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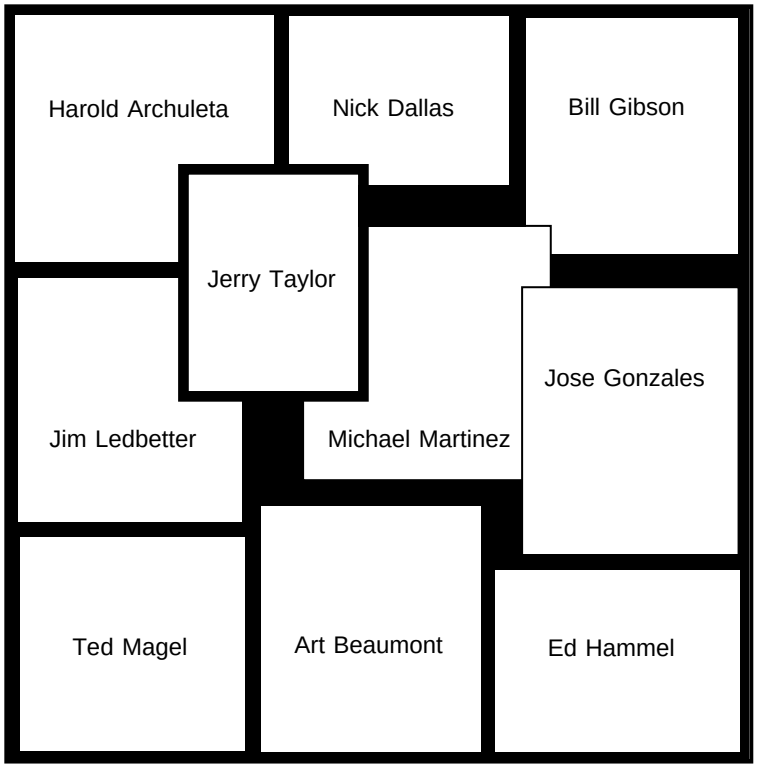
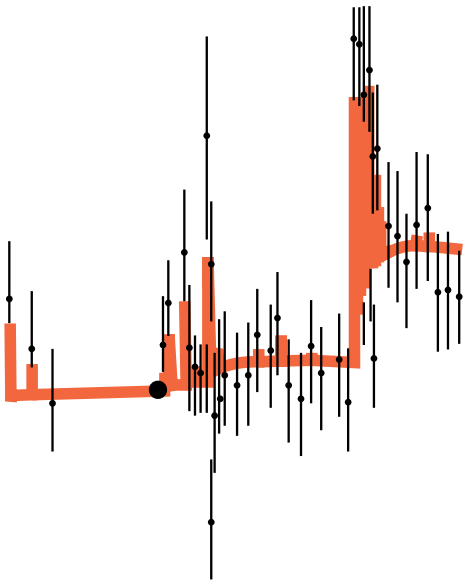
Radiation Protection and the Human Radiation Experiments





On the cover are the images of ten men who have worked with plutonium and now carry measurable body burdens of this radioactive element. Some of those individuals were at Los Alamos during the days of the Manhattan Project, and some of them are here today. In this volume on radiation protection and the human radiation experiments, these men share their experiences with plutonium, the stories of their accidents, and their perspectives on the human plutonium injection experiments. We thank them for their generosity. No doubt their stories will help others who come into similar circumstances.

As much as the plutonium injection experiments were flawed from an ethical standpoint, they did provide the bulk of the data that are now used to estimate the seriousness of an accidental intake of plutonium. Those data relate the amount of plutonium excreted in the urine to the amount retained in the body. The graph (above right) shows data points for the amount of plutonium in the urine versus time for one individual. The fit to that data made using the maximum-entropy method is shown in red. Fifty-year committed doses in rem are calculated from the urine results using biokinetic models of the time-dependent distribution of plutonium in the body. Those models are based on data gathered from the plutonium injectees as well as from the tissues of deceased plutonium workers.

Because plutonium is an ongoing responsibility of this Laboratory, the protection of those who handle that dangerous material is also our ongoing responsibility. This volume is dedicated to openness and to the proper handling of our role in plutonium work.

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Radiation Protection and the Human Radiation Experiments

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Comments from

It is with pleasure that I introduce this volume of *Los Alamos Science*. The volume culminates a two-year effort by our Laboratory's Human Studies Project Team. The team was formed to address questions concerning the ethics and conduct of human radiation experiments that were carried out by Los Alamos researchers from the Manhattan Project days through the 1960s. The credibility and forthrightness of the team's effort has a very special meaning in the context of today's mission and tomorrow's challenges. This Laboratory continues to be the steward of nuclear weapons technology. As the world tries to roll back the number of nuclear weapons and reduce their impact on the community of nations, it is our job to help make that possible by maintaining a credible nuclear weapons technology base in the absence of testing and by developing the specific technologies needed to safeguard nuclear materials and retire them permanently. Working with plutonium and other radioactive materials while limiting radiation exposures thus remains at the heart of our mission just as it was during the Manhattan Project. Concurrently, maintaining public trust regarding environmental, health, and safety issues has become ever more important to the success of our mission. The Human Studies Project Team's review of past work on radiation protection and the human experiments as well as their examination of the current state of knowledge regarding radiation and risk are presented in this volume and represent a major effort by our Laboratory toward achieving public trust through the sharing of experiences and information.

