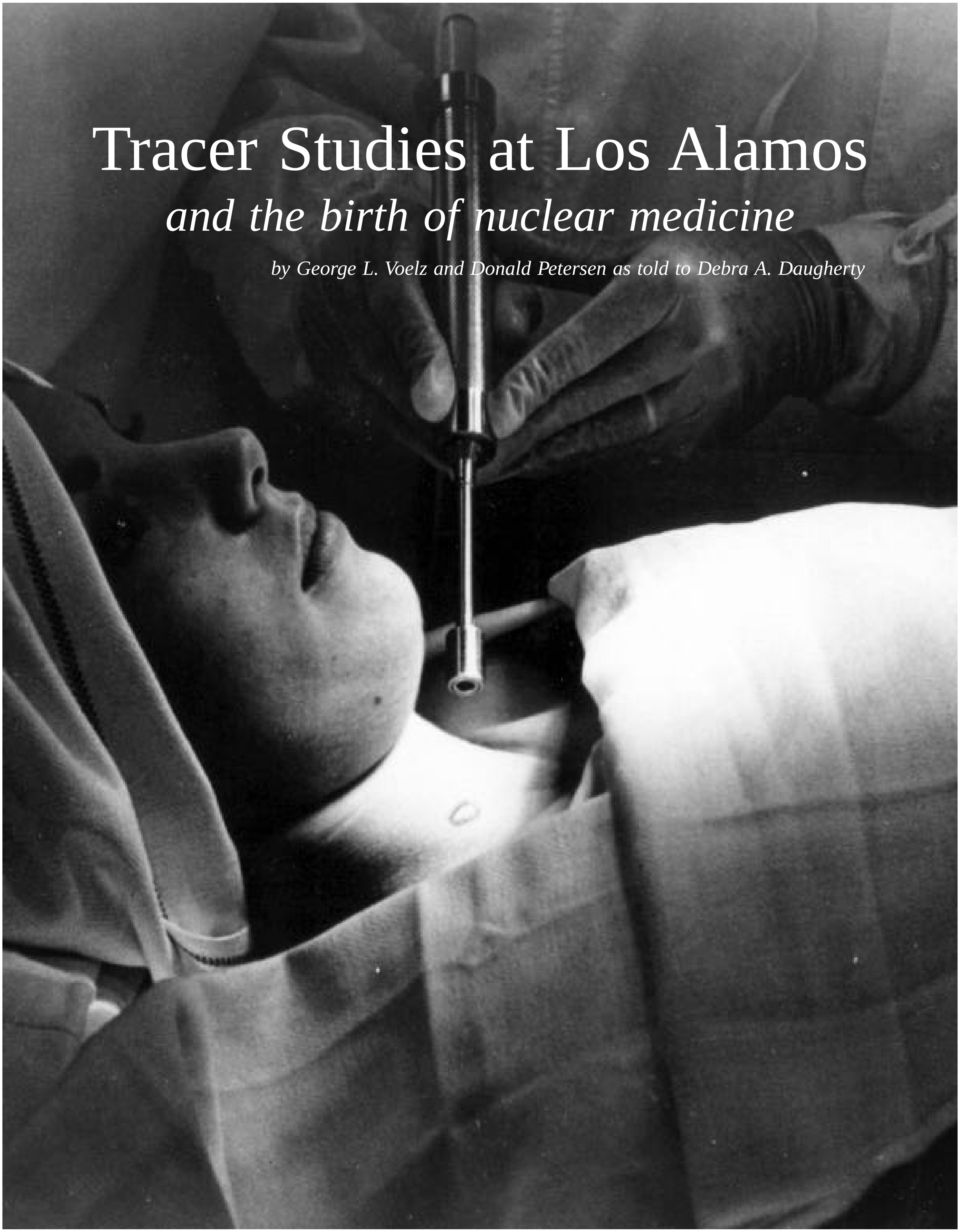
Tracer Studies at Los Alamos
and the birth of nuclear medicine

by George L. Voelz and Donald Petersen as told to Debra A. Daugherty



"He had me put my hand around a Geiger counter," recalled Oppenheimer, "and gave me a glass of water in which part of the salt had radioactive sodium in it. For the first half minute all was quiet, but about fifty seconds after I drank, there was a great clattering of the Geiger counter. This was supposed to show that in at least one complex physiochemical system, the salt had diffused from my mouth through my bloodstream to the tip of my fingers and that the time scale for this was fifty seconds."

The simple, impromptu experiment related above by J. Robert Oppenheimer demonstrated to an amused audience the remarkable ability of radioisotopes to reveal the hidden workings of the human body. The experiment was performed at Berkeley in 1935, not by a biologist or physician, but rather by one of the most prominent physicists of his time, Ernest O. Lawrence. Lawrence, the inventor of the cyclotron, was championing its use as a producer of artificial radioisotopes for medical applications. Strange from today's perspective is the fact that Lawrence performed this experiment spontaneously, without asking for Oppenheimer's consent or even mentioning that the water contained radioactive sodium. But Lawrence knew from prior research that the experiment was safe and would not cause his friend and colleague any harm.

Nearly sixty years later, in December 1993, the Secretary of Energy, Hazel O'Leary, publicly presented her concerns about the ethics and conduct of human radiation experiments that were performed under the auspices of the Manhattan Project and the Atomic Energy Commission. At issue were the rights of the subjects involved: Were the subjects informed about the nature of the experiment and its risks? Did they participate consensually? Moreover, what was the role of secrecy within the government? Did the government use secrecy to abuse unsuspecting individuals and does this persist within government today? To address these concerns, O'Leary decided to organize an "openness initiative."

Figure 1. A Radiosodium Experiment at Berkeley
In the late 1930s, as Lawrence's cyclotron began to produce new, biologically-important radioisotopes, many physicians doubted the wisdom of using these radioisotopes in medicine. However, the pioneer-physicians who either worked or trained at Lawrence's laboratory learned to use radioisotopes safely as powerful tools. This picture shows Dr. Joseph Hamilton (right) starting a timer as Robert Marshak drinks water containing radioactive sodium. In his right hand, Marshak holds a Geiger-Müller counter. The thick lead cylinder surrounding his right arm shields the detector from external radiation. The clicking of the Geiger counter indicates the moment that the radiosodium reaches Marshak's right hand and Hamilton records the time.

As part of this program, O'Leary ordered the release for public review of all Department of Energy documents relating to the use of human subjects in radiation studies including previously classified documents if possible. A team of experts at the Los Alamos National Laboratory searched files and archives for relevant documents throughout 1994 and, ultimately, the Laboratory released over 1600 documents. Although all of the pertinent information regarding the human experiments performed at Los Alamos were in the public domain prior to the openness initiative, we are taking this opportunity to review the story of those experiments and the contributions that were made to science and medicine.

When Oppenheimer became the director of the Los Alamos Laboratory in 1943, he invited Dr. Louis Hempelmann to oversee health, safety, and radiation protection. Hempelmann was among those who had learned to use radioisotopes during the 1930s at Berkeley (see "The Origins of Nuclear Medicine"), and he realized early on that a primary health hazard at Los Alamos was the danger of internal exposure of workers to the radioactive materials that would

The Origins of Nuclear Medicine

The birth of nuclear medicine, it is often said, dates back to August, 1946 when the U.S. national laboratories began to distribute manmade radioisotopes to private researchers and physicians. However, as important as this distribution program was, the principle on which nuclear medicine is founded had been developed years before, in 1913, when the Hungarian scientist, George de Hevesy, invented the "tracer principle." Like many great ideas, Hevesy's tracer principle was born of failure. Rutherford, for whom Hevesy worked in England, challenged Hevesy to "separate radium-D from all that nuisance lead." Hevesy soon realized that the tools of chemistry were quite inadequate for the task and concluded that radium-D, now known as the radioisotope lead-210, and ordinary lead are more or less chemically identical.

Soon thereafter, Hevesy conceived of the "tracer principle," which states that, because radioactive isotopes are inseparable from their stable counterparts, they may be used to trace the progress of stable materials even as they undergo chemical change. In 1923 Hevesy performed the first biological tracer experiment, using thorium-B, another isotope of lead, to trace the movement of lead from the soil into bean plants. In the first animal studies, Hevesy fed radium-D to rabbits and then tracked the movement of the radioactivity through the digestive tract to the bone and finally into the urine.

It was not long before "radiotracers," as they are called, were applied to chart the course of stable atoms and molecules through the human body. In 1926, Drs. Herrmann L. Blumgart, Soma Weiss, and Otto C. Yens at Harvard Medical School were the first to administer radiotracers to humans. In their experiment, bismuth-214 was administered by injection to determine the circulation time of blood in humans in disease and in health. As exciting as this early work was, however, it was seriously limited by the narrow range of properties of the naturally occurring radioisotopes.

George de Hevesy won the 1943 Nobel Prize in Chemistry for his invention of the radiotracer technique, the basis of nuclear medicine diagnostics.

In February, 1934, this all changed when Irene and Frederic Joliot-Curie discovered "artificial radioactivity." The Joliot-Curies bombarded certain light metals, boron, aluminum, and magnesium, with alpha particles emitted by their modest supply of polonium. While the polonium was present, the metals were observed to emit beta particles. When they removed the polonium, the light metals continued to emit beta particles, but the intensity of the activity decayed exponentially with time, *just like natural radioisotopes*. As the Joliot-Curies surmised, the nuclei of the boron, aluminum, and magnesium captured the alpha particles and re-emitted a neutron to become the beta-emitting radioisotopes, nitrogen-13, phosphorus-30 and silicon-27, respectively.

When they heard the news, Ernest O. Lawrence, who invented the cyclotron in 1931, and his colleagues at Berkeley had to kick themselves. Unbeknownst to them, the cyclotron had been producing artificial radioisotopes for the past three years. But because the cyclotron's beam and its Geiger-counter were both powered by the same switch, they both turned off at the same time and the residual radioactivity was never observed. Immediately after they read

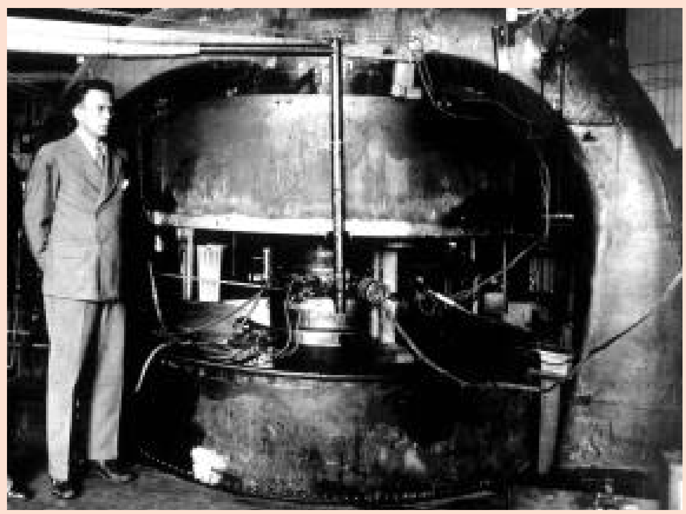
be used to build the first atomic bomb. Although tracer amounts of radioisotopes, like those used in nuclear medicine, were safe, the experience of the radium dial painters during the 1920s and 1930s had shown that larger internal exposures to radium, for example, could lead to bone cancers and fatal anemias (see "Radium—the Benchmark for Internal Alpha Emitters"). Thus, right from the start, the challenge was not only to minimize internal exposure to plutonium and other radioactive materials but also to detect when such exposures occurred and to measure the amount of material retained so that overexposure could be avoided.

The work on internal exposures naturally involved collaboration among physicians, physicists, chemists, and others to develop very sensitive techniques for measuring internal body burdens at levels well below the danger point. It also required radiotracer experiments performed on human volunteers in which small amounts of radioisotope were administered to volunteers internally. By tracing the progress of the radioisotopes as they moved through the body, Los the article by the Joliot-Curies, the scientists in Lawrence's lab rewired the circuits to power the Geiger-counter independently and performed the experiment suggested by the Joliot-Curies in their paper; they bombarded carbon-12 with a deuteron beam. When they turned off the beam, they heard the "click, click, click" of the Geiger-counter and knew that they had created nitrogen-13. One month later, Lawrence's cyclotron began to produce artificial radioisotopes of great value to biomedical science—sodium-24, potassium-42, iodine-128, iron-59, chlorine-34, phosphorus-32, and bromine-82.

