

A TRUE MEASURE OF EXPOSURE

the human tissue analysis program at Los Alamos

by James F. McInroy

The human tissue analysis program, a 35-year-long research program at Los Alamos, has been scrutinized by the local and national news media and, more recently, by the President's Advisory Committee on Human Radiation Experiments. Although this program does not technically fall under the description of "human experimentation," as defined by Secretary of Energy Hazel O'Leary, charges by the news media of DOE's "body snatching," unethical procurement of human tissues and organs, and hiding or withholding resulting data from the next-of-kin and their lawyers mandated that this program be included in the Advisory Committee's investigation and that all documents and other information about the program be made available.

As the leader of the Los Alamos tissue project for 21 years, I will take this opportunity to review the motivations, the manner of obtaining tissue samples, and the most important findings of what the general public, including my wife, sees as a very ghoulish activity. Work on cadavers has been at the heart of medical discovery and medical education for hundreds if not thousands of years. This work is no exception—our program enabled us to quantify the plutonium distribution in the body through

The image at left is an autoradiograph of a tracheobronchial lymph node from a former worker at the Laboratory. It shows alpha tracks radiating in a typical star pattern from tiny alpha-active clumps of material. Chemical analyses of the radioisotopes in this individual's lungs and lymph nodes indicated that those clumps most likely consisted of an aggregate of plutonium particles.

postmortem analysis of tissues from occupationally exposed individuals. Because the risk of cancer is highly dependent on not only the amount of plutonium retained in the body, but also the fraction that goes to specific organs, our discoveries on plutonium distribution have helped to clear away uncertainties about the human metabolism and potential health effects of this radioactive substance.

The plutonium excretion models, which were the main product of the plutonium injection studies, provided an indirect means for estimating the amount of plutonium retained in the body of a living person from the amount excreted in the urine. Those models were crucial because they were the most commonly used means for estimating the body burden and the ultimate risk from accidental plutonium exposures, but they gave no information about the distribution of plutonium in the body, nor were there any independent means to check on their accuracy. The painstaking collection and analysis of tissues from deceased individuals over the last 35 years has provided at least some of the missing information, and that information now serves as a cornerstone of the present models for determining the doses and the risks from plutonium exposure. The early biokinetic models used to estimate body burdens were based primarily on indirect measurements such as urinalysis, fecal analysis, external lung counting, and/or whole body counting. In contrast, the tissue data are direct and definitive. The tissue program has also provided an accurate measure of the general level of plutonium exposure of Laboratory employees and thus a check on the efficacy of industrial hygiene and health

physics measures that are meant to keep plutonium contamination to a minimum.

The author (now retired from the Laboratory) hopes that the tissue results presented here, some of which are relatively recent, will inspire rejuvenation of an effort that can continue to help eliminate the remaining uncertainties characterizing plutonium dosimetry.

Early Studies of Plutonium Metabolism

Bill Moss's article, "The Human Plutonium Injection Experiments," reviews the fact that, in 1944, when plutonium began to be produced in large quantities, nothing was known about human metabolism, retention, distribution, and excretion of this manmade element. The leading scientists and medical doctors in the Manhattan Project, however, were well aware that working with plutonium might pose a serious health hazard. They had done research on using radionuclides for medical diagnostics in the 1930s, and they knew that long-lived radionuclides such as radium are dangerous if they are retained inside the body because they become a constant internal source of radiation. Biomedically, plutonium was assumed to be much like radium. Internal deposits of radium had produced fatal anemias and bone cancers in the radium dial painters of the 1920s, and there was great concern that internal exposure to plutonium and its compounds might be at least as dangerous.

By January 29, 1944, 11 milligrams of plutonium (a fair share of the world's

total supply at that time) had been allocated for animal metabolic studies. The results indicated that the skeleton was the major deposition site, the retention time was long, and the liver had the highest concentration among the soft tissues, followed by the kidneys and the spleen. How appropriate were those animal data for quantifying the distribution and retention of plutonium in humans—and thus for determining the doses and the risks of plutonium exposure?

The human injection experiments were, in part, an effort to answer that question. Excretion data were collected from all subjects following injection of plutonium into the bloodstream, and small tissue specimens from those subjects who were terminally ill were analyzed for plutonium following their death. A number of important observations followed: 1) there were no major differences between humans and the common laboratory animals in the distribution in tissues with the exception of liver; 2) the liver of humans contained 20 to 40 per cent of the total amount retained versus 10 per cent or less for rats when both received the same plutonium-citrate complex; 3) the retention half-time in liver was greater in humans; 4) the retention half-time for whole body in humans was much longer than in laboratory animals; and 5) the excretion pattern in humans was different, especially that a much lower fraction was eliminated in human feces compared to animal feces.

Wright Langham, a radiobiologist in the Health Group at Los Alamos who had planned the analytical protocols for the human injection experiments, used the excretion data to create a model relating the amount of plutonium injected into the bloodstream to the amount excreted in the urine. Thus, the Langham model became the first basis for estimating the amount of plutonium retained in the body as a function of time following an accidental intake of an unknown quantity. By the late 1950s, James N. P.

Lawrence of Los Alamos had modified the Langham model to take into account long-time excretion data from a selected group of Los Alamos workers who had experienced accidental intakes during the Manhattan Project and who had been followed as part of an epidemiological study (some of those men tell their stories in the roundtable "On the Front Lines"). But many uncertainties remained. Most worker exposures were the result of inhaling tiny airborne particles of plutonium into the lung. How did that mode of exposure compare to the injection of plutonium directly into the bloodstream? It was suspected that the patterns of retention, distribution, and excretion, and thus the dose to the body, would change depending on whether the intake was by inhalation, ingestion, or a cut or puncture wound, but no human data were available to check the conjectures. It was also expected that the dose and the ultimate risk of exposure would be affected by the particular chemical form and particle size of the material taken in, the time since exposure, the duration of exposure, and the effects of individual biological variation.

The Beginnings and the Philosophy of the Los Alamos Tissue Program

Our human tissue analysis began spontaneously following the accidental death of Cecil Kelley, a plutonium worker here in Los Alamos. Kelley was exposure to a lethal dose of gamma and neutron radiation on December 30, 1958 and died 35 hours later. The radiation source was a plutonium collection vessel at DP Site that suddenly and unexpectedly went critical during the year-end inventory (see "The Cecil Kelley Criticality Accident: The Origin of the Los Alamos Human Tissue Analysis Program"). As a part of the medical autopsy, the local pathologist Dr. Clarence C. Lushbaugh collected tissues to examine any physical changes that might have been caused by the extreme radiation exposure. Dr. Lush-

baugh, who was also a research scientist at the Laboratory, decided to send several of the organs and bones to the Laboratory for radiochemical analysis to determine the plutonium content.

Kelley had worked with plutonium for a number of years prior to his death and was carrying in his body a measurable plutonium "burden," which presumably had been obtained mostly through inhalation of moderate routine airborne contamination. The estimated whole-body content, based on urine excretion data and the application of Jim Lawrence's PUQFUA (Plutonium Body Burden (Q) From Urine Assays) code, was 18 nanocuries, a little less than half the maximum permissible body burden of 40 nanocuries. The tissue samples represented the first opportunity to determine directly the plutonium burden carried in an individual who had been analyzed for plutonium content prior to death and thus to check the predictive power of the urine excretion models against real data. It was also an opportunity to measure the real efficacy of the industrial hygiene and health physics measures that had been taken to reduce airborne plutonium contamination in the work environment. Those responsible for industrial hygiene at Los Alamos, including Wright Langham, Donald Petersen, and Dr. Lushbaugh, felt it was incumbent on them to take advantage of the availability of that information, even though it resulted from the untimely and tragic death of a colleague.

The Kelley data offered some surprises. Although the whole-body content was found to be 19 nanocuries, in close agreement with the excretion model, that result was considered by Wright Langham to be "undoubtedly fortuitous" because the fraction in the lung and pulmonary lymph nodes was much larger than predicted by the biokinetic models of the day. That surprise led to the initiation of the tissue analysis program at Los Alamos, a concerted effort to collect and analyze tissues from

deceased occupationally exposed workers. The program also included some members of the general public as controls. The hope was to quantify all the variables affecting the distribution and retention of plutonium and then use the data to improve the *in vivo* estimates of internal plutonium exposures.

The most important sources of tissues were the many workers involved with the handling of plutonium in the 1940s and 1950s when most of the serious exposures occurred. Those individuals were fairly young at the time and proved to be a very healthy group. As a result, the collection of human tissues from autopsy or surgery has proceeded slowly.

The plan to include unexposed people as controls eventually grew into a large study of the U.S. non-occupationally exposed general population. The results have produced an accurate determination of the background levels of internally deposited plutonium from atmospheric fallout due to nuclear weapons testing and from accidental release to the environment from nuclear facilities. The results from the general population study are presented in the last section of this article.

The tissue program has also included the study of americium, uranium, thorium, and neptunium, however, the vast majority of the analyses performed on tissues at Los Alamos were for plutonium and americium. As mentioned above, plutonium in the bloodstream was found to be deposited preferentially in the liver and skeleton. If the exposure was from inhalation, the lung and associated lymph nodes would also retain deposited plutonium. If the exposure was through ingestion, the consequences would be reduced because the gastrointestinal tract allows only about one plutonium atom out of ten thousand to pass through the intestinal walls and enter the blood stream. That knowledge of the primary deposition sites led the early researchers to collect tissue

specimens from the lung, tracheo-bronchial lymph nodes, liver, kidney and bone specimens. Later, interest in minor deposition sites and possible consequences, such as potential genetic effects if the radioactive elements were to deposit in gonadal tissue, led to the collection of several additional tissues.