The need for the team became evident in late 1993, when our credibility and integrity were put in question by the widespread publicity regarding the plutonium injection experiments and other human radiation experiments. Challenged by Department of Energy Secretary Hazel O'Leary's openness initiative and encouraged by Dr. Tara O'Toole, the DOE Assistant Secretary for Environment, Safety, and Health, we decided to try to turn the negativity that gripped the media, the public, and many of the Laboratory's employees into a positive force. In my editorial of January 28, 1994, I encouraged all employees to keep open minds because I was certain that the Laboratory and the nation would gain perspective from a thorough review of both the science and the ethics of the human radiation experiments.

Our initial responsibility was to participate in the Department of Energy's openness initiative by gathering information for the agency and for President Clinton's Advisory Committee on Human Radiation Experiments. To that end the Human Studies Project Team, sponsored by the Laboratory's Environment, Safety, and Health Division, was charged with combing the archives and other sources for anything and everything related to human radiation experiments. The team includ-

the Director

Siegfried S. Hecker

ed scientists, physicians, lawyers, ethicists, archivists, and others, some from the Laboratory, some from local universities, and a few representatives from state government. At the beginning there was tension between the retiree experts on the team, who had participated in the radioactive tracer studies done at Los Alamos during the 1950s and were outraged that their mentors Wright Langham and Louis Hempelmann were being maligned by the public, and the younger generation on the team, who had less reverence for the past. But everyone wanted the truth to surface and the team soon became a smoothly functioning body. The documents that were found were reviewed on a weekly basis, decisions were made about removing material that was confidential under the privacy act, and the material was released to the public. That process continued for over 15 months until the entire team was satisfied that all existing documents had come to light. Over 500,000 pages of historical documents were reviewed, and the relevant ones were released with no editing and no editorial comment. It was for the public and President Clinton's Advisory Committee to decide the value and judge the ethics of what had been done. In total, the team released over 1,600 documents. The members also responded to hundreds of specific requests for information from the President's Advisory Committee and from individuals who were concerned about their own exposures. All in all it was an extraordinary accomplishment.

However, there remains a second ongoing job. It concerns our own evaluation of what happened in the past and our efforts to learn from that past. This volume, written by members of Human Studies Project Team in collaboration with the *Los Alamos Science* staff, is dedicated to educating ourselves and the public about radiation, about the human experiments, and about the real consequences of exposure to plutonium. It's also dedicated to saying things as they are. Some of the facts about the plutonium injection experiments are difficult to accept, especially for those of us who take pride in the accomplishments of our Laboratory. We know in retrospect that hospitalized patients were injected with plutonium, and there is no documented evidence that any of them fully comprehended what was being done to them. Most of the eighteen subjects received five micrograms of plutonium, a tracer amount, but nevertheless five times greater than the limit set for workers in the Manhattan Project immediately following the results from the first three injectees and about ten times the amount that we allow today. In general, the health of the injected patients was not followed after the main study was complete even though it was apparent from the experiments that most of the plutonium would remain in their bodies for the rest of their lives. Also, even after the subject of plutonium became declassified, the injectees were apparently never told what was done to them even though a few were called back so additional plutonium excretion data could be gathered. That is not a pretty picture. The President's Advisory Committee came to the conclusion that the injectees and their families had been ethically wronged. We don't believe there are many among us who would disagree with that conclusion, and certainly today, those experiments could not and would not be done in that manner.

But there are mitigating facts. The pressure to gather data for interpreting the results of accidental intakes of plutonium was enormous and immediate. The choice

of the five-microgram injection dose was not an arbitrary one; it was at the limit of detection for the analytical techniques then available. Before the experiments were done, careful work with animals had shown that the injected dose would not be acutely toxic. Also the risk of delayed effects, in particular cancer, were expected to be quite small: The experiences, for example, of the radium-dial painters (many of whom had ingested large quantities of radium, another alpha-emitting radioactive element like plutonium) had shown that only when very large internal doses of radium were present would bone cancers be induced. Thus the researchers at Los Alamos who planned and analyzed the experiments at Oak Ridge and the University of Rochester did not expect the injectees to suffer from their intakes although they admitted to some uncertainty. Fortunately, there is no evidence that plutonium caused harm to any of the patients.

That's an important finding. The press often wrongly states that the tiniest amount of plutonium can kill you. To the contrary, we know from our own plutonium workers that individuals carrying accidental intakes comparable to the amount given to the injectees have lived healthy, vital, and productive lives, some for over 50 years from the time of intake. As part of the effort to educate ourselves, and especially for this volume, the Human Studies Project Team sponsored an informal workshop with ten of those folks and some of our experts in health physics. "On the Front Lines" presents the rather remarkable stories and comments that were shared at the workshop. What may not come across in the telling is the talent and ability of those individuals—many are said to have "golden hands"—and we, and our nation, owe them a debt of gratitude for their skill, their courage, and their dedication in handling very difficult work in the safest and most expeditious fashion. We also hope that their stories will increase our awareness and our respect for each other and for the jobs that we do.

At the end of the workshop, some of the Laboratory experts summarized the safety record in the area of plutonium work as well as the present understanding of the dangers of plutonium exposure. As far as we know, among the thousands of indiviuals who have worked with plutonium, there are only about 50 people in the United States who have plutonium body burdens greater than the maximum permissible level. Of those, there is only one case in which plutonium may have been implicated in the cause of death. That death involved a bone sarcoma in the sacrum, an unusual place to get bone cancer but an area that tends to concentrate plutonium. The exposure records are admittedly incomplete. Nevertheless, it appears that the worker protection standards and the adherence to them have served us well. Remarkably, those standards and the means to implement them were and still are based on the information gathered from the early plutonium injection studies. Those data are used both to calibrate the techniques for monitoring workers and to interpret the amount of accidental intake so that an individual can be taken off the job before the internal body burden becomes dangerous. The article entitled "The Human Plutonium Injection Experiments" presents a definitive review of the motivations, implementation, aftermath, and scientific impact of those experiments. The set of raw data gathered from the injectees, although a rather meager set, constitutes the main source of information on plutonium metabolism in humans. Because it is so important, it has been analyzed and re-analyzed over the years. The article reviews that work and then presents a brand new analysis performed by one of the authors. The new analysis puts to rest many of the ambiguities that have plagued the interpretation of the original data and is yet another accomplishment to emerge from the Human Studies Project.

