:** Newton?
- HARPER:** N-E-W-T-O-N.
- LATHROP:** She went to the west coast someplace, didn't she?
- HARPER:** Yes.
- LATHROP:** A long time ago.
- FISHER:** The Cancer Hospital was involved in, as early as 1953, studies with yttrium-90 to determine whether yttrium-90 might be useful for intracavitary¹⁴⁹ therapy.
- HARPER:** —in rats. You should have had a copy of a paper somewhere that showed the irregular distribution of intraperitoneal¹⁵⁰ colloids. We injected yttrium chloride in saline, at body pH,¹⁵¹ it turns it into hydroxide and distributed in clumps around the peritoneal cavity.
- We also looked at gold[-198] in connection with that study. That did the same thing.
- LATHROP:** I don't think they have the paper, [but] I have a copy of that paper.
- HARPER:** Okay. Well, we have several copies. We can get it for you. Anyway, that's what we did. It got presented at the meeting in Geneva, [Switzerland at the] Peaceful Uses of Atomic Energy [Conference] in 1956.
- FISHER:** What was the extent of your human work with yttrium-90 in the peritoneum?¹⁵²
- HARPER:** Nothing.
- FISHER:** Only [work] in animals?
- HARPER:** Only in animals, rats.

¹⁴⁹ within the cavity of the peritoneum containing the intestines

¹⁵⁰ to the inner side of the peritoneum, a membrane lining the abdominal wall

¹⁵¹ relative value on a scale of acidity and alkalinity, in which 7.0 is regarded as neutral

¹⁵² a membrane lining the abdominal wall

FISHER: What was it that prevented further human application of yttrium-90 intraperitoneally?

HARPER: Lousy localization; it was very irregular. We discovered that the use of ^{32}P in people is just as bad [and] the gold is not very good [(as it failed to localize well in tumors)].

That's why we were led to this project that we're involved in now, because that's the first time we found anything that stayed fairly uniformly distributed in the intraperitoneal [cavity].

FISHER: Did you ever do any sodium-24 studies here at the hospital?

HARPER: No.

FISHER: We came across a publication by Gould, LeRoy, and Okita, on the use of carbon-14-labeled acetate to study cholesterol.¹⁵³

HARPER: They were looking at exhaled—

FISHER: CO [(carbon monoxide)].

HARPER: CO.

FISHER: From cholesterol metabolism?

HARPER: Yes.

FISHER: This work with carbon-14 acetate—

HARPER: We did one study with ^{11}C [(carbon-11)] acetate. It localizes in the heart real nicely. It disappears. (to Lathrop) This you presented in Copenhagen, [Denmark].

LATHROP: Yes.

HARPER: That was the only thing we did with acetate after the dog study that I did when I was a [medical] resident.

FISHER: Do you remember any collaborative studies?

HARPER: I remember using carbon-11.

FISHER: Using carbon-11? Do you recall any collaborative studies with the Los Alamos people on carbon-14-labeled acetate?

HARPER: No, sir.

FISHER: Los Alamos had an interest in carbon-14 acetates injected intravenously.

HARPER: Well, that's what [Bill] Neal and I did. We thought, "We have a world-beater here!" Acetate, you could inject, you could metabolize it into almost anything: [it had] marvelous peripheral alimentation.¹⁵⁴

¹⁵³ R.G. Gould, G.V. LeRoy, G.T. Okita, J.J. Kabara, P. Keegan, and D.M. Bergenstal. "The Use of C^{14} -Labeled Acetate to Study Cholesterol Metabolism in Man." *The Journal of Laboratory and Clinical Medicine*. Vol. 46, No. 3, September 1955, pp. 372-384.

¹⁵⁴ nutritional support by peripheral blood supply

So we tried it [(acetate)] on each other, and it causes—when you inject it into a dog, the dog turns pink, but then he survives perfectly okay.

(laughter)

HARPER: So we tried injecting it into each other, and I was braver than Neal was *(facetiously)*: I injected more of it into him. It causes horrible sensations.

FISHER: For example?

HARPER: Things turn yellow; you feel miserable. This is [with] two or three grams [of acetate].

LATHROP: Are these the chemical effects?

HARPER: Those are the chemical effects of acetate.

FISHER: Of acetate.

HARPER: It would not be a good thing to give for peripheral alimentation.

FISHER: No, no long-term residual effects of this?

HARPER: Oh, no, it's over in a couple of minutes.

FISHER: But it wasn't a pleasant experience?

HARPER: No, it sure wasn't.

FISHER: How did you measure the carbon-14?

HARPER: That wasn't labeled.

FISHER: It wasn't labeled?

HARPER: No, this was after our experiment with dogs, showing it was incorporated into everything, particularly lipids.

FISHER: I see. That was just—

HARPER: So we decided to try it on each other, just as unlabeled acetate.

FISHER: Unlabeled acetate?

HARPER: Yeah.

FISHER: But it's interesting that you would mention this, because that's a good example of a human experiment with a nonradioactive material.

HARPER: Yeah.

FISHER: Which is another thing that is difficult for young scientists to do anymore, and that's conduct any human studies.

HARPER: There was another instance in which human studies should have been done. You're familiar with the strontium-82/rubidium-82 [isotope] generator? The Los Alamos people created one that worked perfectly beautifully in dogs. They would get beautiful, gorgeous pictures of the heart [from the ⁸²Ru images].

But what they eluted it with was strongly buffered ammonium chloride, pH 10 [alkaline]. So we got one of their generators and tried it, and it caused the most awful pain at the site of injection and up the arm from the strongly buffered—

FISHER: Ammonium chloride?

HARPER: Ammonium chloride. So the animal studies were meaningless; it could not be used clinically. I could only stand it for about 30 seconds.

FISHER: Because it was so painful?

HARPER: Yes.

FISHER: Was that due to the hypertonicity¹⁵⁵ of it?

HARPER: Yeah. Well, it was the high pH [(high alkalinity, making the solution caustic)].

FISHER: High pH.

HARPER: So that's another reason for doing things in people, rather than in animals. Before you spend thousands of dollars in an animal project, you ought to try it once on the people, on the investigator himself.

FISHER: There was interesting work on the use of labeled proteins in evaluating multiple myeloma¹⁵⁶ here at the Cancer Hospital.

HARPER: I have no thoughts about that.

FISHER: Using nitrogen-15—[labeled] glycine.

HARPER: Well, that's in the way of getting away from [using] radioactivity.

LATHROP: Who are the authors?

FISHER: Well, it's not easy to determine, but—Hardy and Putnam. Did you know them?

HARPER: No.

FISHER: At the University of Chicago back in early 1950s—Putnam, Meyer, and Miyake.¹⁵⁷

HARPER: No. They escaped us.

FISHER: Working with—would the cyclotron have been the source of the nitrogen-15?

HARPER: That's inert.

FISHER: It's inert? It's a stable isotope?

