The Human Plutonium Injection Experiments

William Moss and Roger Eckhardt

The human plutonium injection experiments carried out during and after the Manhattan Project have received tremendous notoriety in the past year or so owing to the Pulitzer-prize winning journalism of Eileen Welsome in the *Albuquerque Tribune* in 1993. The purpose of those experiments was to develop a diagnostic tool that could determine the uptake of plutonium in the body from the amount excreted in the urine and feces. This tool was essential for the protection of workers who would produce and fashion plutonium metal for use in the early atomic bombs. The idea was to remove a worker from the job if and when it was determined that the he had received an internal dose that was close to or over the limit considered safe.

Although some of the results of the studies were declassified and reported in the scientific literature in the early fifties (and further reports appeared in the seventies), the names of the subjects were not disclosed. Investigative reporting by Welsome uncovered the identities of five of the eighteen subjects and gave details about the circumstances and lives of three of them. The secret nature of the studies and the fact that the subjects may not have been informed about what was being done to them has generated outrage and distrust in the general pubic regarding the practices of the national laboratories. Why were such experiments done? Who allowed them to happen? The Secretary of Energy, Hazel O'Leary, equally disturbed, pledged an era of openness in the Department, promising to make available to the public all information that could be located that was pertinent to those and

Louis Hempelmann

similar radiation experiments with humans.

This article is intended to tell the Los Alamos story of these experiments and their aftermath. The article is based on memos and other documents that were collected by one of the authors (Moss) and were released to the public as a result of Secretary O'Leary's openness initiative. Los Alamos was not directly involved in choosing the subjects for the experiments nor in carrying out the clinical studies. Nevertheless, the motivation for the experiments arose at Los Alamos and scientists at Los Alamos were involved in planning the experimental protocols, preparing the material to be injected in the subjects, and analyzing the results. They were involved both at the time the experiments took place and years later when it became clear that reanalysis was appropriate.

Our intent in reviewing this story is to give enough scientific and quantitative details to bring out two areas that are usually not adequately addressed in the press and other popular reports. The first area is the purpose of the studies. What was to be learned, and how well did the experiments succeed in accomplishing the stated goals? The second area is the significance of the results for the protection of plutonium workers. How have those results aided our current understanding of the uptake, distribution, and retention of plutonium, and how have the results helped us to minimize the risks of internal exposure from plutonium? We will, in fact, show a new analysis of the data from the 1940s that, coupled with a recent human plutonium injection study using plutonium-237, strengthens our understanding of the manner in which plutonium, once it has reached the bloodstream, distributes itself in the body.

But first, we examine motivations and try to reconstruct why things were done as they were. For that we need to go back to the atmosphere of World War

II and the enormous pressures attendant on using unknown and uncharacterized materials to build the first atomic weapons.

The Manhattan Project and Its Need for Plutonium

In planning the development of the atomic bomb, scientists considered using two fissionable materials capable of sustaining a chain reaction—uranium-235 and plutonium-239. Each presented a different set of production and health-related problems.

Uranium-235 was present in natural uranium in small amounts (0.7 per cent). Scientists faced the daunting task of separating kilogram amounts of uranium-235 from the much more plentiful uranium-238 isotope by taking advantage of the slight difference in the mass of the two isotopes. For example, in the gaseous-diffusion method, gaseous compounds of the two isotopes diffuse through porous barriers or membranes at rates that differ by about 6 parts per thousand. Similarly, the electromagnetic method passes a beam of ionized uranium through a magnetic field, and the two isotopes follow circular paths that very gradually diverge.

In 1942, it was problematic whether enough uranium-235 could be separated by such painstaking techniques to achieve the goal of having an atomic bomb by January 1945. It was deemed necessary to pursue plutonium-239 as another possible weapon material. Because plutonium is chemically different from uranium, it was thought that it could be produced in reactors through neutron absorption and then separated easily from its uranium parent and fission products by chemical means.

Scientists had created tiny amounts of plutonium with the cyclotron at the University of California Radiation Laboratory in 1941 and demonstrated its favorable nuclear properties (see "The Making of Plutonium-239"). The physical properties and the chemistry of plutonium were determined using only microgram (micro = 10^{-6}) quantities. Such small amounts and the fact that plutonium emits alpha radiation, which doesn't penetrate the skin, meant the risk of handling plutonium, compared to gamma-emitting radionuclides, was not a major concern. In fact, the alpha activity of these small quantities was the only means to track and account for the material.

The discovery of plutonium led the Office of Scientific Research and Development to inaugurate work on plutonium for a weapon design. The work

was to be directed from the University of Chicago by Arthur H. Compton under the classified wartime name of the Plutonium Project. In January 1942, Compton consolidated the effort by moving many of the separate research projects to the University of Chicago under the cryptic title of the Metallurgical Laboratory. The Met Lab's goals were to demonstrate a nuclear chain reaction using natural uranium and to develop chemical procedures for isolating the plutonium that would be produced in the reactor fuel. From the group of scientists at Berkeley who had worked to discover plutonium (see "The Making of Plutonium-239"), Glenn Seaborg moved from Berkeley to Chicago in April 1942 to head the plutonium chemical-separation effort. Joseph Kennedy, Arthur Wahl, and Emilio Segrè continued their research on the chemistry and nuclear properties of plutonium at Berkeley and then transferred to the Site Y Laboratory at Los Alamos in early 1943. Their colleague, Ed McMillan, was already there, having helped set up the new Laboratory.

The Manhattan Project. As the weapon programs grew in size and complexity, it was decided that the military should coordinate the effort, including spearheading the huge construction projects needed to supply the raw weapons materials. In August 1942, the Army Corps of Engineers formed the Manhattan Engineer District, or Manhattan Project, and took over control of all research on atomic weapons. In September, General Leslie R. Groves was assigned to direct the Project.

At that time, even before the demonstration of a chain reaction at Chicago, plans were already being made for construction of larger reactors to produce plutonium in the kilogram quantities needed for weapons. A pilot reactor would be built in Clinton, Tennessee, and production reactors would be built at the Hanford Engineer Works, a site in southern Washington adjacent to the Columbia River. The Clinton and Hanford facilities would also perform chemical separation of "product" (plutonium) from the reactor fuel pellets; Clinton would develop the process, Hanford would use it on a large scale with automated state-of-the-art facilities.

Right from the start, plutonium was a secret topic, and the Manhattan Project used the code words "product" or "49" to refer to plutonium ("49" was arrived at by taking the final digits in the atomic number, 94, and the atomic mass, 239). During the period from 1941 through 1944, documents discussing "product" were classified Secret Limited. Only personnel with authorization to know were permitted knowledge of plutonium.

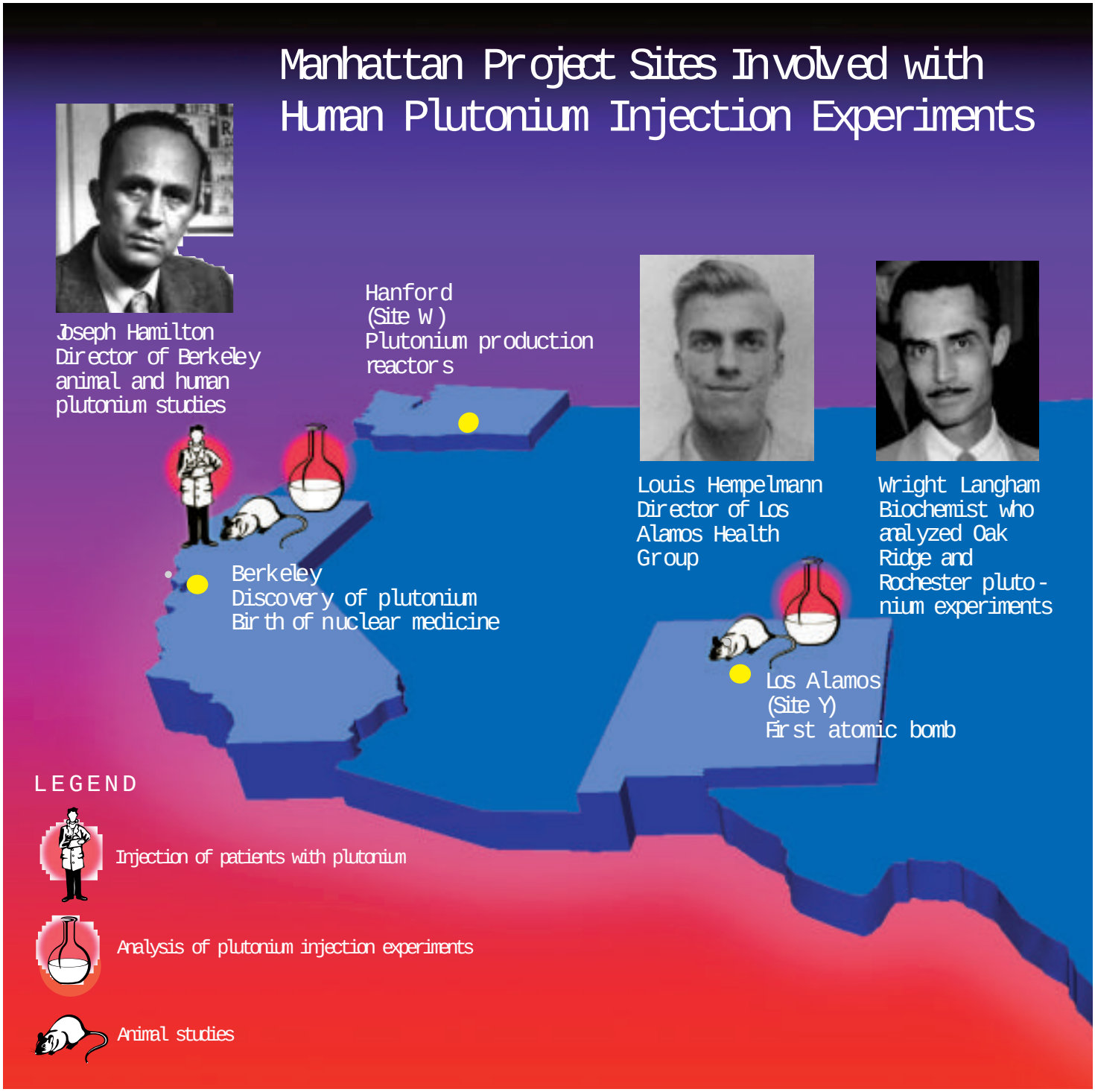
In March 1943, the Los Alamos Project became operational under the direction of J. Robert Oppenheimer. The responsibility of this laboratory was the design of the uranium-235 and plutonium-239 weapons. Two months later, Los Alamos was also assigned responsibility for the final purification of plutonium and its reduction to metal.

Health protection. To protect the thousands of workers at the various sites who would soon be working to produce kilogram amounts of this new element, a Health Division at Chicago was authorized in July 1942, and a team of personnel knowledgeable about the

The Making of Plutonium-239

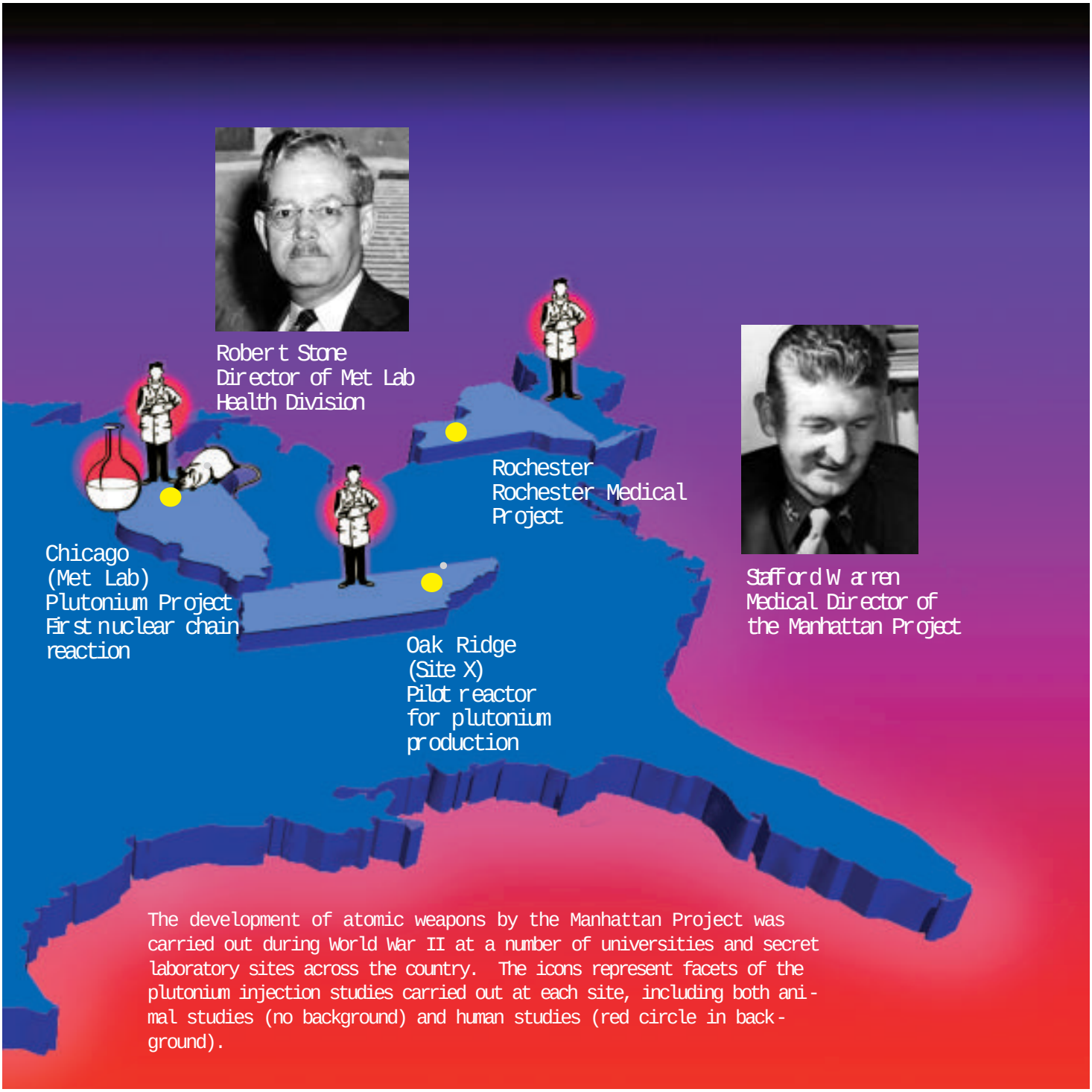
In 1940, Edwin McMillan and Philip Abelson demonstrated with the cyclotron at the University of California Radiation Laboratory in Berkeley that when uranium-238 was bombarded with neutrons, a new element was produced (neptunium-239) that was chemically distinct from the uranium. In 1941, Glenn Seaborg, Joseph Kennedy, Arthur Wahl, and Emilio Segrè, building on the earlier work, isolated the daughter of neptunium-239, an element, also of mass 239, that had been predicted theoretically by Louis Turner. The chemical properties of this material were different than those of neptunium or uranium, and its presence was identified by its alpha activity (about 130,000 alpha disintegrations per minute per microgram, which corresponded to a half-life of about 30,000 years). They then demonstrated that the isotope had the properties predicted by Turner—it underwent fission with slow neutrons with a greater cross-section than uranium-235, making it a potentially favorable material for an explosive chain reaction. The new element was named plutonium by its discoverers in 1942.

The next important step was to demonstrate how to produce plutonium-239 in the quantities needed for a weapon. The key was the construction of a "nuclear pile" that could sustain a chain reaction. In such a reactor, the predominant uranium-238 isotope in the fuel would absorb neutrons from the chain reaction to create uranium-239. This isotope would then decay by two beta emissions to plutonium-239. By December 1942, Enrico Fermi achieved a controlled chain reaction in a graphite-uranium pile under the west stands of Stagg Field at the University of Chicago, thereby completing the first goal of the Met Lab and demonstrating in principle that plutonium-239 could be produced in quantity. It was then up to the Manhattan Project to construct the production reactors and for Seaborg's team at the Met Lab to perfect the chemical techniques that would separate the plutonium from the uranium fuel and the radioactive fission products.



physiological effects of ionizing radiation was assembled under the direction of Robert S. Stone. The intention was to develop health-protection methods for workers involved in the production, purification, and fabrication of uranium and plutonium, including development of ways to monitor personnel for exposures to ionizing radiation by blood tests. In September, research was started to increase information about the toxicity of uranium compounds.

The chemical toxicity of uranium (its radiological risk was unknown) was identified with heavy-metal poisoning related to deposits in the kidney and bone. Plutonium, on the other hand, was an unknown health-risk factor. If plutonium metal or compounds were inhaled or ingested, where would they deposit in the body? What limits should be set on internal body burdens that would be safe? What tests would indi-



The development of atomic weapons by the Manhattan Project was carried out during World War II at a number of universities and secret laboratory sites across the country. The icons represent facets of the plutonium injection studies carried out at each site, including both animal studies (no background) and human studies (red circle in background).

cate when these body-tolerance limits were being approached? As a result of such concerns, efforts in health protection paralleled the growth of the nuclear weapons research (see "The Medical Researchers").

A contract was issued in October 1942 by the Met Lab to the University of California Radiation Laboratory at Berkeley to study the metabolism of the radioactive materials that would result from the fission process in natural uranium piles. These studies, directed by Joseph G. Hamilton, would initially be limited to the metabolism in rats of small quantities of cyclotron-produced fission products (their radioactivity would "trace" their course through the body). As larger quantities of the transuranics became available from the Clinton pilot reactor in 1944, the studies would focus on the assimilation, distribution, retention, and excretion in

rats of neptunium, americium, plutonium, as well as larger amounts of fission products.

When the Manhattan Project took over direction of the weapon programs, it set up its own Medical Office under the directorship of Stafford L. Warren, from the University of Rochester, and this office started medical, health physics, and biological research sections at other centers. In April 1943, the University of Rochester Project was authorized based on the extensive experience of the medical school there in conducting biological studies with cyclotron-produced radioisotopes. In contrast to the Met Lab and Los Alamos, the Rochester Project was not directly involved with the design or production of the atomic bombs. It was responsible for studying the biological effects of various radioactive materials, using animals as the host. Part of that work included determining the comparative toxicity of radium, polonium, and plutonium.

At this same time, it was agreed that the Chicago effort would continue to be responsible for the health programs it already had underway, including the recommendation of health safeguards for other Manhattan Project sites such as Los Alamos and the plants involved with production of weapon materials. The Met Lab's Health Division continued its animal research, including the radioactive tracer studies by Hamilton at Berkeley and, by 1944, acute plutonium toxicity studies at the Chicago site.

Each of the sites within the Manhattan Project established their own group of people to provide on-site health protection. The Los Alamos Health Group was created in March 1943 under the direction of Louis H. Hempelmann and began to plan for the health protection of workers at Los Alamos. Oppenheimer's original intent was to rely on other project sites for the development of the health-protection methods. However, by the summer of 1944, Hempelmann and Oppenheimer found they could not always get the health-protection information they felt was needed, and the Laboratory extended its activities, gradually taking on a role comparable to other sites for health-protection research and development on the hazards of plutonium.

The heads of the various health divisions—Stafford Warren for the Manhattan Project at Oak Ridge, Robert Stone at Chicago, Joseph Hamilton in California, and Louis Hempelmann at Los Alamos—were destined to play a major role in the decision to obtain plutonium metabolic data from humans (see "The Medical Researchers"). All four were medical doctors with strong backgrounds in radiology, and in 1941, three of them—Stone, Hamilton, and Hempelmann—were working at the Radiation Laboratory at Berkeley. They were thus knowledgeable about radiation and its biological effects, including research that involved the administration of small quantities of radioactive materials into humans for biomedical purposes.

By 1942, Stone had gone to the Met Lab in Chicago as head of the Health Division, and Hempelmann had moved back to Washington University in St. Louis (where he had received his medical training). There he was responsible for programmatic uses of that university's cyclotron. By the summer of 1942, both Hempelmann and Hamilton, the latter responsible for operations at Berkeley's cyclotron, were caught up in demands related to the war effort. One of their main responsibilities became the production of plutonium by bombarding hundreds of pounds of uranium nitrate to produce microgram quantities of plutonium-239. The irradiated uranium from St. Louis was sent to the Plutonium Project's laboratories in Chicago where Seaborg's group was learning how to chemically isolate the plutonium from the uranium and the highly radioactive fission products. The uranium irradiated at Berkeley was processed at the Radiation Laboratory under the direction of Art Wahl and Joseph Kennedy, and much of that material eventually went to Los Alamos. The Berkeley and St. Louis groups each produced about a milligram (a thousand micrograms) of plutonium-239 before January 1944, when the first gram amounts of reactor-produced plutonium started becoming available from the Clinton site.

The Los Alamos Health Group. Oppenheimer, at the recommendation of John Lawrence at Berkeley's Radiation Lab, asked Hempelmann to head up the Health Group at Los Alamos in March 1943. Before coming to Los Alamos, Hempelmann visited the Met Lab in Chicago and discussed plans for the organization of the new Health Group. It was the opinion of the Chicago people that changes in blood counts, such as increased numbers of white blood cells, would be the most sensitive indicator of significant radiation exposures. If he was to be the "hematologist-in-chief" at Los Alamos, Hempelmann wanted to learn as much as he could about this subject from Stone and others.

While in Chicago, Hempelmann also met with John Manley, who was responsible for planning for the Los Alamos Laboratory. Manley told him that about fifty to sixty men might be exposed to radiation hazards at Los Alamos and he did not anticipate the hazards being greater than those associated with supervoltage machines, such as cyclotrons. At that time, the Chicago Met Lab was responsible for plutonium research, and Los Alamos was responsible for weapon design. As a result, Manley did not envision an extensive research effort at Los Alamos using plutonium. It would not be long before that would change.

Worries About the Health Hazards of Plutonium

Originally, it was intended that milligram amounts of plutonium would be

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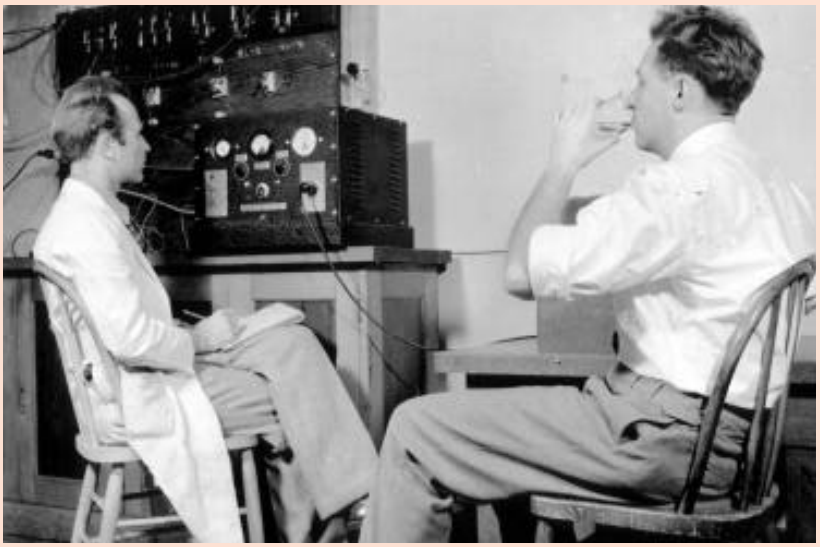
The Medical Researchers

Stafford Warren was educated at the University of California at Berkeley from 1918 to 1922 and received his M.D. from the University of California Medical School at San Francisco in 1922. In 1925, he was appointed as an assistant professor of radiology at the University of Rochester School of Medicine and Dentistry, eventually serving there as the Department of Radiology Chairman. In April 1943, Warren was appointed a consultant to the Manhattan Project to establish the Rochester site. By November, persuaded partly by management at Eastman Kodak, who were running the uranium processing plant at Oak Ridge, Warren was made the medical director of the Manhattan Project with headquarters at Oak Ridge, Tennessee, and was commissioned as a colonel in the Army Medical Corps.

In the mid-thirties, Robert Stone, a radiologist, and Joseph Hamilton, an intern with a degree in chemistry, were recruited by Ernest Lawrence from the University of California Medical School in San Francisco (at that time, part of the UC, Berkeley system) to develop biomedical applications for the Berkeley cyclotron. One application was the direct treatment of cancer, and Stone pioneered the use of cyclotron radiation for experimental treatment of human cancer patients. A second application was to use the cyclotron to produce radionuclides for the internal radiotreatment of disease. By the late thirties, Hamilton and Stone were involved with human metabolic and clinical studies using sodium-24, a short-lived radioisotope. They hoped sodium-24 could replace the long-lived radium isotopes for the internal radiotreatment of certain illnesses. Their studies would involve using human volunteers—patients with leukemia, or other illnesses, and normal healthy subjects—to acquire comparative data and to test for toxic responses and evidence of cures. The amounts of the radioisotope administered to the patients were always well below what were considered toxic levels relative to the then recognized risks from external exposures to x rays and internal exposures to radium (from the use of soluble radium salts to treat a wide range of illnesses).

Louis Hempelmann's medical training was at Washington University in St. Louis, followed by a residency in Boston at the Peter Bent Brigham Hospital. A fellowship brought him to the Radiation Laboratory at Berkeley in 1941, where he studied radiobiology with Stone and John Lawrence (Ernest Lawrence's brother) and worked on the use of cyclotron-produced neutrons for therapeutic treatment of cancer. At that time, Hamilton was doing other research with a variety of radioisotopes, including the cyclotron-produced fission product iodine-131. Many of those studies used both normal human subjects who had volunteered and patients who were then tested for evidence of responses that could lead to medical treatments of illnesses, including cures. In a 1942 article, Hempelmann said that "if the cyclotron finds no place in medicine other than to provide 'tagged atoms' for medical studies, the medical profession will owe Ernest Lawrence an everlasting debt." ■



A Radiotracer Experiment in the 1930s.
Joseph Hamilton (left) performs a tracer experiment in which the volunteer drinks a solution containing radioactive sodium with his hand (out of sight) inside a shielded counter that will detect the arrival of the radioisotope in that part of his body.

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generated in reactors at Argonne (twenty miles southwest of Chicago) and later at Clinton, Tennessee, and that material would be processed into metal at the Chicago Met Lab before being sent to Los Alamos. However, in May 1943, a committee appointed by Groves reviewed the use of plutonium produced by cyclotrons and reactors and decided it was necessary to locate the final production steps for weapons material at the same site that would assemble the bombs. Thus, Los Alamos was assigned the responsibility of the final purification and production of the plutonium metal, starting with the Clinton product in 1944 and, later, with large quantities of the Hanford product (which was sent to Los Alamos in the form of a plutonium-nitrate slurry). The Met Lab would also continue its innovative research for Los Alamos on the physical and chemical properties of plutonium using, in 1944, milligram quantities of the Clinton product.

The new assignment resulted in an increase in personnel in the Chemistry and Metallurgy Division at Los Alamos from about twenty in June 1943 to about four hundred by 1945. It also created an important difference in the type of work at the two sites—the Met Lab research was mainly "wet chemistry," whereas the Los Alamos production effort involved a considerable amount of "dry chemistry," resulting in different types of health hazards, and in particular, exposure to the airborne dust of plutonium and its compounds.

In January 1944, at the same time the first milligrams of reactor-produced plutonium were being shipped from Clinton, Seaborg and others at the Met Lab began thinking seriously about the fact that more and more people would soon be working with gram quantities of plutonium—perhaps thousands of people at Hanford alone. Hamilton had probably informed Seaborg of a 1943 paper by Robley Evans about the dangers of radium and the deaths of radium-dial painters in the 1920s, in this way alerting Seaborg to a potentially similar situation with plutonium. The Evans paper estimated that as little as 1 or 2 micrograms of radium retained in a person's skeleton could cause cancer, a latent radiation effect. It also explained the reasoning behind the occupational tolerance limit of 0.1 micrograms for radium retained in the body (see "Radium—the Benchmark for Internal Alpha Emitters" on page 224 for a fuller discussion of the radium tolerance levels).