During the 1930s, human radiotracer experiments performed with the cyclotron's new radioisotopes yielded breakthroughs in diagnostic and therapeutic nuclear medicine. At Berkeley, Drs. John Lawrence (Ernest Lawrence's brother) and Joseph Hamilton began to use iodine-131 to diagnose hyperthyroidism. In 1936, Dr. J. Lawrence used phosporus-32 to produce the first successful treatment for the disease polycythemia vera. The MIT cyclotron provided radioiodine that Robley Evans and his colleagues used for the diagnosis and therapy of thyroid disease. And Dr. Hahn and his associates at the University of Rochester used radioiron to change our basic understanding of iron metabolism. Yet, as thrilling as this progress was, the cyclotron radioisotopes were produced in such small quantities that they were simply too rare to support continued and widespread growth of the field of nuclear medicine.

In 1941, Enrico Fermi built the world's first nuclear reactor under the stadium of the University of Chicago, and soon thereafter, radioisotopes were produced in abundance. Because the United States was at war, these cheap, plentiful radioisotopes were not distributed for private use until 1946 when the Atomic Energy Act created the radioisotope distribution program, launching the modern field of nuclear medicine.

The national laboratories, however, were not merely the sponsors of modern nuclear medicine. In fact, because the health divisions of the national laboratories were populated with scientists and medical personnel who had been trained in the late 1930s at Lawrence's lab at Berkeley, their work on radiation protection naturally extended into the realm of nuclear medicine and the national laboratories remained in the forefront of nuclear and biomedical research for many years after the war. At Los Alamos during the war years, Dr. Louis Hempelmann, who had trained at the Berkeley cyclotron in 1941, was recommended to Oppenheimer by John Lawrence and became the leader of the health program. It was Hempelmann who set the stage for scientists such as Wright Langham, Ernest Andersen, Ernest Pinson, Chet Richmond, and C. C. Lushbaugh to perform extensive studies at Los Alamos of radioisotopes in humans. ■



Ernest Lawrence stands by the 27-inch cyclotron. It was modified to become the 37-inch cyclotron, which was used to produce artificial radioisotopes for medicine and research during the late 1930s.

Alamos scientists were able to measure certain features of human metabolism: the rate of absorption of the radioisotope, how long it was retained, its distribution in the body, and the rate of excretion. On the basis of this information, they calculated for each of the radioisotopes studied the internal radiation dose that would be received from a given amount retained, and, from that, the maximum amount that could be tolerated in the body without harm.

The human radiotracer experiments performed at Los Alamos can be categorized in three parts: the tritium experiments, the fallout and metabolic experiments, and the medical diagnostic experiments, all of which took place between 1950 and the early 1960s. The tritium experiments were performed to determine the behavior of that radioisotope in the body and to set safety standards for Los Alamos workers, the fallout experiments were performed to assess the impact of world-wide fallout from atmospheric nuclear weapons tests, and the diagnostic experiments were performed for the development of diagnostics for nuclear medicine.

Although the human plutonium injection experiments, which took place between 1945 and 1947, were the first human experiments performed in the interest of protecting workers at Los Alamos, those experiments were not performed at Los Alamos and therefore are presented in a separate article (see "The Human Plutonium Injection Experiments").

The radiotracer studies performed at Los Alamos, although initially motivated by radiation protection concerns, made a significant contribution to the fields of biology and medicine. Not only did the safety limits established at Los Alamos for internal radioisotopes enable physicians to safely administer radioisotopes to humans for research, diagnosis and therapy, but also, the Los Alamos experiments yielded biological and diagnostic information of fundamental interest. Furthermore, in the course of the tritium experiments, Los Alamos researchers developed a sensitive and enormously convenient detector for measuring low-energy beta particles in samples of blood, urine, and other body fluids (see "Los Alamos Radiation Detectors for Biology and Medicine"). Because carbon-14, tritium, and phosphorus-32 are beta emitters and are also the most important radiotracers in biology, the impact of the new beta detector was to revolutionize *in vitro* biochemical research. Today commercial versions of the detector continue to be used at the forefront of research in biochemistry and genetics.

And as for ethics, the Los Alamos human experiments were always conducted with informed volunteers who were either the researchers themselves, employees of the lab and their family members, members of the community, or patients from neighboring cities who were in need of diagnostic exams. All participated consensually, and no one was ever injured in the course of the experiments. Additional discussion of the volunteers, the doses, and the risks appears at the end of this article and in the sidebar "Child Volunteers: One Dad Tells the Story."

Tritium

Soon after the Soviets detonated their first atomic weapon in August 1949, Los Alamos began intensive work on the development of the hydrogen bomb. Along with this work, however, came a new hazard, hydrogen-3. Commonly known as "tritium," this radioisotope emits low-energy beta particles upon decay. Because low-energy beta particles are easily stopped by clothes or skin, tritium isn't a serious threat as long as it remains outside the body. But in the Los Alamos Health Division, scientists were concerned that the tritium might escape into the workplace and find its way inside the body. They knew that if tritium were to escape into the work environment, it would, like hydrogen, form a gas. Most of the tritium would form "tritium gas," HT (where T stands for tritium), while the rest would oxidize to form "tritiated water," HTO, which could be inhaled, ingested or absorbed through the skin. Once in the bloodstream, the tritium would follow a path through the body similar to that of hydrogen and damage neighboring tissues with its beta particles.

No tritium safety standard existed in 1950, and although tritium had been discovered a decade earlier, it was so difficult to detect in biological samples that little was known in 1950 about its behavior in humans. Therefore, to provide radiation protection for its workers, Los Alamos had to start from scratch. They had to develop adequate equipment for the measurement of tritium in biological samples, perform experiments to determine the pathway of tritium in the body, establish safe levels of exposure, and monitor the exposure

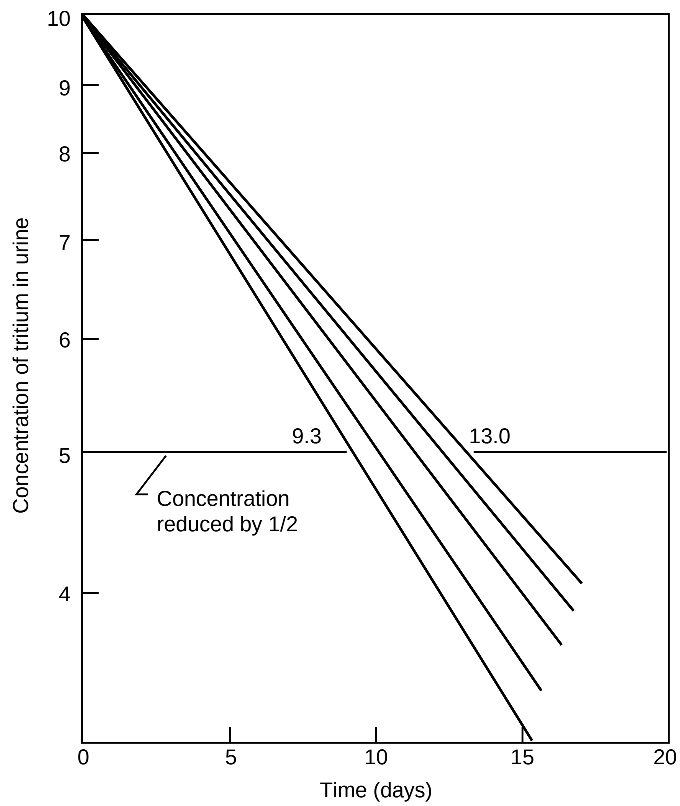


Figure 2. The Tritium Accident
The concentration of tritium in the urine of six accidentally exposed scientists was measured daily for over two weeks. This logarithmic plot of the concentration (arbitrarily normalized to the same initial value) versus time, shows that the biological halftime for tritium varied from 9.3 to 13 days for five of the six scientists. The sixth scientist, who "forced fluids" for four days, was able to reduce his tritium biological halftime from an initial value of 12.5 to only 4.8 days. When this scientist resumed normal water intake, his biological halftime increased to roughly 14.3 days.

of workers, a challenge that was taken by Drs. Ernest C. Anderson and Ernest A. Pinson of the Los Alamos Health Division.

In March 1950, Anderson and Pinson were just finishing their new measurement apparatus when six physicists accidentally inhaled some tritium gas while repairing a leaking tritium target at the Van de Graff accelerator. (One of the exposed scientists, Harold Agnew, became the Laboratory Director during the 1970s . . . evidence that radiation respects no one!) Although Anderson and Pinson had intended to perform their measurements on mice and rats, they rapidly changed their plans. Fortunately, none of the scientists were harmfully exposed, and the occasion was simply regarded as an outstanding opportunity to learn about the behavior of tritium in humans. At this time, written protocols and signed consent forms were not deemed necessary, and because they were just as eager as the investigators to proceed, the six scientists quickly volunteered to become the subjects of the first human tracer experiment performed at Los Alamos. After a brief verbal explanation of the tests to be performed, these six men readily agreed to provide samples of urine, blood, expired air, sweat, and sputum as needed for study during the following six weeks.

Daily urine samples were measured for their tritium content with Anderson and Pinson's apparatus: a Borkowski-type ion chamber connected to an instrument called a "vibrating reed electrometer" for measuring the ion current. The procedure was not easy. First, the urine was distilled to extract the water component that contained the tritium. This water was vaporized and passed over a "reducing agent," powdered zinc. The zinc readily combined with the oxygen in the water vapor and left hydrogen gas as a by-product. To the degree that the urine contained tritium, this hydrogen gas contained HT. The beta activity of the tritium gas caused a cascade of ions in the ion chamber and the ion current was measured by the electrometer. The magnitude of the current indicated how much tritium was present in the urine.

Anderson and Pinson used this arduous technique to determine many features of tritium metabolism, and for that matter, the metabolism of normal water. They determined that the rate of excretion of tritium was fairly constant for a given individual but that it varied widely between individuals. For five of the six subjects, they estimated the "biological half-time" of tritium (see Figure 2), or the amount of time it takes for the tritium in the body to decrease to half of its initial value, and their results ranged from 9 to nearly 13 days. For a certain period, the sixth subject drank as much water as he could during the course of his normal activities and thereby reduced his biological half-time from 12.5 days to less than 5. This technique, called "forcing fluids," is used to this day to reduce the dose from significant accidental intakes of tritium. With this information, Anderson and Pinson were able to determine a safety standard for tritium. In a matter of weeks, their preliminary but fundamentally important work was documented in a laboratory report (LAMS-1099), which was immediately delivered to 38 academic and government institutions.

In 1951 and 1952, Anderson, Pinson, and their colleagues produced a comprehensive account of tritium metabolism by performing controlled human studies on three of the investigators themselves. Not only did this work provide the information required for tritium protection at the lab, but it also determined many facts of biological interest. In one experiment, the three men inhaled some HT gas. They discovered that the HT is oxidized into HTO inside the lung before it is transferred across the lung into the bloodstream. The oxidation rate is so slow that only about 0.004 per cent of the total activity of the inhaled HT is transferred to the body fluid; the rest is simply exhaled. On the other hand, another experiment showed that about 99 per cent of inspired HTO enters the body fluids, and consequently, this mode of exposure poses the greatest hazard to workers.

They also investigated the absorption of tritiated water through the skin and the gut. In one experiment, a man's arm was immersed up to the elbow in water containing some HTO, and the rate at which the water entered the man's bloodstream through his skin was determined to be about the same rate as that of insensible perspiration (exchange of water through the skin when the sweat glands are inoperative). A quick calculation showed that this rate was so small that a man would have to be entirely submerged in pure HTO for a month for this means of exposure to be any serious hazard.

In the course of their work on radiation protection, the Los Alamos researchers also determined a number of facts of biological interest. In one experiment, a man ingested 200 milliliters of water with some HTO in it. They observed that the water began to be absorbed through the stomach into the bloodstream after 2 to 9 minutes and was completely absorbed after 40 to 45 minutes. Because the absorption was roughly linear with time, the rate of absorption was somewhat greater than 5 milliliters per minute. In another experiment, they determined the water content of skin and fat in man, 71 and 20 per cent, respectively.

The tritium studies performed at Los Alamos served as the basis of the tritium standard established by the International Commission on Radiological Protection in 1956, and in 1957, the studies were compiled in the review paper "Physiology and Toxicology of Tritium in Man" (Pinson and Langham. 1957. *Journal of Applied Physiology.).* This classic work was reprinted in the twenty-fifth aniversary issue of *Health Physics*, June 1980, as one of twenty-two articles considered to have made the most important contributions to radiation protection since 1897.*

Lastly, the tritium work stimulated the development of a simple and sensitive radiation detector for low-energy beta particles, the Los Alamos Coincidence-Anticoincidence Model 530 Liquid Scintillation Counter (see "Los Alamos Radiation Detectors for Biology and Medicine").