¹⁵⁵ a condition in which something is lacking in salts equal to those in natural body fluids

¹⁵⁶ a malignancy of bone marrow, marked by abnormal plasma cells; causes fatigue and bone pain and is often fatal

¹⁵⁷ Putnam, F.W., F. Meyer, and A. Miyake. "Proteins in Multiple Myeloma V. Synthesis and Excretion of Bence-Jones Protein." *Semiannual Reports to the U.S. Atomic Energy Commission*. Vol. 1, Parts 1-6, 1954 to 1956. Chicago: Argonne Cancer Research Hospital, pp. 31-37. The University of Chicago, Office of Legal Counsel, Semiannual Reports of the Argonne Cancer Research Hospital.

- HARPER:** Yeah, nitrogen-13 is something else. We had a big project going on that [subject].
- FISHER:** Well, I'm glad you told me that, because I will correct that error. That's stable nitrogen.
- HARPER:** Yeah. Used in the mass spectrometer.¹⁵⁸ There's a fair amount of work going on with carbon-13 and nitrogen-15, doing metabolic studies.
- FISHER:** Well, they also did work with carbon-14-labeled glycine.
- HARPER:** I'm sure.
- FISHER:** It looks like—and compared it to carbon-14, and used L-lysine. All right. Also, here at the hospital, carbon-14-labeled digitoxin was used in some studies [done by] Okita, Plotz, and Davis, do you remember?¹⁵⁹
- HARPER:** (to Lathrop) Do you remember back then?
- FISHER:** Recall any of that work?
- HARPER:** This is out of the Argonne Report. Jake offered to make me Director of the Argonne Cancer Hospital at one point.
- FISHER:** Who did?
- HARPER:** Jacobsen.
- FISHER:** Jacobsen. What was his first name?
- HARPER:** Leon.
- FISHER:** Leon Jacobsen.¹⁶⁰
- LATHROP:** He was the one who was the first director of ACRH.
- HARPER:** He was the [spleen] shielding man. He was a hematologist. He was dean at that point. I said, "I'm sorry, I wasn't interested in other people's research." You have to be, if you're going to direct an operation like that.
- LATHROP:** He was the person who actually got the Argonne Cancer Research started.

¹⁵⁸ a device that uses deflection of ions in an electromagnetic field as a basis for identifying the elements (or elemental components) present in a substance

¹⁵⁹ G.T. Okita, E.J. Plotz, and M.E. Davis. "Placental Transfer of Radioactive Digitoxin in Pregnant Women and its Fetal Distribution." *Semiannual Reports to the U.S. Atomic Energy Commission*. Vol. 1, Parts 1-6, 1954 to 1956. Chicago: Argonne Cancer Research Hospital, pp. 26-30. The University of Chicago, Office of Legal Counsel, Semiannual Reports of the Argonne Cancer Research Hospital.

¹⁶⁰ Leon O. Jacobsen, M.D. (born 1911), specialized in internal medicine. He served as Director of Health, Plutonium Project of the Manhattan Engineer District at the University of Chicago. Jacobsen specialized in hematology, radiation biology, and the effects of chemotherapy and isotopes on leukemia and lymphoma.

Argonne Cancer Research Hospital History (Early '70s)

- YUFFEE:** This might be an aside, but I was curious, in trying to get an idea of the history of the Research Hospital. We know when it started. Then we know, in 1971 it became the Franklin McLean Institute. Is that good?
- HARPER:** That was when DOE [(the U.S. Department of Energy)] took—I mean, Atomic Energy Commission turned into DOE.
- YUFFEE:** Okay, so around '74?
- HARPER:** It was around then that the mission [of ACRH] nominally changed.
- FISHER:** Well, it was ERDA,¹⁶¹ actually.
- HARPER:** ERDA, that's right.
- FISHER:** Energy Research and Development Administration decided—
- HARPER:** I forgot about that, yes.
- FISHER:** —decided not to continue directly funding human therapy at its four hospitals.
- HARPER:** Right.
- FISHER:** One [hospital] of which was Argonne.
- YUFFEE:** Does the Franklin McLean [Institute] still exist under that name?
- HARPER:** Well, it's chiseled in granite on the front of it.
- YUFFEE:** And so it's still—
- HARPER:** It's a geographical term now.
- YUFFEE:** Okay, so it has been included, incorporated, into what general part of the hospital system, now?
- HARPER:** Well, yes; its laboratories.
- YUFFEE:** Oh, I see, so it sort of doesn't exist as its own—
- HARPER:** —not as a hospital. Well, it's—
- YUFFEE:** —geographic.
- HARPER:** The former director thinks it does, but it really doesn't.
- LATHROP:** It's all part of the [University's] Department of Radiology [in the Pritzker School of Medicine] now.
- YUFFEE:** Okay, so now it's included in the Department of Radiology?
- HARPER:** Well, that's only the third—no, Hematology is on the second floor, and other things are on other floors. It's not all Radiology.

¹⁶¹ 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.

YUFFEE: So it just exists now, in a geographic sense, as the Franklin McLean [Institute].

HARPER: That's correct.

YUFFEE: Thank you.

Research on Brain Tumor Imaging Agents

FISHER: Do you remember some work by Tocus, Okita, Evans, and Mullan on the use of iodine-131-labeled fluoroxene as a brain tumor imaging agent?¹⁶²

HARPER: Only very, very vaguely.

FISHER: Did that ever pan out?

HARPER: I don't think so.

LATHROP: No, that predated the brain scanner.

HARPER: Pertechnetate wiped off most of everything in terms of brain scanning agents. [(It was more effective than anything else under study.)]

FISHER: Did it?

HARPER: Yeah. Took a long for Monte Blau—you knew Monte Blau?¹⁶³

FISHER: I didn't know him.

HARPER: He was strongly opposed to the technetium business, because it was "unphysiological." Katherine went and gave a long speech to them.

(laughter)

HARPER: To [our collaborators at Roswell Park Memorial Institute in] Buffalo, [New York,] and convinced them. I presented it at the Nuclear Medicine [Association] meeting in Florida. Monte Blau got up and said, "It's a bad agent, because it doesn't show the tumors, it [only] shows the normal brain."

I said, "Yes, it's a bad agent, but it's the best we've got."

YUFFEE: That's an interesting anecdote.

¹⁶² E.C. Tocus, G.T. Okita, J.P. Evans, and S. Mullan. "The Localization of Octoiodofluorescein-I¹³¹," *Semiannual Reports to the U.S. Atomic Energy Commission*. Vol. 3, Part 101, 1961 and Parts 11-15, 1959 to 1961. Chicago: Argonne Cancer Research Hospital, pp. 104-113. The University of Chicago, Office of Legal Counsel, Semiannual Reports of the Argonne Cancer Research Hospital.

¹⁶³ Monte Blau, Ph.D., professor of Nuclear Medicine and Biophysics, Harvard Medical School. Dr. Blau was active in development of radiopharmaceuticals, counting instrumentation, and magnetic resonance imaging studies.

Collaborative Metabolic Studies

LATHROP: Monte Blau once stated that [you could image anything] with radioactive peanut butter.

(laughter)

HARPER: No, that was the liver and kidneys you could image with radioactive peanut butter; anything goes to the liver and anything goes to the kidneys.