"Tracer Studies at Los Alamos and the Birth of Nuclear Medicine" adds another

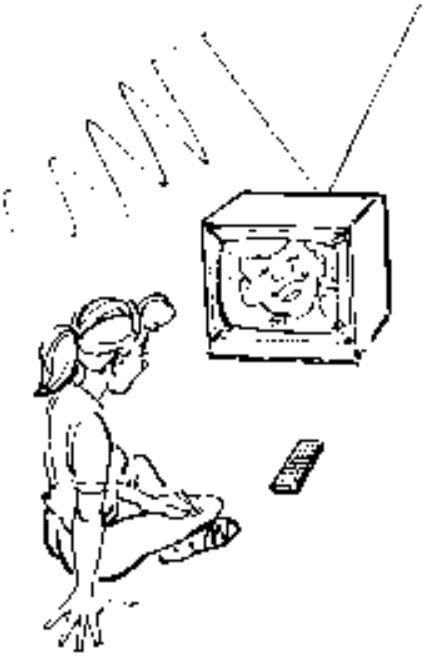
dimension to this story—one for which we can be very proud. The doses involved in the tracer studies were extremely small, the volunteers were appropriately informed, and the studies were important both for radiation protection and nuclear medicine. A most exciting spinoff from the radiotracer work was the invention of a new type of radiation detector made from a liquid scintillator. The device was developed in Wright Langham's Radiobiology Group for the detection of low-energy beta particles from tritium so that the metabolism of tritium in the body could be studied. But word got out, and Fred Reines and Clyde Cowan, Jr., then at our Laboratory, came to the Radiobiology Group for help in designing and building a very large liquid-scintillation detector for neutrinos. Naturally, they got the help they needed from the very talented scientists whom Langham had recruited, and the resulting detector was used to make the first observation of the neutrino. Fred Reines was awarded the 1995 Nobel Prize in Physics for that discovery. In a totally different vein, that large detector became the forerunner of the whole-body counter for *in vivo* monitoring of radioactive fallout from nuclear testing.

This volume is filled with history. It also surveys our present understanding of radiation and the risks associated with radiation exposure. When the story of the human radiation experiments reached the media in the fall of 1993, all kinds of numbers were being quoted to describe the events—picocuries of radioactive iron, 100-millirem doses of iodine-131, microgram quantities of plutonium. Only the experts knew what those numbers meant, and everyone else was baffled. Were those numbers big or small? What radiation exposures are considered acceptable, and how are they measured? What are the known risks from radiation exposures, and how do they depend on the level of exposure? Perhaps the most valuable contribution of the present volume is a three-part primer summarizing what we know about radiation and risk. The first part, "Ionizing Radiation—It's Everywhere!," introduces the physical properties of radiation in a way that should be engaging even to young students and describes various sources of natural background radiation, of which many of us are mostly unaware. The second part, "Radiation, Cell Cycle, and Cancer," presents the latest knowledge regarding the molecular mechanisms of cancer, the mechanisms of radiation-induced cancer, and the body's natural molecular and cellular defenses against radiation damage and cancer induction. That area of research is evolving very rapidly, and the story researched and written especially for this volume has not been told anywhere else at the same level of accessibility. The last part of the primer is a review of all the epidemiological data on radiation effects in humans. The article is entitled "Radiation and Risk—A Hard Look at the Data," and it is just that. We see data for the Japanese atomic-bomb survivors that form the basis for estimating the risk of radiation-induced cancer, we learn the hypothetical risks derived by extrapolating the high-dose risk factors to low doses, and we learn about the epidemiological data that have been gathered at low doses. The data are clearly presented so that anyone can make their own judgement about what is known and where the uncertainties lie concerning the effects of low-level exposures. We hope this volume will take its place on the shelf beside two important reports on the human radiation experiments: the Department of Energy's "Roadmap to the Story and the Records" and the "Final Report" of the President's Advisory Committee on Human Radiation Experiments.

Tara O'Toole helped us to get on this path. Despite considerable discomfort, the Human Studies Project Team took on the task of assessing the science and the ethics of the human radiation experiments. Their openness and commitment can serve as an example for all of us in the Laboratory and elsewhere. It is now up to us to continue. ■

It's Everywhere!