The ethics of our tissue collection process has commanded the most attention during the recent re-examination of the tissue program by the President's Advisory Committee. Our own examination of procedures has shown that for all normal deaths (that is, not involving accidents, suicide, homicide, and so forth), tissue collection was done only after obtaining appropriate authority through a written consent form. For example, during the 1950s and 1960s consent for autopsy and tissue collection were obtained in writing from the next of kin by the floor nursing supervisor or attending physician at the Los Alamos Medical Center.*

Then in 1968 the Atomic Energy Commission (AEC) sponsored the formation of a formal registry to collect medical, exposure, and work histories of plutonium workers on a voluntary basis and to request authority from the registrants for autopsy and tissue analysis at the time of death. Originally called the National Plutonium Registry, it was eventually expanded into two registries, the U.S. Transuranium Registry and the U.S. Uranium Registry. The two are now combined and referred to as the USTUR. They are administered at Washington State University under the sponsorship of the DOE's Office of Health and Environmental Research. The accompanying box "Authority and Collection of Tissues" outlines the procedures followed at Los Alamos in the early days and by the Registries in more recent times to obtain consent and to collect tissues.

* The Los Alamos Medical Center was operated by the AEC until 1964, after which it was purchased by the Lutheran Health Systems of Fargo, North Dakota.

Studies of Occupationally Exposed Workers

Los Alamos Donors. From 1959 to 1978 tissues from 116 former employees of the Laboratory were analyzed. Not all had been exposed to plutonium; many were support personnel such as secretaries, janitors, firemen, truck drivers, and others who had volunteered to be part of the program.

Since our association with the USTUR in 1971, tissues from 60 additional Los Alamos workers with known or suspected exposure to plutonium have been analyzed, including six whole bodies. As of October 1995, there are 42 living members of the Registry from Los Alamos who have given their consent for radiochemical analyses following death; seven of them are whole-body donors. A total of 25 highly exposed workers from all over the country are currently enrolled with the USTUR as whole-body donors following death.

What has tissue analysis revealed about the effectiveness of the Laboratory's efforts to protect its workers from exposure to plutonium? During the early days of the Laboratory's operation, particularly during the war years, we know that the containment and filtering systems were not available or were not used as efficiently as they are today. The higher levels of contamination present at that time were clearly reflected in the tissues we analyzed from a secretary who worked in the original plutonium processing building known as "D" building. Although she probably never worked in a plutonium laboratory, her lungs, liver, and skeleton contained larger concentrations of plutonium than the general public, undoubtedly from inhalation of airborne plutonium during her work hours.

To evaluate the overall exposure of the Laboratory work force, a comparison of concentrations of plutonium in the liver was made between the worker popula-

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Authorization and Collection of Tissues

The charge of "body snatching" by the news media opens up the issue of where and how the Los Alamos tissue analysis program obtained samples for study. During the first twelve years of the program, from 1959 to 1971, all samples were obtained from individuals who had died and/or were given autopsies at the Los Alamos Medical Center. As described in the main text, the first case was Cecil Kelley, who had worked with plutonium and died as a result of a criticality accident. His autopsy was authorized by the Los Alamos coroner, and then the pathologist at the Los Alamos Medical Center, Dr. Clarence C. Lushbaugh, decided to collect tissue samples from Kelley and have them analyzed for plutonium content by the biomedical research group at the Laboratory (Lushbaugh had a joint appointment with that group). After the Kelley incident, Lushbaugh decided to make the collection of tissue specimens for plutonium analyses a routine part of all autopsies performed at the Medical Center. That practice was quite acceptable since, in those days, autopsies were considered a learning tool. They were used to confirm the accuracy of the physician's diagnosis, to determine the effectiveness of certain medical treatments, and, of course, to determine the cause of death, especially in the cases of unattended deaths. Also, autopsy programs measuring plutonium in human tissues were being conducted at other sites in the U.S. and in foreign countries.

Perhaps the more unusual practice was Lushbaugh's attempt to get permission to perform an autopsy on *every* person who died at the Los Alamos Medical Center—Laboratory employees, members of the general population from Los Alamos and surrounding areas, and transient visitors from other parts of the country. Of course autopsies had to be performed on a certain percentage of persons dying in the hospital each year in order to maintain the accreditation of the hospital and hospital staff. Also the members of the Los Alamos community were typically very interested in the science that could be learned from the autopsies and were willing to make this final contribution of themselves in the interest of science.

For routine deaths, the floor nursing supervisor or the attending physician would ask the next of kin to sign the Medical Center's "Authority for Autopsy" form, which stated that the next of kin "authorize(d) a postmortem examination of the decedent, including removal and retention of such specimens and tissues, as the examining physician deems proper for therapeutic or scientific purposes". Few refused consent. Non-routine deaths (accidents, unattended deaths, suicides, homicides, and so on) fell under the authority of the coroner, and so the coroner was asked and would grant consent for the retention and analysis of tissues. In all the cases mentioned above, the next of kin were not necessarily made aware that tissues were being retained specifically for the analysis of plutonium content

Formal consent from occupationally exposed workers. Procedures for obtaining consent became more formal and more explicit in 1968 when the United States Atomic Energy Commission (AEC) established the National Plutonium Registry to function as a national center for the collection of medical, exposure, and work histories for the workers in the AEC nuclear complex. The Registry was an outgrowth of the postmortem tissue sampling program that had begun in 1949 at the AEC's Hanford site near Richland, Washington and continued to collect tissues at autopsy provided permission was given in advance by the occupationally exposed individual. In the original request for funds, the primary purpose of the Registry was stated as "the protection of the interests of the workers, employees, and public by serving as a national focus for acquisition and dissemination of the newest and best information

relative to the effects of the transuranium elements on people." In 1970, the name of the Registry was changed to the United States Transuranium Registry (USTR) but the mission did not change, and by June 1974, 5843 transuranium workers had been identified, of whom 3880 had signed release forms for their medical and health physics records and 819 had given authority for autopsy.

Initially, all tissues collected by the Registry, with the exception of cases originating at Rocky Flats, were analyzed at the Battelle, Pacific Northwest Laboratories, in Richland, Washington. In 1971, the Los Alamos Laboratory was added to the list of "approved" laboratories. The Battelle and Los Alamos laboratories submitted their own research proposals and were funded independently by the AEC for radiochemical analysis of the Registry tissues. In 1978, the Energy Research and Development Agency (ERDA), successor to the AEC, directed that the Los Alamos tissue analyses laboratory become the lead laboratory for analysis of human tissues for the United States Transuranium Registry (USTR).*

Once the Registry was established, physicians in the Industrial Medicine Group at Los Alamos would use the periodic employee medical examinations as a time to introduce the Registry and its purpose to those Laboratory employees who were either known to have, or suspected of having, internal exposure to the transuranium elements. Individuals willing to release their medical, exposure, and work histories to the Registry and to donate tissues following their death were provided additional detailed information and appropriate consent forms. Those forms were generally signed prior to death by the donor, his spouse or nearest next of kin, and a non-related witness. The forms were kept on file and had to be renewed every five years to be valid. Also the next of kin could withdraw the consent for tissue donation at the time of death if they desired to do so.

Potential donors were provided with identification cards to carry on their person that notified the attending physician or hospital staff at the time of death of the individual's desire to donate tissues to the U.S. Transuranium Registry. The card gave a telephone number to be called if death was imminent or had occurred. Once the Registry was notified, they alerted our tissue analysis laboratory, and we sent instructions and shipping containers to the hospital where the autopsy was to take place. Following the autopsy, tissue specimens were individually packaged in plastic bags, frozen, packed in Dry Ice, and shipped to Los Alamos by overnight delivery.

In recent years, the Registry instituted a whole-body donation program in which all internal organs were removed, packaged as described above, and sent directly to Los Alamos, and the cadaver was shipped to Richland for complete dissection. The skin, muscle, and bones were then shipped to Los Alamos for analyses. Because identification cards in wallets were sometimes overlooked, whole-body donors had the additional option of carrying Medic Alert bracelets or medallions so that there would be no delay in notifying the Registry of their death. The fact that the Registry often knew of an individual's death within a matter of minutes following the event, or sometimes prior to death, has led some people to conclude that the Registry was in collusion with the pathologists or contractors for the DOE to obtain tissue specimens. Thus, the charge of "body snatching." ■

*In 1978, the Energy Research and Development Agency funded the establishment of the United States Uranium Registry (USUR). In 1992, the USTR and USUR were combined to form the United States Transuranium and Uranium Registries (USTUR). An excellent summary of the history of the USTUR is given by R. L. Kathren et al in reference 12.

Layman's View of An Autopsy

The author, during the course of his 21 years in the Tissue Analysis Program at Los Alamos, attended numerous autopsies. He is aware that many people do not know what happens at an autopsy, and thought it would be interesting to offer the following lay description.



Lungs from an occupationally exposed worker inflated with dry nitrogen to approximately normal size found in the human chest. The ratio of plutonium to americium was measured in the Los Alamos lung counter and compared with measurements made before death.

Generally, a medical assistant for the pathologist prepares the body by cutting a "Y" shaped incision in the skin and muscle covering the chest and abdomen. The skin is cut back to reveal the muscles and ribs of the thorax (chest) and the opening the abdomen. The cartilage connecting the ribs to the sternum (breastbone) is easily cut with a scalpel, and the sternum along with the connected costal cartilage from the ribs are removed to reveal the lungs and heart. The opening in the abdomen accesses the visceral organs, the liver, stomach, kidneys, small and large intestine, bladder, and so forth.

Pathologists generally remove each of these organs one at a time, beginning with the heart and lungs, and grossly examine them for obvious abnormalities. They then remove small sections of tissue from suspicious areas and preserve them in a special fixative so that the tissues can later be examined microscopically. To observe the interior of large organs such as the lungs and liver, they often "bread-board" them. That is, they make parallel slices about 1/2 inch thick throughout the organ and continually look for abnormalities. Any suspected areas are snipped out and preserved for microscopic examination. In this manner, all internal organs are removed from the body and weighed, and appropriate sections are removed and preserved when, based on training and experience, the pathologist deems it necessary.



A cross section of a lung that had been inflated with nitrogen and frozen to retain its natural shape. The dark area in the center is an enlarged pulmonary lymph node.