YUFFEE: That's funny.

HARPER: He made that [remark] at the Pittsburgh meeting [of the Society of Nuclear Medicine].

FISHER: You mentioned Leif Sorensen. He did a study in 1960 here at the hospital using strontium-85 chloride—

HARPER: No recollection.

FISHER: —administered to seven adult subjects.

LATHROP: For what purpose?

FISHER: To study the metabolism of strontium and calcium.

HARPER: Good heavens.

FISHER: [They] also did some work with calcium-47 together in that study, which you probably weren't aware of that or familiar with.

LATHROP: Strontium is actually where I got started; back in the Manhattan [Project, Metallurgical] Laboratory days, we were doing strontium studies in animals.

But in the course of reading through the literature, I found that there were two people, investigators in England, who had given themselves doses of strontium and then recovered their excreta and analyzed it. So, this is a way of doing things without being radioactive, but it's a lot easier [to study metabolism] if it's radioactive.

FISHER: Absolutely.

HARPER: You left out a couple of big areas [of our research]; are you still planning to come back to them?

FISHER: I don't want to leave anything out, and I would like you to, if you can think of something right now that we haven't discussed, go ahead and bring it up.

HARPER: Well, [our research with] nitrogen-13.

YUFFEE: We actually did have that on the list, the last [question] on the list here.

HARPER: Oh. I [was a] consultant to the people at Sloan Kettering,¹⁶⁴ who have a little [research-size] cyclotron like ours. We were interested in nitrogen-

¹⁶⁴ Memorial Sloan-Kettering Cancer Center (New York, New York); formerly known as Memorial Hospital

13 because we found that we could make, by bombarding methane [to produce] rather impure ammonia, nitrogen-13 ammonia.

The people at St. Louis had been looking at nitrogen-13 ammonia, and they found it went in the liver and brain, but they completely missed the fact that it also goes to the heart. So we started a series of studies of the heart, got the cardiologists interested in this.

And then the people at Sloan Kettering discovered that a much better way to make the nitrogen-13 ammonia was to bombard water protons¹⁶⁵ and get a (p, α) reaction¹⁶⁶ on oxygen. It made nitrate, which could then be reduced to ammonia very easily.

We used this extensively on several hundred patients, collaborating with the cardiologists, looking at fresh infarcts,¹⁶⁷ old infarcts, people with angina, unstable angina, and so forth, doing the sort of studies that one would do with thallium, only with a ten-minute half-life.

So we would make the stuff and run it across the hospital, image the patients; it worked beautifully.

FISHER: By imaging the photon, the 0.511[-MeV] photons.

HARPER: Yes. In order to do this, we had to develop a special collimator¹⁶⁸ for the camera, which we made out of tungsten. The high-energy camera resolution is sufficiently good that it showed the individual holes in the collimator; so we developed a collimator that was a little bit off-center and rotated [while imaging and] that eliminated the hole pattern without hurting the image.

FISHER: Were normal subjects used for some of these nitrogen-13 studies?

HARPER: Only us.

FISHER: Only Dr. Harper and Mrs. Lathrop?

LATHROP: These were the ones we mentioned earlier, about the heart scans.

FISHER: Okay.

YUFFEE: Oh, where they found the lesion?

LATHROP: Yes.

HARPER: The people at UCLA¹⁶⁹ really latched onto this. They've been using it vigorously.

¹⁶⁵ elementary particles in the nucleus of all atoms, carrying a positive charge

¹⁶⁶ a proton-alpha reaction: an isotope is bombarded by a proton in a cyclotron to generate a different radionuclide, i.e., ¹³N from ¹⁶O, with alpha particles as byproducts of the reaction

¹⁶⁷ an area of dead or dying tissues from obstruction of blood vessels supplying the tissue (of the heart muscle)

¹⁶⁸ a device for aligning a beam in a narrow column so that it does not diverge

¹⁶⁹ University of California at Los Angeles, Department of Nuclear Medicine

FISHER: For their PET¹⁷⁰ imaging?

HARPER: Yes.

FISHER: Yes, that's true; they're some of the world leaders in this field.

HARPER: That's right. I think we started it, but they picked up on it, and they had much better equipment for doing it.

FISHER: Well, they're taking advantage of the dual detector system [for positron emission tomography (PET)].

HARPER: Yeah. That's right.

FISHER: In coincidence [(simultaneous detection of both photons from a single decay event)]?

HARPER: Correct.

Selenium Tumor-Imaging Studies (Early '70s)

YUFFEE: I don't think we've talked about metabolism studies with the selenium.

HARPER: Selenium?

FISHER: We will come to selenium.

HARPER: Okay.

I don't think we told the anecdote about how we failed to do the brain scans. This is back in the days when pertechnetate was the new wonderful thyroid imaging agent, and we were working on that. We had a patient who was supposed to have a carcinoma of the thyroid with a brain metastases.

FISHER: What year would this have been about? Do you remember?

HARPER: Well, before we did any brain scanning.

LATHROP: It would have been—

HARPER: It was before the Montreal meeting of the Society [of Nuclear Medicine].

FISHER: Okay.

HARPER: So we did a brain scan on him to see if we could see this carcinoma of the thyroid, [but] no sign of the carcinoma of the thyroid, just what you would expect to see in a normal brain scan. We looked at the brain scan and said, "This doesn't look like a brain scan," and abandoned the whole idea of brain scanning.

(laughter)

¹⁷⁰ 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

LATHROP: Until you looked at—

HARPER: —until we ran across Gottschalk's study with gallium-68 at Montreal.

LATHROP: And then you went back and got out the scan.

HARPER: Yeah, I know, [and] we've been showing it ever since; that was a couple of years there.¹⁷¹

FISHER: Was this ever written up?

LATHROP: No. It just never—

HARPER: No, [but] it has been presented on occasion. [On a trip to Rome, Italy, I sat next to Jim Richards,] and I didn't hear him talking about technetium. [At the time, I was pursuing ¹²⁵I.]

FISHER: Some of the best ideas, Paul, are those that we learn from others and then apply ourselves in some other way.

HARPER: Yeah, it needs to be triggered properly. We decided that the UCLA people had grabbed that and leaped on with it.

YUFFEE: I don't think we finished [talking] about selenium.

FISHER: We're going to go on to selenium-75.

HARPER: *(to Lathrop)* Okay, selenium, that's your department, Katherine.

LATHROP: What do you want to know about selenium?

FISHER: Well, first of all, what were the events—

HARPER: Mrs. Lathrop spent some years in the Poisonous Plant Laboratory¹⁷² at Laramie, [Wyoming] and that's where the selenium story started.

FISHER: Okay, that's where we should begin, then.

(laughter)

LATHROP: Well, I'm not really sure about that. You want to know how selenium got started; is that it?

FISHER: Yes, tell us the selenium story.¹⁷³

¹⁷¹ The significance of this anecdote is that Harper and Lathrop had previously made an important discovery in the science and art of brain imaging without realizing it at first.

¹⁷² The Poisonous Plant Laboratory is part of the University of Wyoming.