Fallout and Other Metabolic Studies

Hundreds of atmospheric nuclear weapons tests have been performed by the United States, the Soviet Union, Great Britain, France and China, mainly in the period from 1945 to 1963. These tests were performed in remote, sparsely populated areas, like the tiny atolls of the Pacific, central Siberia, the Arctic, and the Nevada desert. Yet, fallout, the radioactive debris that is ejected into the environment by a nuclear explosion, does not remain confined to the vicinity of the test. Riding the circulating winds of the atmosphere, fallout radionuclides can be carried a great distance from the original test site before they fall back to earth. Sometimes they fall on grazing or crop land where the radionuclides stick to the vegetation or are taken up by the plants through the soil. These plants are then either processed into foods or eaten by cows, thereby entering the human food chain. As we consume dairy products and foods derived from plants, fallout radionuclides become incorporated into our bodies.

*The same honor was given to two other Los Alamos reports: "Distribution and Excretion of Plutonium Administered Intravenously to Man" (Wright Langham, et al. 1950. LAMS-1151) and "Retention and Excretion of Radionuclides of the Alkali Metals by Five Mammalian Species" (C. R. Richmond. 1958. LAMS-2207.).

Figure 3. An Auspicious Guest Is Measured for Fallout
The study of the worldwide distribution of fallout at Los Alamos benefited from the participation of the numerous laboratory visitors. In this picture, a smiling Prince Ali Khan, son of Aga Khan III, slides into HUMCO I under the supervision of Wright Langham.

Although the short-term effects of nuclear weapons tests were observed from the start, our understanding of the long-term effects developed more slowly. During the early 1950s, when nuclear fallout became the subject of an intense worldwide debate, scientists began to undertake research to predict its long-term impact and to determine how much fallout is too much. Fairly quickly, the radioisotopes iodine-131, strontium-90, strontium-89, and cesium-137 were identified as some of the most important potential hazards. At Los Alamos, two types of human studies were performed to address the question of fallout, both of which were made possible by two highly sensitive and convenient whole-body radiation detectors developed at Los Alamos, HUMCO I and II (see "Los Alamos Radiation Detectors for Biology and Medicine").

The first type of study quantitatively assessed the worldwide distribution of fallout in man, as well as the change of fallout contamination with time. The individuals who volunteered for these experiments were examined in the sensitive whole-body radiation detectors, HUMCO I and II, to determine the amount of cesium-137 present in their bodies. Because the procedure was simple and nonintrusive, volunteers for this study were easy to find. In fact, nearly fifteen hundred persons from around the world participated in the study of the distribution of worldwide fallout, including prominent figures such as the Prince Badouin of Belgium, Prince Ali Khan, son of the Aga Khan, spiritual leader of the Shia Ismaili Muslims (see Figure 3), and the U.S. astronauts. Within the United States, this work confirmed the expectation that the pattern of fallout would trace the pattern of rainfall, such that the California-Arizona region had the lowest level of fallout, whereas the Northeast and Northwest had the highest.

Frequent measurements of the fallout radionuclide cesium-137, present in

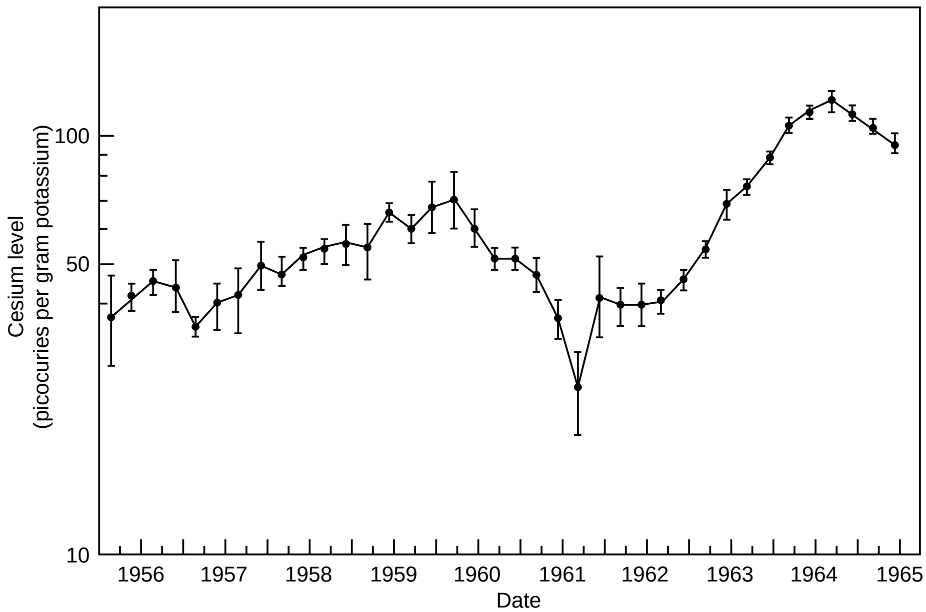


Figure 4. The Rise and Fall of Fallout
To determine the variation in the level of fallout with time, New Mexico residents were measured periodically for the concentration of cesium-137 in their bodies from 1956 to 1965. Because the variations show a delayed correlation with atmospheric nuclear weapons testing activity, this graph and others like it prompted the USSR, Great Britain, and the United States to ban atmospheric weapons testing in 1963.

New Mexico residents between 1955 and 1965, demonstrated the change in fallout contamination with time (see Figure 4). The results of this work showed that by the end of 1960, only three years after the 1958 moratorium on nuclear weapons testing, the contamination in New Mexico had decreased by about a factor of two but began to rise again in 1961 when the Soviets broke the test ban. In part because of studies such as this one, the United States, the United Kingdom and the Soviet Union agreed to an atmospheric test ban in 1963, the effects of which began to show in 1965.

The second type of human studies were performed to determine the radiation dose a given amount of fallout radionuclide would deliver to the body. In these experiments, small amounts of radioisotope were administered to human subjects who were then "counted" in the whole-body radiation detectors, HUMCO I and II. In this procedure, the subject would first slide into the detector (see Figure 5). The gamma rays that were both emitted by the internal radioisotope and able to emerge from the body were then detected by the whole-body counter. The intensity of the gamma radiation was measured at periodic intervals to determine how much of the radioisotope was absorbed by the body and how long it was retained. This information enabled researchers to calculate the dose delivered by each of the different radionuclides. Because they were so sensitive, HUMCO I and II enabled

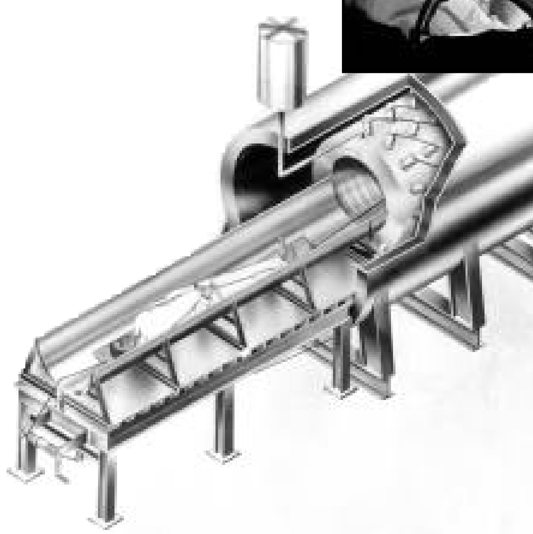


Figure 5. The Human Counter
HUMCO consisted of a cylindrical container filled with 140 gallons of liquid scintillator and surrounded by 108 photomultiplier tubes. The person being measured was placed in a slide and pushed into the detector. Gamma rays emitted by the naturally occurring radioisotope, potassium-40, or the fallout radioisotope, cesium-137, for example, would largely penetrate the inner wall of the detector, excite the scintillator, and be detected. From the rate of the gamma-ray emission, scientists could determine the amount of radioisotope inside the person.

Table 1. Examples of Los Alamos Metabolic Studies of Radionuclides

Radionuclide	Mode of exposure	Average uptake (per cent)	Average biological half-time (days)
cesium-132	intravenous	100	88
cesium-137	oral	,100	135
tritiated hydrogen, HT	inhalation	< 1.6	–
tritiated water, HTO	inhalation and oral	98	11.5
iodine-131	oral	15	,100
iodine-131	skin	0.1	,100
rubidium-86	oral	,100	80
strontium-85	skin	0.4	–
zinc-65	oral	75	154

scientists to perform these experiment with very small, very safe quantities of radioisotope.

In 1963, M. A. Van Dilla and M. J. Fulwyler performed an experiment to accurately determine the absorption and retention of iodine-131 in the thyroid. They held a sodium-iodide detector as close as possible to the front of the neck and measured the intensity of the gamma rays emitted by the iodine-131 in the thyroid. This measurement was used to calculate the amount of the iodine-131 that was absorbed. By repeating the measurement over time, they also determined how long the iodine-131 was retained.

However, there was one difficulty. Because the gamma rays were partially absorbed by the neck and because the measurement was very sensitive to the location of the thyroid relative to the detector, they needed to measure the depth of the thyroid in the neck. Van Dilla and Fulwyler solved this problem by administering *two* radioisotopes of iodine, iodine-125 and iodine-131, that emit photons of different energies. Because the low-energy x rays from iodine-125 are more readily absorbed by the neck tissue than the high-energy gamma rays from iodine-131, van Dilla and Fulwyler were able to accurately determine the depth of the thyroid by comparing attenuations.

Milk is the main pathway by which iodine-131 in fallout is introduced to our bodies. Therefore, it was feared that children, who drink the most milk, might be more seriously affected by this radioisotope than adults. To address this concern, Van Dilla and Fulwyler performed their study on eight children, all of whom were children of scientists in the Health Division between the ages of four and ten (see "Child Volunteers: One Dad Tells His Story"). Each child drank a glass of water containing 11 nanocuries of iodine-125 and 15 nanocuries of iodine-131, only a small percentage of the amount given today in radioiodine diagnostic tests. The results, which showed that, for a given intake, the absorption of iodine per gram of tissue in the thyroids of children is higher than in those of adults, provided a basis for the assessment of the risk posed by iodine-131 in fallout.

Chester Richmond and his colleagues at Los Alamos performed experiments to catalog the biological behavior of a wide variety of radioisotopes in the human body, many of which were relevant to the issue of fallout. This long-term project, sometimes described as "chewing through the periodic table," included experiments to determine the biological half-times of cesium-132, cesium-134, cesium-137, tritium gas, tritiated water, iodine-131, rubidium-86, sodium-22 and sodium-24, strontium-85 and zinc-65 (see Table 1). In one experiment, two volunteers from the Laboratory's staff ingested about one microcurie of cesium-137 and two others ingested cesium-134. The four were then counted in HUMCO I once every week or two. One volunteer was counted for only 15 weeks, another was counted for more than 2.5 years. The biological half-time for the four subjects ranged from 110 to 147 days with an average of 135. Because of this relatively short biological half-time, cesium-137 is much less dangerous than another fallout radionuclide, strontium-90, which remains essentially permanently in the bone.

Richmond also made an "interspecies comparison" in which he showed that animal data can be used to predict the retention of radionuclides in humans when extrapolated by body weight. Studies were made with cesium-137, iodine-131, rubidium-86, sodium-22, tritiated water, and zinc-65. Figure 6 shows the retention of cesium-137 in five mammalian species compared with their body weights.