Similarities with radium. That the health risks for the intake and retention of plutonium might be as dangerous as those of radium was apparent from a comparison of their chemical and nuclear properties. Both elements were heavy metals that were expected to deposit in bone. Both had long half-lives—1,600 years for radium-226 and 24,000 years for plutonium-239—and both decayed by alpha emission. A comparison of their specific activities (1 microcurie per microgram for radium-226 and 0.06 microcuries per microgram for plutonium-239) and the energies of their alpha particles, including those of the daughters of radium, implied that plutonium might be a factor of 50 times less effective than radium at causing physiological damage. But because of the tragic deaths of the radium-dial painters (dating from the use of radium in 1917 to1918), it was imperative to obtain metabolic data on plutonium so that a safe tolerance limit could be established for the Manhattan Project workers.

On January 5, 1944, Seaborg sent a memo to Stone, expressing his concerns. He offered to help set up safety measures for handling plutonium and suggested that "a program to trace the course of plutonium in the body be initiated as soon as possible." Stone replied by explaining Hamilton's planned tracer studies at Berkeley, which would determine the metabolic distribution of plutonium in animals, and Hamilton's need for milligram amounts. Hamilton had apparently been offered microgram quantities of plutonium-239 prior to 1944, but he had informed Stone that "the studies can be much more accurate and much more quickly done" when milligram quantities were available (see "Detection of Internal Plutonium"). He preferred to wait until then to do the plutonium metabolic studies, undoubtedly fearing that experiments with smaller amounts would lead to questionable results that would have to be repeated.

On January 15, Seaborg sent a second memo to Stone.

> *I am seriously worried about the health of the people in my section, for which I am responsible, since they will soon handle such relatively large amounts of plutonium. I wonder whether some plutonium should be made available to Dr. Hamilton for his distribution studies sooner than the couple of months or more indicated in your memorandum. . . . The problem of health hazards assumes even greater importance for Site Y [Los Alamos] where so much plutonium will be handled in so large a variety of operations. It is, of course, also important in connection with the operations which will go on at Site W [Hanford], particularly those involved in its final isolation there.*

In response to those concerns, management at the Met Lab initiated discussions about plutonium and its potential for toxicity, beginning with a meeting of the Project Council at the Clinton Laboratory in Tennessee on January 19, 1944. Compton summarized the delivery schedule for plutonium from the Clinton reactor as 0.5 grams that month, 3 grams in February, and 3 to 4 grams in March and indicated that the Plutonium Project was "still in the lead" in the race with the uranium isotope separation effort.

Tolerance limits. According to the

minutes of the meeting, Stone provided the following information on the toxicity of plutonium:

> *Alpha emitter and is expected to be stored in bones. With Ra, 1 to 2 micrograms sometimes fatal. Pu perhaps less dangerous by factor of 50. Not proven as yet to be accumulative. Radium in body can be identified by radon in exhaled breath or by Geiger counter exploration around body. These methods do not help for Pu.*

Compton added:

> *For moment should consider Pu as potentially extremely poisonous. Investigation necessary. Factor of 50 probably represents worst case and [corresponds to] a tolerance level of stored material of about 5 micrograms.*

Stone's discussion of the "poisonous nature" of plutonium at the meeting resulted in two actions. In the absence of plutonium metabolic data, the management of the Plutonium Project adopted Stone's recommendation of a 5-microgram tolerance limit for plutonium retained in the body. Also, Compton, with Oppenheimer's concurrence, authorized a shipment of scarce plutonium to Hamilton at Berkeley. Ten milligrams of the scheduled February 1 production of reactor plutonium from the Clinton site were to be allocated for metabolism tests in animals at the Berkeley lab.

Early in February, Los Alamos received copies of the minutes of Met Lab information meetings, thereby making personnel at Los Alamos aware of Chicago's concerns about working with plutonium, the proposed tolerance limit, and the current suggestion of using the analysis of urine to monitor the uptake of plutonium relative to the 5-microgram limit. The documents mentioned Hamilton's belief that the "dust hazard was far more serious than oral intake." Based on the known behavior of metallic zirconium, he felt that fifty per cent of inhaled plutonium dust might be retained in the lungs.

Also recorded in the minutes, Cecil Watson, Associate Director of the Met Lab's Health Division, said:

> *Twenty to 30 micrograms [of plutonium] may possibly be a lethal dose. Present laboratory floor surfaces, desk tops, ventilation, laboratory service [are] inadequate to cope with this. May decide to handle under hoods, like Ra. Should plan so that all Pu can be recovered quantitatively if accidentally lost.*

The minutes also mentioned an accident in which an individual had spilled plutonium on his hand. His stools and urine were being examined at the Met Lab for evidence of plutonium that might have passed through the skin into his body.

Learning about the proposed 5-microgram tolerance limit in February, Hempelmann traveled to Boston with other Met Lab personnel to study methods used by the radium industry for handling radium. Meanwhile, Kennedy (who'd been processing cyclotron-produced plutonium at Berkeley the previous year but was now head of the Chemistry and Metallurgy Division at Los Alamos) was anticipating delivery of gram amounts of plutonium from the Clinton site and requested information from Hempelmann about the danger to personnel from inhaled or ingested dry plutonium materials. Hempelmann's response (in an undated memo) said that the risk of biological damage from plutonium would be local in character, a result of energy absorbed by tissues from plutonium's alpha particles. He calculated that the energy absorbed in 10 grams of lung tissue from the alpha particles of a 1-microgram plutonium-239 dust particle would result in a radiation dose that exceeded the daily tolerance limit of radiation for a single organ. In the case of ingestion, he said that 100 to 500 micrograms would constitute a lethal dose, assuming that absorption from the intestinal tract and subsequent metabolism was the same as radium (and applying the estimated factor of 50 difference between the radiological toxicity of the two metals).

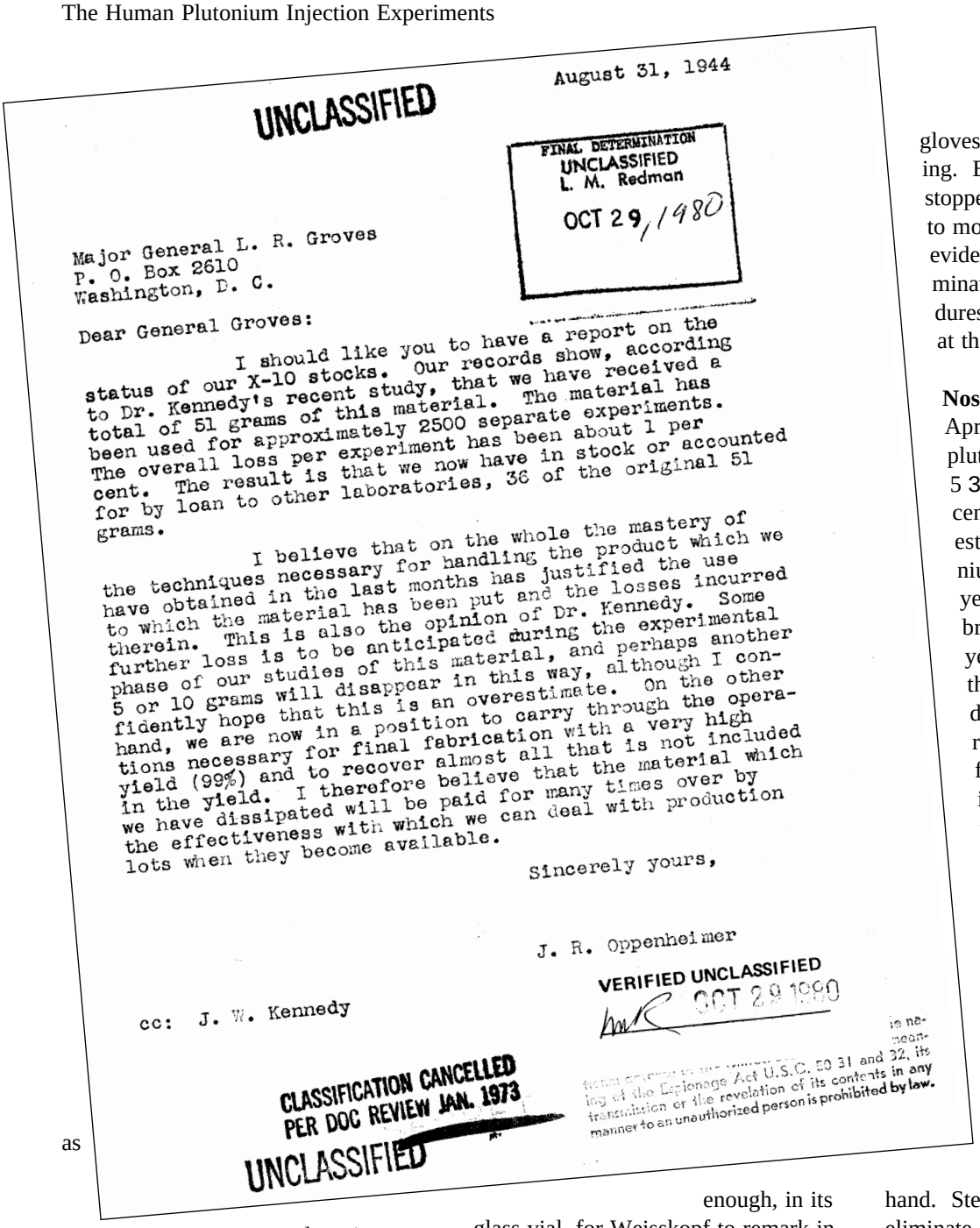
Thus, people throughout the Manhattan Project were aware of the potential dangers of plutonium. But their thinking involved the various assumptions about plutonium's biological behavior and toxicity. Because the number of people working with plutonium was increasing rapidly, the people responsible for their health were forced to develop safe procedures and detection techniques based on best guesses, estimates from the properties of other metals, or whatever useful information could be gleaned from the initial animal studies at Berkeley and, later, Chicago.

Working With Plutonium

The first shipment of cyclotron-produced plutonium sent to Los Alamos arrived in October 1943—650 micrograms of plutonium-239 shipped from Berkeley as a semi-purified, partially decontaminated plutonium salt.* Oppenheimer immediately informed his staff that "purification of the 650 [micrograms] of Pu, at least to the point where the material is suitable for physical work, should be carried out with maximum speed." Several 100-microgram allotments of this plutonium were committed to study the isotope's nuclear properties. The remainder was assigned to Kennedy's Chemistry and Metallurgy Division for research on removal of light-element contaminates.

The first reactor-produced plutonium-239 was shipped from the pilot reactor in Clinton, Tennessee, in January 1944

*In July 1943, 165 micrograms of cyclotron-produced plutonium-239 were lent to Los Alamos from the Met Lab for the study of its fission properties. The plutonium was returned later that same month.



UNCLASSIFIED

August 31, 1944

FINAL DETERMINATION
UNCLASSIFIED
L. M. Redman
OCT 29, 1980

Major General L. R. Groves
P. O. Box 2610
Washington, D. C.

Dear General Groves:

I should like you to have a report on the status of our X-10 stocks. Our records show, according to Dr. Kennedy's recent study, that we have received a total of 51 grams of this material. The material has been used for approximately 2500 separate experiments. The overall loss per experiment has been about 1 per cent. The result is that we now have in stock or accounted for by loan to other laboratories, 36 of the original 51 grams.

I believe that on the whole the mastery of the techniques necessary for handling the product which we have obtained in the last months has justified the use to which the material has been put and the losses incurred therein. This is also the opinion of Dr. Kennedy. Some further loss is to be anticipated during the experimental phase of our studies of this material, and perhaps another 5 or 10 grams will disappear in this way, although I confidently hope that this is an overestimate. On the other hand, we are now in a position to carry through the operations necessary for final fabrication with a very high yield (99%) and to recover almost all that is not included in the yield. I therefore believe that the material which we have dissipated will be paid for many times over by the effectiveness with which we can deal with production lots when they become available.

Sincerely yours,

J. R. Oppenheimer

cc: J. W. Kennedy

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OCT 29 1980

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...is na-... mean-... ing of the Espionage Act U.S.C. 50 31 and 32, its transmission or the revelation of its contents in any manner to an unauthorized person is prohibited by law.

as plutonium nitrate. One-and-a-half milligrams of plutonium went to the Chicago Met Lab on January 6, and six milligrams went to Los Alamos on January 17. The quantity shipped to Los Alamos was ten times larger than the previous 650 micrograms and was large enough, in its glass vial, for Weisskopf to remark in his memoirs: "I held on the palm of my hand the first little grain any of us had ever seen. (I should not have done it, I suppose, because of its radioactivity, but it was such a tiny quantity that it didn't have any detrimental effect.)"* Increasing amounts of plutonium followed in subsequent months.

At the Met Lab, they implemented safeguards for plutonium work by putting linoleum on all the floors and having their people use filter masks, rubber gloves, and outer protection clothing. Eating in the laboratories was stopped. Methods were developed to monitor the air in the labs for evidence of plutonium dust contamination. Similar safety procedures were adopted at Los Alamos at the beginning of March 1944.

Nose swipes. By the end of April, the Met Lab proposed a plutonium air tolerance limit of 5×10^{-10} micrograms per cubic centimeter of air (arrived at by estimating the build-up of plutonium in the lungs over a two-year period for a worker breathing the air 300 days a year). A procedure to detect the inhalation of plutonium dust using nose swipes had already been initiated. A moist filter-paper swab was inserted into the nostril and rotated, then the swab was spread out, dried, and read in an alpha detector. A reading of 100 counts per minute or higher was considered evidence of an exposure.

It was realized early with this procedure that the nose-swipe could easily be contaminated with plutonium from the worker's hand. Steps were included to help eliminate such contamination, and the procedure was changed so that individual counts were taken from each nostril to serve as a check. (Nose swipes are still used for plutonium workers. Nose-swipe counts and air monitoring are the criteria used to decide when medical treatment for the worker, including prompt collection of urine samples and the initiation of chelation therapy, is necessary.)

The new procedure quickly bore results, because on May 30, the Los Alamos Safety Committee informed Kennedy that Ted Magel, one of the

*Victor Weisskopf. 1991. *The Joy of Insight: Passions of a Physicist.* BasicBooks.

workers making the first plutonium metal-reduction runs, had a nose swipe of 11,372 alpha counts per minute. They felt it was apparent that safety rules had been violated, and Magel was instructed to follow those rules in the future. Apparently, in his desire to make sure that a metal-reduction experiment was being set up correctly, Magel had lifted the lid of a crucible containing plutonium without first putting on his respirator and so exposed himself to plutonium dust particles. Magel continued to work with plutonium until he left Los Alamos a couple of months later in August 1944. (A positive urine assay of a sample obtained from Magel in 1945 confirmed the nose-swipe evidence of exposure.)

By the end of August, Los Alamos had received 51 grams of plutonium, and scientists had used the material in over 2,500 different experiments. In a memo to Groves, Oppenheimer stated that "the overall loss per experiment has been about 1 per cent," and that 36 grams remained. One group at the Laboratory was dedicated solely to recovery (and repurification) of the precious metal both from laboratory accidents and from completed experiments. Because they could never be sure what substances or chemicals the plutonium would be mixed with (for example, asphalt floor tiles in a laboratory spill or a mass of burned material from a furnace in a metal-reduction experiment), they had worked out a flow chart for separating plutonium from every other element in the periodic table. In his memo, Oppenheimer continued: "We are now in a position to carry through the operations necessary for final fabrication with a very high yield (99%) and to recover almost all that is not included in the yield." He felt that the loss of 15 grams of plutonium "will be paid for many times over by the effectiveness with which we can deal with production lots when they become available."

There was, of course, great concern about the lost material. In September, Kennedy wrote a memo expressing that concern to the people in his division working with plutonium. Among other things, he said, "the suspicion that several grams of 49 are scattered somewhere in building D is not pleasant. In addition to its great value, this material constitutes a definite hazard to health." He went on to describe efforts to improve handling and recovery.

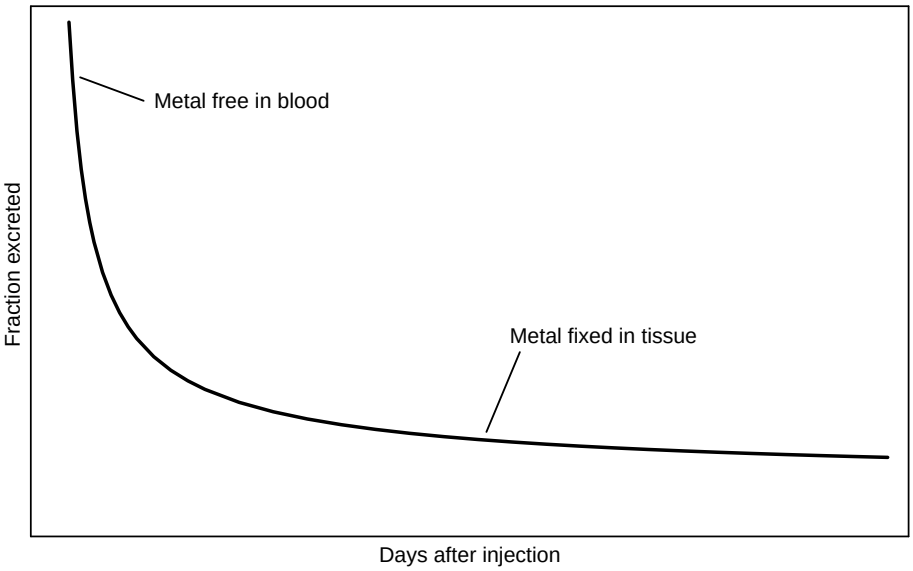


Figure 1. Daily Urinary Excretion for an Internal Exposure

When a person or animal gets a quantity of a metal compound, such as those of plutonium, radium, or zirconium, into their blood, the material may initially circulate in a relatively "free" form. Eventually, however, material that isn't rapidly excreted—within a few minutes, hours, or days—may deposit and become "fixed" in the tissue of various organs and be less available to the blood stream. As a result, a lesser amount will be filtered out by the kidneys and excreted. The two phases (the initial-intake phase and the metabolized phase) will be evident in urine excretion curves as regions with different slopes. The duration and excretion rate of the two phases for a given element will depend on that element's chemical nature and biochemical affinities. The figure shows a theoretical excretion curve.

Plutonium Animal Studies

The quickest way to obtain more realistic information about the toxicity of plutonium was with animal studies. It was hoped that such studies would answer a lengthy series of questions, including how the amount of plutonium taken into the body would depend on the exposure mode (for example, oral ingestion, inhalation, or absorption through the skin), how retention would depend on the chemical, physical, or valence state of the plutonium, and how much of the plutonium that had become internal would be excreted and how rapidly. It was also unknown what fraction of internal plutonium would become "fixed" in tissue in the body (see Figure 1) and how it would be distributed among the various organs.

When Hamilton started his series of animal experiments, his guess was that a plutonium tolerance dose of even 10 micrograms was "very conservative." His reasoning was most likely based on the known excretion behavior of radium, which was very high at first (more than 20 per cent of radium administered as a soluble salt was eliminated in humans the first day) but eventually became very low (less than 1 per cent by the tenth day and less than 0.3 per cent by the twenty-first day). It was thought that the high elimination rate occurred

before the radium was fixed in tissue. Without data to support another conclusion, Hamilton probably assumed that the behavior of plutonium would be similar—much of it would be eliminated quickly.

Hamilton also suggested that "integration of 24-hour urine samples, checked every 2 weeks will give a fairly good indication of intake of Pu by an individual, and so a gauge of Pu deposition in body." This statement is consistent with the assumption that, like radium, plutonium would take time to become fixed in tissue. Thus, an accurate determination of a body burden would require that the measurements be made after the plutonium circulating in the blood was either excreted or fixed. At that later time, only plutonium re-entering the blood from fixed tissue sites would be circulating, and measurements of the fraction excreted would more accurately reflect the level of retained plutonium.

Eleven milligrams of plutonium were diverted to Hamilton at the beginning of February 1944 (about 2 per cent of the total Clinton output of plutonium at that point) to enable him to begin biomedical experiments with animals. The research involved administering soluble 15-microgram portions of plutonium-239 compounds to rats, using different plutonium valence states (+3, +4, and +6) and different methods of introducing the plutonium (oral, intramuscular, intravenous, subcutaneous, and intrapulmonary procedures).

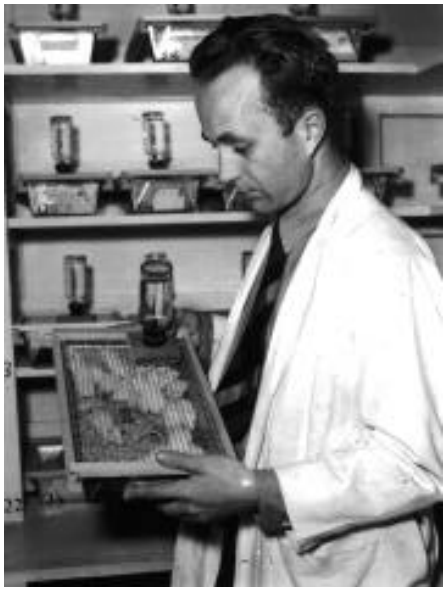
A Met Lab progress report for February containing Hamilton's input stated:

> *Product studies: - Oral absorption of all valence states is less than 0.05%; lung retention high; adsorbed material predominately in skeleton; excretion very small in urine and feces.*

And the report for March noted:

> *Product behaves differently in the three valence states. The plus 4 state is retained to considerable extent at 16 days, the plus 3 is retained to a less degree and the plus 6 to a still less degree.*

By April, Hempelmann was discussing Hamilton's results at Los Alamos, saying that "plutonium in all three valence states is very poorly absorbed when taken by mouth—less than .005%" and "the organ which took up most of the absorbed plutonium was the bone, with more than half of the element going to the skeletal system in each case."



Joseph Hamilton carried out the initial metabolic studies of plutonium in animals.

Additional quantities of plutonium were made available to Hamilton, and he was authorized to extend his research to the uptake of plutonium dust from the lungs of rats. He soon learned that only about 20 per cent of the plutonium originally inhaled was eventually deposited in the skeleton. Almost half was trapped in the upper air passages and eliminated; about 25 per cent remained in the lung, although some of that was slowly eliminated. The actual percentages depended on whether or not the plutonium compound was soluble—plutonium nitrate was quite readily absorbed, whereas the oxide was not absorbed at all.

In the spring of 1944, plutonium was made available for animal studies at the Chicago Met Lab, and research was initiated there on the acute toxicity of plutonium. Those studies involved the injection of microgram and milligram quantities of plutonium-239 into mice, rats, rabbits,.and dogs.
The results of the studies at Berkeley and Chicago showed that plutonium's physiological behavior differed significantly from that of radium. Two facts were particularly alarming: there was significant deposition of plutonium in the liver, and the overall excretion rates were very low (see Table 1). Neither of these facts were anticipated when the tentative 5-microgram tolerance limit for plutonium was adopted early in 1944. Furthermore, the rate of plutonium elimination in excreta differed between species of animals by as much as a factor of five. Such variation made it difficult to estimate what the rate would be for man.

The studies also showed that plutonium was similar to radium in being a bone seeker, but only a little more than half of what was retained went to the bone, compared to 99 per cent for radium. Also, the two metals deposited at different locations. Radium (similar, chemically, to calcium) deposited in mineralized bone, whereas plutonium remained on the surface in the "actively metabolizing" portion of the bone, an area intimately associated with bone marrow and the production of blood cells. (However, because plutonium deposits on the endosteal surfaces of the red marrow and the alpha particles have a limited range, the blood-forming tissue is not irradiated uniformly.)

The initial animal excretion rate for plutonium was low (less than 10 per cent of what had been introduced appeared in the urine and about 6 per cent in the feces over the first *four* days),

which meant the assumptions about rapid initial elimination and slow "fixing" of plutonium in the tissue were not accurate. After roughly 20 to 30 days, the excretion rate appeared to become constant, but again, at much lower rates (about 0.01 per cent in urine). The total excretion rate (urinary and fecal) at 21 days was about 10 times less than that of radium.

The discovery that absorption of soluble compounds of plutonium through the gastrointestinal tract was very low and essentially no absorption occurred through the skin meant that the main routes to internal deposition were absorption from contaminated wounds or inhalation of dust particles. Such considerations led Hamilton, on May 5, 1944, to suggest treatment for puncture wounds.

Hamilton informed Stone that in accidents involving intramuscular injection—such as might occur if closed systems at high temperatures exploded and shards punctured the worker's skin—absorption of plutonium would be slow. Hamilton felt that "only a few percent [of soluble product] would be expected to be taken up within a matter of an hour or so." He realized "that analogies are frequently dangerous for the purposes of comparison, but the superficial similarities . . . to snake bite come to mind." As a result, he suggested a treatment that included, when possible, the use of a tourniquet, which "facilitates the washing out of the material by bleeding and at the same time retards absorption."

Acute effects. By the end of 1945, studies with rodents and dogs had shown that the acute radiation effects of plutonium were less "toxic" than highly toxic chemicals (such as curare, strychnine, and botulinus toxin) but far exceeded any known chemical hazard of heavy metals. The clinical picture of acute plutonium toxicity in dogs was, superficially at least, quite similar to the effect of a single lethal dose of total-body x rays. Although the initial vomiting and depression seen with x rays were absent, weight loss and refusal of food and water in the first days were followed, around the tenth day, by the final "shock" phase that included a rise in body temperature, pulse rate, labored breathing, and various hemorrhages. Changes occurred in the blood as well, including drops in white and red cell counts. However, other animal species showed certain dissimilarities between acute plutonium toxicity and total-body x rays.

The acute lethal dose for animals appeared to be somewhere in the range from 400 to 4000 micrograms of plutonium per kilogram of body weight, depending on the species and, to a lesser extent, on the chemical form of the plutonium. Damage tended to occur more specifically in the liver, kidneys, and spleen and to red blood-cell production in the bone marrow. In rats, about 60 per cent of the retained plutonium ended up in the skeleton and 18 per cent in the liver.

At that time, very little of the experimental work extended over a period of more than six or seven months, so the picture of *chronic* plutonium toxicity was essentially a guess. A few bone tumors and one instance of bone thinning had been observed in rats and mice. It was not at all certain whether the various effects, including those to the blood, were progressive or whether they could be extrapolated to lower doses.

Certainly, extrapolating the results of animal studies to humans had to be done with caution. Experiments with other toxic substances had shown instances of dramatic differences between animals and humans. Rats, for example, will tolerate quantities of deposited radium per unit of body weight that would be lethal to humans, and various inbred mice are capable of surviving huge doses of external gamma radiation compared to humans. Likewise, any study involving skin was particularly suspect because of the very great differences between human skin and those of animals. Thus, the animal studies could only be suggestive of what was expected to happen in humans.

Table 1. The Metabolic Behavior of Radium and Plutonium in Animals

Property	Radium	Plutonium
Initial excretion (rats)		
urinary (first day)	~15 %	~0.7 %
fecal (first day)	~16 %	~2.3 %
Total excretion in 25 days (rats)		
urinary	~23 %	~2.5 %
fecal	~32 %	~25.0 %
Overall deposition		
bone	99 %	~50 %
liver	—	~30 %(at first)
Bone deposition	within the mineralized bone	surface of "active" bone

Planning for the Human Injection Studies

By August 1944, despite the efforts of a full-time chemist at Los Alamos and another at Chicago, no satisfactory method of analyzing excreta that could consistently detect 1-microgram body burdens had yet been devised (assuming the 0.01-per-cent urinary excretion rate suggested by the animal experiments). An ion-exchange method developed by the Met Lab was satisfactory at the 5-microgram level, but Hempelmann was convinced it was important to achieve even lower levels of detectablility (see "Detection of Internal Plutonium").