While the body cavity lies empty, a piece of the vertebrae is sliced off the interior side of the vertebral column with a special bone saw. This bone specimen, called a "vertebral wedge," consists of several vertebral bodies and associated disks. It protrudes into the cavity and is easily removed without destroying the continuity of the vertebral column. Likewise, at this time, a rib and/or piece of sternum can also be removed for examination.

At some hospitals, the organs that have been removed are placed in plastic bags and incinerated. Other hospitals return the organs to the body cavity. In either case, they surgically sew the skin of the abdomen and chest together to restore the body to its "normal" shape so that the mortician can prepare the body for viewing and burial. When prepared by a competent mortician, persons viewing the body are completely unaware that an autopsy has been performed on the deceased.

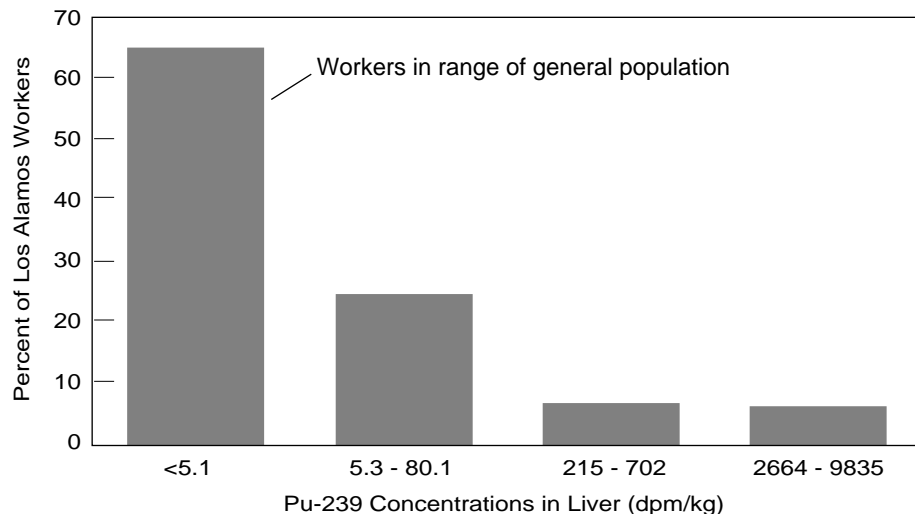
When special circumstances require, the brain is removed by first cutting the scalp from ear to ear and turning back the skin and hair to reveal the top of the skull. A special bone saw cuts through the skull bone to remove the skull cap, without cutting into the brain, itself. The brain is then removed intact, and the bony skull cap placed back into position at the top of the head. The scalp is sutured together, and the sutures are seldom noticeable when the body is prepared for the funeral. The body is then released to the funeral home for embalming or cremation, as the family has directed. ■

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tion and the general population (see Figure 1). The liver was selected because it is a major deposition site for plutonium once plutonium has entered the blood stream and because all or a major portion of the liver could be easily obtained for analysis. Large tissue samples were especially important for evaluating the extremely low levels of plutonium in the general population. Two-thirds of the workers had liver concentrations that did not differ significantly from the general population, who were exposed only to environmental sources of plutonium such as atmospheric fallout from weapons testing. The remaining third fell naturally into three distinct groups. The two groups with the highest liver concentrations (above 80 disintegrations per minute per kilogram) had well documented exposures and consisted mostly of chemists, physicists, and laboratory technicians. Almost without exception, the persons with those high exposures had received them during the earliest days of the Laboratory's existence. The group with intermediate liver concentrations was made up of the same professions as above but also included firemen, health physics monitors, health physics laborers, plumbers, and so on. The latter were probably exposed while passing through or working in a contaminated area for short times. Overall, it is evident that the majority of Laboratory workers have been adequately protected from exposure to plutonium.

One might wonder whether there have been any Laboratory personnel who received really high plutonium exposures, and, if so, whether the exposures have affected their lives or been life threatening. These are questions frequently asked by concerned workers and the general public, alike. (For a discussion of plutonium exposures and their effects see "On the Front Lines.")

Our study was not designed to answer all these questions. It was not an epidemiology study where frequency of disease, causes of death, and life short-



ening are evaluated. However, we can answer some of the questions and refer to other related studies carried out at Los Alamos for answers to some of the others.

Until recently, radiation protection standards for internal exposures were given in terms of the recommended maximum permissible body burden (MPBB) specified in terms of mass (micrograms) or activity (nanocuries). [1 nanocurie = 2,220 disintegrations per minute (dpm)] For plutonium, the MPBB for nuclear industry workers was 0.65 microgram or 40 nanocuries. The MPBB for americium is also 40 nanocuries. The highest depositions measured at the time of death by our program was about 85 nanocuries of plutonium in a former Los Alamos worker, 120 nanocuries of americium in a worker at the Lawrence Livermore Laboratory (the latter is thought to have received his exposure while working as a graduate student at the University of California at Berkeley) and 15 microcuries (more exactly 14,600 nanocuries) of americium in a Hanford Site worker. Did the exposures contribute to their deaths? The Los Alamos worker died at the age of 78 from a heart attack. The Livermore worker died at age 49 of a malignant melanoma. However, it is not believed that americium exposure results in melanoma. The individual from the Hanford Site died at age 76

Figure 1. Plutonium in Workers versus the General Population

This bar chart shows the liver concentrations of former employees of the Los Alamos National Laboratory. Approximately two-thirds of all those employees measured had liver concentrations below 5.1 disintegrations per minute per kilogram (dpm/kg), which is within the range observed in the U.S. general population exposed only to fallout. Individuals having liver concentrations ranging from 5.3 to 80.1 dpm/kg included mainly support personnel (firemen, custodians, health physics monitors, security guards, and so forth) that may have received minor exposures incidental to their job assignments. Individuals with liver concentrations greater than 80 dpm/kg were physicists, chemists, health physics monitors, and metallurgists, all of whom had well documented plutonium exposures.

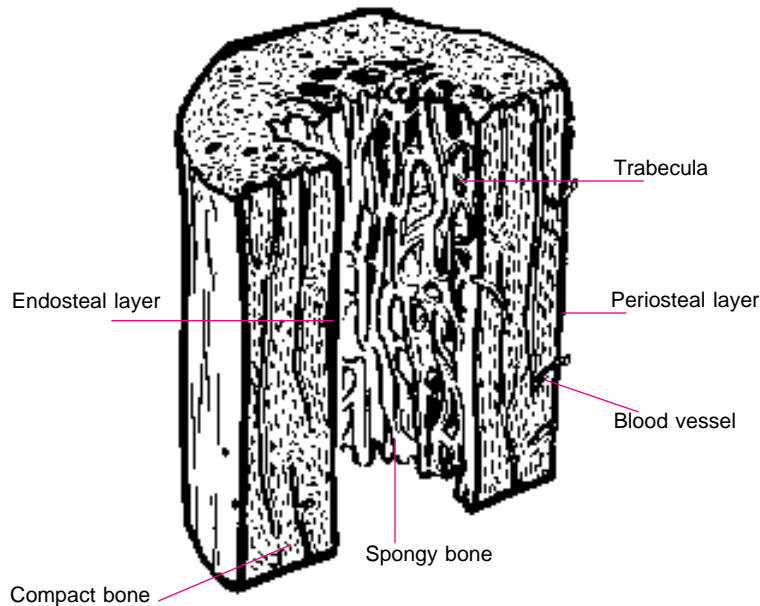


Figure 2. Spongy versus Compact Bone

This drawing shows a portion of a bone from which the marrow has been removed. Bone is composed of two kinds of tissue. One is dense in texture like ivory and is termed compact bone; the other consists of slender spicules, trabeculae, and lamellae joined into a spongy structure, which is called cancellous, or spongy, bone. The compact bone is always on the exterior of the bone, the spongy bone on the interior. The relative quantity of the two kinds of tissue varies in different bones and in different parts of the same bone, according to functional requirements (see *Gray's Anatomy*, page 282).

from cardiovascular disease. Of all the cases analyzed by this program and/or followed by the Los Alamos plutonium epidemiology studies, only one is thought to possibly have died from the effects of their plutonium exposure. That individual, a chemist at Los Alamos during the Manhattan Project, died in 1990 at age 66 of an osteosarcoma (bone cancer). The primary site of the cancer was the sacrum. Osteosarcomas of the sacrum are not common in man but have been observed in animals (beagle dogs) exposed to plutonium. Keep in mind, however, that this is a single case and must be evaluated cautiously. There seems to be scant hard evidence that exposure to plutonium and/or americium at the levels reported above has caused any significant life shortening or disease.

Quantitative results on plutonium deposition and distribution. The data obtained from deceased occupationally exposed workers by the tissue analysis program has been used in many ways. One of the primary objectives of this study was to measure quantitatively the total body burden, or deposition, of plutonium in a person so that models predicting this deposition from urine analyses could be validated and improved. This can be accomplished by

chemically measuring the plutonium content in the major deposition sites, that is, the lungs and associated lymph nodes, the liver, and the skeleton. These three organs contain about 90 per cent or more of the retained plutonium. Determining the lung, and liver content is straight forward, since these organs are easily obtained at autopsy and are small enough to be analyzed in total.

The skeletal content is much more difficult to determine, but is a critical measurement since about half of the systemic burden (internal to the body and exclusive of the lungs) is in the skeleton. Obviously, the entire skeleton is not easily obtained at autopsy. A rib, a vertebral wedge (a block of one to three vertebral bodies removed from within the body cavity), and the sternum were the bones most often removed by the pathologist for our study. That choice was dictated in part by aesthetics—removal of these specimens does not disfigure the body when it is prepared for a funeral and burial. In the early part of the study, the bone specimens were analyzed for plutonium, and the results were extrapolated to represent the whole skeleton under the assumption that plutonium is uniformly distributed in all bones. The average weight of the skeleton in a young (25 to 35 years old), caucasian male weighing 70 kilograms is 10 kilograms, or about 14 per cent of their body weight. The donors to our program were much older men in their sixth or seventh decades. In the current enrollment of the USTUR, 69 per cent of the donors are age 65 or older. (Eighty-five percent are older than age 55.) Body weight proportions change significantly with age. The assumption of a 10-kilogram skeleton, or even a skeletal weight based upon 14 per cent of the body weight, is therefore very uncertain.