Roger Eckhardt

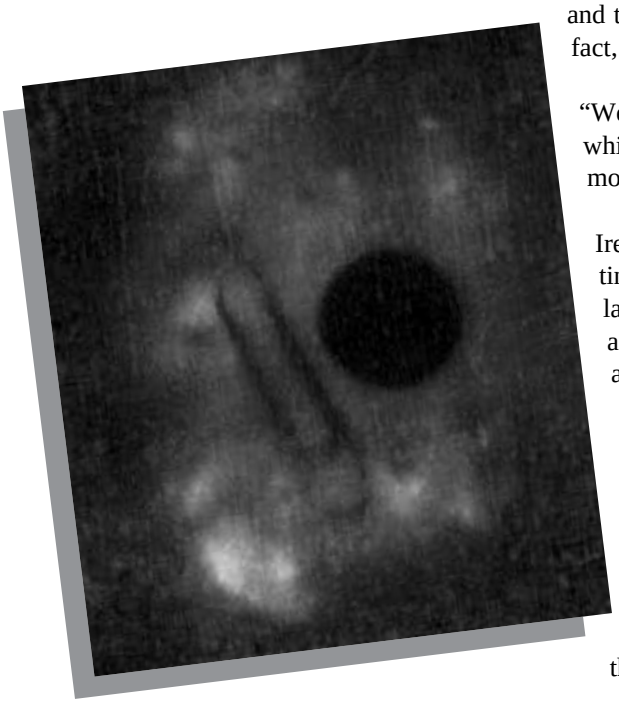


We are surrounded and permeated by radiation—sunlight, radio and television waves, medical x rays, infrared radiation, and the vibrant colors of the rainbow, to name a few. Sunlight drives the wind and ocean currents and sustains life. Radio and television broadcasts inform and entertain us. X rays produce the images needed for medical diagnosis. Infrared radiation warms us and radiates back into space not only the energy brought to the Earth by sunlight but also the entropy produced by life and other processes on Earth. All societies, from the most primitive to the most technological, depend on these various fluxes of natural and artificial radiation.

The dictionary defines radiation as "the emission and propagation of waves or particles," or as "the propagating waves or particles themselves, such as light, sound, radiant heat, or the particles emitted by radioactivity." Such definitions neglect one of the most important characteristics of radiation, its energy. Ultimately, the energy carried by radiation is what makes it so useful to life and civilization.

Because much of the radiation we encounter has relatively low energy, its effect on our bodies is benign. For example, radio waves pass through us with no perceptible effects to our health. However, for many people, the word radiation has a negative connotation—it's linked strongly with danger to life. This association comes from focusing on the so-called nuclear radiations, which are highly energetic, and especially on those generated by the radioactive materials of nuclear weapons and nuclear power plants. It's not always remembered that similarly energetic radiation is generated within the x-ray tubes at hospitals and at particle accelerators in physics laboratories. These radiations are used for medical diagnostics and as a primary therapy for the treatment of cancer. They are thus responsible for helping save many lives every year. The dual nature of energetic radiation, as both a killing and a healing agent, is sometimes difficult to keep in mind.

In this article, we'll attempt to sort through much of the confusion about radiation. We'll use two radiation experts, Irene and Carl, to introduce many of the topics, and they'll illustrate some of the ideas with imaginary experiments. In fact, here are Carl and Irene now. "What are you two up to?" you ask.



"We're repeating Becquerel's experiment with uranium minerals in which he discovered radioactivity," Carl answers. "Except we're using modern film—high-speed Polaroid™."

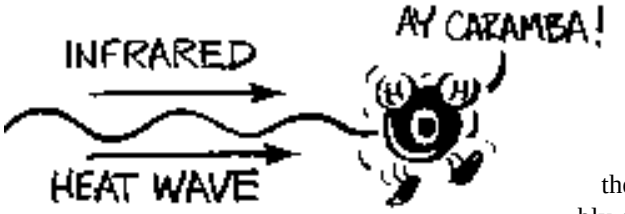
Irene removes the film from under the uranium ore, where it's been sitting overnight, and pulls it through a roller to develop it. A minute later, we see the "picture"—a fuzzy white area with about the same diameter as the lump of ore. There's a blurry outline of a paper clip and a dark, round circle in the middle.

"It worked!" exclaims Carl. "The radiation from the uranium passed into the film except where it was partly blocked by the metal paper clip and the nickel we'd put between the lump of ore and the film."

"Do you know where the radiation is coming from?" asks Irene.

"From atomic nuclei!" Carl answers before you can reply. "From the tiny centers of lots of the uranium atoms."

Radiation emitted by radioactive materials is born deep within atoms—in unstable nuclei undergoing changes that involve strong nuclear forces. As a result, the radiation has very high energies, thousands or millions of times higher than radiation produced by typical atomic processes. Such energetic radiation can create many thousands of ions and molecular fragments by tearing loose electrons from neutral atoms or molecules. Hence, the name, ionizing radiation. In Carl and Irene's experiment, ionizing damage to the film emulsion created the "exposure."



When ionizing radiation traverses living cells, it leaves behind a trail of ions and uncharged molecular fragments, called free radicals, which are highly reactive and can damage other molecules in the vicinity. Such damage disrupts cellular mechanisms and can lead to the death of cells. If the exposure is very high, it will destroy the cells of the immune system and lead to illness and possibly death by infection. Even more massive exposures kill cells in the central nervous system and can cause death within hours or days.

At the lower exposures typically encountered by radiation workers or the general public, the body is able to replace the dead cells with new ones without degradation of bodily functions. The potential danger at those lower levels is mutation, which is damage to the DNA molecules, the genetic material of the cell. Usually the damage is kept to a minimum through DNA repair mechanisms or self-checks that direct the cell to die. However, if the mutation has occurred in the regulatory genes, the cell may survive the self-checks and develop the runaway growth we know as cancer. Finally, a mutation may occur in a germ cell and be passed on to future generations, but the probability of a successful passage is so small that the inheritance of such mutations has not been observed in human populations.

Because of the very specific effects of ionizing radiation, it's helpful to split the subject of radiation into two broad categories—ionizing and non-ionizing. In both cases, the radiation interacts with matter by transferring its energy to molecules and atoms, thrusting them into excited states. However, ionizing radiation breaks chemical bonds; non-ionizing radiation usually only heats the molecules—a more benign process.