People in the Chemistry Division at Los Alamos were concerned "about the inability of the Medical Group to detect dangerous amounts of plutonium in the body." They had already had instances of significant inhalation exposures and one accident in which a chemist inadvertently swallowed an unknown, but small amount of plutonium solution (see "A Swallow of Plutonium"). In addition, there had been five accidents involving wound exposures. They could not afford to continue using guesswork as the basis for transferring skilled workers who had experienced plutonium exposures away from priority work.

As a result, on August 16, 1944, Hempelmann proposed a new research program to Oppenheimer. The first order of business would be "development of methods of detection of plutonium in the excreta." Hempelmann also stressed the importance of determining "the factor by which the amount of plutonium in the excreta must be multiplied to ascertain the amount in the body" and of developing "methods of detection of plutonium in the lung."

Oppenheimer authorized work on the detection of plutonium in both excreta and lungs, but he was concerned about balancing priorities. He said, "in view of the many urgent problems facing the laboratory, it should be carried out with as small an investment of personnel as possible . . . fewer than ten people." In the same vein, he continued: "As for the biological sides of the work, which may involve animal or even human experimentation . . . it is desirable if these can in any way be handled elsewhere not to undertake them here." Los Alamos lacked the appropriate medical research facilities, and Oppenheimer suggested that Hempelmann and he "discuss the biological questions with Colonel Warren at a very early date." Warren, of course, had by now been in charge of the medical programs for the Manhattan Project for over a year. It was logical that biological research should be carried out at a site, such as Rochester, which housed the appropriate staff and facilities.

A three-part plan. Groves, informed of the plutonium exposure problems, apparently made sure that Warren was in Los Alamos about a week later. On August 29, Hempelmann summarized

A Swallow of Plutonium

On August 1, 1944, a sealed tube containing plutonium chloride solution ejected part of its contents while being opened.* Gases had built up, most likely from the dissociation of water by the alpha radiation, and some of the solution shot through the narrow tube out against the wall when the pressure was released and the gases "boiled." Don Mastick, the young chemist working with the plutonium, realized from the taste of acid in his mouth that part of the solution must have bounced off the wall into his mouth.

It was estimated that about 10 milligrams of the material was lost, mostly on the walls of the room, with some on Mastick's face and some swallowed. Although his face was thoroughly scrubbed, the skin remained contaminated with about a microgram of plutonium. His mouth was also thoroughly washed, but for many days afterwards, he could blow at an open-faced ionization chamber across the room and cause the needle to go off-scale—the level of contamination estimated to be about 10 micrograms. (This last fact suggests that the plutonium solution may have had other radioactive contaminants in it since it was later found not to be possible to detect plutonium deposited in the lungs through ionized air molecules.)

Hempelmann pumped out Mastick's stomach to retrieve much of what had been swallowed (analysis of the contents for plutonium registered 4098 counts per minute, which corresponds to only about 60 nanograms). Since very little would have been absorbed through his gastrointestinal tract, Mastick ended up with only a barely measurable body burden. His initial 24-hour urine assays, when the excretion rate was highest, were only 5 to 7 counts per minute, which translates to well below a 1-microgram body burden. Some plutonium was absorbed, of course, and improved assay methods available in the early seventies were able to detect small amounts of plutonium in his urine thirty years later (hundredths of counts per minute).

*The 10 milligrams that were ejected in the accident were not "Los Alamos' entire supply of plutonium," as reported elsewhere (for example, by Eileen Welsome in her 1993 articles in the *Albuquerque Tribune* and in the October 1995 *Final Report* of the President's Advisory Committee on Human Radiation Experiments). In March the first 1-gram reduction of plutonium to metal had been performed at Los Alamos, and by the end of August, the Laboratory was working with over 50 grams of plutonium (5000 times more than the amount sprayed at the wall).

the program that he, Warren, Kennedy, and Oppenheimer had decided upon. Los Alamos would develop "chemical methods of determining plutonium in the excreta and in tissues and of ionization methods of detecting plutonium in the lungs." Experiments at Los Alamos with animals would be used to check the detection methods. The third part of the program would involve "tracer experiments on humans to determine the percentage of plutonium excreted daily."

It was stated that "when satisfactory analytical methods have been developed in this laboratory the problem of carrying out further metabolic studies will be turned over to another medical group, presumably the Rochester group." Initially, Rochester would determine the lethal dose in animals using plutonium supplied by Los Alamos.

The excretion rate. By February 1945, Los Alamos, the Met Lab, and the Berkeley groups all had analytical methods they felt were adequate for the analysis of plutonium in excreta (see "Detection of Internal Plutonium"). They could thus turn to the next puzzle, the ratio of excreted to retained plutonium. Much of the animal data showed that a constant daily urinary excretion rate occurred within two or three weeks that was 0.01 per cent of the initial injection. By March, urine samples from Los Alamos workers were indicating, based on the 0.01-per-cent rate, that some of the workers were approaching or had exceeded a body burden of one microgram. Concern about this situation was mounting.

There were other discrepancies and concerns. Numerous workers with high nose-swipe counts had *no* definite sign of plutonium in their urine. Was this due to hand contamination of the nose, insoluble plutonium particles that had not reached the circulatory sytem, or large particles still lodged in the upper bronchi and nasal passages? The large variations in the animal data for the uri-

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Detection of Internal Plutonium

In 1944, not only were there uncertainties in the animal data, but methods for measuring the amount of plutonium retained in the bodies of workers were not well defined. People realized that because plutonium was an alpha emitter, the radiation was readily absorbed by the surrounding material, and analysis of excreta for plutonium activity offered the most promising route for estimating body burdens of internal plutonium. However, the low excretion rates predicted from animal experiments would make analysis difficult. On the first day after injection, when the fecal and urinary excretion rates were at their highest, the total amount excreted in the urine in 24 hours was less than 10 per cent of the amount injected, and similarly with feces. The excretion rates then dropped rapidly for several weeks, finally leveling off, for urine, at only 0.01 per cent of the injected plutonium.

Although large doses could be injected into animals to insure good analytical results, the same could not be done with humans. If an 0.01-percent daily urinary excretion rate was true for humans, a 24-hour urine sample from a subject with 5 micrograms of retained plutonium would contain only 0.5 nanograms (nano = 10^{-9}) of plutonium (see "Estimates of the Detection Regime").

Excreta samples also had the problem that most of the alpha radiation would be absorbed by the sample mass. Thus, analytical techniques had to be developed to reduce the mass of other material and to concentrate the plutonium by dissolving, evaporating, or ashing the sample and by extracting, precipitating, or plating the plutonium for measurement of alpha activity.

Ion-exchange. That summer, the Met Lab's Health Division developed a urinalysis procedure for isolating and detecting tenths of nanograms of plutonium in urine. The method was based on direct isolation of the plutonium by passing an acidified 100-milliliter urine sample through a cation-exchange resin. After the resin had captured the plutonium, the concentrated metal was eluted from the column and transferred to a counting plate where the alpha activity was measured.

In July 1944, Hempelmann was informed of the Met Lab urinalysis procedure and of the apparent constant 0.01 per cent urinary excretion rate derived from animal studies. Several items—such as his calculation for the dose to the lungs from a 1-microgram plutonium dust particle, early results from the animal experiments, and a difference of opinion of a factor of 10 about what constituted a "safe" alpha radiation dose for tissue cells—were beginning to make him think that detection methods needed to be sensitive to lower levels than the proposed 5-microgram tolerance limit. Also, the Met Lab had determined that blood counts gave evidence of over-dosage but not until a relatively late stage following deposition of the plutonium in the bone. Thus, Hempelmann informed Oppenheimer that analysis of excreta samples in the early stages following exposure, when the excretion rates were highest, was the only method for early detection of overexposure.

Hempelmann assigned a biochemist, Anne Perley, to investigate if the Chicago procedure was suitable for detecting 1-microgram body burdens. By the end of the month, she informed him that the combination of the Met Lab procedure and the Los Alamos alpha counters were inadequate for detection of plutonium levels consistent with 1-microgram body burdens. In fact, attempts to use the

Met Lab procedure to analyze urine samples of four Los Alamos workers who had already experienced instances of high readings from their nose swipes failed to detect concentrations of plutonium alpha activity consistent with the high nose-count records.

As it turned out, one problem with the Chicago procedure was that running a complete 24-hour urine sample (1 to 2 liters) through the column overloaded the resin with organic material. A drop in resin performance altered results and nullified the expected increases in sensitivity. The Chicago method worked well with 100-milliliter aliquots at the activity level of excreted plutonium-239 expected for 5-microgram body burdens. But detection of body burdens of 1-microgram or less would require an analytical procedure that used a 24-hour urine sample and eliminated the organic material and urine salts.

Concerns were heightened by an accident in August in which part of a plutonium-chloride solution sprayed into the mouth of Don Mastick, a young chemist (see "A Swallow of Plutonium"). How much of the plutonium had been absorbed by his gastrointestinal tract? What fraction of a serious dose did the absorbed plutonium represent? Was it safe for him to go back to work at his old job and possibly be exposed again? In fact, to avoid further exposures, Mastick was transferred temporarily to Hempelmann's group "to work on the problem of detection of plutonium in the excreta."

The research team at Los Alamos that attacked the problem of detection methods included Perley, who continued to investigate the Chicago procedure, Robert Fryxell, who studied a method of separating plutonium from urine that used cupferron as the main complexing agent, and Mastick, who investigated various ether extractions. The analytical procedure for isolating plutonium from one liter of urine (a 24-hour sample) was outlined by Arthur Wahl. In September, Roger Kleinschmidt joined the team to investigate methods of isolating plutonium from urine ash samples using a lanthanum-fluoride carrier to precipitate plutonium from the dissolved ash. He would also direct the plating and measurement of the final precipitate with a goal of 90-per-cent chemical recovery of spiked urine samples.

Fryxell consulted with Wright Langham on the cupferron technique for plutonium isolation. Langham was a biochemist who had been transferred to Los Alamos in July 1944. Previously, he had spent a short period at the Met Lab in the analytical chemistry group where he'd been involved in plutonium purification research. Before long, Wright Langham would become one of the major names associated with the detection, analysis, and evaluation of plutonium in humans.

Cupferron extraction. By late 1944, Hempelmann's team had devised a satisfactory technique, using cupferron extraction, for analysis of urine containing tenths of a nanogram of plutonium. After collection, the samples underwent a multistep preparation that included evaporation to dryness, treatement with acid and peroxide to remove organic matter, and the cupferron extraction step. Eventually, the plutonium was carried out of solution as a co-precipitate with lanthanum fluoride, and this final precipitate was transferred to a platinum disc. The activity of the plated sample was measured by placing the disc in an alpha counter.

However, analyzing spiked urine samples—or even samples taken from animals—in a laboratory environment was one thing. Analyzing samples from people working with plutonium on a daily basis was another thing entirely. Early assays of workers yielded surprisingly high results, indicating that if the 0.01-per-cent-per-day excretion rate derived from the animal data were applicable to humans, then these workers had significant levels (greater than microgram amounts) of deposited plutonium.

Sample contamination. An analysis technique sensitive enough to detect tenths of nanograms would easily detect tiny particles of plutonium dust or contaminated skin that, say, dropped from a worker's hand into the sampling flask. As a result, a collection procedure was set up in which the worker to

Estimates of the Detection Regime

Plutonium-239 has a specific activity of 0.06 curies per gram, which means that a nanogram of the substance undergoes about 130 disintegrations per minute ((0.06 Ci/g) (10^{-9} g/ng) (3.7 x 10^{10} d/s/Ci) (60 s/min) < 130 d/min/ng). However, the Hanford "product" contained small quantities of other plutonium isotopes (at the time, it was commonly referred to as 239-240 Pu), and accounting for such impurities increases the rate to about 140 disintegrations per minute per nanogram. If we want to detect a tolerance limit of 5 micrograms of "product" in the body and only 0.01 per cent of the plutonium is being excreted per day (several weeks after the initial exposure), then a 1-liter, 24-hour sample of urine will contain 0.5 nanograms of plutonium. If only 100 milliliters (10 per cent) is analyzed, the test must be capable of detecting 0.05 nanograms of plutonium. A sample at this level emits about 7 alpha particles per minute (0.05 ng 3 140 d/m/ng), which, in an alpha counter with 50 per cent efficiency, corresponds to a reading of 3 or 4 counts per minute. If we want to detect a lower tolerance limit of 1 microgram—one-fifth as large—the counting rate drops to less than 1 count per minute.

be tested was removed from the workplace for forty-eight hours and asked to "wear freshly laundered clothing . . . and to bathe and wash their hands frequently." After this period, the worker was admitted to the hospital, asked to shower, placed in a special room (the "health pass ward"), and checked for contamination. He was instructed to wash his hands and wear white cotton gloves each time he urinated, and the flask and funnel were placed so they didn't have to be touched.

A trial run with plutonium workers vividly demonstrated the need for such care: the average counts per minute when the samples were collected by the workers at home was 20, whereas the average for samples collected using the above procedure was only 2.2 counts per minute! Thus, external contaminates picked up at work made the plutonium excretion rate appear ten times larger than it actually was.

Other problems solved by people at the Met Lab and at Los Alamos were the maintenance of a laboratory free from alpha contamination (including the reagents used in the analysis), the development of a method capable of handling large volumes of urine (1-liter rather than 100-milliliter samples), and the development at Chicago of alpha-counting instruments capable of detecting less than 1 alpha count per minute.

By February 1945, which coincided with delivery of multi-gram amounts of plutonium from Hanford, the urinalysis procedure appeared capable of detecting 0.02 nanogram of plutonium-239 alpha activity in a 24-hour urine sample. If the human urinary excretion rate was equal to the animal rate of 0.01 per cent per day, the method could detect a body burden of less than 1 microgram with 95 per cent confidence.

The method was tested on thirty-six workers at Los Alamos. Fourteen of these people had evidence of previous inhalations of plutonium dust because of at least one high nose-swipe count. These fourteen people had an average of 1.2 counts per minute in their 24-hour urine samples. The urine samples of the other twenty-two people, who had never shown a high nose-swipe count, averaged 0.2 counts per minute. The five most highly exposed people had urine samples with an average of 2.2 counts per minute. Such correlations were strong evidence that development of a sensitive analytical procedure had succeeded at Los Alamos.

TTA extraction. The method developed at Berkeley for analyzing urine samples used extraction with thiophenyltrifluoracetone (TTA). After the sample was ashed, a lanthanum-fluoride precipitation was performed, followed by the TTA extraction step. This method resulted in a negligible sample mass and low background counts.

One of the main sources of alpha contamination in the Berkeley and Los Alamos methods was the lanthanum-fluoride reagent. The Los Alamos procedure *ended* with the lanthanum-fluoride precipitation step, which introduced alpha contaminants and limited the sensitivity of the technique because of a count-per-minute background. In the Berkeley procedure, the lanthanum-fluoride-precipitation step preceded the extraction step, and the alpha contaminants were left behind, which yielded a background of only 0.2 counts per minute.

Each of the three techniques had its advantages and disadvantages, as well as its proponents and detractors, but the Los Alamos, Chicago, and Berkeley sites were each able to acquire highly satisfactory data using their particular method. ■

The Los Alamos Urine Analysis Method

The method developed in 1945 at Los Alamos for the plutonium analysis of urine started by evaporating a 24-hour urine specimen almost to dryness. (It was recommended that people being tested keep their intake of liquids to a minimum—one cup of liquid per meal and little or no liquids in between—to expedite this step.) The residue was then wet-ashed (by repeated additions of concentrated acids and hydrogen peroxide) until a white solid almost completely free of organic matter remained. The solid was dissolved in hydrochloric acid and precipitated as hydroxide. After redissolving the precipitate in hydrochloric acid and adjusting the pH, ferric iron was added as a carrier, and the dissolved plutonium was complexed with cupferron (an organic compound that forms a soluble complex with iron). Choroform was then used to extract the cupferron complex, separating it from other dissolved materials in the aqueous solution. (One of the most critical steps in the process was using a separatory flask to draw off exactly the chloroform layer.) After the chloroform was evaporated, the cupferron residue was digested with nitric and perchloric acids. Finally, the plutonium was carried out of this solution as part of a lanthanum fluoride precipitate, leaving the iron behind. The final precipitate was transferred to a platinum foil, dried, and counted in an alpha-particle detector for thirty minutes. The main reason for these various steps was to concentrate the plutonium while minimizing material that would deposit on the foil and absorb part of the alpha radiation. Control urine samples spiked with plutonium analyzed concurrently with regular samples demonstrated an average chemical recovery of 88 per cent (611 per cent one standard deviation) and a reagent-contaminate background of 1 count per minute.

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nary and fecal excretion rates—factors of 1 to 5 in rodents and 1 to 2 in dogs—cast doubt on whether or not the use of an 0.01-per-cent daily urinary excretion rate for humans was even appropriate. Animal data showed that more plutonium was usually excreted in stools than in urine. Would stool assays be more sensitive than urine assays for humans? The only way to address these concerns was with further studies. But time was critical. Many of the people at Los Alamos were working seven days a week to meet a schedule for the first test of a plutonium weapon in July 1945. There was no time to start another series of animal experiments, and thus, the researchers turned to human studies.

A fact important to the planning of the human injection experiments had been established in experiments with rats at Los Alamos. Five groups of rats had been injected with plutonium doses that ranged from 0.032 to 52 micrograms, and the excretion rate over a 5-day period was determined for each group. Wright Langham, a biochemist and the Biochemical Section Leader under Hempelmann, reported in May 1945 that "the per cent of the total injected dose excreted in the urine . . . is independent of the size of the dose administered." This meant two things: first, a single injection dose, rather than a series of different doses, would be adequate for the study; and second, at a given time after the injection, the amount of plutonium being excreted was simply proportional to the amount injected, and the excretion rate could be used as a direct measure of the plutonim retained in the body. The problem, of course, was establishing accurately the specific ratio for humans.

Hamilton's original work with rats in 1944 had not developed complete excretion curves, but rather pooled samples for chemical analysis at broadly separated intervals (days 4, 16, 32, and 64). On the other hand, Langham's studies with rats had used a daily sampling basis out to 44 days after the injections. Those data, available in July 1945, would have convinced Langham that excretion could be accurately "modeled" using linear plots with the data collected daily for only a few weeks, apparently a key factor in the planning of the human experiments.

Working with the Medical Corps. On March 26, 1945, Hempelmann and others at Los Alamos met with Lt. Colonel Hymer Friedell from the Manhattan Project Medical Section under Warren. In a memo summarizing the meeting for Oppenheimer, Hempelmann stated that they had requested the Manhattan Project Medical Corps "to help make arrangements for a human tracer experiment to determine the percentage of plutonium excreted daily in the urine and feces." They further suggested that "a hospital patient at either Rochester or Chicago be chosen for injection of from one to ten micrograms of material and that the excreta be sent to this laboratory [Los Alamos] for analysis."

The memo also discussed other topics related to the hazards of plutonium, including improvement of protection methods, study of ways to treat overexposed personnel, and development of methods to detect plutonium in the lungs. One of the requests summarized in the memo was "a more satisfactory relationship of this project [Los Alamos] with the Medical Program of the Manhattan District so that the facilities of the Manhattan District will be available for the solution of our problems," and it was suggested "that channels be established through which our problems can be brought to the attention of those individuals who plan the research program of the Manhattan District."

Oppenheimer followed up these discussion with a letter to Warren in which he said:

> *We all have the feeling that at the present time the hazards of workers at Site Y are probably very much more serious than those at any other branch of the Project, and that it would be appropriate that the medical program of the Manhattan District consider some of our problems rather more intensively than they have in the past. . . . Although we would have some ideas of how to pursue all of the topics mentioned, we have, as you know, neither the personnel nor the facilities which would be involved in this. . . . It was our impression that if other workers on the medical program were better informed about what was important from our point of view they would probably be glad to help us out.*

He was reiterating the same point he had made the year before.

The people at Los Alamos were thus ready to move to the third part of the plan that been had agreed upon in August 1944. Warren was also ready. In a December 2, 1944, memo (outlining points for a meeting two days later), he had stated that there was an urgent need both for experiments to establish "the ratios of blood level to urine and fecal excretion following a single intravenous injection of radium and product in rats" and for "[similar] tracer experiments on humans . . . so that the comparison (factor) can be made between the rat data and human data." The three people he identified in conjunction with this work were "Dr. [William] Bale [at Rochester], Dr. Hempelmann, and Dr. [Kenneth] Cole [at Chicago]."

It is easy to get the impression that the human plutonium injections were isolated experiments. However, a number of other studies had been or were being conducted. For example, in 1941, Hamilton's team injected six patients who had bone cancer with radioactive strontium. That metal is also a bone seeker, and Hamilton was studying it as a possible therapeutic agent for the treatment of bone cancer.

Other human experiments involved various toxic heavy-metal radioisotopes that were either materials important for the development of the atomic weapons (polonium and uranium) or were part of a comparative evaluation of health hazards (radium). The polonium studies helped to develop techniques for the similar but later studies with plutonium (see "Polonium Human-Injection Experiments").

One of the main problems in the polonium studies was contamination. Working with the material could easily contaminate laboratory equipment used in the analysis, which, in turn, could bias results or even contaminate samples related to other studies. It was thus anticipated that analysis procedures for plutonium would require laboratories that were absolutely free of alpha contamination. A "clean laboratory" was established at Los Alamos in February 1945 in the Medical Labs Building, and the responsibilities in the plutonium study were split. The Medical Corps or the Rochester Project would handle the clinical work, and Los Alamos would analyze the resulting biological samples.

The First Human Experiments with Plutonium

Reports issued in 1945 show that three human plutonium-injection studies were authorized in April 1945—a study by the Chicago Met Lab Health Group, another by Hamilton's group in Berkeley and San Francisco, and a third study to be done jointly by Warren at the Army Medical Corp Hospital in Oak Ridge (clinical) and the Los Alamos Health Group (analytical). The three approaches would allow using plutonium in two different valence states (+4 and +6), two different chemical forms (citrate and nitrate), and two different isotopes (plutonium-239 and plutonium-238). Each group would be responsible for analysis of excreta samples using their own plutonium analysis technique developed for that purpose (the cupferron-extraction method at Los Alamos, the cation-exchange method at Chicago, and the thiophenyltrifluoroacetone extraction method at Berkeley).

The plutonium-239 dose decided on for the Oak Ridge-Los Alamos and the

At the present time the hazards of workers at Site Y are probably very much more serious than those at any other branch of the Project. . . . it would be appropriate that the medical program of the Manhattan District consider some of our problems rather more intensely than they have in the past.

Chicago studies was 5 micrograms. That quantity would enable the Chicago group to detect plutonium accurately using 100-milliliter urine-sample aliquots of 24-hour collections and would provide appropriate activity levels for the Los Alamos method, which used full 24-hour urine samples. The Berkeley site, however, would use a different isotope, plutonium-238, at a different dose level; the injected mass would only be 0.2 microgram, but because of a much higher specific activivy, it would have 10 times the radioactivity. As a result, the excreta samples at Berkeley would also be expected to have more than ten times the activity of corresponding samples from the other two studies, increasing the accuracy and precision of the alpha measurements on the excreta samples.

Oak Ridge. The first human plutonium injection occurred on April 10, 1945, barely two weeks after the meeting in Los Alamos between Friedell, Hempelmann, and others. The person chosen for the experiment was a 55-year old man and a patient at the Manhattan Project Army Hospital in Oak Ridge. (Although the man was the first patient injected with plutonium, he was later grouped in reports with other patients injected at the Rochester site and was identified as HP-12.)* He had been hospitalized because of injuries in an automobile accident, and bones in his right forearm, left thigh, and right knee were broken. Some of the fractures were "in poor position," which meant an operation to properly set the bones would be necessary. Except for those injuries and "a chronic urethral discharge which he has had for 10-15 years [his clinical record states this may have been due to chronic gonorrhea]," HP-12 had always been employed as a cement mixer and was generally in good health ("well developed, well nourished").

In a report for a conference on plutonium, held May 14 and 15, 1945, Wright Langham stated that "the person was an elderly male whose age and general health was such that there is little or no possibility that the injection can have

*Many of the names of the people who were injected with plutonium have been published elsewhere. However, we did not want to intrude further on the families of those people and so will only identify the patients by case number.

any effect on the normal course of his life." HP-12 was 53 at the time of the injection and lived another 8 years before dying, in 1953, of heart failure. Late radiation effects, such as cancer, were not expected to develop for ten to fifteen years, if at all. For example, the induction period in humans for radium-induced cancer, especially malignancy of the bones, was about 10 to 30 years after exposure. Despite Langham's statement, we cannot, of course, discount the fact that HP-12 might have lived 20 or more years; although in 1945, fifty years of age was considered to be fairly advanced. On the other hand, the GIs at Los Alamos who were heavily exposed to plutonium in 1945 while working in D Building under poor industrial hygiene conditions (see "On the Front Lines" on page 124) were in their early twenties and were at greater risk of developing late radiation effects than was HP-12.

HP-12 was injected with 4.7 micrograms of plutonium (0.29 microcuries) in the chemical form of the +4 citrate salt. The material had been sent to Dr. Friedell at Oak Ridge by Wright Langham, along with directions for its use on a human subject. Langham stated that citrate was chosen "to produce the maximum deposition in the bone . . . [so as to] produce an excretion rate comparable to that of a worker having absorbed the material at a slow rate." Urine samples were collected almost continuously for the first 42 days, and then intermittently until the 89th day after injection. Regular stool samples were collected as well over a 46-day period. In accordance with the plan, the Manhattan District Medical Office conducted the clinical part of the experiment, and the urine and fecal samples were sent to Los Alamos for analysis.

Langham also reported at the May conference that "the excretion during the first day was surprisingly low [0.1 per cent in the urine] and . . . the leveling off of the excretion rate was much slower than with rats." Langham sug-

Polonium Human-Injection Experiments

In 1944, in response to concerns for the risk associated with occupational exposures to polonium, the Army Medical Corps authorized Rochester to undertake a study of the biological behavior of that element. The program was started in August 1944 with animals, and by November, studies with humans had begun. Eventually, tracer amounts of radioactive polonium-210 were injected into four hospitalized humans and ingested by a fifth.

Polonium, the first element isolated by Marie and Pierre Curie from pitchblende in 1898, is an alpha emitter. When alpha particles from polonium-210 collide with beryllium atoms, neutrons are ejected, and polonium-beryllium combinations had already served physicists as a convenient source of neutrons. During the Manhattan Project, it was decided to use that neutron source as an initiator of the chain reaction in the atomic bombs, thus making polonium (and beryllium) an occupational health hazard for the people who needed to develop and build the initiators.

In the Rochester work, the subjects of the excretion studies were volunteers. The problem had been outlined to patients at the Rochester Hospital, who were told that it would involve the intake of tracer amounts of a radioactive substance followed by analysis of their excreta. Because polonium was not classified at that time,* the doctors may have even told the patients what substance they would be injected with. From the group of volunteers, four men and one woman were selected for the studies. They ranged in age from the early thirties to the early forties and were being treated for a variety of cancers (lymphosarcoma and various leukemias). One patient died from his cancer six days after the injection.

Four of the volunteers were injected with doses of polonium in a soluble form that ranged from 0.17 to 0.3 microcurie per kilogram of body weight. The fifth patient drank water containing 18.5 microcuries of polonium chloride, equivalent to 0.19 microcuries per kilogram of body weight. The amount of polonium excreted in urine and feces were analyzed, and blood samples were taken to determine the amount freely circulating in the blood. Autopsy tissue samples were taken from the patient who died to determine the distribution of polonium throughout the body.