¹⁷³ During the early 1970s, investigators at six institutions conducted collaborative studies on the pharmacokinetics of selenium-75 (⁷⁵Se)-L-selenomethionine as a new radiopharmaceutical for imaging the pancreas in nuclear medicine diagnostic exams. A total of 40 subjects, comprising 30 patients with various diseases and 10 normal comparison subjects, participated. Each subject received a single intravenous injection of about 250 microcuries of ⁷⁵Se. Retained activity in the body was measured by whole-body counting of 24 subjects at four institutions over a period ranging from 3 up to 923 days. Selenium-75 concentrations were later measured in tissues obtained at autopsy from a total of 23 subjects at four of the institutions. For a more detailed summary, see UC-42, "Pharmacokinetics of Selenium-75-L-Selenomethionine" in *Human Radiation Experiments Associated with the U.S. Department of Energy and Its Predecessors* (213 pages), DOE/EH-0491, July 1995.

- LATHROP:** All right. From my viewpoint, as far as nuclear medicine is concerned, it got started with Monte Blau.
- FISHER:** B-L-A-U?
- HARPER:** Right.
- LATHROP:** That's right.
- HARPER:** He's one of the people you should be interviewing.
- LATHROP:** Yes.
- HARPER:** He's a pioneer.
- LATHROP:** Because he was looking for something that would localize in the pancreas, and the amino acids¹⁷⁴ have a way of doing this, and he [also] wanted something radioactive. Sulfur does not have a radioactive isotope that was suitable, so he happened onto selenium-75; it worked reasonably well for those times.
- HARPER:** Well, it [(the form)] was as selenomethionine.
- LATHROP:** —yeah, as selenomethionine. He labeled the methionine with selenium in place of the sulfur.
- HARPER:** With the help of yeast.
- LATHROP:** Yes.
- HARPER:** It was a biological labeling[, a natural labeling process rather than one devised by man].
- LATHROP:** Now, I guess this was about the time that the [MIRD] committee was working up to doing dose estimate reports, because, as you know, all the early publications were absorbed fractions of this, that, and the other thing that actually went into—
- HARPER:** Yeah. The selenium, of course, has a 50-day half-life—or it's a 120-day half-life [(biological half-time for excretion)].
- FISHER:** About 120 [days].
- HARPER:** One hundred and twenty. And in the study where you use selenium, you look at it 45 minutes after injection. So this is a little disproportionate [compared to the time selenium takes to clear the body].
- LATHROP:** We had access to the whole-body counter that we talked about this morning, so we decided that we would try to do a study. We did some animal studies and we decided that we would try to do a study [on] Mr. Fields. [That was your patient, wasn't it?]
- HARPER:** No, I don't know whose patient he was, but he ended up being yours.
(laughter)

¹⁷⁴ any of a class of organic compounds that are the building blocks from which proteins are constructed

LATHROP: No, not really, only [for] the study. He was a very, very nice, dignified black man, and we talked to him about what we were doing and the reason we were doing it [(to understand its metabolism rate {retention, distribution, clearance, etc.})].

HARPER: Well, he had the selenium scan [as a routine clinical study].

LATHROP: Yes.

HARPER: [We administered] 200 microcuries of selenomethionine [(⁷⁵Se) to him].

LATHROP: And it [(the selenium scan)] was just a matter of our making use of the selenium that he had; we didn't give it to him just for our purposes. As Paul said, it was for clinical use.

But he came back. First it was day after day, I guess, and then it got to be intervals of weeks, and, finally, a month or so apart. And this went on for almost three years and we were still able to get valid [radioactivity] counts.

We had some problems when we started out [with this research], because of the [low count rate] recovery [of selenium] that we were getting. We found that this was due to the placement of the detectors; that was useful, we [then] wanted to design a better-type instrument.

Paul said something about the Poisonous Plant Laboratory. When I was living in Wyoming, I worked for the Poisonous Plant Laboratory.

In the West, selenium was a big problem, because a herd of cattle would go through a pasture, and maybe half of them would die before they got to the other side of it because of the selenium[, natural in the soil,] that was concentrated in the plants that the animals ate. So I had that interest in selenium too, which made it more interesting to me to do this study on a human. And that is the data, part of which made up the dose estimate report for selenomethionine [(data from the patient study mentioned above)].¹⁷⁵

The other was short-term data that we fed the information that I got from the other contributors to the data.¹⁷⁶

FISHER: How is it [(selenium)] evaluated in humans?

HARPER: Imaging.

LATHROP: Well, no. I think he means if we did—were images made and looked at, or what kind of data of that sort?

HARPER: The only [numerical] data we got out of it was the whole-body count.

¹⁷⁵ "Summary of Current Radiation Dose Estimates to Humans from Se75-L-Selenomethionine." *MIRD/Dose Estimate Report No. 1*. January 1973.

¹⁷⁶ The biological data obtained in these studies were combined for analysis to determine the radiation absorbed dose to the total body and to individual organs from Se75-L-selenomethionine. The information was needed in assessing the usefulness of Se75-L-selenomethionine as a tumor imaging agent. See K.A. Lathrop, R.E. Johnston, M. Blau, and E.O. Rothschild. "Radiation Dose to Humans from Se75-L-Selenomethionine." *Journal of Nuclear Medicine*. Suppl. No. 6, 1972, pp. 10-17.

- LATHROP:** That's all we got out, but what about the people that were doing it clinically?
- HARPER:** Oh, they just looked at pictures.
- FISHER:** So the pictures weren't really used for—
- HARPER:** Quantitation.¹⁷⁷
- FISHER:** Quantitation and liver uptake.
- HARPER:** No.
- FISHER:** Fractional retention, retention half-times?
- HARPER:** No.
- LATHROP:** No, in those days, people were so happy to get an image; that was really all they cared about.
- HARPER:** Now, it's pretty close to the same today.
(laughter)
- LATHROP:** Well, okay, yes, to some extent, because there are an awful lot of things that could be done with nuclear medicine besides making images, [namely studying the biokinetics, pharmaco-dynamics, metabolism, etc., and natural physiological processes in the body. And] they are not being done.
- FISHER:** Did the long half-life of selenium-75 [(127 days)] preclude its use for most studies?
- LATHROP:** No.
- HARPER:** No, the dosimetry [(dose to the patient)] is the limiting factor, and that was okay.
- FISHER:** Is it?
- HARPER:** It doesn't have any primary particle radiation, which helps.
- FISHER:** That's interesting, but it does persist in the human for a long time.
- HARPER:** Oh, yes, it's an essential metabolite; cattle get white muscle disease if they don't have selenium.
- LATHROP:** There's a disease called kwashiorkor; it's a disease where children become very, very thin, and [can] die [from selenium deficiency].
- FISHER:** *(leafing through background materials he had brought to the interview)*
I was going to see if I could find that—here it is: the selenium dose report.
- HARPER:** Yeah, you can see the disappearance curve [(the curve plotting selenium retention over time)] published in there somewhere.
- FISHER:** [Determined by] whole-body counting.
- HARPER:** Yes.