A few Los Alamos studies examined the rate of absorption of radionuclides through the skin. The cutaneous absorption of strontium-85 was measured in two volunteers, sodium-24 in one volunteer, and iodine-131 in one volun-

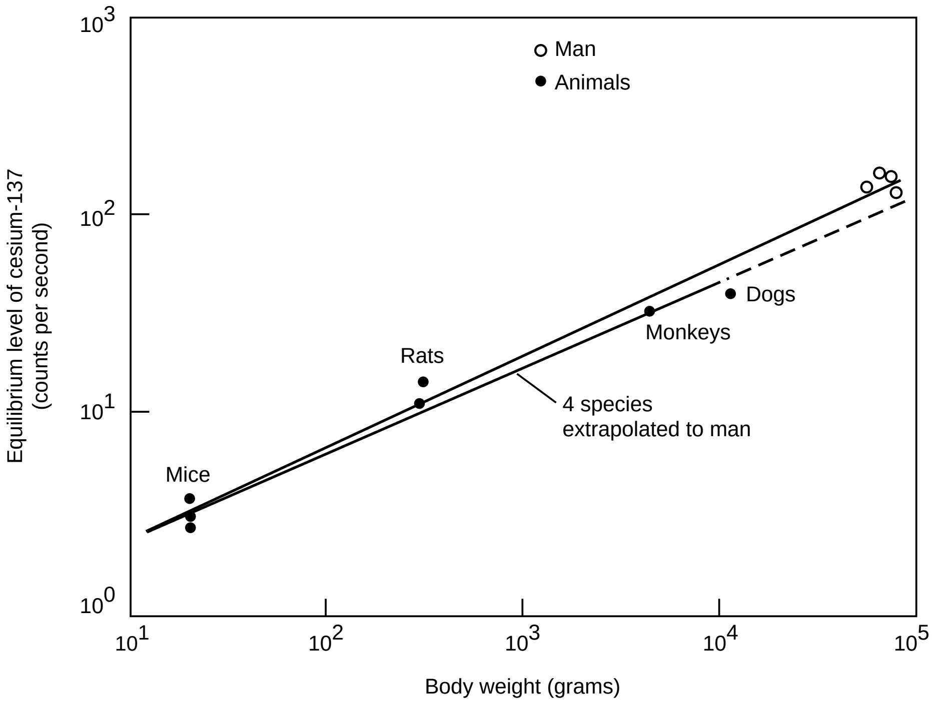


Figure 6. From Mammals to Man

An extensive effort was made by Chester Richmond at Los Alamos to compare the behavior of radionuclides in other mammals with that in man. This is one of Richmond's graphs showing the equilibrium retention of cesium-137 versus body weight for five mammalian species. The lower line was drawn on the basis of the animal data alone and extrapolated to the body weight of man. The upper line was fit to all five species. The small error in the extrapolation suggested that this was a reasonable method of determining the retention of cesium-137 in man.

teer. Absorption through the skin was shown to be too slow to be important.

Lastly, Los Alamos researchers explored the effect of diet and drugs on the retention of deposited radionuclides. For one volunteer, ten milligrams of stable zinc were observed to increase the rate of excretion of zinc-65 by a factor of three during the first 10 days after exposure. In another, two grams of nonradioactive Prussian Blue (ferric ferrocyanide) per day were observed to reduce the biological half-time for cesium-137 from 135 days to about 50 days. And in another, 150 milligrams of stable iodine reduced the biological half-time of iodine-131 to 20 days, rather than 55. These treatments are still used today to reduce exposure to zinc-65, cesium-137, and iodine-131. In 1987, for instance, when forty-six people were seriously contaminated with cesium-137 in Goiania, Brazil, they were treated with Prussian Blue for two months or longer, such that their exposure was only 29 per cent on average of the exposure they would have received without treatment.

Development of Diagnostic Tests for Nuclear Medicine

In the late 1940s, several physicians in the Health Division at Los Alamos, who had established a close working relationship with the physicians at Los Alamos Hospital, began to perform medical diagnostics using sodium-24 and iodine-131. These radiotracer diagnostics had been developed years before (see "The Origins of Nuclear Medicine"), but because they required specialized training and equipment, they were not yet common in hospitals around the country. With the laboratory's radiation detectors and radioisotopes, the physicians at Los Alamos were well prepared to perform these diagnostic tests, and as certain medical needs arose, they responded as they uniquely could. Patients were referred to Los Alamos from miles around to take advantage of these tests, which provided diagnostic information that was not available by other means. These studies were not performed as part of the formal, mandated research of the Health Division but rather as a service to the patient.

Sodium-24 was used to measure the circulation time of the blood, a technique that was first applied in 1924 by Blumgart and his colleagues at Harvard Medical School using radium-C (bismuth-214). Typically, sodium-24 was injected into the patient's right arm after which it traveled in the blood plasma to the patient's left arm. A Geiger-Müller counter held next to the patient's left arm indicated the moment that the sodium-24 arrived and the time was recorded. Circulation times in excess of about 30 seconds might be indicative of arteriosclerosis, frostbite, or any number of circulatory diseases.

Iodine-131 was used to examine thyroid function, a technique developed by Joseph Hamilton during the late 1930s at Berkeley. In this diagnostic, the patient was asked to drink a glass of water containing iodine-131, which enters the bloodstream. From there, the iodine is largely absorbed by the thyroid gland, which uses iodine to produce the hormone thyroxine. The physicians would hold a Geiger-Müller counter near the thyroid to examine both the amount of iodine-131 taken up by the thyroid and its distribution. If the thyroid took up too much, the diagnosis was hyperthyroidism, whereas too little could mean hypothyroidism or thyroid cancer (see "A Successful Diagnosis").

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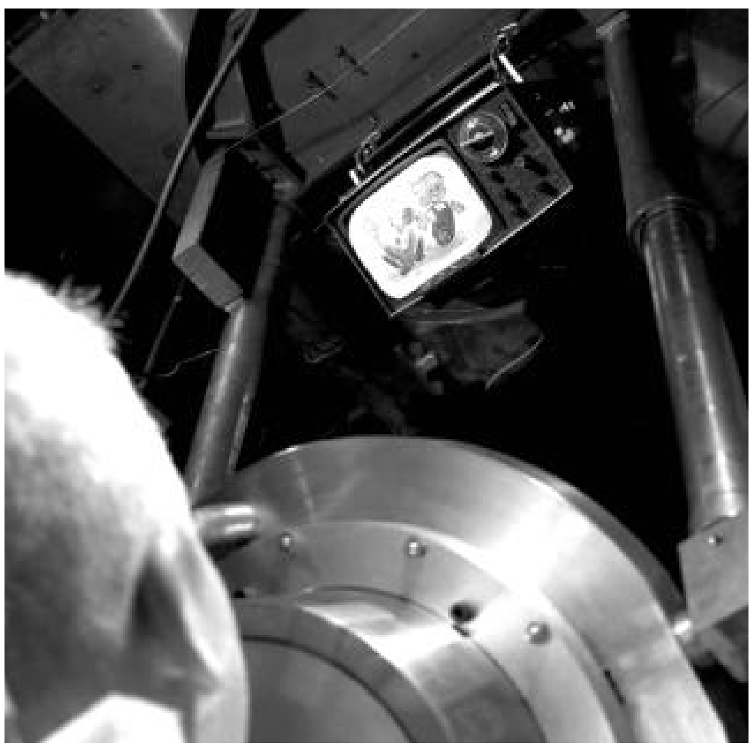
Child Volunteers: One Dad Tells the Story

by Don Petersen

The use of children in human radiation experiments has been a special ethical concern of the President's Advisory Committee on Human Radiation Experiments. At Los Alamos, in 1963, one such experiment was performed in which eight children were given a small amount of radioactive iodine. Responsibility for the children who participated was taken by the parents. Dr. Donald Petersen, a former deputy leader of the Health Division and biochemist at the lab, was one of three parents who invited their children to participate in this experiment. Here is his story.

Almost immediately after the Second World War, the scientific community split into two groups on the issue of radioactive fallout from atmospheric nuclear weapons testing. One said, "We've got to stop. We're going to hurt somebody," while the other said, "We can't afford to stop. We need to test if we are going to survive militarily, even though it might be hazardous." And then there were all shades of opinion in between. The person who really clarified the debate was Willard Libby. Libby realized that neither the people who said, "We've got to stop," nor the people who said, "We've got to do this regardless," had any quantitative information. So, in 1951, as Atomic Energy Commissioner, he started Project Sunshine.

Under Project Sunshine, the Atomic Energy Commission funded the various national laboratories to study fallout. Along with strontium-90 and cesium-137, iodine-131 ended up being one of the most studied fallout radionuclides because it is an abundant fission product, it is highly radioactive, it enters the food chain almost unimpeded, and it concentrates inside the body in a small gland called the thyroid. As the iodine-131 decays, it emits beta particles and gamma rays. The beta particles deposit most of their energy in only a few tenths of a millimeter and so are very effective at damaging the thyroid. On the other hand, the gamma rays are highly penetrating and many of them pass right through the thyroid and surrounding neck tissue. That makes *in vivo* detection of iodine-131 rather easy .



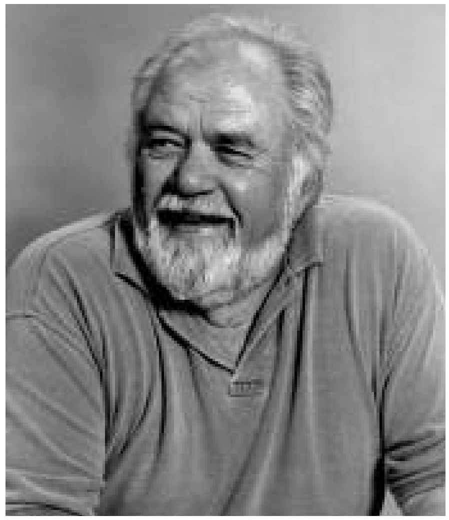
Dennis the Menace provided the incentive for this child to sit still in front of the sodium-iodide detector in Van Dilla's and Fulwyler's radioiodine experiment.

The iodine-131 in fallout was a problem for children in particular. You see, the radioactive iodine produced by nuclear weapons falls on pastures, cows eat the iodine, the iodine is concentrated in the cow's milk, and then people drink the milk. Because the thyroid picks up iodine preferentially, the radioactive iodine in the milk had a straight shot at that tiny organ. Children were potentially at greater risk from iodine-131 fallout than adults because they drink more milk. Also, because they are still growing, it was thought that children's thyroids might take up more iodine per gram than adult's and that they might retain the iodine longer, both of which would enhance the risk for children.

A lot of information had been gathered over the years during the development of medical diagnostic tests on the retention of iodine in the thyroids of adults. But, because the amount of iodine-131 that could be detected by existing techniques was large enough to be of concern, there was little information on children. By 1963, however, measurement techniques had been developed that were able to detect iodine-131 at the level of only 50 picocuries. Therefore, it became safe to perform these experiments on children, and two Los Alamos researchers, Marv van Dilla and Mack Fulwyler, decided to do so.

To make the absorption and retention measurements, they had to administer the iodine-131 and then measure the intensity of the gamma-rays by placing a large sodium-iodide detector right up close to the thyroid. This measurement was repeated periodically to determine how long the radioactive iodine remained in the thyroid. Of course, holding still in front of a large detector for any period of time without fidgeting is very tough for a small child. But the real uncertainty in this experiment was the depth of the thyroid in the neck. The tissue that overlays the thyroid attenuates the gamma rays. Thus, the thickness of this layer must be known to determine the amount of attenuation and, thereby, the actual amount of iodine-131 present in the thyroid. It doesn't take much of a mistake to make a factor of two difference in the calculated radiation dose to the thyroid, which may be enough to conclude erroneously that the child is or is not at risk.

Van Dilla and Fulwyler came up with a very elegant method for determining the depth of the thyroid in the neck and therefore for making an accurate determination of iodine uptake [see main article, p.264]. It was a very neat measurement that could only be done at a place like Los Alamos. Furthermore, it could be done with essentially zero risk to the children because they needed to be given only a few nanocuries, or billionths of a Curie, of iodine. Of course there was an uncertainty in the dose to the thyroid—that's why the measurement had to be made—but the upper limit on the total dose was very low, about 160 millirem to the thyroid. Once they had worked out the details, Marv van Dilla and Mack Fulwyler approached those of their colleagues who had young children and described the experiment. We were all familiar with radiation because we worked with radioactive materials on a daily basis in our labs. When we saw the size of the dose, we realized that it was far below the level at which we would expect any consequences. Convinced that the radiation risk was negligible, the parents went to their children and asked them if they were interested in participating.



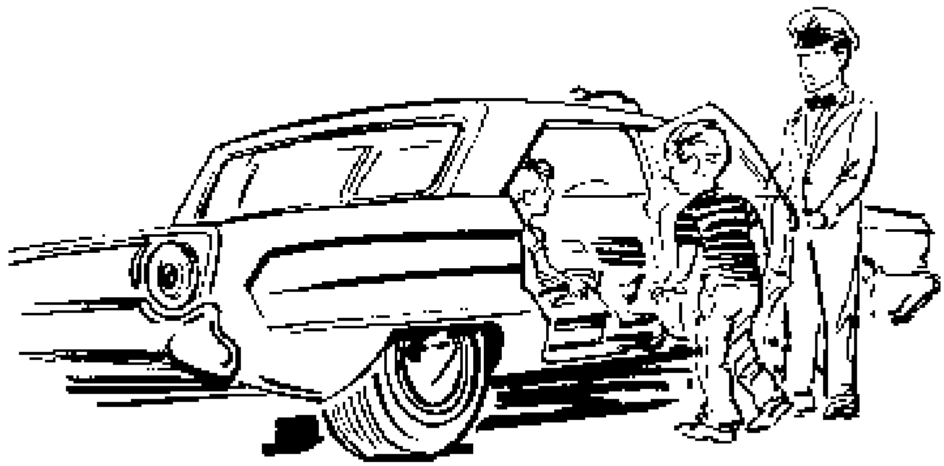
Don Petersen is one of three Los Alamos dads whose children participated in a Los Alamos human radiation experiment.