Polonium-210 has a short half-life (138 days) and very high activity (4,490 microcuries per microgram). The high activity meant very small quantities (of the order of nanograms, a factor of 1000 less than for plutonium) could be administered and detected, so concerns of chemical toxicity were minimal. The short half-life meant the substance would not remain in the body so that concerns about long-term radiation effects were also minimized. In 1945, urine assays corresponding to the tolerance limits were 7 counts per minute for plutonium-239 but 1500 counts per minute for polonium-210.

Such metabolic studies were possible at Rochester University in 1944 because polonium was available at that time. The research yielded important information for the Manhattan Project on the hazards of polonium and helped develop techniques for the similar but later studies of plutonium.

*Polonium was classified in July 1945 and given the code name "postum."

gested that the initial low rate was most likely due to "some metabolic abnormality of the subject." Indeed, it was noted that urine protein tests indicated that HP-12's kidney function "may not have been completely normal at the time of injection." Another explanation was "the stability of the +4 citrate complex"—50 per cent of the injected dose was still circulating in the blood four hours after injection.
One positive note was the fact that the excretion rate seemed to have leveled off after a couple of weeks at 0.02 per cent, rather than the 0.01 per cent predicted from animal data. If the true excretion rate in humans was twice as high as the rate in animals, then earlier urine assays from plutonium workers that had been interpreted using the 0.01-per-cent excretion rate had overestimated the body burden by a factor of two.

When HP-12 was operated on for reduction of the fracture in his knee, biopsies for analysis were taken from the kneecap and the top end of the main bone in the lower leg (tibia) close to the knee. The intent of obtaining those samples was to see how much plutonium had been deposited on the bone in the 96 hours since the injection. At a later date, fifteen of his teeth were removed (it was noted on his initial physical that "patient had marked caries and pyorrhea [an inflammation and discharge of the gums]"), and these also became available for plutonium analysis. Langham reported on the concentrations of plutonium in HP-12's bone and teeth in 1950; they were comparable to the levels in tissue samples from other subjects.

Chicago. Sixteen days later on April 26, 1945, a second human plutonium injection took place at Billings Hospital in Chicago. A sixty-eight-year-old man, later identified as CHI-1, was injected with 6.5 micrograms of plutonium (0.4 microcuries) in the chemical form of the +6 citrate salt. This man had an advanced case of metastasized cancer of the chin and lungs and only lived another 160 days. An autospy was performed after his death, and a series of tissue and bone samples were taken so that the distribution of plutonium in the body could be determined.

The initial 24-hour urinary excretion rate (2.5 per cent) for CHI-1 was much larger than for HP-12 (0.1 per cent). However, within a few days the rates for the two subjects were comparable, and after 21 days, the rate appeared to level off—at about 0.03 per cent of the injected dose.

One of the findings of these first two human experiments was that the amount of plutonium excreted in fecal matter was considerably lower than in animals (compared to some species, a factor of as much as six times lower). In fact, the human feces excretion rate was comparable to or less than the human urinary excretion rate, and so analysis of human fecal matter did not appear to be a more promising way to determine plutonium body burdens, as had been suggested by the animal experiments.

California. On May 14, 1945, a third person, CAL-1, was injected with plutonium at the University of California Hospital in San Francisco. CAL-1 was a 58-year-old house painter that had been diagnosed with stomach cancer and was thus expected to live only six more months. Surgery revealed a firm tumor that extended into the liver and the tail of the pancreas, confirming the diagnosis of cancer, and a large part of his stomach was removed. However,

A Cross-Check of Analytical Procedures

Several weeks after the first Chicago patient had been injected with plutonium, the Met Lab sent to Los Alamos selected sets of aliquots of this patient's urine, including single small aliquots of the first and third voidings collected the first day after the injection. Later, they sent five 100-milliliter aliquots from each of days 40 and 41. When Los Alamos analyzed the two early samples using their procedure, the values (59 and 0.45 picocuries per cubic centimeter, respectively) agreed with those of the Met Lab (58 and 0.4 picocuries per cubic centimer, respectively). Despite the fact the two labs used different plutonium-extraction techniques, this agreement provided evidence of comparable radiochemical proficiency and instrument calibration, at least when the count rates were high (2935 and 31.0 counts per minute, respectively). (A similar comparison was not done with samples from Berkeley.)

The measurements for the ten aliquots from days 40 and 41 (with plutonium concentrations of only about 0.01 per cent of the injected dose) were less satisfactory. The excretion values obtained at Los Alamos ranged from 0.00 to 0.03 per cent of the injected dose, which, although they bracketed the Chicago results (0.011 and 0.009 per cent), were suspect because of the large measurement error. The uncertainty was due to a count rate for the samples (1 to 2 counts per minute) comparable to the background rate of 1 count per minute. This background was a result of the lanthanum-fluoride co-precipitation step, which introduced alpha-emitting impurities. The Chicago procedure did not use lanthanum fluoride, and their background was lower, which allowed them to achieve significant results with 100-milliliter aliquots. Unfortunately, the Chicago procedure would reach the limit of *its* detectability if the plutonium concentrations being measured were any lower because of an inability to analyze large urine samples.

later microscopic examination of the tumor revealed no evidence of cancer and indicated that the diagnosis was incorrect. After another year or so in which no other cancer appeared, the physicians became completely convinced that CAL-1 had had a benign gastric ulcer.

CAL-1 lived for almost another 21 years and died in 1966 from heart disease at the age of 79. Although CAL-1 lived much longer after the injection than expected (based on the original diagnosis), his treatment, including the operation in 1945, was independent of the injection and was not altered because of the plutonium experiment.

The plutonium given to CAL-1 was actually a mixture of plutonium-239 (0.75 micrograms) and plutonium-238 (0.2 micrograms). As noted earlier, Hamilton had proposed using plutonium-238 in metabolic studies because the higher activity of plutonium-238 made it easier to analyze samples. For the sake of comparison, if plutonium were retained in the body, say, at the one-microgram level, urine samples would yield thousands of counts per minute for plutonium-238 compared to 7 counts per minute for plutonium-239.

At the same time, of course, the additional activity of the plutonium-238 increased the radiation dose to the tissue

*Recalculated in 1976 by Patricia Durbin

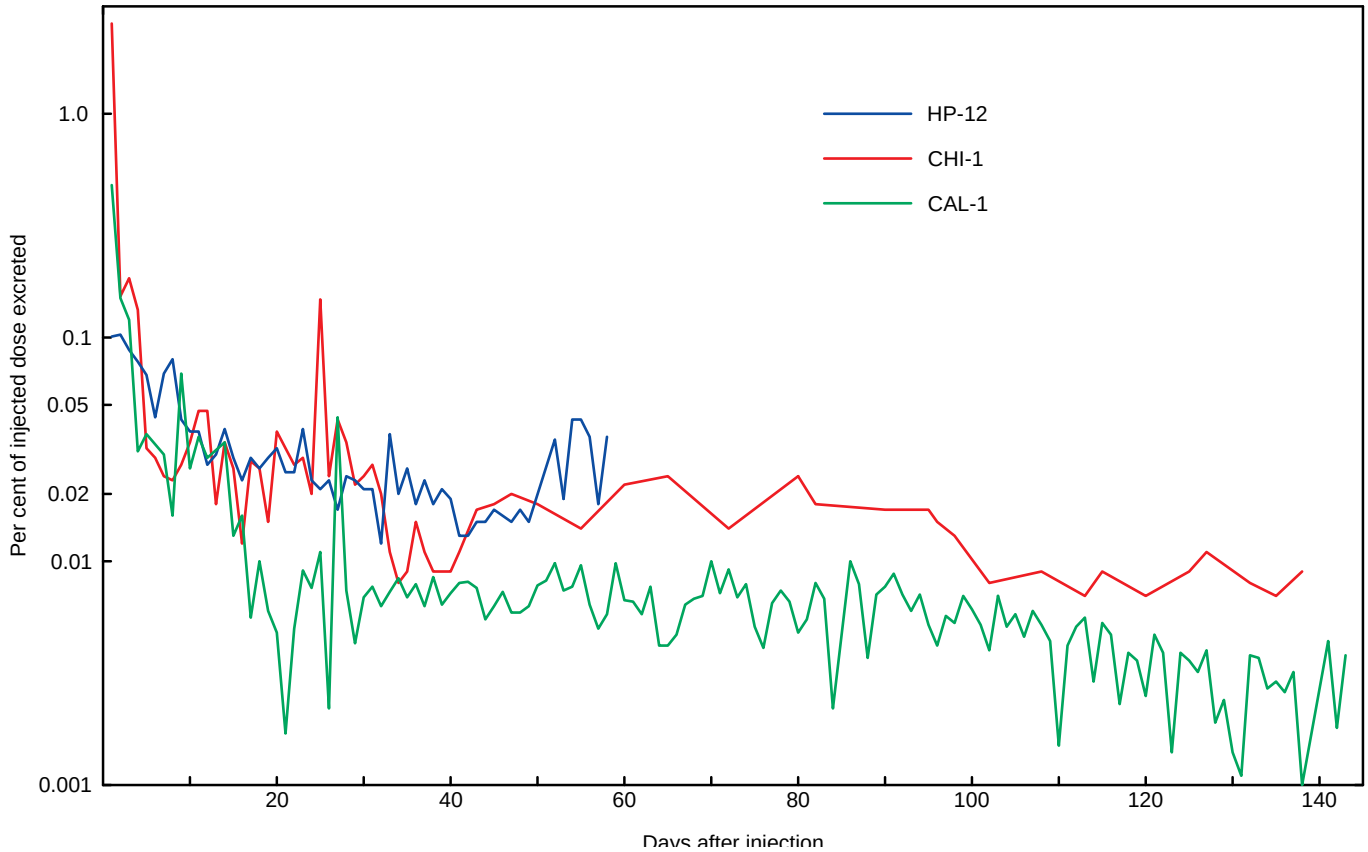

Figure 2. The First Plutonium Urinary Excretion Curves

These urinary excretion curves for the first three injection patients, HP-12, CHI-1, and CAL-1, based on the data as originally analyzed in 1945, illustrate the main features of urinary excretion: a rapid initial rate, but at values much lower than what had been observed for radium, and an apparent leveling off, after about 20 days, at a daily rate somewhere between 0.02 and 0.005 per cent. The curves also illustrate various problems. The initial excretion rate was relatively low for HP-12 (0.1 per cent), which might have been due to his abnormal kidney function. The curve for CAL-1 appears to be consistently lower than the other two; this could have been due to errors in the injected dose (a possible factor of 2), differences in analytical techniques, or differences in the chemical form of the plutonium. It may have also been an indication that the excretion rate varied significantly from person to person. There are instances of unexpected variations in the excretion rate, such as the high values for HP-12 after day 50. As it turns out, the latter values for HP-12 were obtained when researchers at Los Alamos were attempting to improve their analytical procedure and not all the experiments were successful or the results reliable. (Also, after day 42 there were errors in the days-after-injection values—these samples were obtained from HP-12 later than shown, going out as far as day 89). Finally, the long-term data for the CHI-1 and CAL-1 patients suggested that the urinary excretion rate actually continued to fall slowly rather than to stabilize at an 0.01-per-cent daily rate.

for each mass unit of retained plutonium (the total activity of the CAL-1 injection was 3.55 microcuries;* the activity of the HP-12 injection was about 0.3 microcuries). As it turned out, because CAL-1 lived almost 21 more years, he received the highest total radiation dose of the eighteen patients injected with plutonium. His total effective dose-equivalent was 6400 rem, which corresponds to about 309 rem per year, or 858 times what the normal U.S. citizen receives on average every year from natural and manmade radiation sources (0.36 rem).

The urinary excretion rate for CAL-1 started at 0.5 per cent, assumed about the same rate as for the other two patients for the next 12 days, but then reached a constant rate at or below an 0.01 per cent daily rate from about 15 days onward. When data for all three patients were viewed beyond 50 to 60 days after the injection, it appeared as if the "constant" excretion rate actually continued to fall off gradually. For example, by 100 days, the CHI-1 patient had dropped below a daily excretion rate of 0.015 per cent and, between days 130 and 155, was averaging 0.008 per cent.

Hamilton and his group, in a report released a year later on May 31, 1946, stated: "The retention of plutonium in this subject is so great that the loss of this material can be considered negligible. The half time of plutonium excretion is probably greater than fifty years."

The May 31 report also stated that four days after the injection, in the course of the planned surgery, "specimens of rib, blood, spleen, tumor, omentum, and subcutaneous tissue were taken from the patient." Analysis of the bone sample showed that "the major portion of plutonium deposited in the skeleton is to be found in the bone marrow and trabecular [fibrous or spongy] bone." It was also estimated that "87.2% of the plutonium administered was deposited in the skeleton, provided the rib sample is representative of the skeleton generally."

What were some of the main conclusions of the initial injection studies? An August 29, 1946, report of the Chicago work (written by E. R. Russell and J. J. Nickson) stated that:

> *The urinary rate of excretion of plutonium in humans is exceedingly low. The best evidence available at this time would indicate that the "chronic" (150th day) excretion rate does not exceed 0.01 percent per day of the amount fixed in the body.*

In regard to fecal excretion, the report stated:

> *The fecal rate of excretion of plutonium fixed in the body is lower than the urinary rate by a factor of approximately three. What evidence we have would indicate that the rate of fecal excretion does not exceed 0.003 percent per day of the amount in the body.*

The May 31 report of Hamilton's group concluded:

> *This high degree of prolonged retention, together with the tendency of plutonium to become deposited adjacent to the bone marrow in the endosteal and trabecular regions, makes the problem of chronic plutonium poisoning a matter of serious concern for those who come in contact with this material.*

Reduction of tolerance limit. On May 14 and 15, 1945, before the results of the third injection experiment (CAL-1) were available, most of the people involved in this work met at a conference in Chicago to discuss the results of the first two human experiments. They still could not reach a definite conclusion as to what the tolerance limit for plutonium should be.

In a May 21, 1945, letter to Friedell, Wright Langham stated that Los Alamos should "adopt a conservative arbitrary limit [of one microgram] for the maximum tolerance dose and remove all people from further contact with material when they have reached that limit." He agreed with Friedell that "this is probably much too low." Nevertheless, "the urgent need . . . for a working basis and the failure of the Chicago Meeting to establish a limit seems to make it imperative that we adopt a conservative value and go ahead." He thought "it quite likely that further work on the part of other groups will eventually establish a legal tolerance limit of at least one microgram," but in the meantime, the practice of consistently retiring workers below that limit would take care of "the medico-legal aspect" and, "of still greater importance, [reduce the chance of] poisoning someone in case the material proves to be more toxic than one would normally expect."

Langham also suggested that they "continue to collect 24-hour urine samples from [HP-12]—collecting on every third day as long as he is available." He wanted to test extrapolations of the excretion time curve and to have actual samples "with which to try to develop a simpler method of assaying." Because HP-12's kidney function had shown some abnormalities, he also suggested repeating "our human study carefully on an individual whose kidney function has been established as normal beyond question."

Toward the end of June 1945, after data from the first three human-injection experiments were available, the Manhattan District Medical Office lowered the provisional allowable body tolerance for plutonium to 1 microgram. (The Hanford site, because of their operating conditions, such as their new remote-handling facility, was able to adopt an even lower provisional limit of 0.5 microgram.) The rationale for this reduction by a factor of five was based on

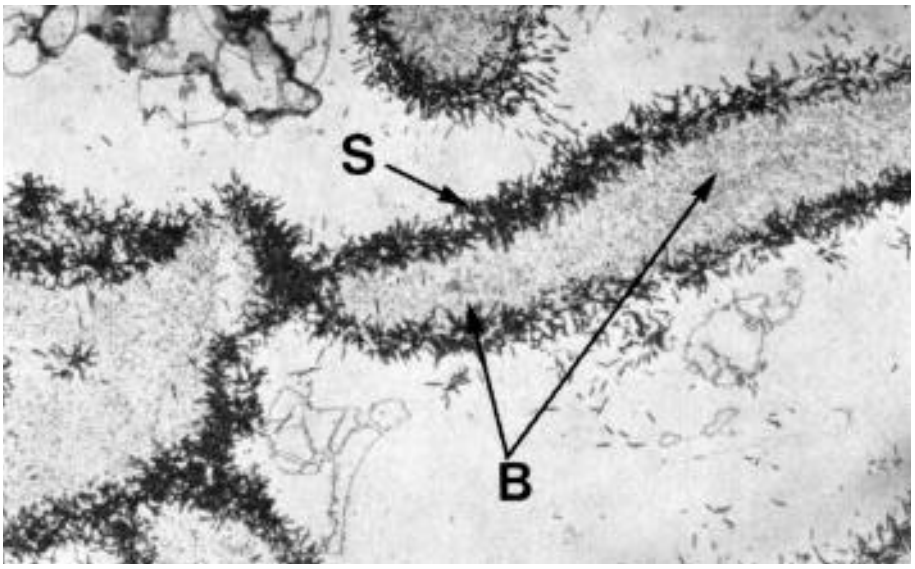

Figure 3. Deposition of Plutonium in the Bone
A neutron-induced autoradiograph (magnified 190 times) of portions of trabecular bone (B) in dog, showing fission tracks from particles of plutonium deposited on the bone surface (S). Radium, in contrast, deposits throughout the bone volume (B). (In *Radiobiology of Plutonium*. 1972. Betsy J. Stover and Webster S. S. Jee, editors. (University of Utah/Salt Lake City: J.W. Press).)

two kinds of experimental results. The first were the results of Met Lab toxicity experiments with animals in which the ability of plutonium and radium to create recognizable and measurable injury, such as death in a certain number of days, was compared. The results of these studies did not agree with the assumption, based on alpha energy deposited in tissue, that plutonium should be about 50 times less toxic than radium. When radium or plutonium were injected in amounts capable of causing death in 30 days, they were essentially equal in toxicity. As the dose was lowered so that the number of days to death increased, plutonium did become less toxic than radium, but the ratio was typically more like 4 than 50.

The second type of experimental result that lead to the reduction in the tolerance limit were autoradiographic studies of bone samples that showed how plutonium and radium were deposited. Much of both ended up in the bone, but radium appeared to be distributed throughout the volume of calcified bone, whereas plutonium concentrated on bone surfaces, especially those surfaces throughout the more biologically active portions of the bone, such as the bone surfaces where the marrow is located (Figure 3).

In a report on the May 14 and 15 conference on plutonium, issued July 23 by the Met Lab, it was postulated that plutonium had a higher level of acute toxicity than expected in relation to radium because of the differences in deposition. A large proportion of the radium buried itself "deep in bony structures where it is relatively innocuous from the standpoint of acute toxicity." On the other hand, plutonium concentrated "in the endosteal layers of bone close to the marrow and (at least to a greater extent than radium) in soft tissues." In fact, these same studies found that another heavy-metal radioisotope, polonium-210, was about 2 to 10 times "as toxic as plutonium per unit of alpha-ray energy dissipated in the body," most likely a result of the fact that polonium concentrated in "highly radio-sensitive soft tissues, such as the hematopoietic and lymphatic tissues themselves."

The Los Alamos Health Handbook. On August 17, 1945, Los Alamos issued the Chemistry and Metallurgy Health Handbook of Radioactive Materials, outlining the hazards and safety procedures for radioactive materials. This handbook put into practice for plutonium what had been learned from the recent animal and human injection studies. The introduction stated:

> *It was deemed essential to indicate to the reader the intensive effort being made to eliminate radiation health hazards: hence, the detailed description of monitoring instruments and, as an example, the chemical assay for 49 [plutonium] and polonium in the urine. . . . The worker exposed to nuclear radiations is emphatically urged to follow the two basic rules: (1) know all the possible radiation hazards in a given job, and, (2) see that proper protective procedures are followed in the job.*

The handbook included a discussion of "tolerance" dose, stating that this "means an upper limit to the radiation energy absorbed per day indefinitely which will be 'absolutely safe,' i.e. which will produce no observable impairment of any function of a large number of healthy humans." The handbook went on to discuss the fact that a "safety factor" was built into the tolerance limit, but that this factor could vary from individual to individual.

> *If the average individual stays within the tolerance limits he can be practically certain of suffering no impairment of any of his functions. If he exceeds the tolerance limits one cannot always predict what the results will be. In general, however if the tolerance limits are not greatly exceeded, the individual need not be considered a "dead duck," for in all probability only minor disability may result.*

The level established for plutonium was

a body burden of one microgram. If a level of more than one microgram was indicated by urine tests, the worker was to be "removed from further contact with the material." This level was established by "a persistent excretion of 7 or more counts per minute per 24 hour sample" (which corresponds to a 1-microgram body burden at an 0.01-percent daily excretion rate and a 50-percent counting efficiency).
In relation to plutonium, the handbook added:

> *For materials such as 49, for which there is not a large experience of long-period human exposure, the tolerance amounts are necessarily set with a conservative view, thus affording the possibility of additional safety factor. Lethal and chronic effects of 49 and Po are being studied extensively in animals. The rate of elimination and the manner of deposition of 49 and Po in tissues of humans is also being studied. At some later time the results of experimentation and experience may lead to an upward revision of the specified tolerance amounts. At present it is safe for the worker to proceed with the presently accepted tolerance values, keeping in his favor any safety factors that may result from conservatism in specifying the tolerances.*

One of the safety factors was the fact that it took several weeks for the 0.01 per cent excretion rate to be reached. For a recent exposure, 7 counts per minute in urine would correspond to a body burden lower than 1 microgram. Thus, there needed to be a "persistent excretion" at that rate before a person was actually removed from work with plutonium.

The handbook also discussed most of what was known about the relative dangers of plutonium and radium, the differences in deposition in the body for these two metals, details of the testing process (both obtaining the urine samples and analyzing them), the various ways plutonium might enter the body and the relative dangers of each pathway, and the fact that plutonium "tends to be deposited on the surface of the bone in close approximation to the radiosensitive cells of the bone marrow."

Hempelmann and his group obviously wanted the people working with plutonium to be as up-to-date as possible about the material and its hazards and to understand what was being done to protect them.

Further Human Plutonium Injection Experiments

By late summer 1945, there were still serious concerns about the Health Group's ability to monitor the plutonium workers adequately and about the type of exposures they were receiving. Hempelmann documented the situation in a memo to Kennedy.

> *This is to confirm our telephone conversation of 22 June 1945 during which we discussed the recent high exposure of personnel in the [Plutonium] Recovery Group. Attached is a list of all urine counts of the people in this group and of high nose counts during the past month. This indicates, I think, that the situation seems to be getting completely out of hand.*

The main concern was the fact that, despite "steps to improve their chemical operations," it was "a grave medical problem." At Kennedy's request, Hempelmann reported these facts to Oppenheimer in a memo on June 26, stating that "as soon as we have evidence that the men have reached tolerance, I shall . . . advise [Kennedy] that they are to be removed from their work."

Also troubling was the fact that the urine assays and nose-swipe counts did not correlate well. It was expected that in some cases, the urine assays would rise. But this would depend on whether a high nose-swipe reading was due to hand contamination or an actual inhalation exposure and then, further, on whether the form of the plutonium was soluble or insoluble.

Likewise, there were questions about the data from the first three studies. The excretion data for CAL-1 appeared consistently lower than the others; HP-12's data were in doubt because of his abnormal kidney function; it was far from certain at what value the excretion rate leveled off, or even if it did; and no autopsy tissue samples had been obtained (CHI-1 would die early in October from his diagnosed cancer). More research was needed—such as a carefully controlled study using about 10 patients in which excretion samples were obtained daily for about three weeks.

On September 5, 1945, Langham and Warren met in Rochester with others of the Rochester group to complete the overall plan for such a series of plutonium injection experiments in humans. A summary of the plan written by Langham states that over three six-week periods, ten patients would be admitted to the metabolism ward at Rochester for the purpose of plutonium injections. The first two weeks of each six-week period would be a control period used to "determine the degree of normalcy of the metabolism of the subject, collect blank feces, get the subject on a standard diet, and get ward attendants and subjects in the habit of collecting all urine and feces." One of the purposes of the control period would be to establish "the normal radioactivity content" of the patient due to elements such as uranium, thorium, and radium that are normally ingested in food.

At the end of the control period, each subject would "be given five micrograms of product in a single intravenous injection. For the next 24 days

Louis H. Hempelmann—1914-1993

Louis Hempelmann (right) with George Voelz looking on.

Louis Hempelmann became interested in the use of the cyclotron in medicine and biology in 1941, and this interest set the stage for an illustrious career in the medical field of radiology, health physics, and epidemiology. His work ranged from the study of radiation effects among plutonium workers at Los Alamos to a monumental follow-up study of thyroid cancer among infants given radiotherapy.

Born in St. Louis on March 5, 1914, Hempelmann followed his father, an internist, into medicine. His undergraduate and medical degrees were earned from Washington University in St. Louis, where he also completed an internship in pathology. In 1941, Hempelmann spent four months as a Commonwealth Fellow with John Lawrence at the Radiation Laboratory in Berkeley, honing skills in the use of the cyclotron for radiotherapy.

Shortly after the war broke out, J. Robert Oppenheimer, Director of the Laboratory at Los Alamos, petitioned John Lawrence for candidates to oversee the health aspects of employees at Los Alamos. Oppenheimer envisioned an urgent need for safety measures for the radiation work being done and had even specified blood tests be taken before there were "any extra neutrons on the Hill." Lawrence suggested Hempelmann, who arrived at Los Alamos in March of 1943, and assumed responsibility for the safety of all technical operations and for directing the Health Group. After the war, Stafford Warren wrote a memo to the Director of the Los Alamos Laboratory, Norris Bradbury, in which he praised Hempelmann:

> *He has done an exceedingly good job. Many men owe their lives to Dr. Hempelmann's sound judgment and the practices which he instituted in a new endeavor. There are no men trained in the field nor even in industrial medicine by which to replace him if he is permitted to resign.*

While at Los Alamos, Hempelmann started the work for which he was best known: he looked for radiation effects among twenty-seven workers at Los Alamos who had received exposures of plutonium and followed them throughout his career. George Voelz, his collaborator, continues this study.

In 1949, Hempelmann published a paper on the danger of using fluoroscopes to fit children's shoes. Shoe-fitting fluoroscopes soon disappeared. In 1950, Hempelmann joined the faculty at the University of Rochester as an Associate Professor of

all feces and urine are to be collected according to a precise sampling schedule and periodic blood samples are to be taken. These are to be carefully assayed for 'product' by the Santa Fe group [Los Alamos]." In other words, blood, urine, and fecal samples taken both during the control period and after the injections would be sent to Los Alamos for determination of plutonium content (or normal radioactivity). The stated purpose of the experiment was "to establish on a statistical number of subjects the relationships existing among such factors as the amount of product in the body, the level of product in the blood, the amount excreted in the urine, the amount excreted in the feces, and the variations of the above with time." Such data would provide "a statistical basis for diagnosing body internal contamination from the analysis of urine or feces, the obvious purpose of which is to retire workers before they have received harmful amounts of the material." Data would be collected for 25 days, a time limit that focused the study on the early excretion rate when it was at its highest level. The early rate, of course, was important to the immediate evaluation of workers who had experienced accidental exposures to plutonium.

Selection of patients. The plan left the selection of subjects "entirely up to the Rochester group." However, the participants at the Rochester meeting "more or less agreed that the subjects might be

Experimental Radiology and served as Chairman of the Department of Radiology from 1960 through 1971. During this period, Benedict Duffy published a paper on a case-series of twenty-eight children who had developed thyroid cancer. Surprisingly, ten of the children had received thymic radiotherapy as infants. Soon after, Hempelmann began his now-famous study of infants who had been given radiotherapy for thymic enlargement. Follow-up surveys of these children, conducted throughout his career, found an advancing excess of thyroid cancers, excessive benign tumors, and possible immunological abnormalities. Such research required abilities in scientific design and the organization of large amounts of data because the work was initiated before standard chronic-disease epidemiology techniques had emerged. The finished study is considered a masterpiece by health physicists, and today, is being continued by Roy E. Shore of New York University.