In addition to being either ionizing or non-ionizing, radiation has other properties that we should know about. For example, most of the radiation we encounter in everyday life, such as visible light and radio waves, consists of electromagnetic waves traveling at the speed of light. Other radiation consists of massive particles with a variety of masses, charges, and energies. We need to be clear about these differences if a whole range of misunderstandings is to be avoided.

The Electron Volt and Ion Pairs

One of the most important defining characteristics of radiation is energy, so we need a convenient measure of energy to facilitate comparisons. For ionizing radiation, a common unit is the electron volt—the kinetic energy a free electron acquires when it's accelerated across an electric potential of one volt. (If you're familiar with mks units, an electron volt is 1.60×10^{-19} joules.)

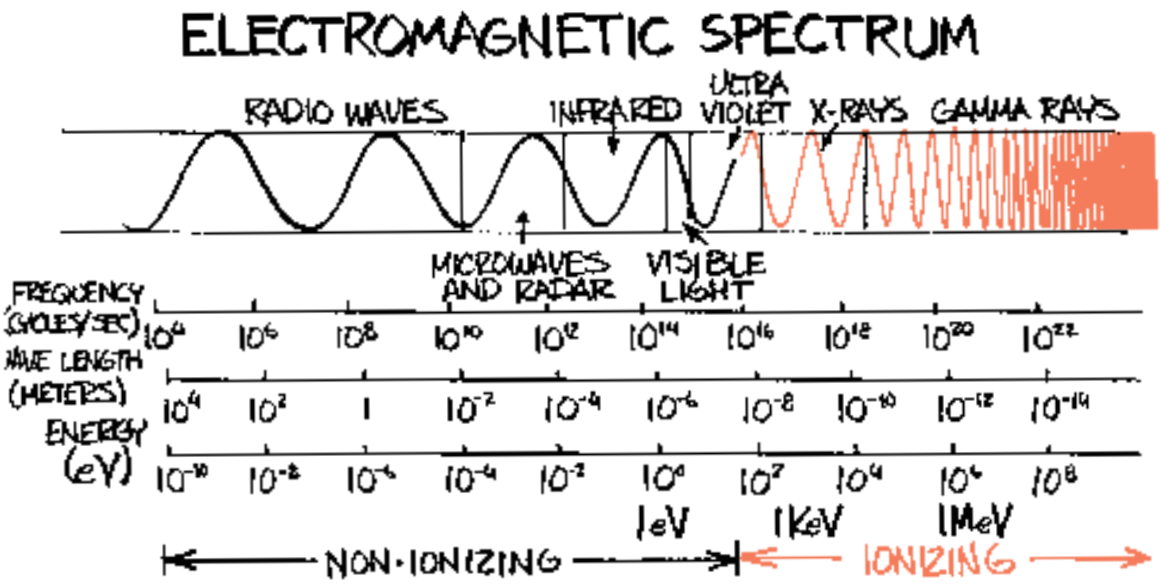
When ionizing radiation ejects an electron from a neutral molecule, a fragment with a plus charge is left behind and the electron with its negative charge speeds off, eventually to add its charge to another molecule. The two charged entities are called an *ion pair*. On the average, it takes about 25 electron volts (25 eV) to create an ion pair in water, although the minimum energy needed is only 12.6 eV. Thus, the electron volt is a very appropriate unit of energy for ionizing radiation.

Visible light has energies of the order of only an electron volt, and so it is non-ionizing. On the other hand, the radiation emitted by radioactive materials has energies of the order of thousands of electron volts (keV, or kilo-electron volts) or millions of electron volts (MeV, or mega-electron volts). Such radiation is capable of generating thousands of ion pairs.

As you can see, the term "radiation" encompasses a variety of emissions, all of which carry energy. The main purpose of this article is to discuss the ionizing radiations emitted by radioactive materials and to explain the physical properties that determine their effects on the body. We'll also explain how radiation doses are calculated, and then survey the ordinary sources that we're all exposed to. Finally, you'll find a guide to help you estimate your own annual dose. But before we tackle ionizing radiation, we'll begin with the more familiar, lower-energy radiations and gradually move to those of higher energies.

Electromagnetic Radiation

The most illuminating of radiation—light!—is a tiny portion of what's called the *electromagnetic spectrum*. The rest of this spectrum consists of a broad range of similar, but invisible, radiations—from radio waves through infrared and ultraviolet to gamma radiation. All these radiations are waves of fluctuating electric and magnetic fields that travel through space at the speed of light and that can be classified solely in terms of a single parameter, such as the frequency of the wave or its wavelength. The arrangement of the different types of electromagnetic radiation along a frequency (or wavelength or energy) scale is called the electromagnetic spectrum.

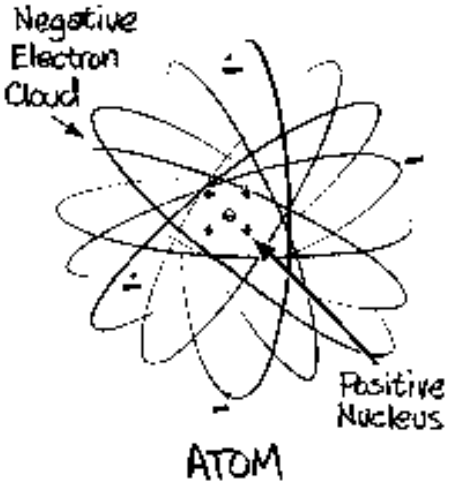


Einstein established that light actually has a dual nature—it behaves both as an electromagnetic wave and as particles, or *quanta*, called photons. The wave particle-duality is captured in the equation:

$$E = h\nu,$$

where E is the quantum energy of the photon, ν is the frequency of the corresponding wave, and h is called Planck's constant. Because energy is directly proportional to frequency, the electromagnetic spectrum becomes a visual guide to the relative quantum energies of the various types of electromagnetic radiation. The energy per photon can be anywhere between zero and infinity. In terms of our unit of energy, the electron volt (eV), some examples are 10^{-10} eV for a photon in the AM broadcast band, 2 eV for a photon of visible light, and on the order of MeVs for a nuclear gamma-ray photon.