An even more important complication in estimating the skeletal content of plutonium was the discovery that, unlike radium, which is distributed somewhat uniformly throughout the bone mineral,

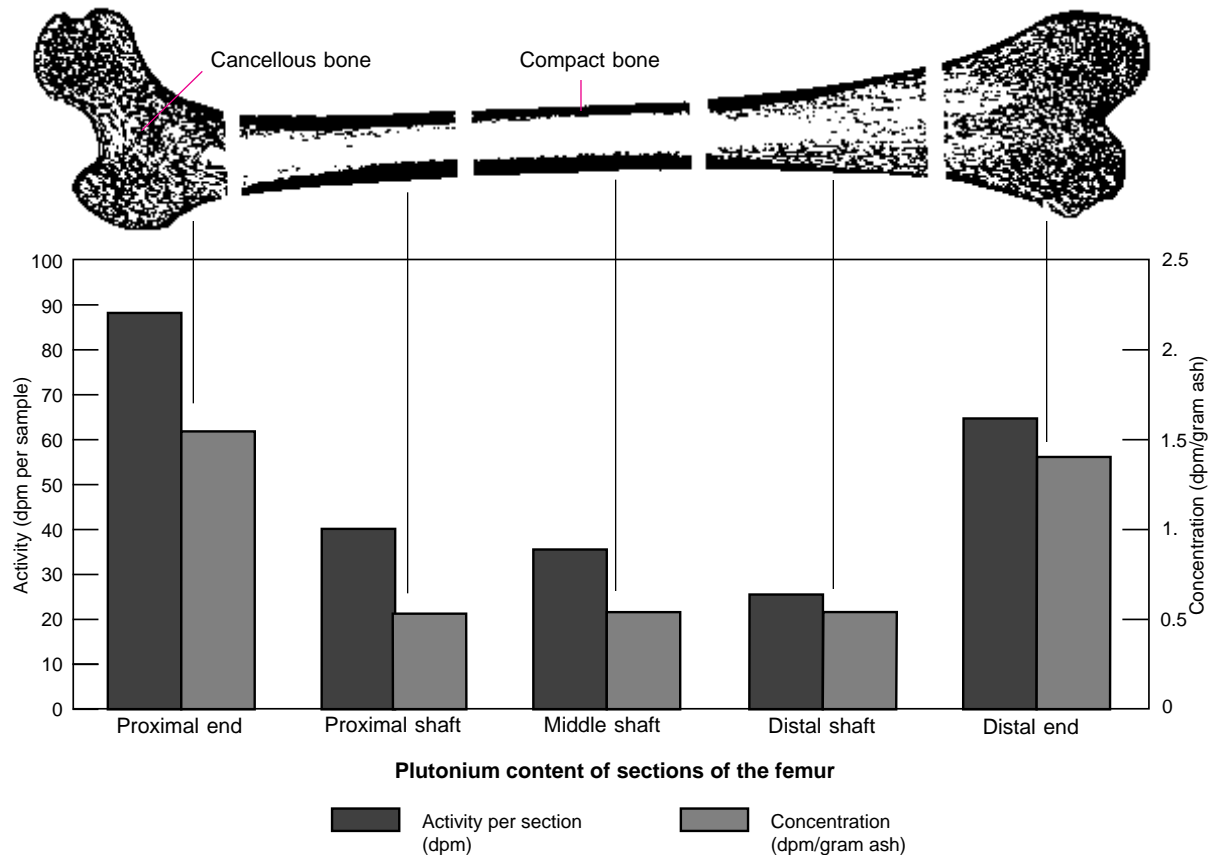


Figure 3. Deposition of Plutonium in a Thigh Bone

The bar chart shows the plutonium-239 content of different sections of a thigh bone (femur) in two ways, the total activity of each section and the concentration, or activity per gram. Plutonium deposits on the bone surface, and therefore, the concentration increases with the amount of surface area. Since the interior of the end sections of the femur contain spongy bone with a high degree of trabecularity and therefore a large surface area, the concentration of plutonium is higher at those ends.

plutonium is deposited on the bone surface. Autoradiographs made from animals given large injections of plutonium citrate demonstrate that phenomenon quite clearly. That means that the concentration of plutonium is greatest where there is a large amount of bone surface compared to bone volume.

Figure 2 shows that the bone is composed of two general types of structure: a very dense structure like ivory on the outside, termed "compact" bone; and a spongy structure on the inside consisting of slender spicules, trabeculae, and lamellae. The cavities of the bone are filled with bone marrow. Yellow marrow is found in the large cavities of the long bones. It consists, for the most part, of fat cells and a few primitive

blood cells. Red marrow is the site for the production of the red blood cells and the granular leukocytes. It is found in the spongy portions of the flat and short bones, the ends of the long bones, the ribs, sternum, and vertebral bodies.

The relative quantity of compact versus spongy bone varies among different bones, and in different parts of the same bone, according to functional requirements. Because plutonium deposits on the bone surfaces, and spongy bone has a high surface area, the distribution of plutonium within a bone is proportional to the distribution of the spongy bone. Figure 3, showing the distribution of plutonium in the large thigh bone called the femur, illustrates this very well. Most of the plutonium is located at the

two ends of the femur, which contain most of the spongy tissue.

Given this pattern of deposition, the primary carcinogenic risk from plutonium in the skeleton is associated with the hematopoietic stem cells (blood-forming cells) of the bone marrow, which fills the spongy structure, and osteoblasts (bone-forming cells) close to the bone surfaces. Plutonium in or near the bone marrow might lead to leukemia, whereas plutonium on the bone surface might lead to osteosarcoma.

Returning to the problem of estimating the amount deposited in the skeleton from the samples taken during autopsy, we note that the ribs, sternum, and vertebral bodies usually sampled at autop-

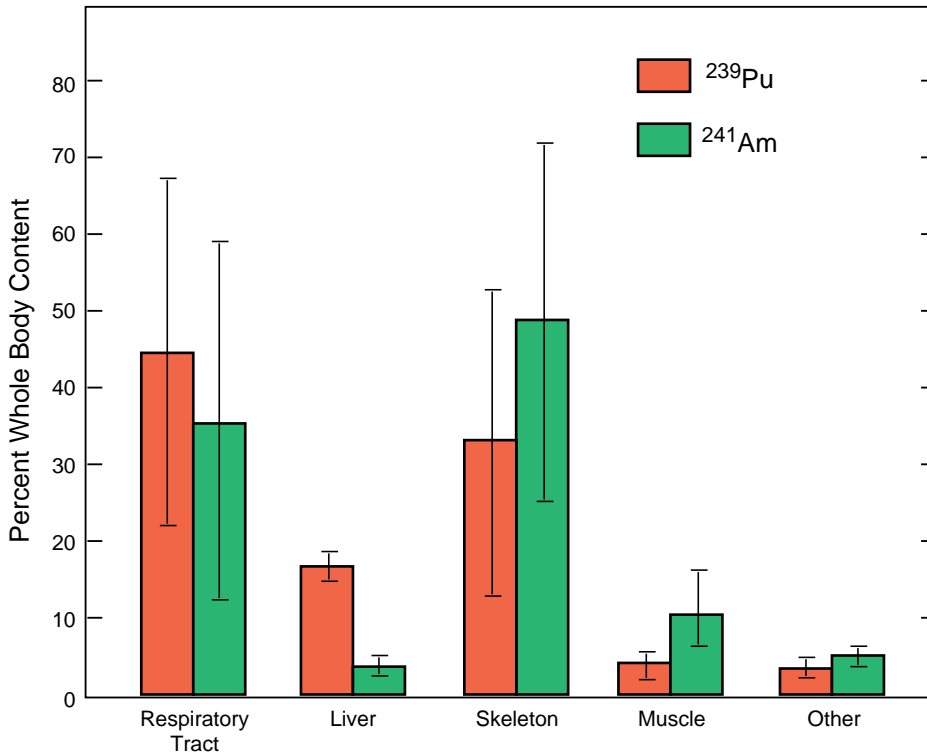


Figure 4. Whole-body Distribution of Plutonium and Americium

The bar chart shows the mean distributions of plutonium-239 and americium-241 in four whole bodies donated to the U.S. Transuranium Registry. All were exposed primarily by inhalation approximately 30 years prior to death. The error bars represent one standard deviation from the mean. The two elements differ most in the liver retention time (plutonium has a residence half-time of 20 years compared to 2 to 3 years for americium). Also the fraction of americium found in the skeleton and muscle is higher than that of plutonium. The large error bars are indicative of individual biological variation and possible variation in exposure parameters.

sy have relatively high proportions of spongy bone and therefore have a relatively higher concentration of plutonium than the entire skeleton. Therefore early estimates of skeletal content derived from analyses of those bone types could easily have overestimated the skeletal content if uniform distribution had been assumed.

Wisely, the USTUR instituted a whole-body donor program in 1979 so that the distribution of the actinides could be determined for the entire skeleton and also for the less frequently sampled soft tissues. As of October 1995, 47 individuals have since consented to become whole body donors. To date, 23 of those individuals have died. Twelve whole bodies have been analyzed in our

laboratory at Los Alamos for one or more of the following elements: plutonium, americium, uranium, and thorium. Six of the twelve analyzed had worked and received their exposures at Los Alamos. Twenty-four donors are still living, and ten bodies are awaiting analyses at the Registries' newly established laboratory at Washington State University in Pullman, WA. One body was not analyzed because the person tested positive for hepatitis-B at the time of death, and we did not want to expose our analysts to that deadly disease.