In 1967, Hempelmann suggested to Fred Mettler, a student who wanted to study radiation effects in humans, that he conduct a study of women who had received x-ray treatments for acute postpartum mastitis 10 to 25 years earlier. They found that among 606 women, there were 13 cases of breast cancer when only about 6 were expected. A number of important studies followed.

At Rochester, Hempelmann and his colleague's research interests included identifying blood and urine that could serve as markers to determine the degree of tissue damage from exposure to ionizing radiation and to clarify the mechanisms involved in the production of radiation-induced creatinuria in animals. In the 1950s and 1960s, Hempelmann's laboratory did studies of cellular destruction and protein breakdown induced by exposure to x rays, the effect of ionizing radiation on the deoxyribonuclease activities of body fluids, the effect of x-ray exposure on the deoxyribonuclease activity of lymphoid tissue, and the effect of x rays on nucleic acid catabolism and collagen metabolism. Many significant publications on the effects of ionizing radiation on animals were written by Hempelmann and Kurt Altman during this time.

Hempelmann authored or co-authored numerous scientific papers throughout his career. The last report, which appeared in 1986, updated his three career-long interests: the plutonium workers, thyroid cancer after thymic irradiation, and breast cancer after postpartum mastitis. The work of this remarkable man remains as significant today as it was critical in the past. ■

chronic arthritics or carcinoma patients without primary involvement of bone, liver, blood or kidneys." It was important that "the subjects have relatively normal kidney and liver function, as it is desirable to obtain a metabolic picture comparable to that of an active worker."

Thought was given to the types of clinical testing that should precede and follow the plutonium injection. For example, hematological tests were needed to see if radiation damage from the plutonium would be obvious in the blood. Other tests might detect changes in bone, liver, and kidney function. Such clinical testing was the responsibility of the Rochester group.

The patients would each "receive a single intravenous injection of 'product'" containing 5 micrograms of plutonium. The stock solutions were to be prepared by Langham at Los Alamos as plutonium nitrate (in the +4 oxidation state), and one of the Rochester doctors would use aliquots of this stock solution to prepare injection solutions of the plutonium complexed with citrate. Before each injection, an assay would be performed with an alpha counter to make sure that there were approximately 5 micrograms of plutonium in every half milliliter of solution.

It was also stated in the plan that:

> *Col. Warren proposed Lt. Valentine as the one to do the injections.*

> *Dr. Fink is to be present at all injections to supervise the calibration tests.*

The calibration tests included five "dummy injections" into volumetric flasks using the same solution and syringe that would be assayed to determine the actual dosage given. "The injection solution, the 'dummy injection' solutions, syringe and needle, and a description of the injection technique" would be sent to Langham so that further assays could be performed as a check on the dosage.

Although it was felt that the injected dose was very small, tests that might reveal any changes due to radiation were to be carried out on a regular basis after the injection. For example, the report states: "Though it is extremely unlikely that such a small dosage will produce any clinical symptoms, those observations that the medical group consider necessary should be continued throughout the experimental period." Also, any clinical chemistry tests of interest could be made even though it was "doubtful as to whether or not such small amounts of radiation [would] produce effects in these organs [bone, kidney, spleen, and liver] that can be detected by chemical means."

The animal data had shown that the excretion rate for plutonium was higher at first. As a result, the report suggested "it would be interesting to take two 12 hour samples the first day after which a straight 24 hour sampling schedule is to be maintained for the next 23 days." It was also stressed that "the timing of the [urine] sampling begin at [the time of the injection]."

Individual stools were to be "collected and analyzed separately during the first four-day period." After that, "feces will be pooled in four-day periods." Even though analysis of feces had been ruled out as a way to monitor the plutonium workers, the fecal samples collected from the patients would allow a determination of the total amount of plutonium being eliminated. Such information was needed for accurate evaluations of plutonium concentrations resulting from accidental exposures, including inhalation and wounds.

It was also decided that because all data "except the 'product' content of blood, urine and feces samples will originate at Rochester . . . this is the logical place to keep the complete record." Thus, Los Alamos would periodically report their analytical results to the Rochester site.

Choice of the size of the dose. What can be said about the Rochester experiments and the choice to continue with 5-microgram plutonium injections despite the fact that the tolerance limit for workers had been reduced to 1 microgram? A year or two after the study, an undated draft report of the work was written (most likely in late 1947 or early 1948 by Dr. Samuel Bassett at the University of Rochester, even though both Bassett and Langham are listed as authors). A section in this report entitled "Choice of size of dose" states:

> *There are no altogether satisfactory criteria at present for estimating the tolerance dose of 94 Pu239. The problem may be approached . . . from several points of view. None of these is free from some criticism since certain assumptions have to be made without support of experimental evidence.*

This section recounts the usual comparison of radium and plutonium alpha energies (resulting in an estimate of a 4.47-microgram tolerance dose) but then goes on to say that there was "another and highly practical consideration," namely that "there was every reason to believe on the basis of animal experiments and one human case, that injected plutonium would be largely retained . . . [and] if the quantity injected was too small, the absolute amount eliminated would [be less] than could be measured with reasonable accuracy by current analytical procedures." One of the sources of such concern, in 1945, was most likely the spread in urine assays, including especially those of CAL-1, which were consistently lower than those of HP-12 and CHI-1 by about a factor of two. (A review of the CAL-1 excretion data suggests that the recorded dose administered to this patient may have been in error on the low side by a factor of 2. Correction by this factor makes the data of CAL-1 appear consistent with the data of all the other injected subjects.)

The study being envisioned for further human injections would involve establishing "on a statistical number of subjects the relationship existing among such factors as the amount excreted in urine and feces and the variations of the above with time." In addition, blood samples and, on occasion, tissue samples would be analyzed when they were obtained at autopsy. Thus, it seemed appropriate that the studies should involve 24-hour urine samples, plutonium doses at the 5-micogram level, and at least 10 sets of data collected over a 25-day period after the injection.

The draft report written by Langham and Bassett in 1947 or 1948 added that "the dilemma of possible late radiation hazard was met by the [selection] of subjects believed to have short life expectancies." They concluded:

> *The several inponderables mentioned in the preceding paragraphs [of their report] have been a source of concern to those who were responsible for the pursuit of this experiment. The data submitted in Section IV supply partial answers to rates of excretion and tissue distribution but leave unanswered the fundamental question of tolerance.*

In a footnote, they mentioned the provisional 1.0-microgram body-burden limit set for the workers by the Manhattan

District.

The Rochester Patients. Eleven patients (HP-1 through HP-11 in Table 2, page 208) were injected with plutonium at the Rochester site during a period from October 1945 through July 1946. The patients included seven men and four women who ranged in age from 41 through 68, with the exception of one 18-year-old. None of the patients were chronic arthritics or carcinoma patients, however, they had various afflictions, ranging from a hormonal deficient disease (Addison's) to alcoholism, that required hospitalization.

In the undated (1947 or 1948) draft report of Bassett and Langham, it was stated:

> *Preference was given to those who might reasonably gain from continued residence in the hospital for a month or more. Special treatments and other therapy thought to be of benefit to the patients were carried out in the usual manner. . . . Patients with malignant disease were . . . omitted from the group on the grounds that their metabolism might be affected in an unknown manner. . . . As a rule, the subject chosen was past 45 years of age and suffering from a chronic disorder such that chance of survival for ten years or more was improbable.*

These last criteria, it was hoped, would avoid "late radiation effects [such as cancer]" and present the opportunity, in some cases, to "obtain post mortem material." There were exceptions to the "rule": three of the Rochester patients were younger than 45 (18, 41, and 44), although the 18-year-old was seriously ill (Cushing's syndrome) and only lived another year and a half.

Ten of the 11 patients were cared for in the special metabolic ward of Strong Memorial Hospital in Rochester (the eleventh was in the hospital but his condition was so serious he was not moved into the ward). The control period lasted about 10 days, during which time the patient was instructed in the quantitative collection of urine and fecal samples and the necessary adjustments were made to the ward routine and the patient's diet. After the patient had proven capable of cooperation, a series of control urine and fecal samples were collected and physical and laboratory

Estimating Effects of the Injection Dose

Several methods were used to estimate the potential effects of the amount of plutonium being injected into the human subjects. These methods were outlined in the various documents written at the time or published later in the fifties, and here, we summarize two of these.

Acute toxicity. An accepted approach, especially for chemical toxicity, was to determine the acute-toxic LD50 dose for animals (the amount that caused death in 50 per cent of the animals) and then set the safe level for humans at least 10 times lower. Plutonium injections in rats showed (on the basis of micrograms per kilogram of body weight): 700 to 1000 micrograms caused half the animals to die in 30 days; 200 to 600 micrograms caused half to die in 150 days; and 10 micrograms caused no deaths after 420 days. The "safe" acute-toxicity dose would thus appear to be 20 to 60 micrograms per kilogram of body weight (1500 to 4600 micrograms total for a 170-pound person). Using acute toxicity is most applicable for terminal cases, such as the three Chicago patients (see Table 2, page 208). The injection dose for CHI-1 was about 0.06 microgram per kilogram of body weight, more than a hundred times lower than the observed no-effects dose in rats. CHI-2 and CHI-3 were each given the maximum injection dose of any patient in the various studies, and this dose was about 2.5 micrograms per kilogram of body weight, still 4 times lower than the no-effects dose in rats and about 10 times lower than the "safe" acute-toxicity dose. The Chicago scientists were thus able to conclude in a report discussing CHI-1 and CHI-2 that "insofar as can be determined the clinical course in neither of the two cases was influenced by the injection of plutonium." (Clinical data for CHI-3 were never documented.)

An alpha-emitter safe dose. In a draft report authored by Bassett and Langham in 1947 or 1948, they stated that an accepted safe dose to irradiated tissue for an alpha emitter was 0.01 rep per day (where 1 rep, a "roentgen equivalent physical," corresponds to the absorption of 93 ergs per gram of tissue). They felt that "a dose of this [size] appears to carry little likelihood of injury to cells." Using the activity of plutonium-239 and the energy of its alpha particles, they calculated that this dose corresponds to 32.6 micrograms of plutonium if the plutonium is distributed uniformly throughout the body and 5.2 micrograms if the plutonium is concentrated in the skelton with a uniform distribution in bone. "Unfortunately," they wrote, "radioautographs reveal a far from uniform distribution of plutonium in bone." Furthermore, "early localization of a large fraction of the dose in the liver . . . is a distinct possibility." They estimated that, in the regions where the plutonium concentrated, a 5-microgram body burden could result in a dose to tissue that was ten times higher than the accepted safe dose of 0.01 rep per day. Thus, they were aware of the fact that a 5-microgram dose most likely exceeded accepted standards, depending on the assumptions regarding distribution in the body.

Wright Haskell Langham—1911-1972

As you can see, I have not made any great contributions to science. I have never been a scientific bride—so to speak—but I have been a bridesmaid at some of the biggest and most interesting scientific weddings in history.

Wright Langham penciled those words on note paper during an interview regarding the book "The Bombs of Palomares." A humble statement from a man who became known throughout the biomedical world as "Mr. Plutonium." Langham was, in fact, one of the great pioneers in what became the modern field of health physics.

Born in Winsburro, Texas, May 21, 1911, and raised in a nonacademic, nonprofessional environment, Langham put himself through every measure of his schooling by hard work. He attended Panhandle A.&M. College (B.S., chemistry, 1934), Oklahoma A.&M. College (M.S., chemistry, 1935), and the University of Colorado (Ph.D., biochemistry, 1943). After receiving his doctorate, Langham joined the Plutonium Project at the Met Lab in Chicago, and in 1944, he came to Los Alamos. Eventually, he went on to become Associate Division Leader for Biomedical Research before his untimely death in a local air-commuter crash in 1972.

Although educated in biochemistry, Langham's major contributions were made in the fields of radiation biology and radiation toxicology. As discussed at length in the main article, Langham helped develop, in 1945, the early bioassay procedures for estimating plutonium body burdens. From the data gathered in the plutonium injection experiments, he determined the universally used "Langham equation" for plutonium excretion. He was active in stimulating and correlating nearly all of the toxicological work on plutonium and related elements for Los Alamos, Argonne, Rochester, and later, the programs at Utah and other laboratories. He took an active part in determining the values for the maximum permissible body burden of plutonium and derived allowable air and water concentrations for exposure to plutonium, figures that stand essentially unchanged today. There is no major work in the field of plutonium toxicology that does not bear the hallmark of his work and

examinations were conducted.
After the plutonium injection, urine and stool samples were collected over a period ranging from 22 to 65 days. Urine was collected as 24-hour samples, except on the first day when two 12-hour samples were taken. Fecal samples were collected daily for the first few days, then generally pooled at 4-day intervals. Blood samples were obtained at "frequent intervals" after the injection. By March 1946, Langham had excretion data from HP-12 at Oak Ridge for 89 days after the injection and from the first seven Rochester patients for some 25 days. After reviewing these data, Langham informed Bassett on March 13 that:

The work here is coming along nicely. I went over some of our data with our medical physicist [Joseph G. Hoffman]. We tried to extrapolate our excretion curves and derive a mathematical expression for calculating the amount of material remaining in the body at ten and fifteen years. He was alarmed and disappointed that we had not followed the excretion further in each case. It is his opinion that the result should be followed to 244 days in order that an accurate mathematical interpretation can be made. This emphasizes to me the necessity of our trying to get each patient back into the hospital for an occasional study if it is possible from your point of view.

In fact, additional urine and fecal samples had been collected in Rochester from three of the patients (HP-2, HP-4, and HP-7) about 80 days after their injections, although Langham did not realize this because of a tabulation error. (The analyses were done in a secure area—"behind the fence"—whereas Langham worked in the "rat lab" outside, and when the data were transferred, the final compilation made them appear to be a continuation of the earlier sequential data after day 25.) In response to Langham's letter, additional urine and fecal samples were collected for HP-8 continuously out to day 65 after the injection and for HP-9 and

ideas, either by direct contribution or by reference to his publications. No major incident involving plutonium contamination went without the benefit of his direct participation or consultation. He was in constant demand by both the military and the federal government in nearly every biomedical phase of the development of nuclear energy.

Langham may well be identified with his plutonium toxicology work, but it must also be remembered he made invaluable contributions in other areas of radiobiology. He participated in studies of the ultimate effects of low levels and high doses of radiation and in an intensive program on the biological effectiveness of diverse types of radiation in a variety of animal species. That work eventually led him to consider the radiobiological problems of manned space flight and similar work for NASA and the National Academy of Sciences Space Science Board. Under the auspices of the Space Science Board, he wrote the definitive volume on radiobiological factors in manned space flight.

Langham authored or coauthored numerous scientific papers and reviews and held positions of leadership on many committees, among them the first Chairman of the National Council on Radiation Protection SubCommittee on Relative Biological Effectiveness from 1957 to 1960. He was a member of the Health Physics Society and served on the board of directors (1958-61) and as president (1968-69).

Langham was extremely efficient, a superb organizer, and could be counted on to speak up for his convictions both as a researcher and as an administrator. For example, he sponsored and encouraged liquid-scintillation-detector development (see "Los Alamos Radiation Detectors for Biology and Medicine," page 274). He was never one to be over-impressed by authority, whether it be by rank, position, or lineage. As told by those who knew him, he would always champion the safety and health of the workers responsible for handling the new-age metal, plutonium. ■

HP-10 through day 36 and day 30, respectively.

Within a year, five of the subjects had died from their diagnosed illnesses and tissue samples were obtained from three of these cases: HP-5, a 56-year-old man with Lou Gehrig's disease who died of bronchopneumonia; HP-9, a 64-year-old male with dermatomyositis (an inflammatory reaction of unknown cause involving degenerative changes of skin and muscle) who also died of bronchopneumonia; and HP-11, an 69-year-old man suffering from alcoholism, malnutrition, dyspnea, and abdominal swelling who was moribund at the time of the injection and lived only 6 more days. These tissue samples were analyzed to help determine the distribution of plutonium in the body.

The injection doses for the 11 patients ranged from 4.6 to 6.5 micrograms of plutonium-239, resulting in effective dose-equivalents that ranged from about 24 to 43 rem per year, or about 67 to 120 times the U.S. average annual effective dose-equivalent from natural and manmade radiation sources. The total dose received by each patient was, therefore, mainly a function of the number of years they lived after the injection. These total doses ranged from 0.6 rem (for HP-11, who lived 6 days) to 1000 rem (for HP-8, who lived almost 30 more years).

Two more Chicago patients. Halfway through the Rochester injection experiments, the Chicago Health Division, on December 27, 1945, authorized the injection of two additional patients with plutonium. Both patients were considered terminal: one was a 56-yr-old woman with metastasized breast cancer who was close to death; the other was a young adult male who most likely had Hodgkin's disease. These two patients, because they were terminal, were injected with 95 micrograms of plutonium-239, the largest amounts (in terms of mass of plutonium and amount of radioactivity) injected into any of the eighteen plutonium-injection patients. Because of the short survival times after injection (17 days and about 170

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Table 2. The Eighteen Patients Injected With Plutonium

Case number and description	Date Injected*	Date of death	Survival time	Age at death*	Cause of death
HP-12 55-yr-old man	April 10, 1945	Apr. 13, 1953	2,925 days (8.0 yrs)	63	heart failure
CHI-1 68-yr-old man	April 26, 1945	Oct. 3, 1945	160 days (5.2 months)	68	cancer of chin, lungs
CAL-1 58-yr-old man	May 14, 1945	Jan. 9, 1966	7,545 days (20.7 yrs)	79	heart disease
HP-1 67-yr-old man	Oct. 16, 1945	Jan. 12, 1960	5,201 days (14.2 yrs)	81	bronchopneumonia
HP-2 48-yr-old man	Oct. 23, 1945	Apr. 4, 1948	894 days (2.4 yrs)	50	brain disease
HP-3 48-yr-old woman	Nov. 27, 1945	Jan. 24, 1983	13,571 days (37.2 yrs)	85	acute cardiac arrest
HP-4 18-yr-old woman	Nov. 27, 1945	Apr. 29, 1947	518 days (1.4 yrs)	20	Cushing's syndrome
HP-5 56-yr-old man	Nov. 30, 1945	Apr. 29, 1946	150 days (4.9 months)	57	bronchopneumonia
CHI-2 56-yr-old woman	Dec. 27, 1945	Jan. 13, 1946	17 days	56	breast cancer
CHI-3 young adult male	Dec. 27, 1945	June 1946	about 170 days (5.6 months)	not known	probably Hodgin's Disease
HP-6 44-yr-old man	Feb. 1, 1946	May 6, 1984	13,974 days (38.2 yrs)	82	natural death
HP-7 59-yr-old woman	Feb. 8, 1946	Oct. 27, 1946	261 days (8.5 months)	60	pulmonary failure
HP-11 69-yr-old man	Feb. 20, 1946	Feb. 26, 1946	6 days	69	bronchopneumonia
HP-8 41-yr-old woman	March 9, 1946	Nov. 22, 1975	10,850 days (29.7 yrs)	71	unknown
HP-9 64-yr-old man	April 3, 1946	July 2, 1947	455 days (1.2 yrs)	65	bronchopneumonia
CAL-2 4-yr, 10-month-old boy	April 26, 1946	Jan. 6, 1947	255 days (8.4 months)	5	bone cancer
HP-10 52-yr-old man	July 16, 1946	June 2, 1957	3,974 days (10.9 yrs)	63	heart disease
CAL-3 36-yr-old man	July 18, 1947	June 30, 1991	16,050 days (44.0 yrs)	80	respiratory failure, pneumonia

*The ages at injection and at death are based on the known dates of birth as determined by Pat Durbin; they differ in a few cases from the ages given by Langham, et. al., in LA-1151. Some of the dates of death are based on information found by Eileen Welsome.

**The injection dose gives an upper limit for the patient's body burden. For example, it is now estimated that after 27 years, about 82.4 per cent of the injected dose would still remain in the body.

Weight of injected Pu-239 (m g)**	Activity of Pu-239 (nCi)	Total effective dose (rem)†	Dose to background ratio‡	Ailments, tissue samples, and remarks
4.7	290	230	80	auto accident victim at Oak Ridge Hospital; bone sample taken in surgery, teeth obtained later
6.5	400	19	120	cancer of chin, metastasis to lungs; near death when injected; autospy samples taken
0.75 (239) 0.20 (238)	46 (239) 3,500 (238)	6400	858	gastric neoplasm; misdiagnosed with stomach cancer; tumor and other tissue taken in surgery
4.6	280	380	74	duodenal ulcer, severe gastrointestinal hemorrhage
5.1	310	80	92	hemophilia and heart disease
4.9	300	880	66	rash, hepatitis, and hypoproteinemia
4.9	300	46	90	Cushing's syndrome, a metabolic disorder
5.1	310	14	95	Lou Gehrig's disease; autopsy samples taken
94.9	5,900	29	1730	breast cancer that had metastasized; autospy samples taken
94.9	5,900	300	1790	Hodgkin's disease
5.3	330	990	72	Addison's disease, a hormonal deficiency disease
6.3	390	30	117	rheumatic heart disease
6.5	400	0.6	100	chronic malnutrition, alcoholism, cirrhosis of liver; moribund at injection; autospy samples taken
6.5	400	1000	94	scleroderma, a chronic skin disease, and duodenal ulcer
6.3	390	52	116	generalized dermititis and weakness; autospy samples taken
2.7 (plus radio-cerium & yttrium)	169	13	52	osteogenic sarcoma, a rare form of bone cancer; bone samples taken
6.1	380	410	104	acute congestive heart failure
0.006 (238)	95	155	10	purportedly bone cancer in left knee; leg amputation removed half the plutonium; bone samples taken; injection was intramuscular

†The total effective dose was calculated using biokinetic models recommended by the International Commission on Radiological Protection, ICRP Publication 30, and all the values represent the dose received by each individual over the period from the time of injection to the time of death.

‡The dose to background ratio was calculated by taking the ratio of the patient's total effective dose to the estimated dose for an average U.S. citizen over the period from the time of injection to the time of death (where the average annual U.S. effective dose equivalent was taken to be 0.360 rem).

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days, respectively), these patients did not receive the highest total doses.

Less than a month after the moribund patient (HP-11) at Rochester had been injected with 5 micrograms of plutonium (on March 13), Langham had written to Bassett, saying:

> *Your letter of February 27 regarding Hp 11 was startling, to say the least. The specimens have already arrived and I am making preparations to analyze them. . . . In case you should decide to do another terminal case, I suggest you use 50 micrograms instead of 5. This would permit the analysis of much smaller samples and would make my work considerably easier. I have just received word that Chicago is performing two terminal experiments using 95 micrograms each. I feel reasonably certain there would be no harm in using larger amounts of material if you are sure the case is a terminal one.*

On March 27, Bassett replied, saying that "this case did turn out to be terminal, but at the time I started the experimental period, there was sufficient uncertainty regarding the outcome to make me feel that the dose should be within the range of tolerance." He added that "if a suitable opportunity occurred and if you are very anxious that I should carry it through, I will see what can be done [about a 50-microgram dose in a terminal patient]." The opportunity never occurred.

The Chicago scientists also studied the gastrointestinal absorption of plutonium by having, on May 13, 1946, six male employees of the Met Lab drink a water solution containing 0.35 nanocuries (or about 6 nanograms) of plutonium-239. That amount was about a factor of a thousand or ten-thousand less than the amount injected into the Chicago patients, so the plutonium excreted in the urine and feces was barely detectable. Besides measuring the fraction of the plutonium absorbed by the gastrointestinal tract, the scientists used the results to improve the interpretation of plutonium exposure and bioassay data collected from occupationally exposed workers.

More California patients. On April 26, 1946, Hamilton and his group at the University of California Hospital in San Francisco continued their studies, injecting 2.7 micrograms of plutonium-239 intravenously in a 4-year-old boy suffering from terminal bone cancer (CAL-2). The injection solution also contained radioactive cerium and yttrium. A week later, surgery was performed and significant bone and tissue samples were taken. The samples were analyzed for the uptake of the radioisotopes and comparisons were made between normal and tumor tissue. Thus, the experiment may have been both a continuation of Hamilton's 1941 research to find a therapeutic treatment for bone cancer and a continuation of the Manhattan Project plutonium metabolism research—the data were applicable to both studies.

On July 18, 1947, a third person, a 36-year-old man, purportedly with bone cancer in the leg, was injected with a mixture of plutonium-238 and tracer amounts of other radioisotopes. That injection was done intramuscularly, rather than intravenously, and after his leg was amputated at mid-thigh, the deposition of plutonium in the bone and tissue was determined. A month earlier, on June 10, a 16-year-old boy with bone cancer had also received an intramuscular injection, but with americium rather than plutonium. Again, part of the patient's leg was amputated and tissue samples were analyzed. Both these experiments may also have been a continuation of the bone-cancer research and were possibly done independently of the Manhattan Project or its successor, the Atomic Energy Commission (AEC).

Such "dual-purpose" research produced further data for the Manhattan Project but also allowed physicians to search for radioisotopes that could be used to treat cancer. The radioisotopes being administered would not have any therapeutic value for the people receiving the injections—the quantities were too small—but the studies might have led to the development of new therapies for future patients.

Results of the Injection Experiments

By 1950, five years after the start of the study, Langham and Bassett, as well as Payne Harris and Robert Carter from Los Alamos, wrote a classified report (LA-1151) that summarized much of what had been learned from the eleven Rochester patients, the Oak Ridge patient, the three Chicago patients, and the first California patient. They concluded that about two-thirds (66 per cent) of the plutonium injected into the bloodstream was deposited in the skeleton and more than a fifth (23 per cent) was deposited in the liver. Thus, "the skeletal system and liver are the tissues of major interest when considering the plutonium tolerance, as these two organs alone account for 90% or more of the total plutonium in the entire body." The level of plutonium in the blood was high at first (35.7 per cent of the injected amount after 4 hours and 15.7 per cent after 1 day) but fell rapidly (1.2 per cent after 10 days and 0.3 per cent after 30 days), which ruled out the use of blood tests "as a means of diagnosing the degree of exposure of personnel."

The Los Alamos report used the accumulated data obtained from the fifteen patients to determine excretion rate equations, which appeared (for both urinary and fecal excretion) to be most easily described by "a logarithmic function:

$$Y = a\,X^{2b},$$

where *Y* is the amount of plutonium (expressed as a per cent of injected dose) excreted in a single day, *X* is the time of observation in days after the injection, and *a* and *b* are constants derived from the observable data by the method of least squares." This equation was what they had been striving for—a general formula describing the amount excreted as a function of time that could be extrapolated back to the amount originally taken in by the body—and it became known as the Langham power-function model.

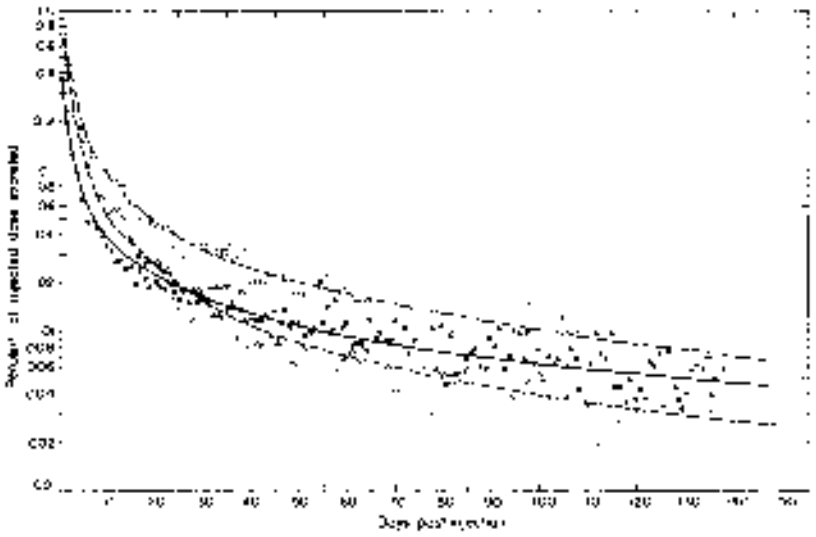

Figure 4. Plutonium Excretion for 138 Days

These excretion data for the human injection experiments, as presented in the original Los Alamos Scientific Laboratory Report LA-1151 and reproduced in a 1980 *Health Physics* article, represent the observed means for the excretion data of the injected patients. A power-function fit is given for urinary (squares), fecal (triangles), and total excretion (circles).