Non-Ionizing Radiation. What happens when electromagnetic radiation interacts with matter? It can be absorbed, reflected, or transmitted—usually a combination of all three. The extent of these interactions depends on the type of material and the frequency of the radiation. For example, glass is transparent to visible frequencies; these photons mainly pass through unaffected, although some are reflected at the surface and a few are absorbed or scattered. On the other hand, glass absorbs ultraviolet wavelengths heavily so that very few of these higher-energy photons penetrate appreciable thicknesses of glass.



What causes such behavior? The wave nature of light helps explain many features of the interaction between electromagnetic radiation and matter. Atoms are made up of a tiny, inner nucleus that's heavy and positively charged and an extended, outer cloud of very light, negatively charged electrons. The total charge of the electrons is exactly the negative of the charge on the nucleus, so the atom as a whole is uncharged. However, the electrons are in constant motion and create fluctuations in the electric charge and localized currents. The electric and magnetic fields of the radiation can interact with these fluctuations and transfer energy to the atom. If the electromagnetic waves happen to be oscillating in resonance with the atom, that is, if their frequency is close to a natural frequency of the atom, they'll transfer energy more efficiently. We see the same thing pushing a child on a swing—you transfer energy most efficiently if you match the natural rhythm of the swing.

Wavelength, Frequency, or Energy?

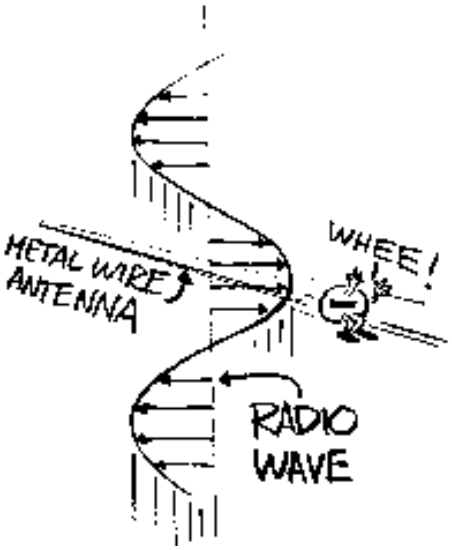
In vacuum, all electromagnetic radiation travels at the speed of light. As a result, there is a one-to-one relationship between the frequency and the wavelength of the electromagnetic waves:

$$\lambda\nu = c,$$

where λ is the wavelength of the oscillation, ν is the frequency, and c is the speed of light ($c = 3.0 \times 10^8$ meters per second).

The choice of parameter characterizing electromagnetic radiation can, thus, as easily be wavelength as frequency. In fact, because radio waves have wavelengths of the order of meters and microwaves have wavelengths of the order of millimeters (milli = 10^{-3}), these radiations are often identified with their wavelengths rather than their frequencies. Similarly, visible light may be characterized by its wavelength, generally in nanometers (nano = 10^{-9}).

At the upper end of the spectrum, very short wavelengths and very high frequencies make both frequency and wavelength cumbersome. It's easier to identify the radiation with the quantum energy of its photons.



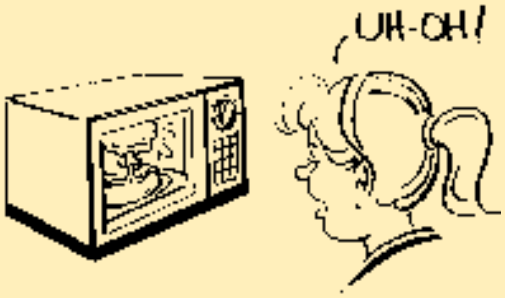
This wave description of radiation is useful for explaining a variety of macroscopic interactions between radiation and matter. For example, waves can help us understand how a metal antenna picks up a radio broadcast. Some of the electrons in metals move easily—after all, metals are good conductors—and the electrons oscillate with the incoming radio waves. The resulting current flow through the radio is detected, amplified, and finally converted by the speaker into the sounds we hear.

What about the dual nature of light? What does it mean for a photon, which is a particle, to be in resonance with an atom or molecule? Electrons bound in an atom or molecule occupy a set of discrete energy levels, which means they can't have energies in between the allowed levels. When a photon collides with the atom or molecule, it can be absorbed if its quantum energy matches the energy difference needed to excite an electron from one level to a higher one. If the photon energy doesn't match any of the energy transitions and is not high enough to cause ionization, then the photon will continue through the material unimpeded.