Van Dilla and Fulwyler made sure that the kids who were interested would be available for the length of the study because you wouldn't want the children to leave in the middle of the experiment to go on vacation. In the end, four of one of the investigator's kids, two of my kids, and two of someone else's kids participated. My children were quite young, ages five and seven, so there was no point in trying to explain to them, in physical terms, about radiation. I just described the kind of physical environment they would be in, that they would have to go into a dark room and sit very, very still for a substantial period of time, like 15 or 20 minutes. Because the doses were so low, van Dilla and Fulwyler couldn't get a good count, a statistically significant count, unless the children sat for a fairly protracted period. The children would then come back three or four times, spaced about eight days apart, since eight days is the physical half-time of iodine-131.

. . . with Sarah

Christy

Hans



The experiment showed that the depth of the thyroid in the children's necks ranged from about half a centimeter to nearly one centimeter and, from this measurement, van Dilla and Fulwyler were able to derive an average correction factor for the attenuation. This experiment was a "one time only" deal. Once the correction factor was determined, it could be applied to all future measurements of iodine absorption in children, not only fallout measurements but also measurements involved in children's medical diagnostics. This work also demonstrated that the biological half-time for iodine was similar in children and adults and that the fraction of the administered iodine that was taken up by the thyroid was about the same for children as in adults. Unfortunately, this implies that children, whose thyroids are smaller than those of adults, receive a higher dose for a given amount of iodine-131 intake.

The children who participated were "subjected" to certain amenities. For example, their daddies didn't drive them over to be counted—instead they got picked up at the front door of their house by a Zia taxi. There was also a really neat technique to keep them still—a little Sony television sitting right on top of the sodium-iodide detector. It took no time at all for those kids to figure out that the best counting times were when the best cartoons came on. The children were never physically restrained. But they were told to hold very, very still and the cartoons assisted in that. You could get good counts even from a five year old. Three of my children were the right age for the study, but only the older two, who were 5 and 7 at the time, participated. The youngest one just didn't want to hold still and so she said no. She was kind of an ornery little kid at the time anyway!

Yet, as much as I feel that participation in this experiment was completely safe and appropriate for my children, I am not sure how to deal with the strong feelings of the general public or our Human Studies Committee here at Los Alamos or the President's Advisory Committee. When I testified before the President's Committee, someone in the audience suggested that we, the parents of the children involved, should be incarcerated. What bothers me the most about that kind of statement is that it's completely at odds with my understanding of the concerns that guided our actions. I remember those times, and I remember the attitudes of the people involved in the experiment. As in the Hippocratic Oath, which says do no harm, everybody performing these experiments performed them with ground rules that said, "We're not going to hurt anybody." Everyone was trying to help. In particular, the studies that were performed at Los Alamos were always driven in the direction of reducing doses and minimizing risk.

The children who participated were "subjected" to certain amenities. For example, their daddies didn't drive them over to be counted—instead they got picked up at the front door of their house by a Zia taxi.

I am concerned that in the 1990s people are beginning to equate the kinds of biomedical activities that took place in this country immediately following World War II with the things that Nazi doctors were being tried for at Nuremberg. There have actually been accusations that the experiments were similar. Others have claimed that we should have been much more aware of the Nuremberg Code. As I recall, nobody involved in tracer studies at Los Alamos saw even the remotest connection between our work and the things being discussed at Nuremberg. The Nazi physicians used people against their will and in a harmful manner that included causing horrible deaths. Our work was done from the premise that we would hurt no one, and we never did.

To get back to the issue of child volunteers, obviously, if there had been any radiation hazard to my kids, I wouldn't have allowed them to take part in the iodine experiments. It is true that high radiation doses can cause severe consequences including cancer and subsequent death. But the doses required are thousands of times larger than the tracer doses used in diagnostic medicine, and that's what we're talking about here in the case of the children. ■

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With the success of these early radiotracer diagnostics behind them, Los Alamos physicians went on to perform more experimental medical work. About 400 diagnostic tests, a number of which are summarized below, were conducted between 1956 and 1966 either upon request or as part of the development of new diagnostic procedures. Although these diagnostics were experimental, the physicians used their prior experience to ensure that they were conducted safely with radiation exposures kept to a minimum.

A Successful Diagnosis

In 1994, when the Los Alamos information phone number was publicized as part of the openness initiative of the DOE, a woman called to tell the story of her diagnosis at Los Alamos. In 1948, when she was only 14 years old, her private physician in Albuquerque had arranged for her to have a diagnostic test for her thyroid in Los Alamos. The test revealed a "cold nodule," a section of her thyroid that failed to absorb the iodine-131, and she was diagnosed with thyroid cancer. Surgery successfully cured her cancer and now, 46 years later, she is the mother of two healthy daughters. Although she expressed no particular concern about the radiation dose involved, she did recall with trepidation the breakneck speed at which her doctor drove on the dirt roads to Los Alamos! It was a different time, a time when physicians would personally chauffeur their patients two hundred miles for a diagnostic test.

Improving upon Hamilton's technique, Dr. C. C. Lushbaugh and Dorothy B. Hale developed an advantageous whole-body counting technique for the diagnosis of thyroid disease using iodine-131. Their technique was both more sensitive and more accurate than the earlier method using the Geiger-Müller counter. In addition to measuring thyroid function, they used their technique to determine the effectiveness of various therapeutic drugs for both hyper- and hypothyroidism, to assess the completeness of thyroidectomy, and to watch for the recurrence of thyroid cancer.

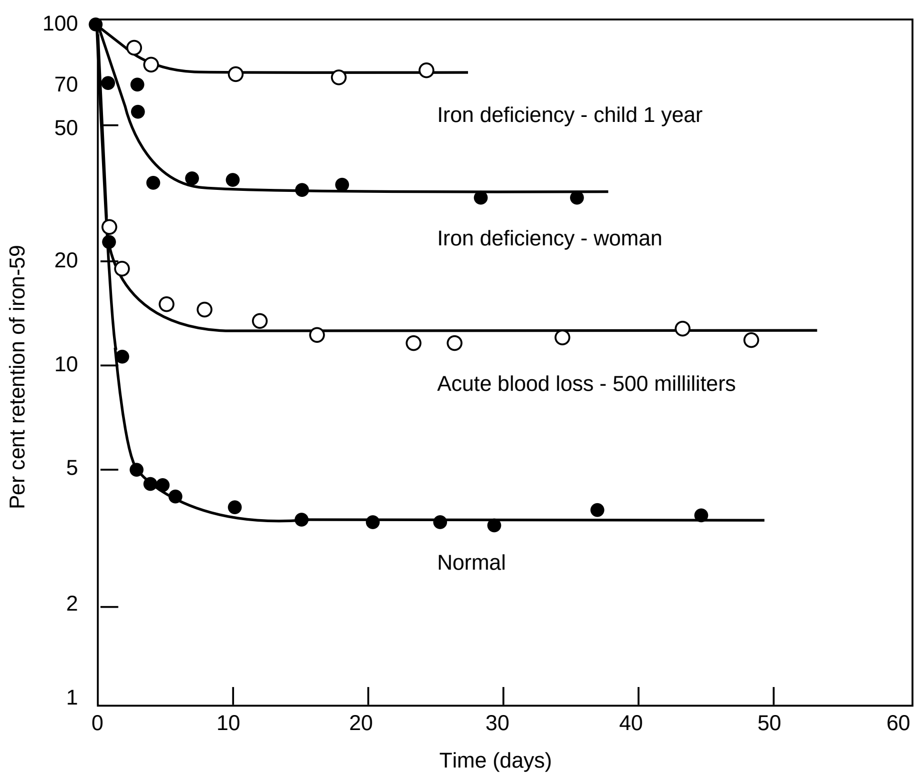


Figure 7. Anemia and Iron Retention

The retention of iron-59 can be used to differentiate between healthy and diseased states. This graph shows the typical patterns of iron retention for a healthy man, a man after giving 500 milliliters of blood, a moderately anemic woman, and a severely anemic child.

Iron is an essential part of hemoglobin. Therefore, Lushbaugh and Hale used iron-59 to study the formation rate of red blood cells in people with disease and in healthy people. They measured the retention of iron-59 in 66 volunteers, some of whom were healthy, others of whom were patients suffering anemia, various cancers, traumatic or surgical blood loss, and a variety of other conditions. The absorption of the iron differed significantly among the volunteers (see Figure 7). The variation in the absorption of iron-59 with different amounts of dietary iron was also examined in healthy volunteers and compared with that of patients. One important discovery was that healthy women absorb and lose iron about twice as fast as men but that women with menorrhagia (abnormally profuse menstrual flow) absorb and lose iron almost ten times as quickly.

In contrast with iron, which is only absorbed by the youngest members of the red-blood-cell population, chromium is present in red cells of all ages. Therefore, chromium-51 is useful in determining how long red blood cells

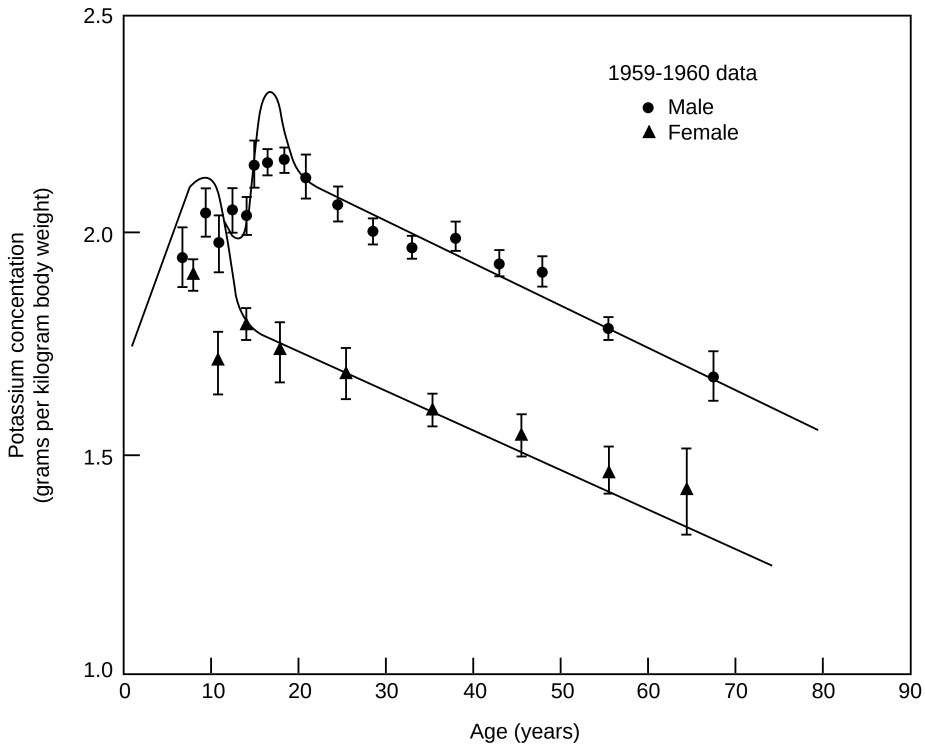


Figure 8. Muscle Mass by Age and Sex

Because potassium concentrates in muscle, the amount of potassium in the human body is proportional to the body's muscle mass. In 1959, Wright Langham and Ernest Anderson measured the amount of potassium-40, a naturally-occurring gamma-emitting radioisotope, in 1590 people using HUMCO I. From this measurement, they calculated the total amount of potassium in each person's body and divided by their body weight. Their results are plotted on this graph, which shows the variation in potassium concentration with age and with sex.

survive. In one study at Los Alamos, some red blood cells were removed from each of a group of volunteers, tagged with chromium-51, and injected back into the subject. The retention of chromium-51 was measured with the whole-body counter and urine samples were taken to determine the excretion rate. Red blood cells were shown to live approximately 120 days in healthy subjects.