They were able to fit the mean daily excretion data from fifteen patients to this type of expression for 138 days after the injection (see Figure 4). However, if only the first ten days of data were used, the best fit gave a different exponent (-1.0 rather than -0.77). They felt that "this difference . . . may be due to the clearance of the injected plutonium from the blood during this early period after injection." Thus, if a worker was receiving chronic but variable exposures to plutonium, an initial screening assay could be used to determine if he should be removed from further exposures, but a precise value for the body burden could only be determined from later assays, after the first ten days. At that time, the initially higher excretion rates for any recent exposures would no longer be masking the lower excretion rates of the less recent exposures, and the assays would reflect the actual amount accumulated in the body.

Beyond 138 days, extrapolation of the Langham power function "introduces increasing uncertainty with increasing values of X," which made it difficult to determine a "biological half-life" for plutonium. For those reasons, they had felt it "important to supplement the urine excretion data beyond 138 days to the greatest possible extent." As a result, they had obtained additional urine samples from two of the Rochester patients (four consecutive daily urine samples from HP-6 a year-and-a-half after the injection, and four consecutive daily urine samples from both HP-6 and HP-3 four-and-a-half years after the injection). Those longer-term data showed an excretion rate consistent with that predicted from the power-function model derived from the 138-day data, which gave Langham confidence that a one-term power-function model was a satisfactory way to treat even long-term data.

Los Alamos workers. The plutonium workers at Los Alamos were another source of long-term urinary excretion data. Between 1944 and 1950, over 6000 urine analyses were made on workers, and of these men, 27 excreted measurable amounts of plutonium. For this latter group, the exposures had all occurred in the early work between 1944 and 1946, and the records showed one or more instances of high nose-swipe counts in each case. (Four of these men had been removed from further exposure to the substance in 1945; twenty-two of the twenty-seven left Los Alamos after 1946; and only a couple remained working with plutonium after 1946). Body burdens were estimated for the 27 workers using the 0.01-percent excretion model, and the values ranged from 0.1 to 1.2 micrograms. (These men are referred to as the UPPU club—see "On the Front Lines." A study of their health has been conducted from 1952 to the present, first by Langham and Hempelmann and, later, by George Voelz.)

One of the sources of concern to Hempelmann and Langham was the fact that, for some of the men, there was a poor correlation between an apparent inhalation exposure, as indicated by a high nose-swipe count, and subsequent positive urine assays. The poor correlation could have been due to hand contamination of the nose or the result of an exposure to insoluble plutonium particles that took awhile to be absorbed into the circulatory system and, thus, detectable in the urine. They concluded that the nose-swipe data should be treated as supplementary information to the urine assays and moved ahead

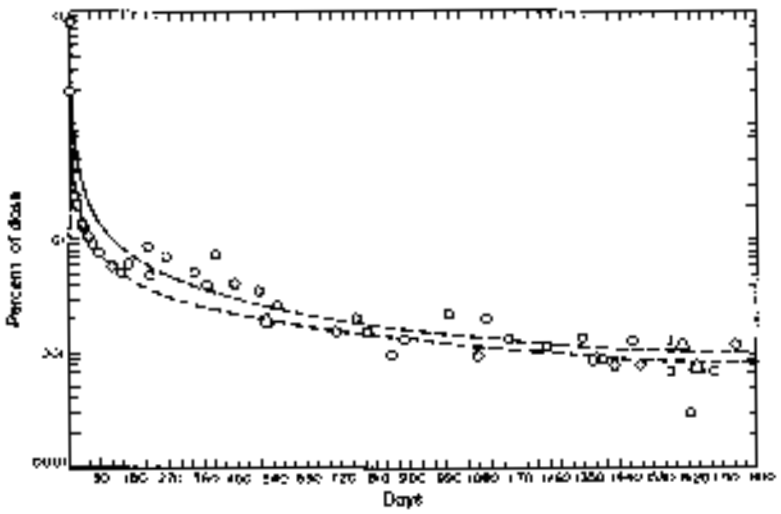

Figure 5. Plutonium Excretion for 1750 Days

These plutonium excretion data, as presented in the original Los Alamos Scientific Laboratory Report LA-1151 and reproduced in a 1980 *Health Physics* article, include the additional long-term points for the plutonium injectees HP-3 and HP-6 (circles) and data for three Los Alamos plutonium workers (triangles). The top curve represents total (urinary plus fecal) excretion; the lower curve, urinary excretion.

with their analysis, not knowing in many cases the date of the primary exposure to the worker.

Although the plutonium body burden in a given worker was the result of multiple unknown doses that had built up over an indefinite period rather than a single, measured exposure, the chronic exposure could be treated in terms of an *effective* single dose given at some *effective* time during the period the worker was exposed in 1945. The 138-day power-function model was used with the urinary excretion data of three workers to calculate their body burdens (two measurements separated enough to be significantly different, and with no exposures in between, were used in the calculation). Then the data of the workers were combined with the additional long-term data of the injectees to produce a longer excretion curve (Figure 5). The urinary-excretion equation derived from these data through 1750 days (almost 5 years) was:

$$Y_u = 0.20\, X^{20.74}.$$

A similar equation was obtained for fecal excretion, but it was based only on data from the patients through 138 days. This expression, plus a few observations of fecal excretion at later times, indicated that roughly equal amounts of plutonium are excreted in the urine and the feces over the first month. By the end of a year, however, although both excretion rates have dropped in absolute terms, there is about four times as much in the urine as in the feces. The equation for total excretion of plutonium was obtained by adding the separate expressions for urinary and fecal excretion.

By integrating the expression for total excretion of plutonium, it was determined that only about 8.7 per cent of a single plutonium dose is excreted in the urine and feces over a five-year period and 12.7 per cent in 20 years. This very slow rate of elimination led the authors to conclude that it would take about 118 years for the body to eliminate half of the plutonium (the biological half-life). Futhermore, there was "no practical significance . . . in permitting the return to work of an individual who has reached the maximum permissible body burden." In other words, "once a worker is retired from work with plutonium . . . it must be assumed that he is retired . . . for the balance of his lifetime."

What happened to the injectees? Of the 18 people in Table 2 who were injected with plutonium, 11 died less than 10 years later, before any long-term effects should have been seen. Eight of those 11 died within two years of the injection; a ninth died about 2.5 years after the injection. The 8 people who lived much longer survived for times ranging from 10.9 years to 38.2 years. HP-6 lived the longest, dying when he was 82 years old. In fact, four of the patients lived into their eighties and two into their seventies.

There is no evidence that any of the patients died for reasons that could be attributed to the plutonium injections (one cause of death is unknown). Ten of the patients died from the disease for which they were admitted to the hospital prior to their injection (or from complications related to that disease). Of the others, there is evidence that several of them benefited from their stay in the hospital. For example, the patient with Addison's Disease (HP-6), the result of insufficient steroid hormones, had access in the clinic to steriods and the close observation needed to achieve proper regulation of a hormone-supplement regime. A woman patient (HP-3) suffering from an unexplained weight loss was thought to have some undiagnosed chronic disease; however, the close medical scrutiny permitted the physicians to recognize that she was instead suffering from severe depression. The increased attention she received at the hospital may have helped her because she apparently recovered and lived another 37 years.

On the other hand, with the end of the war in 1945, many of the health physics researchers throughout the Manhattan Project moved on to other jobs and organizations or became in-

volved in other studies. For example, many of Hempelmann's staff were commandeered late in 1945 to study the effects of the atomic bombings in Japan, and on their return, many of those were released from service. By 1946, Langham was deeply involved in studies of the fallout from atmospheric testing of weapons in the Pacific. Stone returned to Berkeley, and both Bassett and Warren eventually went to the University of California in Los Angeles. The attention of the researchers was thus diverted away from the injection studies.

In addition, the transfer, in January 1947, of the Manhattan Project to the newly formed Atomic Energy Commission caused the injection studies to be viewed in a different light—a senstive, potentially embarrassing one. As a result of these various forces, no one followed up the ten remaining plutonium injection patients, the only people with well-characterized plutonium doses, to determine the impact of plutonium on their health. Likewise, the eventual long-term study of Los Alamos plutonium workers with significant body burdens was not started until 1952.

The impact on workers. What was the impact of the injection studies on the people working with plutonium at Los Alamos? In July 1945, five Los Alamos plutonium workers were judged to have body burdens equal to or above the 1-microgram tolerance limit (calculated by applying the 0.01-per-cent excretion model to their urine assays). These workers were removed from further work with plutonium. When World War II ended in August 1945, all plutonium-related research at Los Alamos was discontinued pending completion of a new plutonium laboratory then under construction (see "Middle Years—1952 to 1978 at DP Site," page 134). The new facility was fully occupied by November 1945, and the improved working conditions reduced the probability of serious accidental exposures. After that, very few workers received significant plutonium exposures, especially those involving inhalation.

Meanwhile, the 0.01-per-cent excretion model continued as a straightforward way to estimate a worker's accumulated plutonium burden (firmly established by a 1946 summary of the human injection data by Russell and Nixon). For example, several editions of the *General Handbook for Radiation Monitoring* published by Los Alamos (LA-1835) after the war stated that measuring 14 disintegrations per minute for plutonium-239 in a 24-hour urine sample collected about a month after exposure would correspond approximately to a permissible body burden. That activity was equivalent, for a 0.01-per-cent excretion rate, to a 1-microgram (or 63-nanocurie) body burden.

Chronic exposures. The primary exposure for workers in 1945 was not a single acute dose, as it was for the patients injected with plutonium. Rather, the main concern was chronic inhalation of low levels of plutonium dust, followed by gradual absorption into the body of a fraction of the plutonium that had built up in the lung. Determining body burdens for this latter type of exposure was more complicated because the total excreted plutonium was actually a sum of excretions from many individual exposures (or absorptions of material from the lungs). Using the Langham power-function equation to estimate an effective body burden was highly sensitive to the selection of data used to make the calculation. As a result, it was important to determine if the picture of plutonium distribution and excretion based on the injection studies of humans and animals was an accurate one for plutonium workers.

On December 30, 1958, an accident occurred in the plutonium processing facility at Los Alamos in which an experienced chemical operator, Cecil Kelley, received a sudden burst of intense neutron and gamma radiation. It was later estimated that Kelley received a total dose to his body of 4000 to 5000 rad (around 12,000 rem), a tremendous amount of radiation, and he died about 35 hours later.

Kelley had been a plutonium worker for two-and-a-half years from 1946 to 1949 and, again, for three-and-a-half years from 1955 through 1958. During that time, especially the early years, he had been exposed to plutonium dust on a regular basis and had a record that included 18 instances of high nose-swipe counts and ten instances of minor exposure, for example, during the cleanup of a plutonium spill or from a slight skin laceration. Throughout that period, regular urine assays had been performed that usually showed slight amounts of plutonium. Records were also available on the average low-level concentrations of airborne plutonium in the areas where Kelley had worked.

Kelley's tragic death, thus, became an opportunity to compare an individual's extensive health and exposure records, including urine assays, to a postmortem analysis of tissue. Autopsy samples were taken from throughout Kelley's body so that plutonium concentrations could be measured. (The accident itself, an exposure to neutrons and gamma rays, had no impact on the levels or distribution of plutonium in his body.) It was found that about 50 per cent of the plutonium was in the liver, 36 per cent in the skeleton, 10 per cent in the lungs, and 3 per cent in the respiratory lymph nodes. Intravenous injection of plutonium in humans had shown a somewhat different distribution: 65 per cent in the skeleton and 22 per cent in the liver, for example. The investigators (Harry Foreman, Wright Langham, and Bill Moss) felt that such differences might have been a result of differences in the chemical and physical nature of the plutonium (a soluble salt versus dust particles). Finally, the total plutonium in Kelley's body was estimated to be 18 nanocuries (equivalent to 0.29 micrograms of plutonium-239).

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Consent in the Human Plutonium Injection Experiments

Did the patients who were injected with plutonium in 1945 and 1946 give any form of consent? This is a question that probably cannot be answered unequivocally. None of the people directly involved in the experiments are living now, and documents that would shed light one way or another on this question are scattered and incomplete. Here, we review some of the evidence that has come to light coupled with a few speculative thoughts.

One fact is almost certain—the patients were not told that they were being injected with plutonium. Up until the end of the war, the word plutonium was a secret. Even in the classified documents of the time, plutonium was referred to with the code words "49" and "product."

Were the patients told they were being injected with a radioactive substance? Possibly not. Although research with radioactive tracers was publicized before the war, reference to radioactive materials in the context of the Manhattan Project may have been considered a security risk as well. But we do not know this for sure.

Is informed consent still possible if the patients are *not* told that the material under study is radioactive plutonium? Many experts feel the answer is yes, because these two words, especially in the forties, would not have done anything to help the patient assess the risk. Moreover, it would be possible to give the patient a practical understanding of the risk and benefits of the study without mentioning radioactivity or plutonium. The medical personnel in charge would emphasize that the patient would be involved in a research study important to the war effort, their participation was voluntary, and there was some personal risk, which the researchers, to the best of their knowledge, felt was small. The nature of the experiment could have been described as follows:

> Each of you will be injected with a material that will circulate through your body and then be slowly excreted. Blood and other clinical tests will be done and all your excreta will be collected for a period of time. Most of the material will remain in your body, making it a long-term risk, but at a level close to what is considered safe for people now working with the material. Previous experiments on animals have given us an idea of the acute toxicity of the material, and what you receive will be hundreds of times lower. The purpose of the study is to learn the fraction of material excreted as a function of time so we can tell when a worker is getting too much in his body.

Would the investigators have told the patients something along these lines? Quite possibly. Participants were required to collect their urine and feces for a month or more, as well as to submit to clinical examinations, blood tests, dietary regulations, and so forth. Something surely was said about the necessity for these indignities, and what better way to motivate them than to emphasize that the study was important to the security of a nation at war. Because of the collection period required for the study, patients that would benefit from a stay in a hospital ward were more suitable than normal subjects, such as workers or wives.

The Polonium studies. Along these lines, we have some evidence of what was told to patients at the Rochester site in 1944 when the earlier human injection study on polonium was done. An article in *Biological Studies with Polonium, Radium, and Plutonium,* published in 1950 after the war, states:

> *The general problem was outlined to a number of hospital patients with no previous or probable future contact with polonium. Of the group who volunteered as subjects, four men and one woman were selected for the excretion studies . . .*

Taking these statements at face value establishes a precedent for the manner in which patients at Rochester were treated. There is no reason why the investigators could not have continued the same practice with the plutonium injectees. Whether they did or not is not clear.

A 1946 memo. We now turn to evidence that supports the possibility that no consent was given. About five months after the last Rochester patient had been injected, authority was being transferred from the Manhattan Project to the new Atomic Energy Commission, and research programs involving human injections with radioactive tracers were being scrutinized. T. S. Chapman, Chief, Operations Branch, Research Division, in a December 30, 1946, memo to the Area Engineer in Berkeley, California, refers to a proposal for research at the University of California Hospital in San Francisco and states that "preparations were being made for injection in humans by Drs. [Robert] Stone and [Earl] Miller [Stone came to San Francisco after the war]." The second paragraph continues:

> These doctors state that the injections would probably be made without the knowledge of the patient and that the physicians assumed full responsibility. Such injections were not divergent from the normal experimental method in the hospital and the patient signed no release. A release was held to be invalid.

The memo also states that the Medical Division of the District Office had referred reports on the project "to Colonel Cooney [the new Medical Director of the Manhattan Project] for review and approval is withheld pending his opinion." In fact, six days earlier, Colonel Nichols of the Manhattan Project, after discussions with

Cooney, signed a letter to the Area Engineer in the Berkeley Area in regard to "the intravenous administration of certain Manhattan District products to human subjects" that bluntly stated:

> *It is therefore deemed advisable by this office not only to recommend against work on human subjects but also to deny authority for such work under the terms of the Manhattan contract. You will take immediate action to stop this work under this contract, and report to this office upon compliance.*

We can speculate that the first memo reflects the attitude of the physicians in charge of the human plutonium injections that took place in 1945 and 1946. If consent *had* been obtained throughout the program of earlier plutonium experiments, it seems unlikely that the practice would have suddenly been discontinued for the studies proposed in the memo. Stone was head of the Chicago medical effort during those years and, after the war, he became Chairman of the Division of Radiology at the University of California School of Medicine where he was able to continue his work. Although he, of course, was not directly involved with the study of the Oak Ridge patient or any of the Rochester injections, it is reasonable to think that similar practices in regard to consent took place at all the Manhattan Project sites. Thus, the 1946 memo is indirect evidence that consent was not obtained from the plutonium injectees.

What research was taking place in the Berkeley area at this time? In a document entitled "Scope of Research Programs M. E. D. As of 1 December 1946," the research items listed under a University of California heading included "studies of the metabolism of plutonium, uranium and fission products in rats and man" as well as tracer studies of fission products and studies on the "metabolism of radium, actinium, americium & curium in animals and man." The last plutonium injection took place at the University of California Medical School in San Francisco after the date of the 1946 memo—on July 18, 1947. Thus, some observers feel the last injection was actually not part of the Manhattan Project work but was, instead, a continuation of research by Hamilton's group to locate a radioactive isotope suitable for the treatment of bone cancer.

In 1969, Patricia Durbin, a biophysicist at the University of California, Berkeley, began re-investigating the human plutonium injection studies and visited Christine Waterhouse, a medical doctor who had studied under Bassett at the Rochester metabolic ward. In notes summarizing her visit, Durbin stated:

> *More important, they do not know that they received any radioactive material. [Waterhouse] is of the opinion that to tell them at this late date would do no good but might very likely do them substantial psychological damage.*

This statement does not rule out the idea of consent in terms of an explanation of risks, but does agree with what we have already suggested: that the patients were not told they were being injected with a radioactive substance.

Durbin visited Langham in December 1971 to discuss the information summarized in LA-1151, which had been classified for many years following the war. After her visit, Durbin reported:

> *Classification (prolonged) and the passage of many years before even classified publication of the findings led to [Langham's] eventual responsibility for analysis and publication of the results. He is, I believe, distressed by this and other aspects of the study itself—particularly the fact that the injected people in the HP series were unaware that they were the subjects of an experiment. . . . Dr. Langham has been associated in the minds of many in the radiation protection field with only this one aspect of the subject . . . I believe he grew very weary of attending meetings and conferences at which he was expected to discuss this material over and over again. . . . [Langham felt] the information to be gained [from access to the early data] would be of great value, but he did not wish to be responsible for locating it. I think this sums up the matter, although my prose can hardly do justice to what are obviously deeply held doubts about the study itself and to my strong impression that he justifiably resents the pervasive influence on his whole professional life of Pu in general and the human study in particular.*

In October 1995, the *Final Report* of the President's Advisory Committee on Human Radiation Experiments stated:

> *It is possible that some of the patient-subjects agreed to be used in nontherapeutic experiments. But the picture that emerges suggests otherwise. . . . With one exception [CAL-3], the historical record suggests that these patients-subjects were not told that they were to be used in experiments for which there was no expectation they would benefit medically, and as a consequence, it is unlikely they consented to this use of their person.*

Much of the basis for the Committee's conclusion apparently comes from the *lack* of documented evidence that consent was given. Few experiments from that era documented what was said to the patients or what level of consent, if any, was given by the patients. Thus, there is a definite, possibly unbridgable, gap between the statement that we have been unable to find any documented evidence that sheds light on the consent process and the statement that the subjects were injected without their consent or knowledge. It is quite possible that the patients were completely in the dark about the potential risks, but we will probably never know for sure one way or the other. ■

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Changes in production methods between Kelley's first and second stints as a plutonium worker had considerably increased the ratio of plutonium-238 to plutonium-239 in the material being handled. This fact, coupled with the record of nose counts and exposures, allowed them to distinquish somewhat the "early" from the "late" plutonium and, thus, to trace qualitatively the movement of plutonium from the lungs to other organs. An article discussing the findings stated:

> *[The] observations suggest (a) a relatively rapid clearance rate for plutonium in the lungs, compared to that in bone and lymph nodes; and (b) that a relatively small percentage of the material deposited in the lungs must migrate to the latter tissues. . . . [Also,] the rate of clearance from the lungs to the liver must be relatively fast and the retention time in the liver must be longer than in the lungs.*

The body burden. Equally important, of course, was checking the reliability of estimating a plutonium body burden from urinary excretion data when the exposure had been primarily through inhalation. Using a computer program developed by James N. P. Lawrence of the Los Alamos Health Physics Group (see "A Computer Analysis of Plutonium Excretion"), a body burden was calculated for Kelley of 19 nanocuries (equivalent to 0.30 micrograms of plutonium-239). This value was extremely close to the autopsy estimate of 18 nanocuries (or 16 nanocuries if the 10 per cent in the lungs was subtracted). In the discussion, Foreman, Langham, and Moss concluded that "the . . . agreement between body burden from tissue analyses and estimated burden from urine assays is so very satisfactory that it is undoubtedly fortuitous." Nevertheless, the agreement was a very strong indication that the execretion modeling approach was, indeed, close to the mark.

Changes in the Maximum Permissible Body Burden

We have already discussed the fact that in July 1945 the provisional tolerance limit for plutonium was lowered from 5 micrograms to 1 microgram because of the results of acute toxicity experiments with animals and because of the deposition pattern of plutonium in bone and soft tissue. In September 1949 at the Tripartite Permissible Dose Conference at Chalk River, Canada, Austin Brues presented the results of experiments on rats and mice on the comparative chronic toxicity of plutonium and radium. His results indicated that plutonium was 15 times as damaging as radium-226 when both were injected in microcurie amounts.

Those results prompted the Conference to recommend lowering the maximum permissible body burden to 0.1 microgram. Langham later reported that "this value placed an extremely stringent restraint on air tolerance in such facilities as Los Alamos." The Laboratory's plutonium work would have been seriously delayed. The same month as the Conference, Truman had announced the Russians' first test of an atomic bomb, and arguments were building for development of the hydrogen bomb, which would need plutonium for its "fission-bomb trigger."

After the conference at Chalk River, Brues pointed out two mitigating factors. First, the 15 to 1 toxicity ratio for plutonium versus radium was based on injected amounts. However, about 75 per cent of the plutonium was retained in rodents versus only about 25 per cent for radium, which meant the ratio in terms of retained dose should be a factor of 3 less. Second, fifty per cent of the radon from radium decay was retained in man versus only 15 to 20 per cent in rodents, which meant the ratio should be reduced by at least another factor of 2. The combined factor of 6 meant that the fixed body-burden limit for humans should be set at 0.6 microgram rather than 0.1 microgram.

On the other hand, Langham's analysis had shown that only 8.7 per cent of a plutonium body burden was excreted after 5 years and 12.7 per cent after 20 years. Those results supported the acceptance of a lower tolerance dose for plutonium.

Early in 1950, the Atomic Energy Commission authorized an official maximum permissible body burden of 0.5 microgram (32 nanocuries) for plutonium-239. In 1951, the International Committee on Radiological Protection (ICRP) recommended 0.6 microgram (40 nanocuries), and by 1953, both national and international committees were recommending this limit. The main doubts about this limit concerned use of the maximum permissible body burden for radium-226 as the cornerstone for calculating the plutonium burden. Although the critical organ for radium was the skeleton, that might not be the case for plutonium—especially when the main exposure route for workers was chronic inhalation. That type of exposure appeared to result in higher concentrations in the respiratory lymph nodes, lung tissue, and liver than in the skeleton.

In 1962, Langham, Lawrence, Jean McClelland, and Hempelmann published data on the analysis of autopsy samples from eight Los Alamos plutonium workers who had died of natural causes, as well as the samples from Kelley. The body burdens estimated from urine data using Lawrence's PUQFUA code ranged from 0 to 20 nanocuries (0.0 to 0.3 microgram of plutonium-239), and in fact, the three workers with the highest estimated body burdens also had the highest concentrations of plutonium in their tissue. Calculation of body burden from the tissue samples was not done; in some cases, only a few samples had been obtained.

In regard to distribution of plutonium in the body, the tissue samples, ranked in

the most frequent order of descending plutonium concentrations, were respiratory lymph nodes, lungs, liver, and bone. In the two cases where urine assays definitely indicated a significant positive exposure and analyses of both lymph nodes and bone were possible, the lymph nodes had plutonium concentrations 50 times higher per gram of tissue than the bone. Thus, inhalation exposures resulted in the entry of plutonium into the respiratory lymph nodes, a phenomenon that should obviously not have been seen (and was not seen) in the injection studies. (For a summary of what has been learned from autopsy studies, see "A True Measure of Exposure—the Human Tissue Analysis Program at Los Alamos.")

Additional Data from the Plutonium Patients

In 1969, Patricia Durbin, a biophysicist at the University of California, Berkeley, was involved with metabolic work on various radioisotopes, including americium, that led her to the published work on plutonium. Wanting to learn more, she began investigating the records and data on the plutonium human injections and trying to locate further information about the patients. In a letter, dated April 23, 1969, to Dr. John Howard, an administrator at the University of California Medical Center in San Francisco, she said:

> *Most of the patients injected with Pu were studied at other hospitals around the country, and although most were elderly and expected to have short life expectancies at the time of injection, some were misdiagnosed. Because of this, there was an understandably great uproar when the civilian A.E.C. took over from the Manhattan Engineer District. As a result, the human data thus obtained was classified "Secret", and so it remained for some years. All efforts to follow up on those persons who had been*

A Computer Analysis of Plutonium Excretion

One of the problems in applying the Langham power-function model to urine assays for plutonium workers was how to work backwards from the data to an estimate of the body burden. Urinary excretion data were usually low-level values with considerable scatter. Was a jump in a person's excretion rate due to analytical variations, physiological changes, or the result of a recent exposure? A method was needed that eliminated suspect data and then weighted all the remaining data in the determination of the effective dose, or body burden, and the effective exposure time for the Langham power-function.

In 1960, James N. P. Lawrence at Los Alamos devised a computer program (called PUQFUA), based on the plutonium excretion power functions, that attempted to account for multiple or continuous exposures occurring over a period of time. Basically, the work period was split into intervals between urine samplings and each interval was treated as a separate exposure incident. Using the Langham power function, the dose for that interval was calculated from the observed increase of plutonium in the urine over what was expected from previous exposures. If there was no increase, the exposure for that interval was set to zero, and if there was a decrease from what was expected, the previous data point was rejected, which helped eliminate contaminated samples (later versions of the code rejected data more than 2 standard deviations from the expected value). The total excretion at any given moment was then effectively the sum of many Langham power functions, one for each interval, each on its own time scale. The retained plutonium at any given time was the sum of all the original exposures corrected for excretion losses.

One advantage of the PUQFUA method was that essentially all the urine data were used to calculate a body burden rather than, as previously, using either a single urine assay or an average over a time interval. Individual assay points could fluctuate greatly (because of analytical variations, contamination, or physiological changes). Lawrence's approach weighted all but the rejected assays equally and, thus, was more likely to arrive at a reasonable estimate.

It should be emphasized that this approach, or any approach based on the excretion equations, was pertinent only for plutonium that had entered the blood stream and could be excreted by the kidneys. The program could, thus, calculate an effective measure of internalized plutonium, but the result did not give any indication of how much plutonium might be trapped in the lungs. Only when such plutonium had worked its way into the blood stream would a fraction of it appear as excreted plutonium.