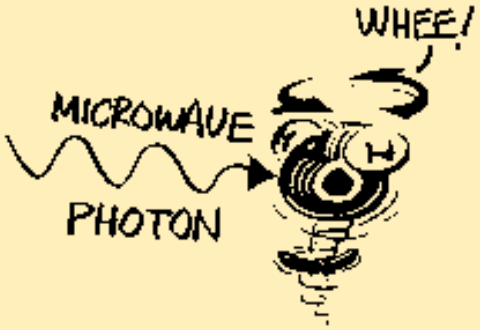
The frequency dependence of the interaction of photons with matter is responsible for a variety of things. For example, microwave ovens operate at a frequency chosen to be in resonance with an energy transition of the water molecule. Thus, microwave energy is effectively absorbed by most foods. If the radiation were "out of sync," it would simply pass through without losing intensity or heating the food. Certain regions of the spectrum are absorbed by the atmosphere, whereas other regions penetrate to the surface of the earth. The sky is blue because blue light is more effectively scattered out of the direct path from the sun than other colors. Plants appear green because chlorophyll selectively absorbs in the red and blue portions of the spectrum, leaving the green light to be scattered. The energy of the absorbed light is used by the plant in photosynthesis, thereby converting electromagnetic energy to stored chemical energy.

Some Health Effects of Common Radiations

Characterizing radiation by the quantum energy it carries can help make its potential effects less mysterious. We'll illustrate with examples of common forms of electromagnetic radiation.



Much of the public is apprehensive about the harmful effects of microwaves. In fact, many people say "Let's nuke it!" when they put food in the microwave. Although colorful and expressive, the phrase is misleading because the energy of microwave photons (about 0.001 eV) is even lower than those of infrared heat radiation or visible light. Thus, microwaves are non-ionizing and have nothing to do with the radiation of nuclear weapons. The occasional explosion of hot-dogs in a microwave oven from trapped steam may have something to do with the genesis of the phrase.



The real danger of microwave radiation lies in its efficient heating of tissue. The frequencies generated by microwave ovens match the rotational frequencies of water molecules, spinning them up like little tops. Because water is the most common substance in cells, the microwave energy is quickly absorbed and converted to heat energy as spinning molecules collide randomly with their neighbors. Possible health effects of direct exposure to microwave radiation range from "cooking" of tissue to changes in cardiac rhythm, damage to nervous systems, and cataracts. Microwave ovens are generally well shielded, and proper use results in minimal exposures. However, each of us should take mental note of the real dangers when we "nuke" our next meal.

Most people are much better informed about ultraviolet radiation (3 to 124 eV). The widespread use of sun block to prevent skin cancer is a rational response to the danger of the damaging effects of ultraviolet radiation. Such protection is even more important now that there's evidence of a thinning ozone layer in the upper atmosphere. The ozone layer serves as "nature's sun block," absorbing much of the ultraviolet radiation before it reaches the surface of the Earth.

The public's concern about the number and extent of medical x-ray exposures is also well-founded. X rays are of higher energy (tenths to hundreds of keV) than ultraviolet, and are definitely ionizing. They quite readily penetrate soft tissue, which is made mostly of light atoms, but are absorbed more efficiently by material containing heavier elements, such as the calcium in bone or most metals. This property makes x rays useful for examining the human skeleton or luggage in airports. There is also more absorption in denser soft tissue, making x rays useful for detecting tumors and tuberculosis. The danger, of course, is the possibility that the ionizing properties of the x rays can damage the exposed cellular material.

The health dangers of x rays are very real and well documented. Early scientists in the field quickly seized on obvious clinical and scientific applications of x rays but only gradually understood the full health implications of x-ray exposures. Researchers were carried away by the excitement of what the rays could reveal and frequently ignored warning signs from high exposures, including loss of hair, inflammation, and skin burns. Although these visible effects were usually only temporary, the massive ionization damage of frequent exposures overwhelmed normal cellular repair mechanisms. The long-term effects of the practice were numerous cases of cancer and radiation-induced diseases among the researchers. Several hundred people died before safety practices became prevalent.

These early experiences taught us that the more frequent and intense the exposures, the higher the probability of lasting damage. Also, cells undergoing rapid growth—such as those in the fetus—are more susceptible to permanent damage. Modern guidelines for the safe use of x rays stress the lowest practical dose per exposure, exposures administered infrequently and only when needed, and avoidance of exposures for pregnant women. Damage under such circumstances is minimal and usually is repaired easily by the cells. Our society has decided that, in most cases, the benefits from such use of ionizing radiation outweigh the hazards. (See the next two articles, "Radiation and Risk" and "Radiation, The Cell Cycle, and Cancer," for detailed discussions of the risks and biological effects of ionizing radiation.) ■

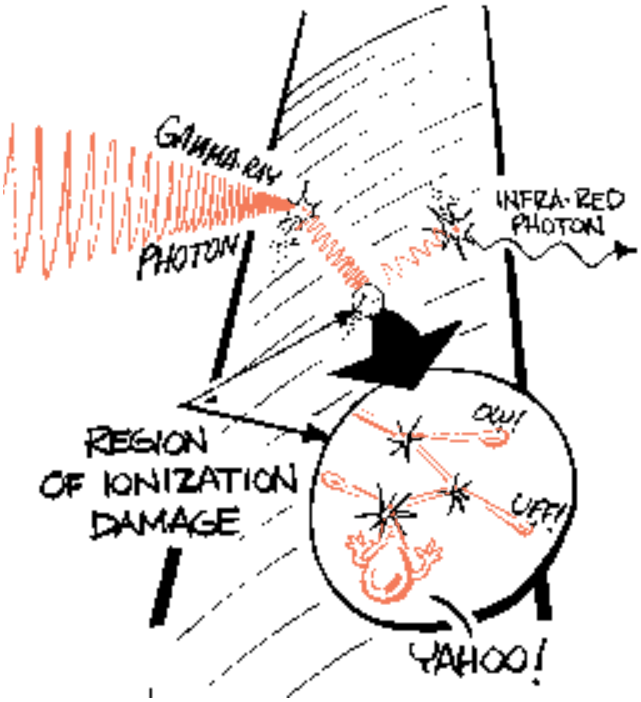
Ionizing Radiation. "But now," you ask, "where in the spectrum does electromagnetic radiation first become ionizing?"