Potassium concentrates in the muscle of the body, so potassium-40, a naturally-occurring radioisotope, can be used to measure the body's muscle mass. Such measurements were made in men and women ranging in age from less than 1 to 79 years (see Figure 8). Those measurements demonstrated that muscle mass increases steeply before puberty and then declines steadily beyond the age of 20. Potassium-40 measurements were also used to compare the lean body mass of athletes with that of sedentary people and yielded the expected result.

And finally, a number of diagnostics were performed using radioisotopes as labels for compounds of interest. Iodine-131 was used as a radioactive label on albumin to diagnose internal bleeding, on fat to diagnose fat malabsorption, and on Rose Bengal to measure the liver function in a recovering hepatitis patient. In one very noteworthy case, cobalt-60 was used as a label for vitamin B-12 to diagnose a patient with the life-threatening illness lateral-column disease. The patient ingested the labeled vitamin, and the scientists measured the amount of radioactive cobalt in the patient's blood. The amount turned out to be miniscule, demonstrating that the patient absorbed very little of the vitamin B-12 through the gastrointestinal tract. For treatment, the patient was injected with large amounts of vitamin B-12, and before the doctor's very eyes, the patient revived and went on to live in good health for another 30 years.

Synthesis of Labeled Compounds

In addition to the tritium, fallout, and diagnostic studies, Los Alamos performed a few human experiments with specifically labeled organic compounds. These experiments were a natural outgrowth of a program in organic synthesis that began at Los Alamos in 1947. As part of this program, organic compounds were labeled in specific positions within the molecule for use within the biomedical community. This work culminated in the comprehensive text *Organic Syntheses With Isotopes*, by Arthur Murray, III, and D. Lloyd Williams, which remains a landmark reference in the field to this day.

Los Alamos scientists participated in three experiments using Los Alamos labeled compounds, all in the early 1950s. Dr. Harry Foreman and Theodore Trujillo conducted one study that focused on EDTA, a chelating agent used to remove deposited actinides, such as plutonium, from the body during the forties and fifties. Carbon-14 labeled EDTA was used to determine the retention of EDTA, information that enabled scientists to determine optimal dosage schedules. Another study conducted by Dr. Irene Boone focused on a drug called isoniazid, which, in conjunction with antibiotics, virtually eliminated tuberculosis in the late 1940s. In this study, isoniazid was labeled in specific positions to determine how a certain compound, para-aminosalycilate, affected drug interaction with the tubercle bacillus.

The third study was performed jointly between Gordon Gould at Los Alamos and researchers at the University of Chicago. These scientists used tritium-labeled cholesterol and carbon-14-labeled acetate to study the cause of atherosclerosis, a disease commonly known as hardening of the arteries. The patients ingested the cholesterol and acetate after which the lesions of their arteries were examined. Interestingly, they discovered that the vast majority of the cholesterol found in the lesions was labeled with carbon-14, whereas a minor amount contained tritium. An interpretation made a decade later was that the cholesterol in the lesions was synthesized in the patient's liver from the carbon-14-labeled acetate whereas dietary cholesterol played only a minor role in the disease.

Figure 9. Peering Into HUMCO I

HUMCO I was not designed with the comfort of the claustrophobic in mind. However, in the interest of the volunteer, a "panic button" was installed on the interior wall of the detector. If the volunteer pressed the button, the detector operator would stop the measurement and let them out.

The Volunteers

The experiments described above were performed between 1950 and 1967, just as the fields of radiation protection and nuclear medicine were coming of age. In all, approximately 2000 volunteers participated. Nearly 1500 were simply "counted" to measure the radioactive fallout in their bodies, approximately 400 were referred patients seeking medical diagnosis, and about 130 were volunteers for radiotracer experiments. These 130 were administered radionuclides in the course of experimental research, and the circumstances of their involvement are directly relevant to the ethical issues being discussed as part of Secretary O'Leary's "openness initiative."

At Los Alamos, the vast majority of the volunteers in the radiotracer experiments were employees of the Laboratory; some were simply the investigators themselves. These volunteers understood the experimental objectives as well as the biological effects of ionizing radiation. It is interesting to note that many Laboratory employees willingly participated in more than one study, some receiving more than one radionuclide. The remaining volunteers were family members of Lab employees as well as 27 volunteers from the community of Los Alamos, 12 firemen and 15 women from the Hospital Auxiliary.

The large, formidable detectors and the unfamiliar laboratory surroundings prompted the volunteers from outside the lab to ask many questions and their consent was contingent upon thorough explanation of the experimental procedures. When children were involved, the experiment was explained to the parents and usually to the children as well. On the basis of the explanation, parents consented to let their children participate only if their children were interested and willing. Unlike today, obtaining the volunteer's consent in the 1950s and 1960s was informal, and typically, no papers were signed. Although this procedure of informing the volunteer and obtaining his or her consent was considered adequate at the time, it would not meet current regulatory standards.

Certainly, the personal rapport between the investigators and the volunteers made a difference. Furthermore, the volunteers were treated with consideration. For example, volunteers for the fallout studies were instructed in the use of the "panic button" before entering the small central compartment of the detector (see Figure 9).

At Los Alamos, proposals for human experiments were always reviewed internally by the director of the Los Alamos Health Division, Dr. Thomas Shipman. Today, that safeguard has been replaced by an Institutional Review Board according to the requirements of federal policy for the protection of human research subjects. In 1956, guidelines for human radiotracer research were issued by the AEC Division of Biology and Medicine that specified, "doses for research shall be a microcurie (a millionth of a curie) or less and administered to informed patients by a physician." Because of the strict precautions taken, no human experiment performed at Los Alamos violated this guideline, even those performed prior to 1956.

The Doses

The $64,000 question asked by volunteers was, "What is the risk to my health from this radiation exposure?" The investigators answered that there was no risk associated with the low doses involved in the experiment. No follow-up studies of the volunteers' health were made to verify this claim. Now, decades and many radiation studies later, this answer has been re-examined by Bill Inkret of the Los Alamos Health Division. Inkret recalculated the range of doses received by volunteers in five representative Los Alamos experiments. He used current models of internal dosimetry recommended by the International Commission on Radiological Protection as well as the quantities of radionuclides administered in the various studies according to published reports. The results are listed in Table 2. For tritium, Inkret has calculated the range of *cumulative* doses from all of the tritium studies, which involved only three volunteers.

Because the vast majority of the dose from iodine-131 goes to the thyroid, it is more appropriate to compare the dose with that of thyroid diagnostic tests than with the natural background. The largest dose received in the iodine-131 experiments, 13,000 millirem, is comparable to that of thyroid diagnostic tests in the 1950s. Of all the people who have had thyroid diagnostic tests, no detrimental effects have been observed, including no excess thyroid cancer. In light of this, the answer to the volunteers' question is still "none."

Table 2. Radiation Doses to Volunteers

Nuclides	Number of volunteers	Doses (mrem)*
hydrogen-3 (tritium)	3	200 - 900
cesium-137	4	50 - 70
iodine-131	117	1 - 400†
zinc-65	4	10
sodium-22	3	1 - 10
rubidium-86	3	1 - 10

*effective doses
†the thyroid doses range from about 30 millirem to 13,000 millirem

The doses given in Table 2 are "effective doses." This means that the dose has been calculated so that it is equivalent, in terms of health risk, to an equal dose of uniform whole-body gamma radiation (see "Effective Dose," page 31). All effective radiation doses to the volunteers in the Los Alamos experiments were less than 1 rem—a very low dose. To get a general idea of the risk involved with levels of exposure such as that, it is useful to compare the effective doses in Table 2 with the natural background radiation. The U.S. national average of the natural background radiation is about 300 millirem per year. Out of all the Los Alamos human experiments, the largest effective dose to volunteers was 900 millirem, or the equivalent of about three years of exposure to natural background radiation, and typically, the doses were equivalent to a small fraction of one year of natural background. No health effects have ever been observed at such low levels of exposure.

In Retrospect

Looking back over the hundreds of reports and publications pertaining to Los Alamos human experiments, one could ask many questions. Was the effort worthwhile? Was the work appropriate? Would researchers do it again?

These were the questions we asked ourselves at the time. To ask them again is like asking, if you had your life to live over, would you change anything? Now, from the vantage point of experience, most of us could think of a few things we would like to change, and the same answer holds true for research. Certainly past research experience has pointed out the need for people of different backgrounds and training to carefully review experimental procedures. It has also shown the benefit of obtaining consent from volunteers in a formal setting in which the volunteer feels comfortable to ask plenty of questions.

Learning from the past is only natural and those changes are not intended to be confused with regrets. There is no doubt that the use of human volunteers in medical and biological research has been a valuable and well-justified resource.

As for the volunteers, the fact of the matter is that people *want* to be helpful, sometimes to help themselves, but also to help others. This is a wonderful quality of our human nature. Therefore, in the future, when information about humans is required, there is little doubt that human volunteers will respond eagerly, as they did in the fifties and sixties at Los Alamos. ■

Further Reading

E. C. Anderson and W. H. Langham. 1959. Average potassium concentration of the human body as a function of age. *Science* 130: 713,714.

M. A. van Dilla and M. J. Fulwyler. 1963. Thyroid metabolism in children and adults using very small (nanocurie) doses of iodine-125 and iodine-131. *Health Physics* 9: 1325-1331.

C. C. Lushbaugh and D. B. Hale. 1959. Clinical applications of whole-body scintillometry. I. retention of orally administered iron. Los Alamos National Laboratory Report, LA-2445-MS.

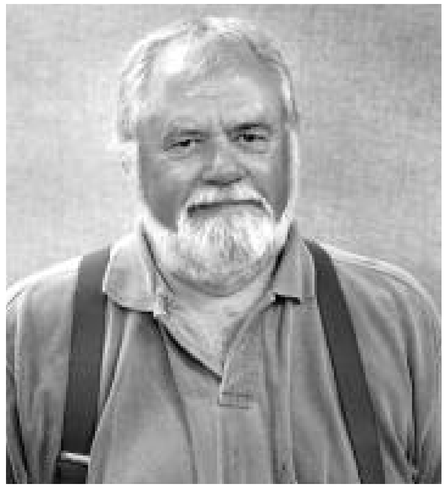
E. A. Pinson and W. H. Langham. 1980. Physiology and toxicology of tritium in man. *Health Physics 25th Aniversary Issue* 38: 1087-1110. This article is a reprint of the original published in *Journal of Applied Physiology* 10: 108-126 issued in 1957.

E. A. Pinson. 1952. Water exchanges and barriers as studied by the use of hydrogen isotopes. *Physiological Reviews* 32: 123-134.

C. R. Richmond, J. E. Furchner, and W. H. Langham. 1962. Long-term retention of radiocesium by man. *Health Physics* 8: 201-205.

R. G. Thomas., E. C. Anderson, and C. R. Richmond. 1979. Cesium-137 whole-body content in a normal New Mexico population: 1956 - 1977. *Health Physics* 37: 588-591.

George Voelz, a native of Wisconsin, received his M.D. degree in 1950 from the University of Wisconsin Medical School followed by an internship at the University of Oregon Medical School Hospital and Clinics. In 1951 George completed an Atomic Energy Commission Fellowship in Occupational Medicine at the Kettering Laboratory of the University of Cincinnati and in 1952 completed a Fellowship at the Los Alamos Scientific Laboratory. From 1957 to 1970, George was the Medical Director at the National Reactor Testing Station for the U.S. Atomic Energy Commission, Idaho Operations Office, where in 1967, he organized and became Director of the Health Services Laboratory. George returned to Los Alamos in 1970 to serve as Health Division Leader until 1982. For the next five years, George served as Assistant Division Leader of the Health Division, primarily in administration of research programs. From 1987-1990 he led the epidemiology section in the Occupational Medicine Group. Since then he has continued his studies on the health of workers in the nuclear industry with a special interest in the effects of plutonium exposure. George has been certified as a diplomat of the American Board of Preventive Medicine since 1959 and has served on numerous committees including a lifetime Honorary Council Member of the National Council on Radiation Protection and Measurements. He has served as a committee member for the International Commission on Radiological Protection, and in 1994, participated as a member of the Laboratory's Human Study Project Team. George retired from the Laboratory in 1990 but has actively continued his research as a Laboratory Associate.