Detailed data from six whole bodies have been published. Figure 4 shows the relative distributions of plutonium and americium in four of the bodies.

For the inhalation cases, greater proportions of plutonium-239 and americium-241 are found in the respiratory tract than are predicted by the International Commission on Radiological Protection (ICRP publications 30 and 48). Early models based upon animal data had proposed a 500-day half-time for the retention of plutonium in the lungs. The data in Figure 4, derived from individuals who died approximately 30 years following their exposure, show very clearly that the half-time in the lungs of humans is much longer. Another finding is that americium is cleared much more rapidly from the liver than is plutonium, whereas early models used the same clearance time for both elements. The liver-clearance half-time for americium is two to three years whereas the liver-clearance half-time for plutonium is 20 years (ICRP publication 48). After long-term exposure, significant fractions of the systemic plutonium-239 and americium-241 are found in muscle and other soft tissue, which suggests that those tissues function as a long-term depot for those nuclides.

How do the body burdens measured from our radiochemical analyses of whole-bodies compare to the body burdens predicted by applying biokinetic models to excretion data? Table 1 presents a comparison that Ron Kathren and I published in 1991. Measurements of the systemic deposition (all organs except the lung) and the whole-body deposition of plutonium-239 in four whole bodies are shown in red. Also listed are 13 different theoretical estimates of the deposition. Each theoretical estimate was calculated by applying a different biokinetic model to the urinary excretion data obtained during the lives of those four individuals.

Table 1 shows that the plutonium burdens estimated from the older biokinetic models were many times greater than the measured values. The results of two models are within a factor of two of the tissue analysis results for all four

Table 1. Tissue Results on Whole Bodies Compared with Estimates of Biokinetic Models

Biokinetic Model	Date	Systemic Burden of Plutonium-239* (nanocuries)			
		Case 193	Case 208	Case 213	Case 242
Langham	1950	27.0	56.5	55.9	94.6
Healy	1956	23.2	40.0	43.0	80.0
Durbin	1972	13.0	30.5	61.1	47.8
Rundo et. al.	1976	3.0	10.0	5.9	15.1
Parkinson & Henley	1981	8.9	31.6	17.8	42.4
Leggett	1984	3.8	4.0	11.6	29.7
Jones	1985	5.7	11.9	8.1	20.0
Leggett & Eckerman	1987	4.9	8.4	6.8	11.6
Revised Langham per Legett & Eckerman	1987	3.2	5.9	8.1	16.2
PUQFUA		(7.3)	(15.5)	(13.5)	(23.3)
Tissue Analysis	1988	3.1	3.8	6.7	24.3
Tissue Analysis (whole body)		(6.6)	(6.1)	(8.2)	(75.7)

*Systemic burdens refer to the content of all organs excluding the lungs, whereas whole-body burdens include the lung content.

cases: the Langham power function model as modified by Leggett and Eckerman and the two component exponential model proposed in ICRP publications 19 and 30. In all four cases in Table 1, exposure was primarily by inhalation. Jim Lawrence's PUQFUA code is also a modification of the Langham equation and was used at Los Alamos for many years. The code estimated the whole-body deposition including the lung, and therefore, the PUQFUA results should be compared with the radiochemical estimate of whole-body contents shown in parentheses. Lawrence continuously used the tissue analysis estimates of plutonium deposition in deceased workers over the years to verify and improve his model.

One of the other new studies done on

the whole bodies was an investigation of the amount of plutonium in the bone marrow. Animal studies had shown that myeloid leukemia as well as osteosarcomas (bone cancer) can be induced in laboratory animals by plutonium in bone given appropriate exposure conditions. As a result, there was some concern that a high bone marrow concentration might increase the risk of leukemia above that calculated by the ICRP bone model.

We attempted to evaluate the leukemia risk from plutonium exposure in humans by separating the bone marrow from mineral bone. The separation was accomplished by washing the marrow out of the bone cavities with a jet of water and then measuring the plutonium in the bone-mineral and bone-marrow components. As expected,

most of the skeletal plutonium was associated with the mineralized bone. Concentrations of plutonium were more than ten times greater in the mineralized portions than in the organic fraction. Approximately 3 per cent of the total skeletal plutonium was estimated to be resident in the marrow, with the concentration in the red marrow several times greater than the concentration in the yellow marrow. Our result suggests that the radiation dose to the mineralized portion of the bone and to osteoblasts in the periosteal layers and endosteal layers of the bone (see Figure 2) may be an order of magnitude or more than the dose to the red marrow. The implication of these findings is that the risk of bone tumors is several times greater risk than the risk of leukemia.

General Population Studies

Origin and procedures. From the beginning in 1959 the tissue program included non-occupationally exposed individuals who died at the Los Alamos Medical Center. At first the collection and analysis of tissues from that general-population sample was meant to determine background levels for comparison with the levels found in plutonium workers. The community and the Laboratory were also interested in determining whether or not any plutonium had been released from the Laboratory and was causing internal exposure of people living in Los Alamos and near-by communities.

A more global concern was the impact of the more than 320 kilocuries (approximately 5,000 kilograms or 11,000 pounds) of plutonium-239 that had been distributed worldwide, mostly in the northern hemisphere, from atmospheric testing of nuclear weapons. Reliable data were not available on how much had been deposited and retained in tissues of the general population, nor whether there were significant differences in exposure depending on where a person lived. It was obvious even at the start of the tissue study that answering those questions would be a natural and important extension of the research effort if and when the opportunity arose.

The Los Alamos general population study expanded its borders somewhat accidentally when, in 1968, tissues from 36 individuals from New York City (unclaimed bodies) were sent to Los Alamos and, at the request of the AEC's Health and Safety Laboratory, analyzed for fallout plutonium. In 1970, the Colorado Department of Health wanted to evaluate the extent of off-site plutonium contamination that was suspected to have occurred as the result of a major fire in 1969 at the Rocky Flats plutonium processing and fabrication facility. They requested that



Figure 5. Geographic Distribution of General Population Study

The map shows the states of origin of the 1187 individuals from the general population from whom tissues were collected and analyzed over the course of the Los Alamos tissue analysis project. Major collection sites were near the DOE nuclear facilities at Los Alamos, the Rocky Flats Facility in Colorado, the Savannah River Facility, and the Hanford Facility in Washington State. Control populations were collected from areas not near nuclear facilities in Pennsylvania, Illinois, and New York. A few other individuals from other states died in one of the participating hospitals and were included in the sampling process.

Los Alamos analyze tissues from individuals living in the Denver-Boulder area. Local hospitals collected the tissues, which were then picked up and sent to Los Alamos by personnel from the Colorado Department of Health. Tissue collection from the Denver-Boulder area continued until 1985.

With the cooperation of the Medical Director at the plutonium production plant at Savannah River Plant, contact was made with local pathologists and tissues were collected, from 1972 to 1979, from the areas around Augusta, Georgia and Aiken, South Carolina to establish the background levels of environmental plutonium and evaluate the possible release of plutonium from the Savannah River Plant. Realizing the samples collected from the Los Alamos, Rocky Flats, and Savannah River areas may have been contaminated by local releases from these nuclear facilities, we sought control populations from areas far away from existing nuclear facilities. As a result, we added the Illinois-area residents to the study

in 1973 and the Pennsylvania-area in 1974.

Before setting up those programs, we investigated the legality of having pathologists send tissues to Los Alamos and found it to be within the limitations included in the autopsy consent form used by most hospitals. Although consent forms vary from hospital to hospital, they are all similar. In particular, the "Authorization for Autopsy" form published by the American Medical Association states in part, "I (we) authorize the removal and retention or use for diagnostic, scientific, or therapeutic purposes of such organs, tissues, and parts as such physicians and surgeons deem proper."^{*} This authority was granted subject to any special restrictions by the next of kin, but it generally provides for the release of tissues for a scientific study such as ours. With a few exceptions, individuals whose tissues were sent to us were not identified

^{*}Form 44 in "Medico-legal Forms with Legal Analysis" (American Medical Association, Chicago, Illinois, 1961).

Table 2. Results of Hypothesis Testing for Geographic Differences**1974-75**

Kidney	<u>PA</u>	<u>LA</u>	<u>CO</u>	<u>GA</u>	<u>NM</u>	
	(0.114)	(0.108)	(0.081)	(0.075)	(0.063)	
Liver	<u>LA</u>	<u>NM</u>	<u>GA</u>	<u>IL</u>	<u>PA</u>	<u>CO</u>
	(2.399)	(2.123)	(1.942)	(1.461)	(1.398)	(1.276)
Lung	<u>NM</u>	<u>LA</u>	<u>GA</u>	<u>CO</u>	<u>PA</u>	<u>IL</u>
	(0.535)	(0.447)	(0.316)	(0.301)	(0.271)	(0.104)
Lymph Node	<u>LA</u>	<u>NM</u>	<u>CO</u>	<u>PA</u>		
	(6.553)	(6.500)	(2.917)	(1.923)		
Rib	<u>LA</u>	<u>NM</u>	<u>PA</u>			
	(1.125)	(0.966)	(0.460)			
Vertebrae	<u>NM</u>	<u>CO</u>	<u>GA</u>	<u>PA</u>	<u>LA</u>	
	(0.673)	(0.631)	(0.400)	(0.363)	(0.213)	
Female Gonad	<u>CO</u>	<u>PA</u>	<u>LA</u>			
	(2.769)	(1.000)	(0.667)			
Male Gonad	<u>LA</u>	<u>PA</u>	<u>CO</u>	<u>NM</u>	<u>GA</u>	
	(0.568)	(0.319)	(0.063)	(0.053)	(0.042)	
Spleen	<u>LA</u>	<u>PA</u>	<u>GA</u>	<u>NM</u>	<u>CO</u>	
	(0.350)	(0.164)	(0.160)	(0.147)	(0.101)	
Thyroid	<u>LA</u>	<u>PA</u>	<u>CO</u>	<u>IL</u>	<u>NM</u>	<u>GA</u>
	(1.303)	(0.749)	(0.363)	(0.286)	(0.00)	(-0.194)

1967-68

Liver	<u>LA</u>	<u>NM</u>	<u>NY</u>
	(1.823)	(1.730)	(1.500)
Lung	<u>LA</u>	<u>NM</u>	<u>NY</u>
	(1.272)	(1.165)	(0.668)
Vertebrae	<u>NM</u>	<u>NY</u>	<u>LA</u>
	(4.557)	(1.539)	(0.769)

The table summarizes the results of statistical testing for geographic differences in the plutonium content of different tissues. The two-letter abbreviations stand for states, except for LA, which stands for Los Alamos. For each tissue listed, the distribution from those states underlined with the same line do not differ significantly. Median values in units of disintegrations per minute (dpm) per kilogram are given in parentheses. Even where statistically significant differences exist from one state to the next (in which case the states fall on two different lines), the differences in median are quite small, on the order of 1 dpm per kilogram of tissue, so that the measured differences probably have no practical consequence.