¹⁷⁷ determination of the quantity of something, especially with precision

FISHER: That's interesting.

LATHROP: We also did excreta collections on that one [(selenium-75)] too, in the early part of the [study].

FISHER: Is this a compound that's used very much anymore?

LATHROP: No, not for some years.

HARPER: Oh, no, it has been abandoned long ago. This brings us to a whole new question about, how do you deal with the pancreas?

FISHER: Yes.

HARPER: Because of this interest in the pancreas, we had a major interest in looking at possible agents.

As Mrs. Lathrop mentioned, the amino acids go to the pancreas. We worked up a number of amino acids with carbon-11 and put them in mice, [and] every single amino acid we made went to the pancreas in the mouse.

Then we formed a [collaboration] with one of our surgeons here who was enthusiastic [and] was willing to tackle carcinoma of the pancreas by excision [(surgical removal by cutting out)], which is something that has been pretty-well abandoned, [yet] he was still enthusiastic about it.

So, in the course of this, we collected maybe 100 patients that he allowed us to image, and we used various different amino acids we [had] synthesized with carbon-11 in the carboxyl position. The one that worked best we [studied] in one patient. We went through the business of separating out the optical isomers using a column [(to use a pure preparation of the designed amino acid)].

FISHER: *(smiling)* The one patient being Katherine Lathrop.

HARPER: *(smiling)* Yes.

FISHER: Why was she different than the others?

HARPER: *(smiling)* She was available. So we [used] D-tryptophan, L-tryptophan, and D-L-tryptophan [(various amino acids)].

LATHROP: There was something that I particularly wanted to do—

HARPER: And the localization with D and L is markedly different. [D-form] goes a lot to the liver, a lot to the kidneys; the L-form goes to the pancreas and not to the kidneys and not to the liver. And so, this turned out to be the ideal imaging agent.

Well, it turned out that pancreas imaging had moved ahead so that CT [(computerized tomography)]¹⁷⁸ studies and MRI ¹⁷⁹ studies and ultrasound¹⁸⁰ studies [had replaced] nuclear studies.

LATHROP: If you're looking for a mass—

FISHER: —in the pancreas.

LATHROP: Yes. But if you're looking for physiologic function, nobody is interested.

HARPER: Nobody was interested in looking at physiologic function in the pancreas so that [research] died; but it *was* interesting.

LATHROP: But it's still out there. Maybe some day, somebody will [continue the research].

FISHER: You know, but this whole story of investigating selenium, selenomethionine, is very interesting.

(reading from a reference book) I see how we spell kwashiorkor: K-W-A-S-H-I-O-R-K-O-R, "a protein malnutrition disease of animals."

LATHROP: —and people.

FISHER: Oh, I'm sorry—"and children." All right.

HARPER: Okay.

Other Isotope Research

FISHER: What are some of the other interesting isotopes that you've worked on that you haven't mentioned?

HARPER: Indium.

FISHER: Indium-111?

HARPER: No, indium-113m.

FISHER: -113m?

HARPER: It's short-lived—[(It has a short half-life.)]

LATHROP: Shall we tell him the story about that?

HARPER: We're about to.

LATHROP: Okay, well, go ahead.

¹⁷⁸ high-resolution imaging by rotating a fine x-ray beam around a patient and using computer analysis to reconstruct the image

¹⁷⁹ magnetic resonance imaging (a process of producing images of the body regardless of the presence of bone by means of a strong magnetic field and low-energy radio waves)

¹⁸⁰ the practice of reflecting ultrasonic waves off interior body structures to produce a visual image, or sonogram, for diagnostics

HARPER: Indium-113m, this was Henry Wagner's favorite isotope; it's the daughter of a tin [isotope].

LATHROP: Tell them how he started using it.

HARPER: I don't know how he started using it.

LATHROP: Well, Dr. Harper mentioned [the surgical resident] George Andros earlier, who worked with us on technetium. George's wife was an artist, [and] George was sort of impressed by all these radionuclides that we would have, so his wife made up a poster that said, "Isotope of the Week," and she would have [on] it whatever [isotope] we happened to be working [with]. [So], she made up a poster that indium was the isotope of the week. Henry Wagner's chemist came by for a visit, I forget his name right now, and he saw this [poster] on the wall, but he didn't say very much about it. But it wasn't too long until Henry Wagner was working on indium [and] he was making quite a big thing of it; it was going pretty well.

(to Harper) Now, do you want to tell him the part about the comparison paper?

HARPER: Yes.

LATHROP: Okay.

HARPER: Well, there were three short-lived isotopes with long-lived parents that were possible to make into generators [for] general use; indium-113m was one of them. Somebody finally figured out how to put it on a [chemical-separation] column so that the tin stayed and the indium came through.

Gallium-68 was another one, with germanium as the parent; then there was technetium[, but] there was some question which would be the best one to use, other things being equal.

So we made up a bunch of phantoms,¹⁸¹ imaged them with these different isotopes using [the] appropriate methods. [Then, we] calculated the radiation dose and the figure of merit being the statistical probability of detecting the material in a lesion like this and a background like this.

The figure of merit, divided by the dose, gave you a figure for comparing the various agents; indium didn't do very well, and Henry Wagner never forgave us [for letting our poster lead him to think indium-113m help special promise].

(laughter)

FISHER: I was wondering what the attraction was with indium-113m.

HARPER: It's a short-lived isotope.

FISHER: It has a 97-minute half-life.

¹⁸¹ material that serves as a surrogate for a human being during calibration of radiological counters

HARPER: Yeah, well, that's okay. It also has a huge amount of conversion electrons.

FISHER: Right.

HARPER: But it [(indium-113m)] was used very widely: commercial generators were peddled, and it had a long half-life parent, so it could be used for a long time.

FISHER: That's right.

HARPER: So it was a useful agent, but the [photon] energy was pretty high, so it was hard to image well.

FISHER: About 392 keV [thousand electron-volts]?

HARPER: That's right, and it's difficult to image anything that way [with] commercially available collimators.

FISHER: Did you do work with [the] indium-111 I mentioned that just a little bit earlier?

LATHROP: We did some work with indium-111, some placental studies with it.

HARPER: Yeah, Mrs. Lathrop was unable to sell the hard-nosed gynecologists on the specific localization in the placenta of indium.

LATHROP: Early on in the use of indium, somebody said that it was just blood pools that they were seeing [in radiological images] when indium was in the placenta, but it really isn't: it actually localizes there.

FISHER: In embryonic tissues?

HARPER: In the placenta.

LATHROP: In the placenta itself.

FISHER: In the placenta itself?

LATHROP: Yes.

FISHER: Why is that? I don't know the mechanism for that.

LATHROP: I don't know why.

HARPER: It was an observation.

FISHER: But it's clearly the placenta?

HARPER: Yes.

LATHROP: Oh, yeah, we did lots of animal studies [that involved] taking out the placenta.

HARPER: [In] guinea pigs, you could see half a dozen little placentas in the pregnant [animal].

LATHROP: I have a nice slide of that someplace.

HARPER: But the gynecologists never bought it—they started using ultrasound instead.