Donald Petersen was born and raised in South Dakota. He received his Ph.D. from the University of Chicago in 1954 and remained on the faculty in the Department of Pharmacology for two years. In 1956 he became a staff member of the Biomedical Research Group H-4 in the Los Alamos Scientific Laboratory's Health Division. In 1963 he became section leader of a new effort in cell biology and remained involved in research on the regulation of cell growth and division until 1970. When the Cellular and Molecular Biology Group was formed in 1970, he became the Group Leader and continued to expand the cell-cycle studies and investigations of chromosomes in normal and malignant cells. He became Deputy Health Division Leader in 1974 with responsibilty for the Laboratory's Biomedical Research Program ranging from very basic studies of cell-cycle regulation to the carcinogenesis of plutonium particles and genetic effects of radiation. When the Health Division was split in 1979, he organized the Life Sciences Division and served as the Division Leader until 1982. From 1982 until his retirement in 1989, he was the Program Manager for Department of Defense Health Effects Programs and a member of the Advanced Concepts Group. He has served on editorial boards, committees and advisory panels on radiation effects, radiotherapy, and other interests of the U.S. Army Medical Research and Development Command. In 1994, he became a member of the Laboratory's Human Studies Project and actively continued his involvement in research related to military health issues.

Los Alamos Radiation Detectors

In 1940, Otto Frisch and Rudolph Peierls wrote a memorandum to the British government warning of the possibility of a German atomic bomb. In it, they impressed upon the British government the importance of determining, in the aftermath of the explosion of an atomic bomb, "the exact extent of the danger area, by means of ionizing measurements, so that people can be warned from entering it." Even as Frisch and Peierls made the first serious consideration of an atomic bomb, they were mindful of the need for radiation detectors to define the boundaries between hazard and health. This concern for radiation protection, which was articulated well before the Manhattan Project was even conceived, was inherited by the workers who built the atomic bomb.

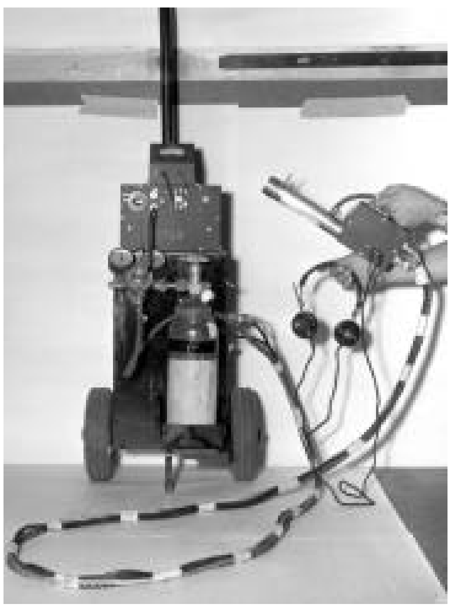


Figure 1. Supersnoop
This early alpha-particle detector, called Supersnoop, was produced at the Chicago Metallurgical Laboratory and distributed to places such as Los Alamos for the detection of plutonium, uranium, and polonium in the work environment. However, because of the shortage of instruments like this one, Los Alamos began a detector development program of its own. By 1945, the program yielded a sensitive light hand-held alpha detector called Pee Wee.

Radiation detectors were needed at Los Alamos to delimit safe and dangerous areas and, even more challenging, to monitor internal exposures to plutonium and other radioisotopes. In 1943, when Los Alamos first opened, Los Alamos scientists were preoccupied with research on the atomic bomb and, therefore, relied upon the Chicago Metallurgical Laboratory to supply the radiation detectors needed to monitor uranium and plutonium in the work environment. Yet, despite heated correspondence between Los Alamos and the Met Lab, the detectors were not forthcoming. Los Alamos suffered an acute shortage of radiation detectors well into 1944 and, in the interest of the workers, began a detector development program of its own. At the forefront of this work was Richard Watts of the Electronics Group in the Physics Division who developed a number of alpha-particle detectors—culminating in the portable "Pee Wee"—named for its mere 19 pounds, to detect uranium and plutonium in the work environment. This work initiated detector development at Los Alamos and set the stage for later work. After the war, Los Alamos began the development of some very special radiation detectors for monitoring internal exposure to radioisotopes. Wright Langham, the leader of the Radiobiology Group of the Health Division, organized a group of scientists of diverse and complementary talents to produce detectors that not only provided radiation protection but also had a great impact in the fields of biology and nuclear medicine.

During the late 1940s, while Los Alamos was busy maintaining its newly acquired nuclear capability, a number of discoveries led to the rebirth of a promising class of detectors called scintillation counters. In 1903, scintillation counting was first used by Sir William Crookes to detect alpha particles emitted by radium. Every time an alpha particle struck the scintillator, zinc sulphide, the scintillator would emit a flash of light. With his eye, Crookes counted the flashes and, with a pen, he recorded the tally. Because this technique was so laborious and uncertain, scintillation counters fell into disuse in the 1930s as Geiger-Müller counters and ion chambers, which produced electronic output, took their place. Two events revived scintillation counting in the forties and fifties: the development of the photomultiplier tube (an instrument that converts light into an electrical pulse) and the discovery of a variety of new types of scintillators, liquid and solid, organic and inorganic, each with their particular advantage. Scintillation counting developed through the 1950s to produce the most versatile, sensitive, and convenient detectors of the time.

Los Alamos scientists became involved in these developments in the early 1950s

for Biology and Medicine

Donald Petersen

as they began intensified research on the hydrogen bomb and boosted fission bombs. This work involved tritium, the radioactive isotope of hydrogen. As a result the Los Alamos Health Division began to develop techniques to monitor internal exposures to this low-energy beta-emitting isotope. Unlike gamma rays, low-energy beta particles cannot penetrate the body, and therefore internal tritium exposures must be monitored by measuring the tritium in samples of body fluids such as blood and urine. The beta particles are hard to detect even in the body fluids because they tend to be "self-absorbed" before they reach the detector. Consequently each sample had to be prepared in many tedious steps, including complete distillation or combustion followed by vaporization and reduction (see "Tracer Studies at Los Alamos"), before its tritium content could be measured with a standard detector, either an ion chamber or Geiger-Müller counter. Furthermore, those standard detectors were fairly inefficient at measuring the very low-energy (less than 18 keV) beta particles emitted by tritium.

Once discovered, it was immediately clear that liquid organic scintillators would eliminate many of the problems associated with tritium detection in biological samples. Self-absorption would not be a problem because the blood or urine was directly mixed into the liquid scintillator such that the tritium beta particles would immediately collide with scintillator molecules. Depending on the energy, the beta particles would excite thousands or possibly millions of scintillator molecules. The excited molecules would quickly re-emit the absorbed energy in the form of photons, which would travel freely through the transparent scintillator to a photomultiplier tube where they would be converted into an electrical pulse. The scintillation counter was also highly efficient.

Wright Langham, who had been an investigator in the tritium human studies, was well aware of the advantages of liquid scintillation and decided to put the exceptional talents of his scientific staff to work on a liquid scintillation counter. F. Newton Hayes—a brilliant organic chemist who discovered the "*p*-terphenyls," a family of organic chemicals which yielded many of the best liquid scintillators ever known—produced the scintillator. Ernest C. Anderson, Robert Schuch, and Jim Perrings—who were familiar with the difficulties of low-energy beta detection from their work with Willard Libby and Jim Arnold at the University of Chicago on radiocarbon dating—did the instrumentation.

Even the earliest liquid scintillation counters were several times more efficient than the ion chamber and very convenient, requiring minimal preparation. Yet, for all these advantages, there was one serious problem: the false signal, or "noise," produced by the photomultiplier tube. This noise was so large that it could easily overwhelm the signal from a typical biological sample. Richard Hiebert and Watts, the experienced detector physicist who developed the much needed alpha detectors during World War II, were the first to rectify this problem. Instead of using only one photomultiplier tube to detect the light emitted by the scintillator, they used two and created a "coincidence circuit" to eliminate background noise. Signals that appeared in both photomultiplier tubes at the same time were counted, whereas signals that occurred in only one photomultiplier tube were thrown away. Of course, occasionally the false signal from the two photomultiplier tubes would occur at the same time and be counted in the

Figure 2. The Early Version . . .
As big as a refrigerator, the early Packard TriCarb Liquid Scintillation Counter of 1954 was a marked improvement on existing techniques for the detection of tritium and other beta-emitting radioisotopes, such as the biologically important carbon-14 and phosphorus-32.

Figure 3. . . . and the New Version
Sleek and computerized, the modern Packard Liquid Scintillation Counter still uses the original basic design developed at Los Alamos. This detector, or a detector like it, can be found in virtually every biochemistry or genetics laboratory around the world.

data. However, this technique immediately reduced the noise from 10,000 to 20,000 counts per minute to only 10 counts per minute in the Los Alamos Coincidence-Anticoincidence Model 530 Liquid Scintillation Counter.
As has so often been the case, once the basic design was worked out, industry began to produce commercially successful models of the liquid scintillation counter. In 1953, Gordon Gould was collaborating with George LeRoy at the University of Chicago on a study of the role of cholesterol in atherosclerosis, or hardening of the arteries. Cholesterol and one of its building blocks, acetate, were labelled at Los Alamos with tritium and carbon-14, both low-energy beta emitters. Although they did not use the liquid scintillation counter in this study, Gould informed LeRoy about the work done at Los Alamos on the Model 530. LeRoy was so enthusiastic about the detector that he went to Lyle Packard and asked him to build him one of these detectors. This interaction resulted in the first commercially successful version of the Los Alamos Tritium Counter, called the Packard Tricarb. The value of this detector extended well into the fields of biochemistry and nuclear medicine and, in fact, a modern equivalent is found in every biochemistry or genetics laboratory to this day (see "DNA Repair and the Scintillation Counter" for examples of how these counters were used to make major discoveries in molecular biology).

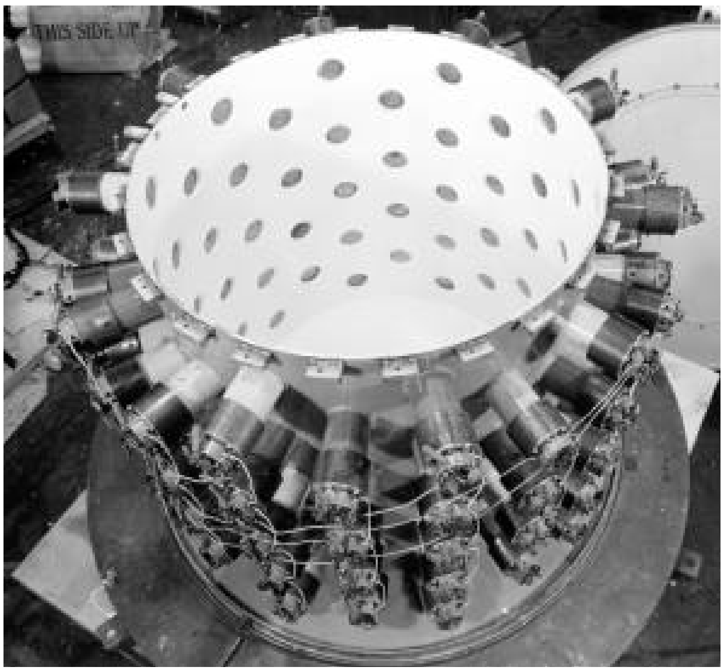


Figure 4. The Neutrino Detector
This top view of the giant Hanford neutrino detector shows the interior of the ten-cubic-foot vat for the liquid scintillator and the 90 photomultiplier tubes peering inside. This detector was the first step toward the discovery of the neutrino, work for which Fred Reines (see Figure 5) earned the 1995 Nobel Prize in physics.

At more or less the same time that the Model 530 scintillation counter was being developed, an elusive particle called the neutrino brought about the development of a second branch of liquid scintillation counters at Los Alamos: the whole-body counters, HUMCO I and II. The existence of the neutrino had been hypothesized by Wolfgang Pauli as early as 1930, but the particle had never been "observed," and Fred Reines and Clyde Cowan of the Los Alamos Physics Division decided to test Pauli's theory. Because neutrinos interact extremely weakly with other matter, they needed to build a colossal, high-density detector and put it near a nuclear reactor, where the flux of neutrinos was expected to be high. Liquid scintillators, which are quite dense and can be produced in large quantities, were perfect for the job. Reines and Cowan approached Wright Langham with their idea and were apparently so persuasive that Langham "loaned" them Hayes, Anderson, and Schuch. They built a cylindrical vat, 10 cubic feet in volume, and filled it with liquid scintillator. They surrounded the vat with 90 photomultiplier tubes, connected them to a coincidence circuit, and placed the detector beside the Hanford nuclear reactor. This work produced a tentative confirmation of Pauli's neutrino in 1953 and in 1956, after some modifications on the original detector, the first positive observation of the neutrino (see Figure 4).