In the analysis, we tried to eliminate the dependence on age at death and year of death by considering only very short time segments, namely, the year of death, and subtracting out the age trends found during those time periods. The two time periods chosen (1974-75 and 1967-68) were selected because they included the major portion of the data and because they were the only periods where data was available from certain geographical locations. A Kruskal-Wallis non-parametric test of significance of among-region differences at the $\alpha = 0.05$ level was used. If this test indicated overall significance, Mann-Whitney tests were performed for all pairwise comparisons of the geographic regions (at the $\alpha = 0.05$ level). If the Kruskal-Wallis test was not significant, then all pairwise comparisons were declared not significant.

by name, only by hospital identification number or autopsy number. We believed that the standard autopsy clause was adequate to release tissues for our plutonium study, and we left it to the discretion of the pathologist or their representative to do whatever additional explaining to the next of kin they deemed necessary and appropriate. (That means we did not follow up to

determine if the next of kin were told specifically about our plutonium analyses of the donated tissues.) Pathologists were generally reimbursed a small amount (\$25 to \$100) to cover their cost of collecting the tissues, packaging each tissue individually, freezing them for storage, packing them in Dry Ice, and finally arranging to have them shipped to us. (We also paid the ship-

ping charges for sending the tissues to us by air freight).

Between 1959 to 1985 samples were collected in that manner from 1848 individuals in seven geographic areas throughout the United States. Figure 5 shows the number of individuals from whom we analyzed tissue for each of the 27 contributing states.

In 1978 Los Alamos was named the lead laboratory for analyzing tissues donated by occupationally exposed workers to the U.S. Transuranium and Uranium Registries. At that time our general population study had to be discontinued because of funding constraints. By then, one or more tissues had been analyzed from 1,254 of the individuals who had contributed autopsy specimens. Results from approximately 900 individuals (approximately 4,400 tissues) were reported in the open literature through three major reports. Unfortunately, in 1990, a freezer failure resulted in the loss of the unanalyzed tissues and they had to be destroyed by cremation.

What has been learned? Most importantly, the data showed that levels of plutonium in the U.S. general population are small and that populations living near major nuclear facilities did not have significantly higher plutonium levels than those living far from such facilities. The analyses also confirmed that major deposition sites of fallout plutonium were the respiratory tract, the liver and the skeleton. The measured deposition patterns and retention factors are critical for identifying the level of hazard to the general population.

The data also show that liver concentrations increase slightly with age and skeletal concentrations decrease. Evidently, as time passes a remobilization of the bone mineral releases plutonium from the skeleton, which then deposits in the liver.

No significant differences in tissue deposition of plutonium between males and females were evident.

The data were also examined for geographic differences (see Table 2). To eliminate any influence of the year of death, we examined tissues from individuals who died during a certain short time period and we subtracted out the age trends found in that time period. For the time span 1967-68, the data

showed no geographic differences in any of the tissue concentrations of plutonium. For the time span 1974-75, the data showed no regional differences in plutonium concentrations in the vertebrae, kidney, spleen, and female gonads, but, as shown, there were small regional differences in all other tissues (liver, lung, lymph node, rib, male gonad and thyroid).

How have the data been used? The 1981 report "Deposition and Retention of Plutonium in the United States General Population" evaluated the data as a function of time and compared the results with the predicted organ concentrations estimated using the ICRP lung model and the annual air concentrations of fallout plutonium measured by DOE's Environmental Measurements Laboratory in New York City (formerly AEC's Health and Safety Laboratory). According to the ICRP Publication 48, "The Metabolism of Plutonium and Related Elements," those data showed "reasonable agreement between computed and measured values for lung. Computed values for skeleton were about three times lower than measured values in vertebrae and rib. . . . The computed values for liver were also somewhat lower than the measured values. . . . The computed content of fallout plutonium-239 in lung-associated lymph nodes is an order of magnitude higher than the measured content. The half-time values used in the [ICRP] model were based upon data from beagles; monkeys, and rodents accumulated less plutonium than beagles in their lymph nodes, and are more consistent with human data. These findings emphasize the need for careful extrapolation of animal data to predict human metabolism."

Based to a large extent on the Los Alamos general population tissue study program (the ICRP referenced four major Los Alamos reports and one personal communication from me in their Publication 48), the ICRP has recommended changes in their lung model that reduce the retention parameters for

plutonium in lung and liver. In the general conclusions of the above reference, they stated "...there is considerable evidence to suggest that both the 40-year half-time for plutonium in liver and the 100-year half-time for plutonium in the skeleton recommended in ICRP Publication 19 (ICRP72) and employed in ICRP Publication 30 (Part 1), (ICRP79), are too long. Values of 20- and 50-years for retention times in liver and skeleton, respectively, now seem more reasonable." The ICRP report stated further: "The more recent information on the behavior of inhaled plutonium, or other actinide compounds, in animals, and on the behavior of inhaled particles in man [from the Los Alamos Tissue Study], is not always consistent with the assumptions of the ICRP Lung Model. These discrepancies are being considered by the Task Group on Respiratory Tract Models."

The ICRP further stated that "Since the appearance of ICRP Publication 19, much more information on the tissue contents and retention of plutonium and americium in humans has become available. Much additional information can be obtained from continuing the measurements of fall-out plutonium in autopsy material. . . ." ■

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James F. McInroy earned a M.Ed. in physical science from Pennsylvania State University in 1959. He taught chemistry and physics for ten years in the public school system in Pennsylvania and New York with an additional five years at Slippery Rock University, Slippery Rock, PA. McInroy earned a M.S. in 1969 and a Ph.D in 1973 from Colorado State University in health physics and radiobiology. His doctoral research involved evaluation of possible exposures to the general population via the food chain, should there be an accidental release of polonium-210 during the launch of satellites containing nuclear powered electronic sources (SNAP devices). McInroy joined the Health Research Division of the Laboratory as project leader in 1972 following funding by the Atomic Energy Commission of the human tissue analysis program and remained in that position until his retirement in 1993. From 1979 to 1984 he was deputy group leader of Health Division's Epidemiology Group. McInroy was instrumental in the organization and establishment of the International Conference on Low Level Measurements of Actinides and Long-Lived Radionuclides in Biological and Environmental Samples, and was Chairman of the Technical Planning Committee for their meetings in Sweden, Japan, India, and Brazil. He also played an instrumental role in the development of the National Bureau of Standards (now NIST) natural matrix reference materials containing metabolized actinide elements in human tissues (lungs, liver, and bone). McInroy has been a member of Sigma XI, the Health Physics Society, the Radiation Standards Committee of the Health Physics Society, and the Bioassay, Analytical and Environmental Chemistry Conference. McInroy became a member of the Human Studies Project in December 1993 and was responsible for making available all documents associated with the Human Tissue Study Project.

The Cecil Kelley Criticality Accident

On December 30, 1958, an accident occurred in the Los Alamos plutonium-processing facility, where plutonium was chemically separated, or “recovered,” from various compounds. In this facility, plutonium compounds were dissolved and mixed in a large tank with chemical reagents to concentrate and purify the plutonium. On the day of the accident, Cecil Kelley, an experienced chemical operator, was working with the large mixing tank. The solution in the tank was supposed to be “lean,” typically less than 0.1 grams of plutonium per liter, but the concentration on that day was actually 200 times higher. In fact, the tank contained enough plutonium (3.27 kilograms) in an upper layer of organic solvent to be very close to criticality—that is, capable of sustaining a chain reaction. When Kelley switched on the stirrer, the liquid in the tank formed a vortex, or whirlpool. The lower, aqueous layer was pushed outward and up the walls of the tank, as if forming a bowl; the upper, plutonium-containing layer flowed into the center of this “bowl,” which increased the thickness of the layer. In this new configuration, the plutonium went critical, releasing a huge burst of neutrons and gamma radiation in a pulse that lasted a mere 200 microseconds.

Kelley, who had been standing on a foot ladder peering into the tank through a viewing window, fell or was knocked to the floor. Confused and disoriented, he apparently turned the stirrer off and on again, then ran out of the building. The two other operators on duty at the time saw a bright flash of light, like that of a flash bulb, and heard a dull thud. Quickly, they rushed to help, and found Kelley outdoors. He was ataxic (lacking muscular coordination). All he could say to the operators was, “I’m burning up! I’m burning up!” Assuming he’d had a chemical accident, the

two operators led Kelley to a shower. One operator turned the stirrer off as they went by.

Within five or ten minutes, a nurse, supervisors, and radiation monitoring staff were all on the scene. Kelley was evidently in shock and virtually unconscious, but rather innocently, the nurse noted that Kelley had “a nice pink skin.” Because the nature of the accident was unknown at the time, it was not understood until later that Kelley’s pink skin was erythema (a redness of the skin, like that from a sunburn) caused by his radiation exposure.