- LATHROP:** In a way, it's too bad, because there again, it shows the physiology that the [ultrasound] images won't show.
- HARPER:** Yes, we had this monkey with a sick placenta [on which] we demonstrated [the problem] before we took it out.
- FISHER:** Now *that's* interesting.
- HARPER:** I don't know if we worked with anything else diagnostically.
- FISHER:** Well, I'm going over—you've worked with so many different isotopes.
- HARPER:** Which ones have we dropped through the cracks?
- FISHER:** It's hard to know which ones we haven't really covered. I would like to just ask another question about cesium-131—
- HARPER:** Oh, yes.
- FISHER:** —and wonder if you could say a few more [words] about that.
- HARPER:** Oh, cesium-131, that dates back to when we were redoing implants,¹⁸² and it was a nice agent to fit into an implant, because it has low-energy emissions—pure electron catheter.
- FISHER:** I read the paper on that.
- HARPER:** We also had a go at cesium-130 [when] we were trying to look at the heart. Cesium localization in the heart is slow, [because] it's not first-pass localization, the way many of the agents are. [It localizes in the heart muscle, which is viable.]
- FISHER:** What was the chemical form of the cesium?
- HARPER:** Ionic; it's a potassium analog. [It behaves in the same way as potassium.]
- FISHER:** I was wondering if you didn't have a lot of background [mass to serve as contrast] from normal muscle.
- HARPER:** There isn't much normal muscle in the chest wall.
- LATHROP:** There was an interesting story about the cesium, no fall in the production of it. *(to Harper)* You remember the discrepancy on the isotope tables?
- (Harper chuckles.)*
- FISHER:** *(to Harper)* That brings a chuckle from you.
- HARPER:** Yeah, [because] the Segrè¹⁸³ chart had a cross-section value for cesium and—for barium-131, but the [precursor]—the thermal neutron capture

¹⁸² The implants were used for brachytherapy, use of devices into which isotopes are inserted for cancer therapy.

¹⁸³ At Los Alamos Scientific Laboratory in early 1944, Emilio Segrè had developed Little Boy, a lighter, smaller version of a uranium bomb that used a plutonium gun design. Little Boy was dropped, untested, at Hiroshima on August 6, 1945.

cross-section was such and such, and it turned out it [(the chart's prediction)] was quite wrong, and we were able to demonstrate it.

LATHROP: He started working on it, and then he decided he would go out to ANL and talk to the people out there.

HARPER: Yeah, they looked at the Segrè chart and looked at me pityingly and said, "You don't really want to do this, do you?" But the Oak Ridge isotope catalog had the correct cross-section.

FISHER: You know, I don't think this interview would be complete unless we discussed alpha emitters and your interest in alpha emitters as a therapeutic—

HARPER: Well, these are the last couple of months [that we have been doing that research].

FISHER: Well, what is your age?

HARPER: How old am I? Close to 80.

FISHER: Close to 80 and still branching into new research. I think that's remarkable.

Alpha emitters are particularly effective in cell killing, so they offer something that beta emitters don't.

HARPER: Right, well, we talked a little bit about auger emitters; I got into those first.

FISHER: But not so much on this order, this was during our lunch.

HARPER: Okay, it's not on the auger emitters?

LATHROP: The alpha emitters, that's where you're interested in, isn't it?

FISHER: Well, we're interested in both.

HARPER: Okay.

FISHER: Let's start with auger emitters, then. What auger emitters have you worked with, other than iodine-125?

HARPER: 123.

FISHER: Iodine-123?

HARPER: That's because it's available, and you can use it, although it's pretty expensive. We've [also] been trying to make bromine-80m. Arnie Friedman thought [this] up. Arnie was not as fussy about [the hazards of] his isotopes as we were; he didn't object to the fact that the 4-hour bromine-80m had a 17-minute daughter, bromine-80, which had strong beta and gamma emissions.

So we decided to go ahead with that and ignore the daughter. We thought possibly, that if the bromine-80m were attached to an estrogen and got into a cell, disintegrated, that probably the excitation would [have] an

effect sort of like the [Szilard–Chalmers] reaction:¹⁸⁴ It would release the daughter bromine so it would go out and circulate around the body, and be vastly diluted, and probably wouldn't cause too much trouble.

Dr. DeSombre in the Ben-May Laboratory has been pursuing this to some extent, along with Jeff Schwartz. They've been able to demonstrate clearly that bromine-80m, when it's incorporated into the DNA¹⁸⁵ molecule as BUdR¹⁸⁶ is vastly destructive to the [DNA and] produces lots of chromosome breaks.

FISHER: It has a high LET?¹⁸⁷

HARPER: Of course.

FISHER: At the short-range?

HARPER: That's right, it's similar to the heavy-charge particle with just a very short range. DeSombre has also shown—I think he used ¹²³I for this, or the estrogen ¹²⁵I—when it's localized in the estrogen receptor, which is in the cell adjacent to the DNA, [it] will also cause significant cell killing.

FISHER: Now, the obvious applications for this would be—

HARPER: —well, tumors that carry estrogen receptors.

FISHER: Ovarian?

HARPER: —ovarian, breast.

FISHER: Cervical?

HARPER: Not cervical, [but] endometrial¹⁸⁸ [tumors are another application].

FISHER: I see, endometrial.

HARPER: And I think, vaginal, [but] I'm not sure about that. And then there are, of course, prostate [tumors, whose treatment] might work with androgen. These are things that are being thought about.

FISHER: Have any of these studies advanced to the clinical stage?

HARPER: No, no, this is still all at mouse and cell level.

FISHER: But it sounds very productive for the future.

¹⁸⁴ The reaction was used for making high-specific-activity material in a nuclear reactor: With organic arsenic in neutron flux, the activated isotopes are excited and move from organic binding to an inorganic phase for separation as high-specific-activity isotope.

¹⁸⁵ deoxyribonucleic acid—a type of nucleic acid, particularly found in cell nuclei, that is the basis for heredity in many organisms. DNA molecules are constructed of a double helix held together by hydrogen bonds.

¹⁸⁶ 5-bromodeoxyuride, an analog of the DNA base thymide. BUdR is a halogenated pyrimidine; it is used as a radiation sensitizer, to make cancer cells more sensitive to radiation.

¹⁸⁷ linear energy transfer: as measured along a charged particle track, the relative specific ionization per unit track length in units of KeV/micrometer

¹⁸⁸ endometrial—of the endometrium, the inner lining of the uterus

Alpha Emitter Studies Using Radioactive Isotopes

HARPER: Yeah. Well, it's sort of in parallel to the alpha emitter studies.

FISHER: Which I would like you to talk about a little bit now.

HARPER: Atcher¹⁸⁹ was running this.

FISHER: Robert Atcher.

HARPER: And the gynecologists, mostly Jacob Rotmensch.¹⁹⁰

FISHER: Rotmensch?

HARPER: This group was working at Argonne for eight or ten years, I think and were hopefully bringing it to clinical use. I got into the act when they were doing biodistribution studies here. They hadn't done them out at Argonne; they did the toxicity studies.