The neutrino detector was developed out of pure academic interest, yet it yielded the practical rewards of HUMCO I and II. In the course of their work on the neutrino detector, Reines and Cowan decided to determine the degree to which the natural gamma ray activity of the materials used to shield the neutrino detector would add noise to the experiment. They built a large "top hat" about 23 centimeters in diameter and 75 centimeters high and inserted it, top down, into the cylindrical vat of scintillator. The shielding materials were placed in the concavity of the top hat. Most of the gamma rays emitted by the materials would penetrate the top hat, enter the scintillating material, produce photons, and be detected.

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DNA Repair and the Scintillation Counter

Before the invention of the liquid scintillation counter, there seemed to be a conspiracy in nature against the biochemist, that tritium and carbon-14, two of the most important radioisotopes to the study of biology, were also some of the hardest to measure. The scintillation counter, which was developed in the 1950s, made the detection of these low-energy beta-emitters simple and efficient. Consequently, tritium and carbon-14, along with phosphorus-32, soon became the backbone of biomedical research. A few of the contributions to our understanding of DNA repair of radiation damage that were made possible by the scintillation counter are given below.

In 1964, R. B. Setlow and W. L. Carrier at Oak Ridge National Laboratory used a scintillation counter to produce some of the first biochemical evidence that cells repair ultraviolet damage to DNA. Earlier in the 1960s it had been demonstrated that ultraviolet radiation induces chemical bonds between two neighboring pyrimidine DNA bases (thymine and cytosine), forming pyrimidine “dimers.” Those dimers distort the normal helical shape DNA, stop DNA synthesis, and prevent cells from replicating. Setlow and Carrier examined the cellular response to pyrimidine dimers in a culture of bacterial cells.

The cells were grown in a medium containing tritium-labeled thymidine, which was incorporated into their DNA. After irradiation, the DNA was degraded into single bases, dimers, and other DNA fragments, which were analyzed by process called “paper chromatography.” In this process, bases and dimers separate onto different locations on a piece of paper by virtue of their different solubilities. The paper was cut into segments containing single bases and others containing dimers, and the segments were tossed directly into a scintillation counter. Fortunately, because of its broad range of sensitivity, the scintillation counter was able to measure the activity of both the bases and the dimers, even though they may differ by as much as a factor of one hundred thousand.

Setlow and Carrier observed fewer dimers in the DNA of cells that were allowed to incubate, indicating that those cells somehow repaired the dimers, and they also demonstrated that the cells cut the dimers out of the DNA, the first step in a type of genetic repair called “nucleotide excision repair.”

In 1964, David Pettijohn and Philip Hanawalt at Stanford University demonstrated the second step of the repair, the replacement of the excised piece of DNA. In this experiment, two labels were used: carbon-14-labeled thymine and a higher-density, tritium-labeled thymine analog. The cells were grown in the presence of the first label, irradiated, and allowed to incubate in the presence of the second label. The DNA was broken into fragments of similar length and separated in a centrifuge by density. Then the DNA was dried on filter paper and put it into a scintillation counter. They observed that the higher-density thymine analog was incorporated into the DNA in the small quantities that demonstrated the replacement of the excised piece of DNA.

In 1966, R. A. McGrath and R. W. Williams of Oak Ridge National Laboratory used the scintillation counter to produce the first evidence that cells repair “single-strand breaks,” or breaks in one side of the DNA double-helix, caused by ionizing radiation. The cells were grown in tritium-labeled thymidine and irradiated with x rays. The cells were divided into batches and allowed to incubate for different amounts of time. The DNA from the cells was then divided into its two single strands, such that it fell into pieces at the single-strand breaks. Using a centrifuge, they separated the long molecules of DNA from the short molecules. The DNA was dried on small disks of filter paper which were then thrown into the scintillation counter. McGrath and Williams observed that the DNA from the cells that were allowed to incubate was in large pieces, not very unlike the DNA of unirradiated cells, while the DNA from the cells that were not allowed to incubate was in short pieces. Clearly, the DNA had been significantly repaired during incubation.

The scintillation counter has continued to produce breakthroughs in the study of cellular repair of radiation damage since then and remains as important today as when it first became available in the 1950s. ■

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Figure 5. Getting Down to Work
Wearing his characteristic tie, Wright Langham was the only one small enough to be lowered into the "top hat" inside the neutrino detector. Fred Reines (left) and Kiko Harrison do the honors.

Schuch was the one who suggested making a larger insert, 51 centimeters in diameter, so that they could put a small person inside and use the detector to measure the gamma activity of people. Before trying it out with a person, a dog was lowered into the insert and counted before and after injection of a solution containing 10^{-7} curies of radium. It was concluded that a radium body burden of about 5 x 10^{-9} curies could be detected, an immediate improvement by a factor of about 100 on the sensitivity of Robley Evans' early instrument for measuring the body burden of the radium dial painters (see "Radium—the Benchmark for Alpha Emitters").

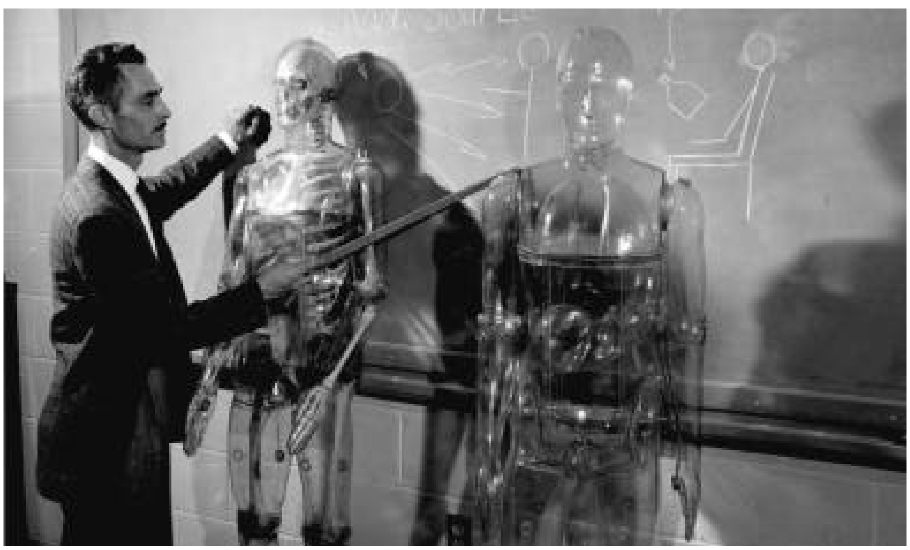

Figure 6. A Captive Audience
Wright Langham lectures on the uses of Remab (left) and Remcal in the calibration of the whole-body counters, HUMCO I and II. These plastic "phantoms" enabled the researchers to perform "human" experiments to determine the efficiency of the detectors.

By crouching, a small person could also fit into the top hat and Langham, as the smallest one around, was the first person to try (see Figure 5). He was counted twice, once with an external 0.1 millicurie radium source and once without. Later, a water "human phantom" (see Figure 6) was made and radioactive potassium salt was dissolved in it. With this phantom, the scientists determined that the detector efficiency for potassium-40 was 10 per cent. That was very useful because potassium-40 is a naturally-occurring gamma-emitting radioisotope which is found in humans. A number of people were counted to determine the amount of potassium-40 in their bodies, and given the ten per cent efficiency of the detector, these measurements agreed well with expected results.

This preliminary work was rapidly brought to fruition. By September 1954, a collaboration between Schuch and Anderson at Los Alamos and Marvin van Dilla at the University of Utah resulted in the development of the K-9, otherwise known as the "dog counter." This detector was used to perform radiation experiments on animal subjects, and it also served as an intermediate step before the development of a whole-body detector for humans. In January 1956, Anderson, Schuch, Perrings, and Langham developed the Human Counter or HUMCO I, a whole-body gamma detector for people. Because it was highly sensitive, this detector made it possible to measure the amount of potassium-40 in a person in only a minute and 40 seconds with a 5 per cent error.

Immediately, the detector was put to practical use. By 1959, the potassium-40 concentration had been measured in 1590 men and women from the ages of 1 to 79. Because potassium-40 resides largely in muscle, the amount of potassium-40 in the body is proportional to the body's lean mass. The measurements were mainly for the benefit of the public, but they also revealed the fundamental facts about the evolution of muscle mass with age for men and women (see "Tracer Studies at Los Alamos," page 270). At the same time, under Project Sunshine, HUMCO was used to study the worldwide distribution of fallout and the change of fallout with time. The concentration of gamma-emitting fallout radionuclides was measured in dried milk from three New Mexico dairies as well as in New Mexico residents and laboratory visitors. The sensitivity of the whole-body counter not only made those measurements quick and accurate, it also enabled medical tests and biological experiments to be performed on people using very small amounts of radionuclide—so small in fact that diagnostic tests could be performed safely even on newborns. In 1962, HUMCO I was superceded by HUMCO II, which had nearly ten-fold greater sensitivity and therefore made measurements that much safer and quicker.

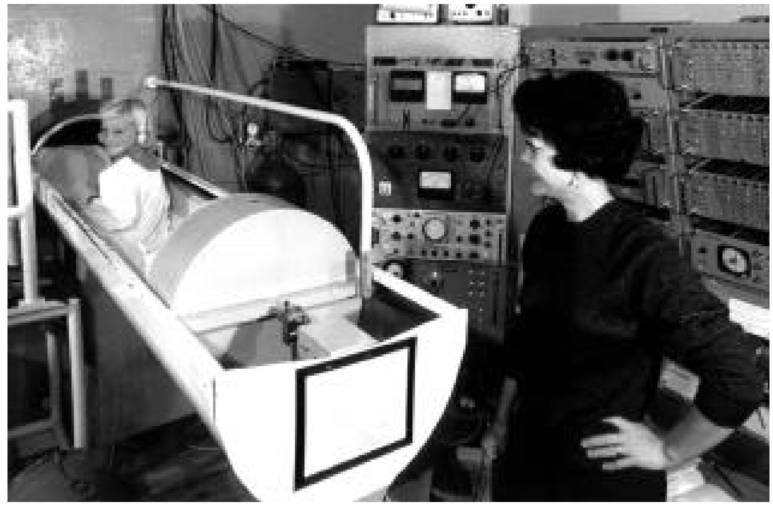

Figure 7. A Young Volunteer
Many New Mexican residents were monitored for the level of fallout radionuclides in their body. Here, a young resident enters the cylindrical opening of HUMCO I under the supervision of the attendant, Annie Hargett. Several young volunteers were counted weekly to determine their cesium-137 body burden.

This story is a good illustration of the benefits of the interdisciplinary approach to problem solving that was common at Los Alamos at the time. If an investigator had an interesting idea, he was not required to seek permission from his superior or consult him to see if the idea was worthwhile. He would simply talk to scientists in the fields that related to his idea, perhaps perform a preliminary experiment, and then, if the idea seemed promising, he would begin research. That approach to problem solving was in stark contrast to the strong disciplinary segregation that was the fashion in academic institutions, and, in light of stories such as this one about the Los Alamos liquid scintillation counters, it proved quite successful. ■

Further Reading

F. N. Hayes and R. G. Gould. 1953. Liquid scintillation counting of tritium-labeled water and organic compounds. *Science* 117: 480-482.

R. D. Hiebert and R. J. Watts. 1953. Fast-coincidence circuit for hydrogen-3 and carbon-14 measurements. *Nucleonics* 12: 38-41.

E. C. Anderson, R. L. Schuch, J. D. Perrings, and W. H. Langham. 1956. The Los Alamos human counter. *Nucleonics* 14: 26-29.

M. A. van Dilla, R. L. Schuch, and E. C. Anderson. 1954. K-9: a large 4π gamma-ray detector. *Nucleonics* 12: 22-27.

C. L. Cowan, Jr., F. Reines, F. B. Harrison, H. W. Kruse, and A. D. McGuire. 1956. Detection of the free neutrino: a confirmation. *Science* 124: 103-104.

R. B. Setlow and W. L. Carrier. 1964. The disappearance of thymine dimers from DNA: an error-correcting mechanism. *Proceedings of the National Academy of Science* 51: 226-231.

R. A. McGrath and R. W. Williams. 1966. Reconstruction *in vivo* of irradiated *Escherichia coli* deoxyribonucleic acid; the rejoining of broken pieces. *Nature* 212: 534,535.

D. Pettijohn and P. Hanawalt. 1964. Evidence for repair-replication of ultraviolet damaged DNA in bacteria. *Journal of Molecular Biology* 9: 395-410.