The possibility of a criticality accident had been considered so remote that the radiation monitoring staff began their investigation by searching for plutonium in the work environment with alpha detectors. They found no widespread activity. It was only as Kelley was leaving in an ambulance, eighteen minutes after the accident, that the circumstances of his accident became clear. The monitoring staff had just begun gamma radiation measurements. When they saw the high level of gamma radiation in the vicinity of the large mixing tank (tens of rad per hour), the investigators quickly realized what had happened.

The symptoms Kelley displayed at the plutonium-processing facility, characterized by collapse and mental incapacitation, were the first stage of his clinical course (what is now known as the most severe form of acute radiation syndrome). The second stage began when he arrived in the emergency room of the Los Alamos Medical Center. It was dire. Kelley was semiconscious, retching, vomiting, and hyperventilating. His skin was cold and dusky reddish-violet, and his lips had a bluish color that indicated poorly oxygenated blood. He was immediately wrapped in blankets and

surrounded by hot water bottles. His blood pressure and pulse were at first unobtainable. He had shaking chills, and the uncontrolled movement of his extremities and torso necessitated restraint by the nursing staff. Kelley’s anxiety and restlessness were eased only by Demerol. After about ten minutes, the nurses were able to measure Kelley’s pulse (160 beats per minute) and his blood pressure (80/40). His body emitted a small but measureable amount of gamma rays, and his vomit and feces were sufficiently radioactive to give a positive reading on the detector.

One hour and forty minutes after the accident, Kelley entered the third stage, which was both the longest and most encouraging. Kelley regained coherence, and although he complained of severe abdominal cramps and occasionally retched and vomited, he seemed considerably improved overall. He was transferred from the emergency room to a private room, placed in a bed that was on “shock blocks,” and enclosed in an oxygen tent. Kelley’s first blood samples were drawn at this time. Because Kelley had been irradiated with neutrons, the sodium and other light metals in his blood were “activated,” or transformed into radioisotopes such as sodium-24. His average whole-body dose was first estimated by measuring the radioactivity of his blood. It appeared to have been massive—in the range of 900 rad from fast neutrons and 2,700 rad from gamma rays, giving a total of 3,600 rad—and certainly lethal.¹

Six hours after the accident, the lymphocytes virtually disappeared from Kelley’s peripheral circulation, which

¹ After his death, Kelley’s radiation dose was better estimated, again using biological indicators of the neutron dose and inferring the gamma dose. The results were somewhat greater than the estimate made during Kelley’s period at the hospital: 900 rad from fast neutrons and 3,000 to 4,000 rad from gamma rays, giving 3,900 to 4,900 rad.

The origin of the Los Alamos Human Tissue Analysis Program

was taken as a grave sign. Twenty-four hours after the accident, a sternal bone marrow biopsy was performed. The marrow appeared watery, rather than bloody, and no excessive bleeding occurred. The marrow was almost completely acellular, edematous, hemorrhagic fatty tissue. From that observation, along with the rapid onset of lymphopenia (depression of the lymphocytes in the bloodstream overall), it was clear that Kelley would not survive long.

During the second evening after the accident, Kelley entered the fourth stage. The pain in his abdomen became difficult to control. He became increasingly restless despite medication—so much so that the intravenous infusions were inadvertently interrupted. He began to sweat profusely, his color became ashen, and his pulse irregular. About 35 hours after the accident, Kelley died.

Kelley had spent about half of his 11.5 years at Los Alamos as a plutonium-processing operator (from 1946 to 1949 and, again, from 1955 through 1958). During that time, he underwent several minor exposures to plutonium, including regular exposure to moderate levels of airborne plutonium in various chemical forms. Therefore, his tragic death became an opportunity to determine certain factors crucial to the protection of workers. By analyzing the tissues of his body, researchers could determine Kelley's total plutonium body burden and compare it with the result obtained from periodic urine assays during his life. Furthermore, they could determine the distribution of the plutonium in Kelley's body. Because certain tissues are more sensitive to radioactivity than others, the distribution of the plutonium was important in determining the effective dose. That result could be applied broadly to other individuals who were exposed to plutonium largely by inhalation over a prolonged period.

Kelley's exposure record included 18 instances of high nose-swipe counts and 10 instances of minor exposures, such as being involved in the cleanup of a plutonium spill or getting a slight laceration. Urine assays taken during that period usually showed slight amounts of plutonium. Analysis of those assays indicated that Kelley's plutonium body burden was 19 nanocuries (see "The Human Plutonium Injection Experiments"). Kelley's records showed that all of his exposures occurred during his early plutonium work (1946-1949) and it was very likely that most of his plutonium burden was accumulated during this period from chronic inhalation exposure to low-level airborne plutonium.

Autopsy samples were taken from throughout Kelley's body to measure plutonium concentrations. (The accident itself, an exposure to neutrons and gamma rays, had no impact on the amount or distribution of plutonium in his body.) The tissue analysis showed that Kelley's total plutonium body burden was 18 nanocuries. This compared extremely well with the value of 19 nanocuries determined from urinalysis. Wright Langham stated that the above agreement "was so very satisfactory that it is undoubtedly fortuitous." In addition, it was found that about 50 per cent of the plutonium was in the liver, 36 per cent in the skeleton, 10 per cent in the lungs, and 3 per cent in the respiratory lymph nodes. Plutonium Injection Experiments in humans had shown a somewhat different distribution: 65 per cent in the skeleton and 22 per cent in the liver, for example, most likely the result of differences in the chemical and physical nature of the plutonium (the experiments used a soluble salt of plutonium whereas Kelley inhaled plutonium dust particles).

Another interesting factor in Kelley's analysis was that they were able to de-

termine relative timescales for the movement of plutonium through the body and within organs. This was possible because changes in plutonium production methods between Kelley's first and second stints as a plutonium worker had considerably increased the ratio of plutonium-238 to plutonium-239 in the material being handled. This fact, coupled with the record of nose counts and exposures, enabled them to distinguish the "early" plutonium from the "late" plutonium and, thus, to trace qualitatively the movement of plutonium from the lungs to other organs. They found that plutonium cleared relatively rapidly from the lungs compared with the clearance from the bone and lymph nodes. Much of the plutonium in the lungs migrated to the liver whereas only a small percentage migrated to the bone and lymph nodes. Finally, the rate of clearance from the lungs to the liver must be relatively fast and the retention time in the liver must be longer than in the lungs.

A memorandum written by Jean McClelland and Bill Moss, chemists in the Health Division, presented the results of Kelley's tissue analysis. Those results showed that plutonium was retained in the lungs and pulmonary lymph nodes much, much longer than contemporary models had predicted. Because this was unexpected, it was decided to collect tissues from other exposed individuals to confirm this phenomenon. They also stated that tissues from non-occupationally exposed individuals would be collected as controls. Thus, the Los Alamos tissue analysis program was begun. ■

Further Readings

T. L. Shipman, C. C. Lushbaugh, D. F. Petersen, W. H. Langham, P. S. Harris, and J. N. P. Lawrence. 1961. Acute radiation death resulting from an accidental nuclear critical excursion. *Journal of Occupational Medicine: Special Supplement*. (March 1961): 145-192.

The Karen Silkwood Story

Karen Silkwood died on November 13, 1974 in a fatal one-car crash. Since then, her story has achieved worldwide fame as the subject of many books, magazine and newspaper articles, and even a major motion picture. Silkwood was a chemical technician at the Kerr-McGee's plutonium fuels production plant in Crescent, Oklahoma, and a member of the Oil, Chemical, and Atomic Workers' Union. She was also an activist who was critical of plant safety. During the week prior to her death, Silkwood was reportedly gathering evidence for the Union to support her claim that Kerr-McGee was negligent in maintaining plant safety, and at the same time, was involved in a number of unexplained exposures to plutonium. The circumstances of her death have been the subject of great speculation.

After her death, organs from Silkwood's body were analysed as part of the Los Alamos Tissue Analysis Program. Silkwood's case was important to the program because it was one of very few cases involving recent exposure to plutonium. It also served to confirm the contemporary techniques for the measurement of plutonium body burdens and lung burdens.

After her death, organs from Silkwood's body were analysed as part of the Los Alamos Tissue Analysis Program at the request of the Atomic Energy Commission (AEC) and the Oklahoma City Medical Examiner. Silkwood's case was important to the program because it was one of very few cases involving recent exposure to plutonium. It also served to confirm the contemporary techniques for the measurement of plutonium body burdens and lung burdens. The following account is a summary of Silkwood's exposure to plutonium at the Kerr-McGee plant and the subsequent analysis of her tissues at Los Alamos.

In the evening of November 5, plutonium-239 was found on Karen Silkwood's hands. Silkwood had been working in a glovebox in the metallography laboratory where she was grinding and polishing plutonium pellets that would be used in fuel rods. At 6:30 P.M., she decided to monitor herself for alpha activity with the detector that was mounted on the glove box. The right side of her body read 20,000 disintegrations per minute, or about 9 nanocuries,¹ mostly on the right sleeve and shoulder of her coveralls. She was taken to the plant's Health Physics Office where she was given a test called a "nasal swipe." This test measures a person's exposure to airborne plutonium, but might also measure plutonium that got on the person's nose from their hands. The swipe showed an activity of 160 disintegrations per minute, a modest positive result.

The two gloves in the glovebox Silkwood had been using were replaced. Strangely, the gloves were found to have plutonium on the "outside" surfaces that were in contact with Silkwood's hands; no leaks were found in the gloves. No plutonium was found on the surfaces in the room where she had been working and filter papers from the two air monitors in the room showed that there was no significant plutonium in the air. By 9:00 P.M., Silkwood's cleanup had been completed, and as a precautionary measure, Silkwood was put on a program in which her total urine and feces were collected for five days for plutonium measurements. She returned to the laboratory and worked until 1:10 A.M., but did no further work in the glove boxes. As she left the plant, she monitored herself and found nothing.