[They were working with the thorium-228, radium-228, lead-212, and bismuth-212 in dogs.]

FISHER: Dogs.

HARPER: And what turned up was a vastly irregular localization of their [agent in the peritoneal] cavity, such as one I showed you in the rats.

FISHER: With iodine-131? Yttrium-90; I'm sorry.

HARPER: No, the ones that I showed there are yttrium-90 and gold.

FISHER: Gold-198.

HARPER: We looked at the ³²P localization as chromic phosphate. There are some publications in the literature showing images that are, again, vastly irregular.

That, plus the fact that our technologist came to me and said, "Gee, this sample that's supposed to have a 10-hour half-life is"—this was lead-203 and -212—"is still hot [(radiologically active)] after several months! What will I do with it?"

So he went back to the chemists at Argonne who [had] made the generator, and it became obvious that what we were dealing with was thorium.

And we calculated [that] a microcurie of thorium, had approximately the same energy emission over its decay period as 10 millicuries of the lead-212, due mostly to the half-life difference. That didn't seem like a good thing to put in people.

¹⁸⁹ Robert Atcher, Ph.D., a radiochemist (born 1951) currently working at the University of South Alabama at Birmingham; formerly at the University of Chicago, Argonne National Laboratory, and National Cancer Institute (Bethesda, Maryland). Atcher conducted research on the production of short-lived isotopes for medical applications, the development of radiopharmaceuticals using radioactive metals, and the radiobiology of therapeutic radionuclides.

¹⁹⁰ Jacob Rotmensch, M.D., a professor at the University of Chicago and clinician with an interest in ovarian carcinoma

The people in Argonne came up with an answer to this [problem]. Using the Spec resin, which binds strongly to lead, made it possible to milk the radium generator that made the lead. Then, after the lead came off and went through the column, the lead was fixed and the impurity traces could be washed off successfully. [Finally,] the bismuth daughter could be removed from the lead, or, if you wanted to, you could strip the lead off the column with ammonium carbonate, and use it in that form. We haven't done that.

FISHER: Bismuth-212 has a short half-life?

HARPER: One hour.

FISHER: That makes it difficult to work with in some applications.

HARPER: Well, we took that into consideration as a possible advantage. We didn't know whether the bismuth would form clumps or not, but we thought that, possibly, it took a while for the clumps to form if you put it in the peritoneal cavity. That short-half-life material would float around more-or-less uniformly; and if clumps formed later on, it wouldn't matter, because the radioactivity would be gone.

FISHER: Perhaps for that application it's ideal.

HARPER: That's what we thought might be the case.

FISHER: If you can get it into the cells or in close proximity to cells that you want to irradiate—

HARPER: Well, we tried this in animals, in rabbits, putting in ionic bismuth, not colloidal material, and 80 to 90 percent [of] it had apparently stayed in the peritoneal cavity in the two-hour period during which most of [the radiation dose] takes place.

We were able to recover [injected activity] by washing out the peritoneal cavity, measuring the activity which was still [present] there.

So it looked as though it would be the ideal agent for killing cells floating around in the peritoneal fluid or just sitting on the peritoneal surfaces. This, of course, we will have to confirm [later].

Some studies had been done out at Argonne by Rotmensch some years ago, using bismuth to kill tumor cells in mice. He was able, without killing the mice, to get some permanent survivors, so there is reason to suspect that this will be efficacious.

FISHER: Roger Maeklis,¹⁹¹ when he was at Harvard, also did something like this with tumor mice and found effective irradiation of those tumors.

HARPER: With what?

FISHER: With bismuth-212.

¹⁹¹ Roger Maeklis, M.D., a cancer specialist, is currently director of Radiation Oncology at the Cleveland Clinic Foundation, Cleveland, Ohio.

HARPER: He did?

FISHER: I think. Or was it astatine-211?¹⁹²

HARPER: I think it was astatine.¹⁹³

FISHER: It must have been.

HARPER: Astatine is the ideal agent, but it's too hard to get hold of.

FISHER: It must have been astatine-211.

HARPER: I think it was astatine. That was done at the Brigham [and Women's Hospital, Boston]?

FISHER: Yes.

HARPER: Yeah, I think they were working on that there.

FISHER: I think he had that flown over from England on the Concorde [(supersonic jet airliner)].

HARPER: Might be. Twelve-hour half-life on that [(astatine-211)].

FISHER: Seven hours.

HARPER: Seven hours, you're right.

FISHER: You're close.

HARPER: Not that close.

FISHER: That's really interesting. But, as far as you know, the bismuth-212 hasn't been used in any humans so far in this country?

HARPER: I don't think so.

FISHER: I think astatine-211 has been used in England.

HARPER: It may well have been.

FISHER: On one or two humans.

HARPER: Well, that's hard to make; you have to bombard bismuth with just the right energy, or you get a lot of polonium.

Yeah, well, [about] 27 MeV.¹⁹⁴

FISHER: Something like that.

HARPER: One of the things that impresses me about this account of what our accomplishments is the fact of how frequently we're presented with a problem, and it isn't for a long interval, maybe years, before, suddenly, the solution leaps out.

¹⁹² Note: It was actually bismuth-212, not astatine-211.

¹⁹³ a heavy, rare element of the halogen family

¹⁹⁴ million electron-volts

Difficulties Involved With Using Human Volunteers

- FISHER:** What have you found to be the most difficult aspect of working with radioactive materials in human subjects; first of all normal human subjects and then, patients with cancer?
- HARPER:** No real problems, short of the regulations, which we didn't have to face at first.
- FISHER:** Did you develop your own techniques for radiation protection and handling of isotopes [and] waste disposal?
- HARPER:** No, we did what was conventional at the time.
- LATHROP:** Well, to some extent, we did develop techniques.
- HARPER:** We made one horrible mistake once: we disposed of our excess radioiodine into a big carboy [(plastic jug)] under the hood, overlooking the fact that it was full of acid.
- FISHER:** And it vaporized.
- HARPER:** And, after a while, anything we touched—
- LATHROP:** After a while, it [(the evaporated acid)] was a big [radioactive] background that kept bothering when we were counting.
- HARPER:** Yeah. Anything you touched came up hot.
- FISHER:** [The acid] volatilized the iodine.
- HARPER:** Right. Well, that's the sort of mistake you shouldn't make, but there wasn't anybody around to point it out to us at the time.
- LATHROP:** But at least we were—
- HARPER:** —we recognized it when it happened.
- LATHROP:** Yes.
- FISHER:** Did you go to the next step and do any thyroid counting¹⁹⁵ on yourselves to see if you had iodine uptakes?
- HARPER:** No.
- LATHROP:** We were pretty sure we did have some, but it wasn't [a large amount.]
- HARPER:** We were aware that it takes 100 millicuries to ablate¹⁹⁶ a thyroid, and we weren't anywhere near that.
- FISHER:** That's true.