Calculations with PUQFUA indicated that the body burdens of twenty-six Los Alamos plutonium workers (occupationally exposed at Los Alamos between 1944 and 1946 and in the UPPU study of Langham, Hempelmann, and Voelz) were 60 per cent higher than Langham had estimated with his approach, which suggested that Langham's power-function method underestimated plutonium retained in the body. However, we now know that the overestimate is due to long-term urinary excretion that is truly higher than what is predicted by the Langham model. When a modified version of the PUQFUA code is used that properly accounts for long-term data (10,000 days), the predicted body burdens are consistent with the values obtained from tissue analysis studies.

injected ceased abruptly, and no other human being has been deliberately injected with Pu since. Gradually the classification was downgraded, and the bulk of the data now appear in the open literature. Unfortunately, the material from three of the four patients injected by Dr. Hamilton [CAL-2, CAL-3, and the patient injected with americium] has never been made available to anyone. . . . Today, the production of Pu is enormous, and all indications are that it will increase. More people in the nuclear energy field are being exposed to Pu and more are expected to be world-wide. Still—all of our knowledge about Pu behavior in man rests on the sketchy results [of] the patients injected in the early days. None of the records are complete.

Durbin felt that, meager as they were, the human plutonium data, gathered 25 years before, represented nearly all their "human plutonium experience." Thus, it was time to re-examine the data, especially in light of newer knowledge (such as long-term animal data), and bring together under one cover as much as possible of the original detail.

Durbin visited many of the people associated with the plutonium work, including Langham and Christine Waterhouse who, in 1971, still saw two of the surviving Rochester plutonium patients. She and Waterhouse discussed the possibility of obtaining further excretion and blood samples and of performing physical examinations and other tests. The motivation behind the study of long-term excretion was, of course, to determine the radiation dose to a person who had had an intake of plutonium. The dose depended critically on the amount of plutonium retained in the body.

In 1972, Durbin brought all the known information about the patients together and summarized the data in a review article. Because the excretion rate out to several thousand days appeared to have several regions with different slopes, Durbin felt these regions might be related to physiological changes, and she fit both the urinary and fecal data to equations that were a sum of exponentials, one for each region. The exponential equations predicted total amounts of plutonium excreted that were somewhat larger than the amounts predicted by Langham's power function (for example, 8.8 per cent versus 6.3 per cent after a year). Durbin attributed the increase mainly to the fact that she had used data only from patients with normally functioning excretory systems (to better model healthy workers).

Durbin summarized the dynamics of plutonium in the body as follows:

Pu initially present in soft tissues other than liver is cleared rapidly; the major fraction is redistributed to bone and liver, and a small fraction is excreted. Pu deposited in the skeleton is mobilized in the normal course of bone remodeling; some is redeposited in bone, some is deposited in liver, and a small fraction is excreted. Pu deposited in liver is eventually transformed from relatively soluble forms in hepatic cells into insoluble hemosiderin deposits and sequestered in reticuloendothelial cells. Therefore, liver Pu is likely to be lost as slowly as, or more slowly than, bone Pu . . . The loss rate from the liver may eventually become the rate-limiting process for Pu disappearance from the whole body.

Thus, the picture of plutonium in the body was much more dynamic than that of simply "fixed" plutonium. Although plutonium appeared to be lost from the bone faster than had originally been thought, the consequence was an increase in liver plutonium with time. Durbin concluded that "liver is as critical an organ for Pu as is the skeleton."

Twenty-seven-year excretion data. In 1973, John Rundo at the Argonne National Laboratory in Chicago, working with additional long-term urine and fecal samples obtained by Durbin from two of the Rochester subjects (HP-3 and HP-6), developed new equations for the excretion data. The new data, taken about 10,000 days (27 years) after the plutonium injections, did not agree with predicted values—both the urinary and fecal excretion rates were more than a factor of ten higher than those predicted by the models. In fact, when data on the plutonium workers at Los Alamos were included, the values not only appeared to be higher than predicted but the curve turned upward (the values at 10,000 days were higher than at 1600 days), which raised questions about the validity of the models.

Deviations from the original equations proposed by Langham were, in one sense, not surprising. The main aim of the original human-injection studies was to gather enough short-term data to interpret urine assays a few weeks at the most after an accident and decide if plutonium workers had signficant internal doses of plutonium. Trying to apply equations describing short-term data out to almost 30 years went well beyond reasonable expectations. Not only were such data very meager, but the techniques used to analyze urine samples had changed several times over the years, and so the data points were not necessarily consistent. The data that were available—especially the urine assay data of plutonium workers—indicated that more plutonium was being excreted than had been predicted by Langham's model, and thus the expected long-term dose would be lower than previously thought.

Health effects. In 1976, R. E. Rowland, from Argonne, and Durbin reported what they had learned about health effects on the various injectees, especially those who had survived for many years and thus were more apt to show the radiation effects of plutonium.

None of the patients who had died had bone- or liver-related malignancies as the listed (or even the contributing) cause of death on their death certificates, unless that was the diagnosed disease at the time of the injection. And those patients who were still living also did not show any plutonium-related effects.

Eight of the 18 cases had survived at least twice as long as the four-year period established as the shortest induction interval for a radium-induced bone tumor. Using known cases of bone tumors from radium, Rowland and Durbin estimated that "the lowest average endosteal [bone surface] dose at which plutonium might induce bone tumors in man to be of the order of 600 rad." Four of the patients injected with plutonium had considerably higher endosteal doses (7420, 1280, 1790, and 973 rad); the other four had significant fractions of that dose (141 to 448 rad). Although, one to three cases of bone cancer were possible in the group, none had appeared (which might indicate a higher threshold dose for bone cancer or simply be a result of the smallness of the group). In regard to doses to the liver, all but one of the cases had estimated doses that were smaller than what appeared necessary, in comparison to radium, to cause liver cancer. Thus, it was not surprising that no liver tumors had appeared.

A Recent Analysis of the Excretion Data

One outcome of the openness inititative pledged by the Department of Energy and the subsequent review of documents was a re-analysis of the plutonium injection data by one of the authors (Moss) and Gary Tietjen. A careful review of the original notebooks at Los Alamos has revealed some errors in the urinary excretion data for the Rochester patients. Some of those errors were mistakes, others were simply needed adjustments for chemical recovery and elapsed collection time. For example, failure in the Rochester metabolic ward to properly time the urine sampling from the time of injection led to uncertainties in the initial excretion rates. Likewise, some of the data were not corrected for the analytically measured per cent recovery of plutonium, including an 88-per-cent recovery rate of plutonium for all the Rochester urine data.

Bill Moss and Eileen Welsome

When there was insufficient information to check the values, Moss and Tietjen discarded the data. In many cases, however, careful documention allowed the original data to be corrected and included in the subsequent analysis. (After 1956, a different urinalysis procedure, based on a nuclear-track method developed at Hanford, was implemented at Los Alamos, and data from that time onward are much more accurate and consistent. Today's analytical methods routinely detect body burdens at the 0.1-microgram level.) As a result of the re-examination of original data, it is apparent that the increase in excretion rate noted by Rundo was, in fact, only an artifact, the result of urine assays that were not corrected for chemical yield or for alpha-counting instrument calibration bias.

Also included in the re-analysis were several consecutive daily samples that had been collected from each of HP-3, HP-4, HP-6, and HP-9 about a year after their injections. Although these data were recorded at Los Alamos, for some unknown reason Langham may not have been aware of them; they were not used in his analysis even though they were consistent with the data he did use (the 500-day data obtained from HP-6).

In addition to corrections, new data have become available from a recent study. Talbot, Newton, and Warner in England injected plutonium-237 into two healthy male volunteers and analyzed the excreta using modern analytical methods. Plutonium-237 has only a 45.3-day half-life and decays by the relatively benign electron-capture mode, which made this isotope a negligible health concern compared to plutonium-239. Moreover, x rays emitted in the decay enabled patterns of organ uptake to be studied during the experiment. This approach was not used earlier because it has been too difficult to eliminate other plutonium isotopes with long half-lives. In this case, the researchers were able to use a variable-energy cyclotron at Harwell and adjust the conditions of the irradiation of uranium-235 with helium ions to make relatively pure plutonium-237.

Moss and Tietjen used the new excretion data together with the corrections to the original plutonium-239 data to do another analysis of plutonium urinary excretion. Based solely on empirical grounds, they expanded Langham's original power function by adding a second term. The urine data for the two plutonium-237 subjects from day 5 through day 15 are remarkably linear on a log-log plot, whereas the data for days 1 through 4 are more variable. Thus, only the data for days 5 through 14 were used to obtain the first power-function term. When they compared the slope for that term to the slopes for ten of the Rochester patients (HP-1 through HP-10), the comparison, for the most part, was very close.

Moss and Tietjen next used the sparse

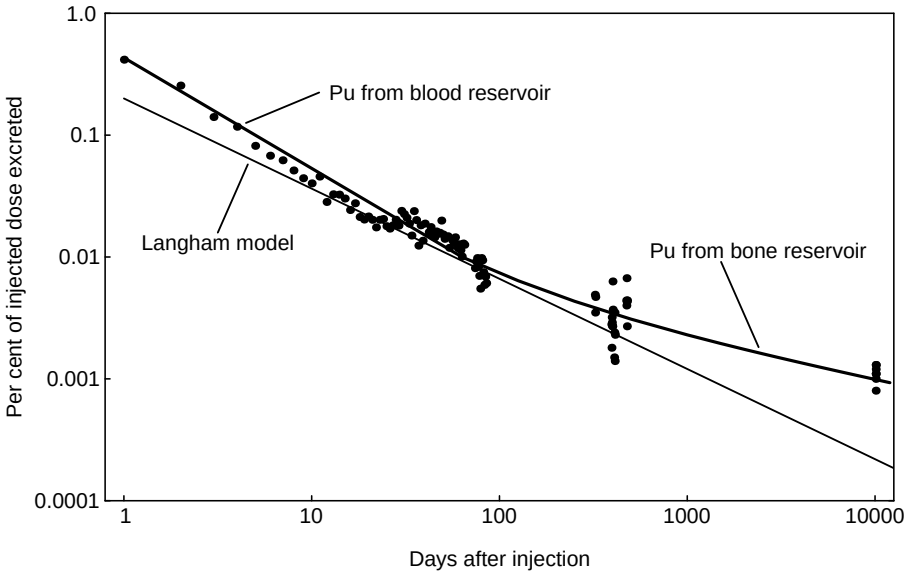

Figure 6. A Re-analysis of the Plutonium Urinary Excretion Data

The data are the median values for urinary excretion in the human injection studies after rejection of suspect data and correction for chemical yield. The solid curve represents the two-term power function that results when the slope of the curve determined from the early data (5 through 15 days) is used to fix the exponent of the first term of the function and the late data are used to determine the exponent of the second term. The curve shows two distinct regions that probably correspond to an early release of plutonium from a blood reservoir followed by a slower release from a bone reservoir. The original Langham power-function model is also shown (dashed line); the apparent poor fit is, of course, a result of the recent adjustments of the data.

"late" data (80, 300, 400, 500, and 10,000 days) to obtain the exponent for the second power-function term for urinary excretion. (The 1600-day data were analytically suspect and were discarded; those data, and data from the workers in the same time frame, were influential in Langham's extension of his power function to 1750 days.) Fixing the slope (in a log-log plot) for the late data meant the early data would not have undue influence. Once the slopes in the two regions were fixed, the coefficients of the two power terms were found from a weighted nonlinear least squares fit, using the medians (rather than the raw data or the means) to cut down on any undue influence from outliers. A similar analysis was done for fecal excretion, although Moss and Tietjen did not have to constrain the data. The final results are:

$$Y_u = 0.4132\,X^{2\,1.0615} + 0.0187\,X^{2\,0.3217},$$
$$Y_f = 1.1481\,X^{2\,1.4400} + 0.0058\,X^{2\,0.2039}.$$

The dependence of the excretion function on two power terms is obvious in the log-log plot of the data (Figure 6), which has two distinct regions of different slopes. The second region is especially obvious because of the data at 10,000 days, which has less scatter because of improved analytical methods. However, the corrected data around day 80 and days 300 to 500, when plotted on an individual basis for each patient, also strongly indicate the different slope of the second region, despite the much greater scatter of those data evident in the figure.

Table 3. 10,000-day Excretion of Plutonium

	Moss-Tietjen function	Langham function
Urinary excretion:	17.4 %	7.8 %
Fecal excretion:	14.6 %	4.3 %
Total excreted:	32.0 %	12.1 %
Amount remaining:	68.0 %	88.9 %

Excretion of plutonium. The equations have allowed new estimates to be made of the amount of plutonium that would be excreted over the long term (see Table 3), and it turns out that this is more than twice the amount of what had been estimated earlier with Langham's single-term power function. For example, after 10,000 days (27.4 years), a total of 32.0 percent of internal plutonium will have been excreted compared to the 12.1 per cent estimated from Langham's function. This fact helps explain why body-burden values derived from autopsy studies of plutonium workers tend to be less than that previously estimated from the urine data. However, because 68.0 per cent of the plutonium remains (versus 88.9 per cent), the conclusion about removing workers from further exposure once they have reached the maximum permissible limit remains as true today as it was in 1945.

On the other hand, the implications for dose estimates are significant. After fifty years, almost half the plutonium will have been excreted. Thus, the results of a tissue analysis on a worker that died 50 years after his exposure would extrapolate to an initial body burden almost twice that estimated from the Langham function. The increase in body burden translates, in turn, to an increase in the radiation dose to the person over the rest of his life.

Two physiological regions. Physically, the importance of a two-term power function is that it likely corresponds to two different physiological processes. Moss and Tietjen believe that for the

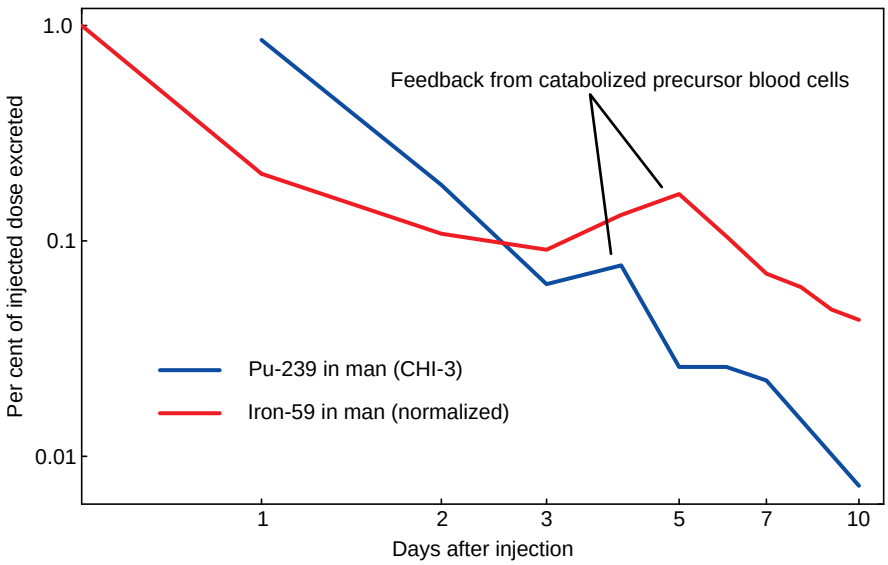

Figure 7. The Four-day Peak for Red Blood Cells

Many of the urinary excretion curves for the human plutonium injection studies show a small peak around day 4 (the blue curve above uses the excretion data of CHI-3). This peak corresponds to the release of plutonium back into the blood when about 10 per cent of newly forming red blood cells, which started their life cycle at the time of the injection, are destroyed (catabolized). A similar peak is observed in studies with iron-59 in man (red curve), as well as for plutonium-239 in dogs (not shown).

first couple of weeks, most of the excreted plutonium is coming from a blood reservoir. For later times, the plutonium is being released more slowly from a bone reservoir with some contribution from the liver. Such behavior had been postulated in 1972 by Betsy Stover from an analysis of long-term plutonium excretion in dogs, and Langham had conjectured about this type of physiological change as well. However, the human data did not appear, until recently, to follow the same pattern. Now, the dog and human data are consistent.

These results form an interesting contrast with radium. After intake, radium is almost immediately deposited in the bone. To be excreted, it has to be metabolized and returned to the blood. So there is only one region, and the excretion rate, although initially very high, drops off in a log-log plot with no apparent changes in slope. A single-term power function is adequate to describe the full excretion behavior for radium.

Although our two-term power function fits the general trend of the initial excretion of plutonium, there has always been some variability in the first four days, which, as it turns out, has a physiological basis. Typically, there is an increase in the excretion rate at about four days (Figure 7) corresponding to a turnover in red blood cells. Soluble plutonium has been shown to combine with the iron-transport protein in the blood, transferrin, where it is incorporated into developing red blood cells. However, after four days, catabolization, or destruction, of about 10 per cent of the developing red blood cells, including all those containing plutonium rather than iron, are released back into the blood, which increases the amount available for excretion. Such a peak in the excretion data cannot, of course, be modeled with simple, one- or two-term power functions. But recognizing why a peak occurs at the four-day mark is a satisfying check of our understanding of the metabolism of plutonium in humans. Perhaps more important, though, noting the existence of the peak in most of the original human excretion curves helps substantiate the sensitivity and, thus, the importance and relevance of that fifty-year-old data.

Additionally, the iron-transport bound plutonium that is released back into the blood is not incorporated into mature red blood cells. Some fraction of this plutonium is excreted and the rest is redeposited in tissue. A cycle of this sort continues on and on, which gradually brings small amounts of plutonium into the blood to be excreted.

Implications of the Plutonium Injection Studies

In the years that have passed since the human plutonium injection studies, the data have been endlessly analyzed, discussed, and re-analyzed by the community of health physicists concerned with the protection of plutonium workers. What has been learned and what impact has this knowledge had on health protection for plutonium workers?

The determination of a radiation dose to workers from plutonium (or the toxic dose from any material, for that matter) requires a biokinetic model that describes, in mathematical terms, how a known intake of plutonium translates to a time-dependent distribution of plutonium throughout the body. For example, an inhalation exposure to plutonium dust would need expressions that describe, as a function of time, the fraction of plutonium retained by the lung, the fraction that enters the bloodstream, the fraction that is coughed up, swallowed, and passed through the gastrointestinal tract, the fraction in the blood that goes to various organs, such as the liver and bone, the fraction of plutonium that is filtered out by the kidneys and excreted, and so forth. The human plutonium injection studies coupled with autopsy results yielded considerable data that were applicable to the calculation of the time-dependent distri-

bution of plutonium in the body. Urine assays of plutonium workers, again coupled with occasional autopsy results, increased that knowledge.

The usual problem, however, is the inverse: urine data are available but the amount of intake, and perhaps the time of intake, is not known. In this case, the current approach typically uses two biokinetic components for plutonium inhalation exposures: the first describes how inhaled material enters the blood system; the second relates the amount in the blood to the amount excreted. These two components translate urine assays to a realistic estimate of the amount of intake, and then the complete biokinetic model is used to determine the distribution of that plutonium throughout the body, which, in turn, serves as the basis for calculation of radiation dose to the individual.

The most uncertain step is this last one—the calculation of a dose from a known plutonium distribution. For example, although it is well established that much of the plutonium in the bone is concentrated on the endosteal surfaces, there is still a great deal of controversy about how to calculate the actual dose from this deposition. Plutonium that is directly on top of the surface will impart a much higher dose to the osteocytes (bone cells) than plutonium that is buried in the bone matrix, even if only by a few hundred micrometers. The only evidence that actual doses may be less than was originally assumed is the fact that none of the human plutonium patients and none of the plutonium workers (with one possible exception) who lived many years with plutonium in their bodies have exhibited any evidence of plutonium-induced tumors. This outcome is in high contrast to radium, where many cases of tumors were obviously present above certain threshold levels.

What about the one possible exception? In 1975, George Voelz, a medical doctor in the Los Alamos Health Division published a study of the Los Alamos plutonium workers, which discussed the fact that one of the radiation effects of radium poisoning was the development of osteogenic sarcoma, a rare bone cancer. He stated that "the age adjusted death rate in the U.S. from all bone tumors, including osteosarcoma, is only about 1 per 100,000 persons per year." The appearance of 2 bone sarcomas in 15 cases of radium poisoning was evidence that the sarcomas were, indeed, a result of the radiation. In 1989, one of the 26 Los Alamos workers, exposed to plutonium in 1945 and 1946, had an osteogenic sarcoma. Bone sarcomas had been observed in plutonium studies with animals, including inhalation studies at plutonium levels comparable to the maximum permissible lung dose for workers. In a 1991 paper by Voelz and Lawrence, it was stated that the "dose estimate for our case . . . is similar to the lowest range of doses for dogs that have developed bone tumors when exposed to Pu . . . but is much below the dose for the lowest Ra-exposed person with a bone tumor." To insure a full understanding of this one case, a new dose calculation based on the two-term power function is warranted.

However, this is the only possiblity to date of a plutonium-induced cancer. Most of the workers have lived longer than average. It would seem important to continue studying the plutonium workers. Much could be learned for little cost.

It is also important to remember that occupational health protection for plutonium was approached with the radium tragedy in mind, which resulted in practices and standards being adopted that made it much more unlikely that the threshold for tumors would be reached with plutonium. The almost total absence of such tumors indicates that the practices established for plutonium workers were, in the main, successful, even though, from a statistical point of view, the number of cases on which conclusions can be based is too small to be conclusive. But that in itself speaks to the fact that the radium industry was a situation in which the workers, early on, were in an unregulated and unknowingly hazardous environment, whereas even though the plutonium workers, early on, were working under hazardous conditions, they were nevertheless kept apprised of the dangers and given whatever safety equipment became available. As soon as it was feasible, the work was moved into a highly controlled environment in which the safest procedures available were practiced and in which the equipment, analysis techniques, and work procedures were constantly upgraded as they became available.

A great deal has been learned from the human plutonium injection studies, but much is left to be learned. However, the early studies were valuable enough to enable our country to perform its weapons research and production at the end of World War II and into the cold war with confidence that the workers doing the work were being protected and that the estimates of their plutonium doses would be accurate. The potentially tragic consequences of working with a new and unknown substance never came to be. For this, we are greatly indebted to the radiologists concerned with insuring safety during the Mahattan Project and are even more indebted to the patients who were injected with plutonium (see "'Ethical Harm' and the Plutonium Injection Experiments" on page 280). ■

Acknowledgements

Bill Moss would like to thank Darrell Fisher for his encouragement and support, Gary Tietjen for his work on the re-analysis of the data as well as many helpful comments, and George Voelz, Payne Harris, and especially Julie Langham Grilley for their willing help and valuable comments.

Further Reading

A collection of copies of the documents gathered

by the Los Alamos Human Studies Project Team are available to the public in the Los Alamos Public Reading Room next to the Bradbury Science Museum in Los Alamos. Also, the Department of Energy Office of Human Radiation Experiments has information about many of the documents on its home page on the World Wide Web (www.ohre.doe.gov).

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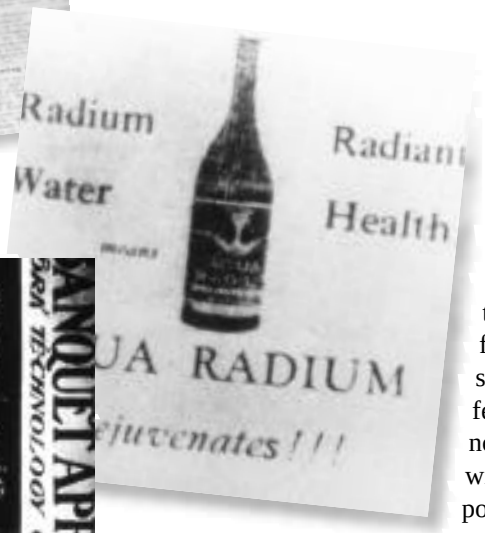
William D. Moss came to the Laboratory in 1953 after receiving his B.S. in biology and chemistry from Sterling College, Kansas, in 1950. In 1958, he became a staff member in the Industrial Hygiene Group where he was responsible for developing analytical chemical procedures for analyzing low concentrations of inorganic and organic compounds and radioelements. He was sent on assignment to Madrid, Spain, in 1966 to assist the Spanish Nuclear Energy Board with their evaluations of plutonium contamination at the Palomares site. In 1975, Bill was named section leader of the Bioanalytical and Chemistry Section, and from 1984 through 1990, he was section leader of the Radiochemistry Group. His research interests included the behavior and characterization of airborne radioactive aerosols in the working environment and concentrations of radioactive elements in human tissues. Bill has co-authored numerous publications and has served as a member of the Health Physics Society and the American Industrial Hygiene Association. In 1994, Bill joined the Laboratory's Human Studies Project Team and was responsible for re-evaluating the human plutonium injection experiments conducted in the mid-forties. Bill retired from the Laboratory in 1990 and has actively continued his research as a Laboratory Associate.

Roger Eckhardt. See biography at the end of "Ionizing Radiation—It's Everywhere!"

Radium–the Benchmark



Over the past fifty years, thousands of workers in the United States have handled plutonium. Of those workers, only about fifty, all from the nuclear-weapons complex, have been exposed to plutonium at levels above the maximum permissible dose. Because so few people have high-dose exposures, we have little direct information about the risk of plutonium in man. This leads to the ironic situation that the better we protect our workers, the less we know about their risk. What then do we use to base our decisions about the risk of plutonium and the precautions we need to take to safeguard workers against that risk?

Much of our understanding of the health risk posed by plutonium is based on another element, radium. Like plutonium, radium is an alpha-emitting radioisotope, but it is created naturally as a decay product, or daughter, of uranium. As described below, thousands of people were exposed to radium before 1932, and the effects of the many high-dose exposures became apparent after just a few years. That grievous situation none-the-less provided scientists with a group of people who were exposed internally to an alpha-emitting radioisotope, and who could be observed, evaluated, and studied. In 1944, the risk associated with the new manmade element plutonium was therefore estimated by scaling the risks associated with radium. That initial estimate was soon modified to take into account new animal data on the comparative toxicity and distribution in the bone of radium versus plutonium. But even today, much of our understanding of the risk of plutonium to humans and much of the public's perceptions about the dangers of radioactive materials are grounded in the story of radium.

That story began in 1898 when Marie and Pierre Curie discovered radium. The announcement at the French Academy of Science of a new radioactive material followed just two years after Henri Becquerel's discovery of radioactivity in uranium. Radium was only the third radioactive element to be identified (polonium was the second—also discovered in 1898 by the Curies). Radium was very scarce; after four years of hard labor, the Curies were able to separate only 100 milligrams of the pure element (roughly equivalent in volume to the the head of a match) from several tons of uranium ore. It was therefore very expensive, and as late as 1921, one gram of radium cost $100,000. However, the extraordinary attributes of radium made it worth the cost. The half-life of radium is 1600 years, as opposed to only 138 days for polonium and 4.5 billion years for uranium (see "Ionizing Radiation—It's Everywhere!" pages 24-25, for a discussion of radioactive half-life). Radium was thus a stable source of radiation for hundreds of years

for Alpha Emitters

with an intensity three-thousand times greater than an equal amount of uranium. In other words, radium combined a long life with radioactive intensity far better than the other known radioactive materials, and it was eagerly put to a great number of uses.

Marie Curie (1867-1934), photo taken circa 1920.

Inset: Pierre Curie (1859-1906).

Cancer treatment was among the earliest and most beneficial applications of radium. The idea derived from an incident that occurred in 1901 in which Becquerel, eager to carry out some impromptu demonstrations, carried a tube of radium that was loaned to him by the Curies in his shirt pocket for six hours. Ten days later, he developed a small erythema, or reddening of the skin, identical to that produced by x rays. It was clear that emanations from the radium sample could affect skin tissue, and that perhaps, like x rays, such emanations could be used as a treatment for cancer.