Silkwood arrived at work at 7:30 A.M. on November 6. She examined metallographic prints and performed paperwork for one hour, then monitored herself as she left the laboratory to attend a meeting. Although she had not worked at the glovebox that morning, the detector registered alpha activity on her hands. Health

¹ 1 nanocurie = 2,220 disintegrations per minute

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physics staff members found further activity on her right forearm and the right side of her neck and face, and proceeded to decontaminate her. At her request, a technician checked her locker and automobile with an alpha detector, but no activity was found.

On November 7, Silkwood reported to the Health Physics Office at about 7:50 in the morning with her bioassay kit containing four urine samples and one fecal sample. A nasal swipe was taken and significant levels of alpha activity were detected (about 45,000 disintegrations per minute (dpm) in each nostril and 40,000 dpm on and around her nose). This was especially surprising because her left nostril had been almost completely blocked since a childhood accident. Other parts of her body also showed significant alpha activity (1,000 to 4,000 dpm on her hands, arm, chest, neck, and right ear). A preliminary examination of her bioassay samples showed *extremely* high levels of activity (30,000 to 40,000 counts per minute in the fecal sample). Her locker and automobile were checked again, and essentially no alpha activity was found.

Following her cleanup, the Kerr-McGee health physicists accompanied her to her apartment, which she shared with another laboratory analyst, Sherri Ellis. The apartment was surveyed. Significant levels of activity were found in the bathroom and kitchen, and lower levels of activity were found in other rooms. In the bathroom, 100,000 dpm were found on the toilet seat, 40,000 dpm on the floor mat, and 20,000 dpm on the floor. In the kitchen, they found 400,000 dpm on a package of bologna and cheese in the refrigerator, 20,000 dpm on the cabinet top, 20,000 dpm on the floor, 25,000 dpm on the stove sides, and 6,000 dpm on a package of chicken. In the bedroom, between 500 and 1000 dpm were detected on the pillow cases and between 500 and 2,000 dpm on the bed sheets. However, the AEC estimated that the total amount of plutonium in Silkwood's apartment was no more than 300 micrograms. No plutonium was found outside the apartment. Ellis was found to have two areas of low level activity on her, so Silkwood and Ellis returned to the plant where Ellis was cleaned up.

When asked how the alpha activity got into her apartment, Silkwood said that when she produced a urine sample that morning, she had spilled some of the urine. She wiped off the container and the bathroom floor with tissue and disposed of the tissue in the commode. Furthermore, she had taken a package of bologna from the refrigerator, intending to make a sandwich for her lunch, but then carried the bologna into the bathroom and laid it on the closed toilet seat. She remembered that she had part of her lunch from November 5 in the refrigerator at work and decided not to make the sandwich, so she returned the bologna to the refrigerator. Between October 22 and November 6, high levels of activity had been found in four of the urine samples that Silkwood had collected at home (33,000 to 1,600,000 dpm), whereas those that were collected at the Kerr-McGee plant or Los Alamos contained very small amounts of plutonium if any at all.

The amount of plutonium at Silkwood's apartment raised concern. Therefore, Kerr-McGee arranged for Silkwood, Ellis, and Silkwood's boyfriend, Drew Stephens, who had spent time at their apartment, to go to Los Alamos for testing. On Monday, November 11, the trio met with Dr. George Voelz, the leader of the Laboratory Health Division. He explained that all of their urine and feces would

Dr. Voelz reassured Silkwood that, based upon his experience with workers that had much larger amounts of plutonium in their bodies, she should not be concerned about developing cancer or dying from radiation poisoning. Silkwood wondered whether the plutonium would affect her ability to have children or cause her children to be deformed. Dr. Voelz reassured her that she could have normal children.

be collected and that several whole body and lung counts would be taken. They would also be monitored for external activity.

The next day, Dr. Voelz informed Ellis and Stephens that their tests showed a small but insignificant amount of plutonium in their bodies. Silkwood, on the other hand, had 0.34 nanocuries of americium-241 (a gamma-emitting daughter of plutonium-241) in her lungs. Based on the amount of americium, Dr. Voelz estimated that Silkwood had about 6 or 7 nanocuries of plutonium-239 in her lungs, or less than half the maximum permissible lung burden (16 nanocuries) for workers. Dr. Voelz reassured Silkwood that, based upon his experience with workers that had much larger amounts of plutonium in their bodies, she should not be concerned about developing cancer or dying from radiation poisoning. Silkwood wondered whether the plutonium would affect her ability to have children or cause her children to be deformed. Dr. Voelz reassured her that she could have normal children.

At the request of the AEC and the Oklahoma State Medical Examiner, Dr. A. Jay Chapman, who was concerned about performing an autopsy on someone reportedly contaminated with plutonium, a team from Los Alamos was sent to make radiation measurements and assist in the autopsy.

Silkwood, Ellis, and Stephens returned to the Oklahoma City on November 12. Silkwood and Ellis reported for work the next day, but they were restricted from further radiation work. After work that night, Silkwood went to a union meeting in Crescent, Oklahoma. At the end of the meeting, at about 7 P.M., she left alone in her car. At 8:05, the Oklahoma State Highway Patrol was notified of a single car accident 7 miles south of Crescent. The driver, Karen Silkwood, was dead at the scene from multiple injuries. An Oklahoma State Trooper who investigated the accident reported that Silkwood's death was the result of a classic, one-car, sleeping-driver accident. Later, blood tests performed as part of the autopsy showed that Silkwood had 0.35 milligram of methaqualone (Quaalude) per 100 milliliters of blood at the time of her death. That amount is almost twice the recommended dosage for inducing drowsiness. About 50 milligrams of undissolved methaqualone remained in her stomach.

At the request of the AEC and the Oklahoma State Medical Examiner, Dr. A. Jay Chapman, who was concerned about performing an autopsy on someone reportedly contaminated with plutonium, a team from Los Alamos was sent to make radiation measurements and assist in the autopsy. Dr. Voelz, Dr. Michael Stewart, Alan Valentine, and James Lawrence comprised the team. Because Silkwood's death was an accident, the coroner did not legally need consent from the next of kin to perform the autopsy. However, Silkwood's father was contacted, and he gave permission for the autopsy over the telephone. The autopsy was performed November 14, 1974, at the University Hospital in Oklahoma City, Oklahoma.

Appropriate specimens were collected, preserved, and retained by Dr. Chapman for his pathological and toxicological examination. At the request of the coroner and the AEC, certain organs and bone specimens were removed, packaged, frozen, and brought back to Los Alamos for analysis of their plutonium content. Because Silkwood had been exposed to plutonium and had undergone *in vivo* plutonium measurements, her tissue was also used in the Los Alamos Tissue Analysis Program to determine her actual plutonium body burden, the distribution of the plutonium between different organs of her body, and the distribution within her lung. On November 15, small samples of the liver, lung, stomach, gastrointestinal tract, and bone were selected and analysed. The data, shown in Table 1, indicated clearly that there were 3.2 nanocuries in the liver, 4.5 nanocuries in the lungs, and a little more than 7.7 nanocuries in her whole body. These measurements agreed well with the *in vivo* measurements made before Silkwood's death (6 or 7 nanocuries in the lung and a little more than 7 nanocuries in the whole body).

There was no significant deposition of plutonium in any other tissues, including the skeleton. The highest concentrations measured were in the contents of the gastrointestinal tract (0.05 nanocurie/gram in the duodenum and 0.02 nanocurie/gram in a small fecal sample taken from the large intestine). This demonstrated that she had ingested plutonium prior to her death.

With the exception of the left lung, the remaining unanalyzed tissues were repackaged and kept frozen until it was determined whether or not additional analyses were required. The left lung was thawed, inflated with dry nitrogen until it was approximately the size that it would have been in the chest, and re-frozen in that configuration. It was packed in an insulated shipping container in dry ice and sent to the lung counting facility at the Los Alamos Health Research Laboratory. The data were then compared with the *in vivo* measurements made prior to her death. As expected, without the ribs and associated muscle attenuating the x rays from the americium-241, the results for the left lung measured postmortem were about 50 per cent higher, but not inconsistent with the *in vivo* result.

Some of the most interesting observations made during Silkwood's tissue analysis were: 1) the distribution of plutonium-239 within her lung and 2) the concentration of plutonium in the lung relative to that in the tracheobronchial lymph nodes (TBLN). After the frozen left lung was returned to the Tissue

Analysis Laboratory, the superior lobe was divided horizontally into sections. Those sections were further divided into two parts: the outer layer of the lung (pleura and sub-pleural tissue) and the inner soft tissue of the lung (parenchyma). The plutonium concentrations in the inner and outer parts of Silkwood's lung were about equal, in stark contrast with another case examined under the Tissue Analysis Program in which the concentration in the outer part of the lung was 22.5 times higher than that in the inner part. That difference was an indication that Silkwood had probably been exposed within 30 days prior to her death, whereas the other case had been exposed years prior to death. Furthermore, the concentration of plutonium in Silkwood's lung was about 6 times greater than that in the lymph nodes, whereas in typical cases that ratio would be about 0.1. Both of those results indicated that Silkwood had received very recent exposure and supported the view that the plutonium tends to migrate from the inner part to the outer part of the lung and to the lymph nodes over time.

The saga of Karen Silkwood continued for years after her death. Her estate filed a civil suit against Kerr-McGee for alleged inadequate health and safety program that led to Silkwood's exposure. The first trial ended in 1979, with the jury awarding the estate of Silkwood \$10.5 million for personal injury and punitive damages. This was reversed later by the Federal Court of Appeals, Denver, Colorado, which awarded \$5000 for the personal property she lost during the cleanup of her apartment. In 1986, twelve years after Silkwood's death, the suit was headed for retrial when it was finally settled out of court for \$1.3 million. The Kerr-McGee nuclear fuels plant closed in 1975. ■

Table 1. Amounts of Plutonium-239 in the Organs of Silkwood

Organ	Plutonium-239 (nanocuries)	Concentrations (picocuries/gram)
lung (whole)	4.5	4.6
parenchyma	4.5	4.6
pleura	0.01	0.004
liver	3.2	2.4
lymph nodes (TBLN)	0.02	0.80
bone	~ 0	~ 0