¹⁹⁵ counting the rate of radiation emissions from radionuclides inside the thyroid, using radiation detection instruments

¹⁹⁶ to remove or destroy by radiation

LATHROP: Rather early in my career in working with radioactivity, I developed a thyroid nodule,¹⁹⁷ and the physician wanted to [do a thyroid scan]; [it turned out that] it had nothing to do with my working with radioactivity. I come from a family that has thyroid disease. My grandmother had a beautiful, great big tumor down here (*points to her neck*) on her thyroid; at one time, this was thought to be [a tumor.]

HARPER: You've got the Oak Ridge paper, with the figures in it [of this]?

LATHROP: At one time, this protuberance in the neck was thought to be a sign of beauty, that was back, several centuries ago. But anyway, I developed a thyroid tumor—

HARPER: —upper right-hand corner.

LATHROP: This was discovered on a routine health examination at the Argonne National Laboratory, and they urged me to see a physician. I did, and the first thing they wanted to do was to give me [a thyroid scan using ¹³¹I].

HARPER: A millicurie?

LATHROP: Oh, a millicurie of ¹³¹I, for a scan?

(*laughter*)

LATHROP: This seemed to me like it was something that I really didn't want to do; so, anyway, the nodule was removed. Another thing—

FISHER: Was it removed surgically?

LATHROP: Yes.

FISHER: Rather than with iodine-131?

HARPER: It was a "cold" nodule [(not actively producing hormone)].

FISHER: A cold nodule?

LATHROP: Yes. [So it wouldn't have taken up activity.] But also, in addition to that—talking about the use of radioactivity—when I first came to Chicago, my two oldest children, the only ones we had at that time, were four and six years old, I think, something like that.

We had been, as I told you, living in Wyoming. We came to Chicago, where there were all sorts of diseases that we hadn't been exposed to, and all of us were having frequent respiratory diseases. The doctor that was seeing the children wanted to give them radiation, and I had learned enough by that time that I was a little scared about this.

I consulted Dr. Lisco, who was an M.D., in the Biology Division. He said "No," he thought it would be better not [to do it]. And I've never regretted that we didn't have it done.

FISHER: It sounds like—

¹⁹⁷ a small, rounded mass or lump

HARPER: I have an experience, an anecdote about that. I was on a panel once; we were discussing this sort of thing, and I brought up the question of radiation of the neck leading to thyroid disease, thyroid carcinoma.

The [person] sitting next to me was a therapist, and he jumped up and said, "This is absolutely ridiculous! There is not a possibility! We do this all the time!" Six months later, his son turned up with carcinoma of the thyroid [following x ray to the neck.]

FISHER: His own son?

HARPER: His own son, whom he had treated.

YUFFEE: Tough way to learn your lesson.

FISHER: It sounds like each of you have, although you've worked extensively with isotopes, tracers, [and] radioactive materials, that you've developed a cautious respect for the hazards associated with radiation, and you've treated these with some care to protect not only yourselves, but others, from radiation, unnecessary exposures to radiation.

HARPER: But we're not paranoid.

FISHER: Not paranoid to work with them.

HARPER: No.

FISHER: And not paranoid to use them—

HARPER: —to accept modest amounts of radiation.

FISHER: —where they can be used as tools for diagnosis of disease—

HARPER: Right.

FISHER: —for therapy of otherwise untreatable cancer and other applications. I was impressed with both of you and your scientific curiosity and your willingness to explore new options for solving problems in medicine using isotopes.

HARPER: One of the things that one hears from time to time is that some young man makes a great discovery and then will waste the rest of his life working out the details of his great discovery.

The opposite principle is, when you've made a great discovery, abandon it and go on to something else.

(laughter)

HARPER: We've conformed to this last idea more than the former, I think.

FISHER: Perhaps that is one reason why anyone reading your résumé cannot help to be impressed by the breadth of your knowledge and experience.

HARPER: Yeah. And that's why I've been called a phenomenologist.¹⁹⁸

¹⁹⁸ one who classifies and describes phenomena

FISHER: And not just a surgeon, but an interesting scientist. I've also been impressed with this more-than-40-year collaboration between you and Katherine Lathrop.

HARPER: I told you earlier how I phrased that. ["I provided the ingenuity and Katherine provided the scholarship."]

LATHROP: Well, it just worked.

FISHER: *(to Yuffee)* Michael, can I ask you if you have any more concluding questions before we finish?

YUFFEE: I don't. I basically wanted to close out with a few more personal comments, which we have. So I guess that's it.

Thank you for agreeing to speak with us, and we appreciate your time.

HARPER: I've been doing some historical reading recently about the problems of science—physics and astronomy and so forth—and it has been absolutely amazing how the great people in the past have had absolute blind spots toward future developments.

[Sir Arthur Stanley] Eddington¹⁹⁹ refused to accept anything about black holes, even though [astrophysicist Subrahmanyan] Chandrasekhar²⁰⁰ [at the University of Chicago] was working in his laboratory. This pattern is repeated and repeated and repeated, all through physics and chemistry, over the centuries.

Well, we really can't make a judgment about that. It's going to take more years than we have.

HARPER: Well, we've done it ourselves.

LATHROP: Well, we've overlooked a few things.

HARPER: The brain scan that we didn't recognize as a brain scan. The technetium we didn't recognize as the way of the future.

FISHER: Who would have guessed that technetium-99m would become the most used radionuclide in the world?

HARPER: Dr. Gottschalk had an interesting comment about that once when he was making an introductory speech somewhere for the Society [of Nuclear Medicine.] (I think that's when he was president,) that if somebody came to a funding agency with a new isotope that nobody had ever heard of with a mode of decay that nobody had ever heard of before and a half-life that was only a few hours, no way would he have gotten funding.

(laughter)

¹⁹⁹ Eddington (1882–1944), an English physicist, astronomer, and mathematician, studied the motion, structure, and evolution of stars. He was one of the first to discuss the theory of relativity.

²⁰⁰ Chandrasekhar (1910–93) was an Indian-born, U.S.-naturalized astrophysicist who, with William Fowler, won the 1983 Nobel Prize in Physics for formulating the currently accepted theories on development of dwarf stars. He was on the faculty at the University of Chicago starting in 1938 and was known to Lathrop and Harper.

FISHER: Yes, I can relate to that, Dr. Harper, because of my interest in radium-223.

HARPER: Of course.

FISHER: Which no one is using yet, and has had not clinical or animal applications since the 1950s.

HARPER: Well, you'll have to cure some mouse cancers with it before [it flies].

FISHER: Well, certainly, the alpha emitters have great promise for therapy of cancer.

I think, with that, we'll thank you and Katherine Lathrop. May I first, before we turn off the tape, ask what your age is, Katherine?

LATHROP: Same as his.

FISHER: Seventy-nine?

HARPER: Seventy-nine in July.

FISHER: Seventy-nine in July.

LATHROP: He's in July and I'm in June.

FISHER: So you're both the same age, still collaborating at the University of Chicago Hospital, both of you at the age of 79, and still doing very productive work. Katherine a member of the MIRD Committee, Paul still active in the Society of Nuclear Medicine.

Thank you very much.

HARPER: Not active in the Society, but active in—

FISHER: In the field?

HARPER: In the field. □