That idea proved to be successful, and in 1906, the Biological Laboratory of Paris for the practice of “radium therapy" was established. Applicators containing radium salts were applied directly to the surface of benign and malignant tumors to shrink or eliminate them. Such use of radium dramatically improved the quality of many lives (see Figure 1) and helped found the modern medical field of radiotherapy. However, the radiation that penetrated the applicators were mainly gamma rays from the radioactive daughters of radium decay. Once other gamma-ray-emitting radioisotopes, such as cesium-137, became available from nuclear reactors during the 1960s, the use of radium as a radiation source for cancer treatment gradually declined and eventually ended.

During its heyday, however, radium’s use as a cure for cancer was widely publicized in the press. The element assumed an aura that was both mysterious and fascinating, and it was celebrated in Europe and America. Audiences drew around storytellers describing the danger of radium’s emanations, while at the same time, it was touted as a miracle cure for many diseases. The young indulged themselves with radium-laced candies and sodas. Women sought youthful beauty in radium-containing facial creams, while the fatigued restored their vigor

in radium baths. For the early part of the 20th century, radium enjoyed a tremendous, albeit curious, popularity.

But that popularity gradually turned to disdain. In 1925, a man fraudulently titled "Dr." William Bailey patented and promoted a nostrum of radium-laced water called Radithor. Bailey seems to have been motivated by a desire for easy money as well as a personal obsession with radioactivity. His oral medication, a solution containing the two radium isotopes radium-226 and radium-228 (the latter called mesothorium), was touted as a cure for "dyspepsia, high blood pressure, impotence, and more than 150 other 'endocrinologic' maladies." Whatever truth lay in those claims, Radithor in large quantities proved lethal. In 1927, Eben Byers, a millionaire socialite and amateur golf champion, began to take Radithor on the recommendation of a physician to treat the chronic pain in his arm. Byers reported feeling rejuvenated and invigorated by the nostrum. However, in 1932, four years and about 1000 to 1500 bottles of Radithor later, Eben Byers died, having suffered severe anemia and weight loss, massive destruction of the bone in his jaw, skull, and entire skeleton, and finally kidney and bone-marrow failure.

Figure 1. A Miracle Cure Brought about through Radium Treatments

These three photographs show the miraculous results that were obtained using radium applicators. The first image is a baby girl immediately before radium treatment in December 1923. The next two photographs show the young girl in April 1926 and then at 10 years old. She was treated at the Institut-Curie, Paris. (Reprinted wih permission from the Institut-Curie, Paris.)

National press coverage of Eben Byers' horrible death brought the danger of internal deposits of radium to the attention of the general public. It also inspired the Food and Drug Administration to campaign for broader jurisdiction over the uses of radium. Although that outcome was a very positive result from Byers' death, it is painful to realize that his death was avoidable. Two years prior to Byers' ingestion of his first bottle of Radithor, the health risks associated with radium had been identified within a select group of radium workers, and "radium poisoning" had been recognized as a deadly occupational hazard. The story of the radium dial painters is a tragic, yet crucial episode, in the development of radioactive risk assessment.

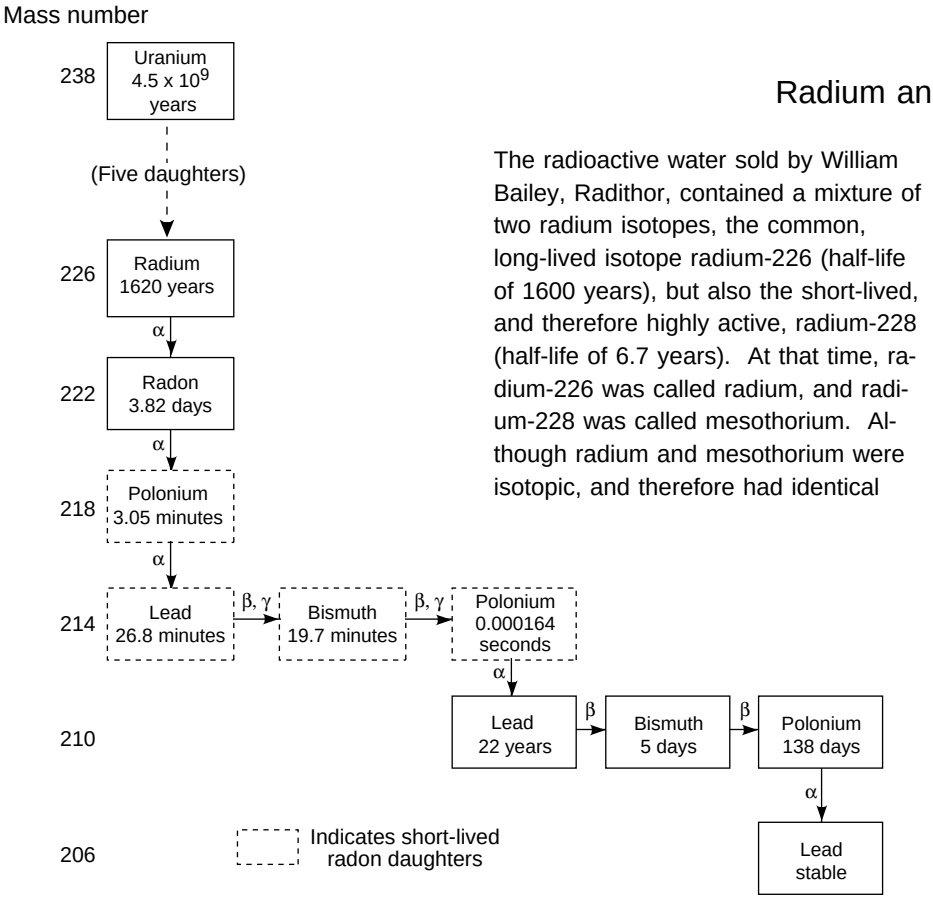
During World War I paint containing radium was widely used to make self-luminous dials for watches, clocks, and military instruments. The "glow-in-the dark" paint was first developed in Germany around 1908 and began to be made in the United States by about 1913. This "self-luminous compound," as it was frequently called, contained fine crystals of zinc sulfide mixed with radium salts. When alpha particles from radium collided with molecules of zinc sulfide, the latter would "scintillate," or emit light.

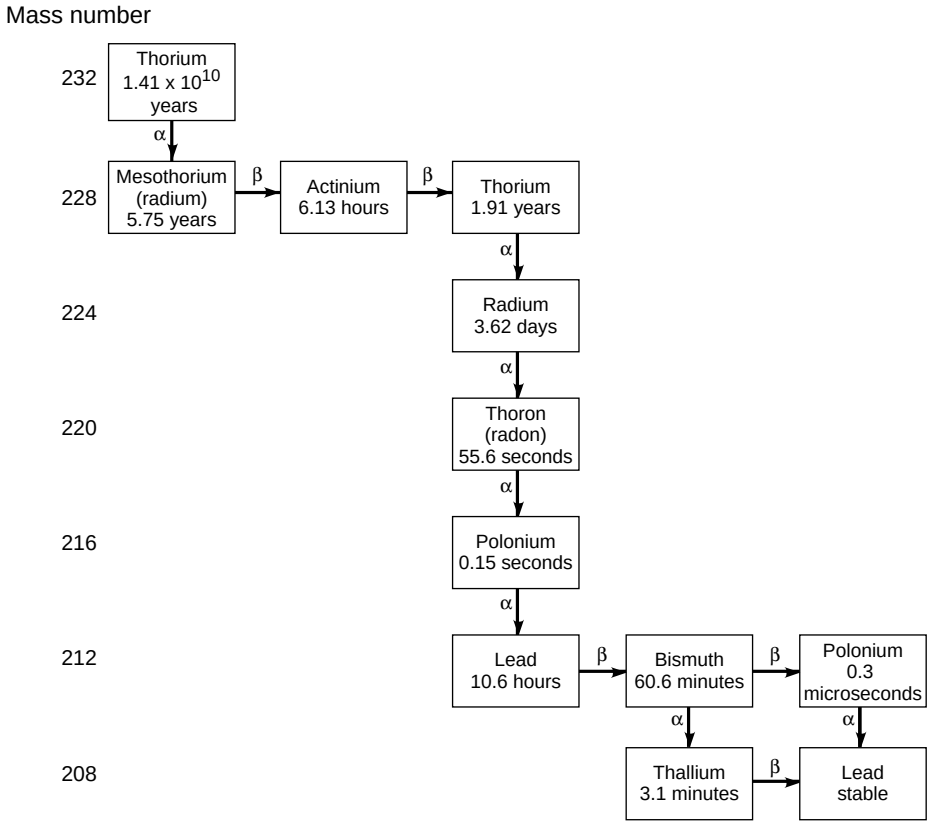
When the United States entered the war in 1917, a factory in Orange, New Jersey, became a major supplier of radium-dial instruments to the military. The factory employed hundred of workers, most of whom were very young women. Those women were in the practice of "tipping" their brushes, that is, using their lips to shape the brush into a sharp point, which enabled them to paint fine lines and numerals. As a result, many women inadvertently ingested small but significant quantities of radium. From 1922 to 1924, nine young dial painters, most of whom

Radium and Mesothorium

The radioactive water sold by William Bailey, Radithor, contained a mixture of two radium isotopes, the common, long-lived isotope radium-226 (half-life of 1600 years), but also the short-lived, and therefore highly active, radium-228 (half-life of 6.7 years). At that time, radium-226 was called radium, and radium-228 was called mesothorium. Although radium and mesothorium were isotopic, and therefore had identical chemical properties, they belonged to different radioactive decay chains and had distinct radioactive characteristics. Unlike radium, which was the sixth daughter in the uranium-238 decay chain with a 1600 year half-life, mesothorium was the first daughter of thorium-232 and decayed with a 6.7 year half-life.

Mesothorium became commercially available in about 1916 as a by-product of the thorium "gas mantle" industry. By 1917, both radium and mesothorium were primary ingredients of a self-luminous paint that the military used to produce glow-in-the-dark instrument faces. Mesothorium was preferred to radium because it was cheaper, but the supply of mesothorium was erratic. Some batches of paint contained only radium whereas others had a high proportion of mesothorium. This variability in the isotopic composition of the paint became an issue when it was discovered that the paint was a severe health hazard and attempts were made to correlate a person's physiological harm with the amount of radium retained in that person's body. Mesothorium activity decreased more rapidly than that of radium due to its much shorter half-life. Consequently, when body-burden measurements were made years after intake, the mesothorium activity was very low and couldn't be distinguished from the radium activity. Not until the late 1950s, when high-resolution gamma-ray detectors became available, could the residual mesothorium be measured and accurate doses be determined. Those doses were within the same range as the radium-226 doses, and thus they did not alter the radium standard, which had been set in 1941 with a large margin of safety relative to the radium-226 doses that were known at that time.





had been diagnosed with oral lesions, necroses of the jaw, and anemia, died early and painful deaths.

That ominous coincidence prompted a very quiet, factory-management-sponsored investigation in 1924. In 1925, a second (though this time not so quiet) investigation was conducted by Dr. E. L. Hoffman, a physician working on behalf of the New Jersey Consumers' League. Hoffman suggested that the deaths signaled a new occupational disease probably caused by the radioactive materials in the paint.

Young women in the radium-dial painting industry in the 1920s.

Dr. Harrison S. Martland, the local county's chief medical examiner, began an independent investigation of Hoffman's hypothesis. He examined two young dial painters with jaw necrosis and severe anemia, and when they died some months later, Martland performed the autopsies. He found radioactivity in both bodies. Martland also discovered radioactivity in the body of a company physicist who died at about the same time. He studied five other patients with symptoms of jaw necrosis and anemia, and based on the detection of radon gas (a decay product of radium) in their breath, diagnosed them as probably having the new disease. The findings of the three investigations were published in 1925, and all came to the same conclusion: The ingestion of radioactive materials in the luminous paint was the probable cause of a new type of occupational poisoning. Although the diagnosis and the conclusion were initially resisted by company members and others, more deaths quickly confirmed that the cause of the disease was poisoning by either the inhalation or ingestion of radium compounds. The habit of licking the brushes was forbidden, and other practices at the dial-painting plants were sufficiently modified such that very few new cases of occupational radium poisoning occurred after 1930.

Dr. Martland, in his 1925 paper, was correctly able to outline the origin, symptoms, and pathology of radium poisoning. Unlike ordinary poisons, such as arsenic, which impair or kill an organism through chemical action, radium causes injury through its radioactivity. Most of the radiation emitted is in the form of energetic alpha particles. In living tissue, alpha particles typically travel about 50 microns, or about 5 to 10 cell diameters, and deposit their energy within the cells

through ionization processes. The resulting damage can result either in direct cellular death (necrosis), or possibly in the generation of genetic mutations that initiate the development of cancer or tumor formation. (Alpha particles are not much of a biomedical threat if the radium or other radioactive source is outside the body. Barriers such as our clothing or the outer dead layers of our skin are effective shields against alpha bombardment.) When radium is ingested, the majority of material is rapidly excreted. However, since radium is chemically similar to calcium, a significant fraction is absorbed into the bloodstream and deposited mainly in the skeleton. The amount that remains within the body is called the "body burden," and it is effectively an internal radiation source. The continual alpha-particle bombardment of the bone-forming and blood-forming cells evidently caused the severe bone lesions and anemias seen in the dial painters.

In a 1929 paper, Martland observed that the cases of radium poisoning fell into two distinct groups: those acute cases in which symptoms appeared relatively soon after the exposure and ended in a rapid death and those cases in which the disease seemed to follow a much slower course. In the first group, later designated as cases of acute radium poisoning, the patients exhibited severe necrosis of the jaw bone, osteomyelitis (inflammation of the bone), crippling lesions of the bone, and severe anemia and leukopenia (depletion of white blood cells). Patients exhibited those symptoms anywhere from 1 to 7 years after having worked steadily in the industry for at least one year, and death came within months of the appearance of the symptoms. Acute radium poisoning was associated with body burdens (mostly deposited in the skeleton) of from 10 to 100 micrograms of radium and mesothorium. The body burdens of those fatal cases were estimated in rather rough fashion during post-mortem examinations.

The second group of patients, followed by Martland and other colleagues well into the 1950s, were identified as suffering from chronic radium poisoning. Those dial painters appeared to be in good health for about 5 to 15 years after exposure. During that time, however, they were harboring a silent, slowly progressing bone necrosis that would lead to rarefactions, holes, and mineralization within the skeletal system. The frank clinical symptoms that eventually appeared included the loosening of the teeth, followed by infection of the jaw bones, pathological bone fractures that occurred spontaneously or as a result of trauma, that healed very slowly, and that produced bony deformities, and finally cancers of the bone and adjacent structures. The cancers appeared anywhere from 12 to 23 years after exposure and were very often fatal. Those that suffered chronic radium poisoning were found to have residual body burdens of radium between about 0.7 and 23 micrograms, which was much lower, on average, than those associated with acute radium poisoning.

In the late 1920s the diagnosis of radium poisoning was done by Martland and others on the basis of the detection of radioactive gases, either radon (radon-222) or thoron (radon-220), in the breath of patients. Those inert gases are produced in the skeleton by the decay of radium-226 and radium-228 (mesothorium), respectively (see "Radium and Mesothorium"). From the bone, the gases diffuse into the bloodstream where they are transported to the lung and exhaled. Martland used his measurements of radioactive gases as a sort of flag that indicated whether or not a patient had been internally exposed to radium. He did not use this method to quantitatively assess the amount of radium inside the patient.

A sensitive quantitative means for measuring the radium body burden was not developed until Robley D. Evans entered the nascent field of radium toxicology. In

Robley Evans in his laboratory at MIT.

1932, Evans was a graduate student in physics under the famous Robert Millikan at Caltech. His thesis work involved, among other things, the development of highly sensitive accurate techniques for measuring radium and radon in geophysical samples. Following the scandal associated with Eben Byers' death, a representative from the Los Angeles County Health Department, inquiring about how to prevent such occurrences in California, was referred to Evans.

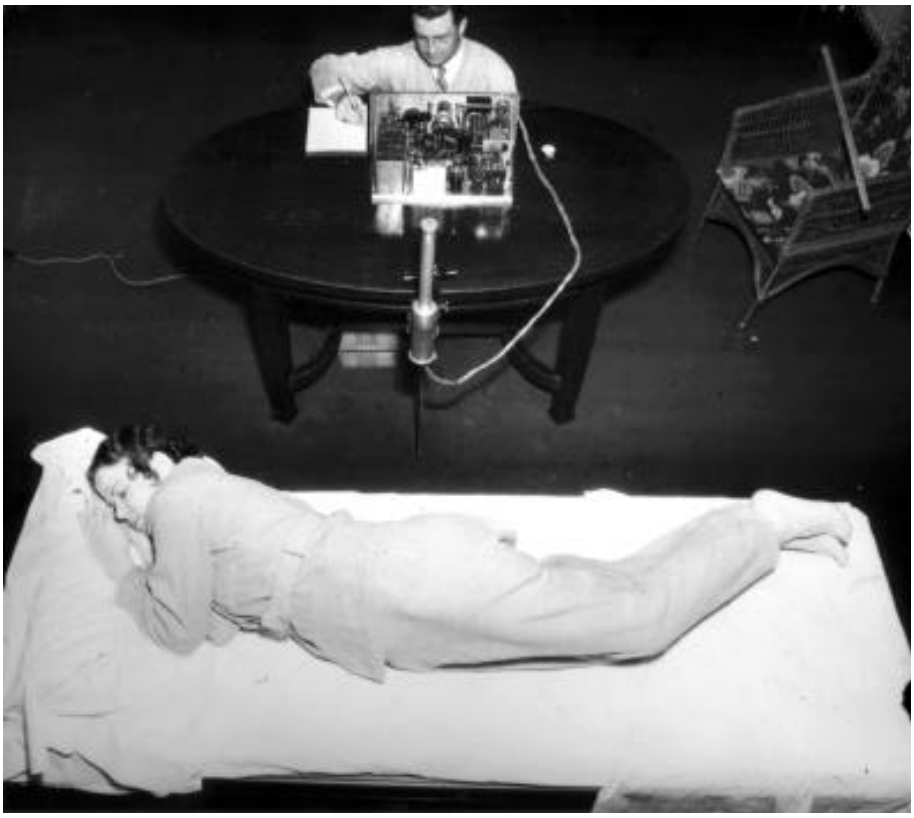
Evans became interested in the uptake, metabolism, and excretion of radium in living persons and realized that the key to studying those problems would be the ability to accurately measure the amount of radium present in the living body. However, the alpha particles emitted by radium are only weakly penetrating and cannot be used to measure the radium body burden; they simply do not make it out of the body. Therefore, Evans' idea was to measure what became known as the *in vivo* body burden by an indirect approach. Instead of measuring the alpha particles from radium, Evans would make measurements pertaining to three of the daughter products of radium (see "*In Vivo* Measurements of Radium"). Evans developed the technique in 1934 at MIT. It was many times more sensitive than previous techniques, allowing measurement of body burdens as small as 0.1 microgram. It was also easy to apply and was eventually used by all those involved in clinical studies of radium poisoning, including, of course, Dr. Martland.

Toward the end of 1940, the United States was gearing up for World War II, and radium-dial instruments were being produced in large quantities. Evans was again approached, this time by the U.S. Navy, about the subject of radium standards. (It is said that a captain in the Navy Medical Corps paid Evans a visit and insisted that he either provide the Navy with safety standards for radium-dial painters or face being inducted into the service where he would be forced to produce them.) Evans became part of nine-member committee formed by the National Bureau of Standards. Also on that committee were Martland and two other researchers who had done quantitative work on radium toxicity.

By February 1941, the committee had collected accurate information on the residual body burdens of 27 persons as well as their state of health. The 20 persons with radium body burdens in the range of 1.2 to 23 microcuries of activity, or 1.2 to 23 micrograms by weight (by definition, 1 gram of radium has an activity of 1

In Vivo Measurements of Radium

The technique by which Evans measured the *in vivo* radium body burden required two measurements, one involving the rate at which radon is expired in the breath and another involving the intensity of gamma rays emitted from the body. Together, these two measurements provided all the information that was needed to determine the amount of radium in a patient's body.



Radon, the first daughter of radium, is an inert gas. As such, it tends to diffuse from the skeleton into the bloodstream where it is transported to the lung and exhaled. Since one gram of radium is known to produce 2.1×10^{-6} curies of radon per second, the rate of radon exhalation can be used to measure the amount of radium in the body that produces the expired radon. Evans therefore developed a precise version of Martland's "breathalyzer test" to make an accurate measurement of the rate at which radon is exhaled. Exhaled air was collected and its radon content determined in an ionization chamber by measuring the alpha emissions from the radon decay.

That technique only measured a fraction of the body burden because some of the radon decayed before it could be exhaled. To determine the total body burden, a second measurement was necessary. Evans had to look farther down the decay chain of radium, past radon, to two gamma-emitting radioisotopes, lead-214 and bismuth-214. Because gamma rays are penetrating, they are easily detected outside the body. Evans used a "homemade, copper-screen-cathode" Geiger-Müller counter to measure the intensity of the gamma-ray emissions from the whole body and then worked backwards to determine the amount of radium required to produce that intensity. By adding the results of Evans' two measurements, the total *in vivo* radium body burden was deduced.

The photograph above shows the breathalyzer test used by Evans to measure the amount of radon being exhaled per second. That amount turned out to be about 50 per cent of the total radon produced per second and thus reflected about 50 per cent of the total radium body burden.

The photograph at left illustrates the "meter-arc" method for measuring the fraction of the radium body burden that could not be determined from the radon test shown above. The body of the radium patient was positioned along an arc so that the gamma-ray detector was about 1 meter from the forehead, shoulder, abdomen, knees, and toes. The detector measured the gamma rays emanating from the patient's body. Those gamma rays were produced by lead-214 and bismuth-214, radioiosotopes located below radon in the radium decay chain. Thus, they originated from radon that decayed before reaching the lungs.

curie), showed various degrees of injury, whereas the 7 persons with body burdens less than 0.5 microcurie showed no ill effects at all. Evans proposed to the committee that the tolerance level for the radium body burden in radium-dial painters be set "at such a level that we would feel perfectly comfortable if our own wife or daughter were the subject." With that thought in mind, the nine members unanimously decided to set the tolerance level at a factor of 10 below the level at which effects were seen, or 0.1 microcurie. On May 2, 1941, the standard for radium-226 was adopted in the National Bureau of Standards Handbook, seven months before Pearl Harbor and two months after the then secret discovery of plutonium.

Although the tolerance level of 0.1 microcurie was based on residual body burdens measured 15 to 20 years after intake, in practice it was used as the maximum permissible body burden at the time of intake. The initial body burdens of the subjects in Evans' study were typically about 10 to 100 times larger than the residual burdens he measured. Therefore, an additional safety factor of about 10 to 100 was built into the standard. In 1981, 40 years after the standard was set, Evans reported that no exception to the standard had been found among some 2000 observed radium patients. That is, no symptoms were ever observed for persons with body burdens of 0.1 microgram or less. That conclusions still holds today.

In 1944, when plutonium began to be produced in kilogram quantities, the experiences with radium forewarned scientists about plutonium's probable toxic effects and provided an essential quantitative basis for the creation of a plutonium standard. Robert Stone, the head of the Plutonium Project Health Division, made the earliest estimate of a permissible burden for plutonium by scaling the radium standard on the basis of the radiological differences between radium and plutonium. Those included the difference in their radioactivities and that of their daughters and the difference in the average energy of their alpha particles. The result indicated that, gram for gram, plutonium was a factor of 50 less toxic than radium, and the standard was set to 5 micrograms.

In July 1945, Wright Langham insisted that the 5-microgram standard be reduced by a factor of 5 on the basis of animal experiments that showed that plutonium was distributed in the bone differently, and more dangerously, than radium. Thus, the maximum permissible body burden for plutonium was set at 1 microgram. That limit was chosen to protect plutonium workers from the disasters that had befallen the radium-dial painters. As part of the effort to understand how to measure the plutonium body burden in living persons and to remove them from work if the burden got close to the limit, the human plutonium-injection experiments were carried out. (The story of those experiments is told in "The Human Plutonium Injection Experiments.")

Following those experiments, discussions at the Chalk River Conferences in Ontario, Canada, (1949 to 1953) led to further reductions in the plutonium standard to 0.65 micrograms, or 40 nanocuries, for a maximum permissible body burden. Since then, no further changes have been made, in part because no ill effects from plutonium have been observed in any exposed individual with the exception of one person—an individual with a body burden around the permissible level who died of a rare bone cancer that possibly was caused by plutonium.

As stated in the introduction, there is a dirth of information about the risks of plutonium. Consequently, the risks for plutonium-induced cancer of the bone, liver, and lung are based on the human data gathered for radium, radon, and thorium, respectively. The data gathered for radium-induced cancers (see Figure 2) are very

interesting in that they appear to have a threshold—no bone cancers exist below a cumulative skeletal dose of 1000 rad, or 20,000 rem, which would be the 50-year dose from a body burden of about 2 microcuries per kilogram of body weight. This is the best data available on the induction of cancer from a bone-seeking alpha-emitter, and so it is natural to suspect that similar threshold-like behavior may exist for plutonium. Fortunately for those who work with it, the truth of that conjecture may never be determined.

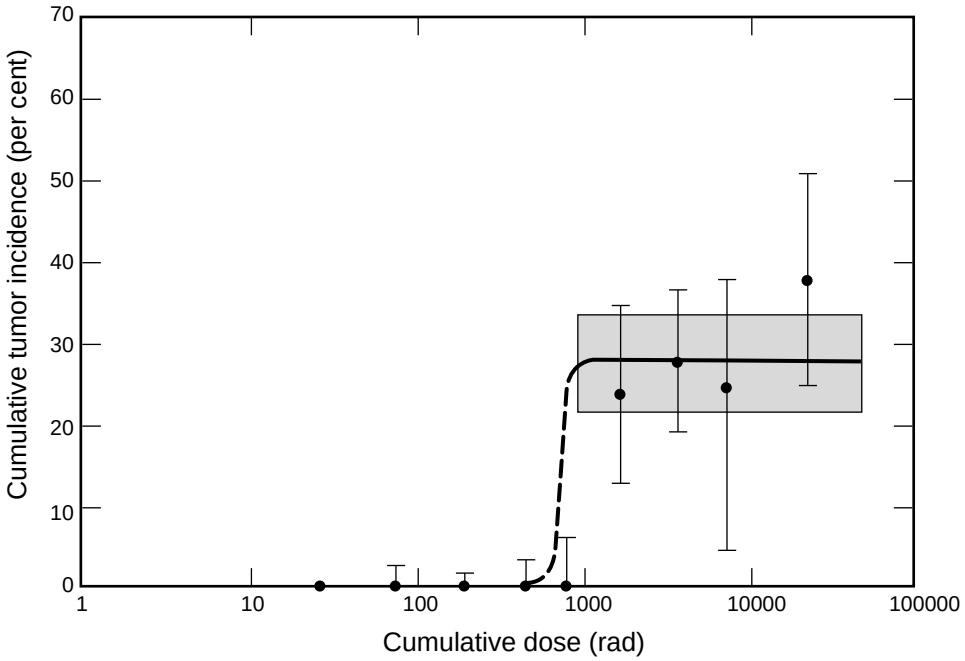


Figure 2. Radium-induced Cancers

This plot, as originally presented in a 1974 article by Robley Evans, shows radiation dose versus incidence of radiation-induced bone and head carcinomas in over 600 radium cases studied at MIT. The plot suggests a threshold of 1000 rad, or 20,000 rem, to the skeleton for the induction of bone and head cancers. Because the latency period seems to increase with decreasing dose, Evans suggested that this result be interpreted as a "practical threshold"—at lower doses the latency period might be longer than the lifetime of the individual so that malignancies never become manifest. Evans' idea of a practical threshold is still considered viable, although two cases of bone cancer with doses below 1000 rad have appeared in a cohort of 4000 individuals exposed to radium (see "Radiation and Risk," pages 100-101).

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