"Well, the dividing point is a bit fuzzy, but we can use what we know about the spectrum to sort it out," Carl suggests.

As we move up the frequency scale, we reach a point at which the energy per photon is sufficient to break molecular bonds—a few electron volts. Ultraviolet light of this energy is responsible for skin aging and cancers, for example. Farther up the scale near 10 eV, an ultraviolet photon has enough energy to eject an electron from a molecule and leave behind a positively charged ion. It takes an energy of at least 12 eV to ionize water or oxygen molecules, or 15 eV to ionize nitrogen. Thus, radio waves, microwaves, infra-red radiation, visible light, and low-energy ultraviolet light are all non-ionizing. High-energy ultraviolet, x-rays, and gamma-rays and beyond are ionizing.

At photon energies of thousands of electron volts (kilovolts, or keV) and higher, the ejected electron itself may have enough kinetic energy to damage molecular bonds along its track by colliding and knocking free additional electrons. When this happens, a *region* of ionization damage is created, not just a single ion pair.

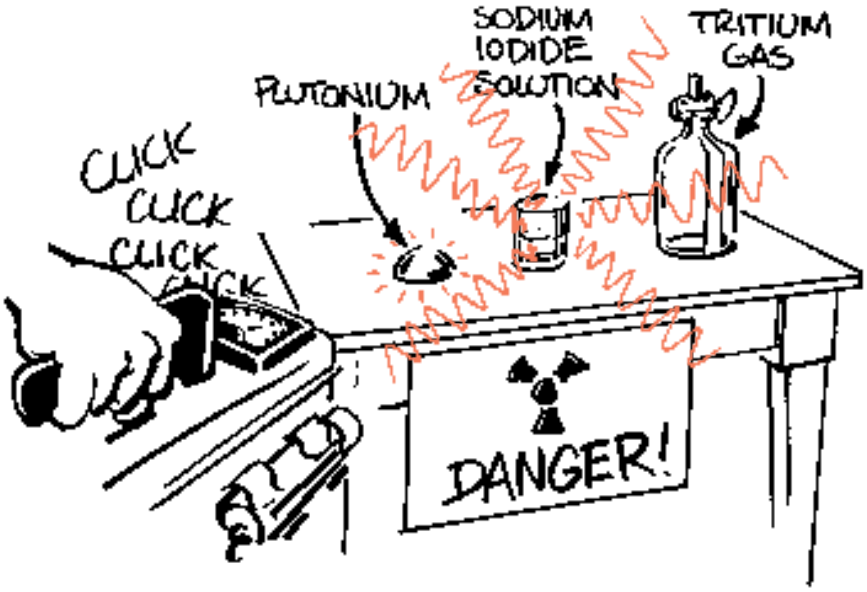
What happens to the photon in this process? When the photon has just enough energy to eject an electron, it's almost always completely absorbed. At higher quantum energies, such as the hundreds of eVs for x-rays, the photon is more likely to lose only part of its energy to the ejected electron and then continue on as a lower-energy photon until it collides again. Each such collision creates another region of ionization until either the photon passes out of the material of interest or approaches the threshold energy, ejects one last electron, and is completely absorbed. Because usually not all the energy of the photon is lost in a single scattering, the pattern of energy deposition is more complicated than for non-ionizing radiation. The number of unscattered photons drops off exponentially (as for non-ionizing radiation), but because the photons continue with reduced energy, energy deposition by ionizing photons must be treated as an exponential drop-off times a "build up factor," which, typically, has a value of one to ten.



What is the source of the high quantum energy of ionizing radiation? At the turn of the century, when Becquerel discovered that uranium ores were radioactive—that they emitted ionizing radiation in the absence of any external energy source—this question was the great mystery. How could radioactive materials, such as uranium and radium, continually emit quantities of energetic radiation with no apparent diminishment? Why didn't they "burn up?" Was radioactivity a violation of the conservation of energy? Well, as we'll see, they do in fact burn up. Becquerel just happened to be dealing with materials that took such a long time to do so that he could not detect the gradual decrease in radiation being emitted by the source.

Radioactivity—What Is It?

Now, imagine yourself in a room with your new friend and radiation expert, Irene. Also, imagine very relaxed safety standards. The two of you are standing next to a table that holds a round lump of silver-gray metal, a small beaker of colorless solution, and a large, clear glass bottle closed at the top with a valve. The only thing that alerts you to the fact that these are not ordinary materials is the standard magenta and yellow trefoil symbol for radiation.



Irene tells you that the metal is plutonium, a heavy, radioactive element and one of the last in the periodic table. More specifically, Irene says the metal is called plutonium-239—the same kind used to power two of the first three nuclear explosions in 1945—the one at Trinity Site and the Nagasaki bomb.

Next, Irene explains that the glass jar contains a special form of hydrogen, called tritium, or hydrogen-3. Hydrogen is a colorless gas, and a very light element—in

Plutonium Metal

Plutonium is a soft, silvery metal that's highly reactive. It oxidizes so easily that a fine powder of the pure metal will burn in air spontaneously. Such high chemical reactivity is one of the reasons plutonium is difficult to work with.

In real life, the lump of plutonium you're looking at would probably have been coated with something, perhaps a thin layer of platinum-rhodium alloy. This coating would seal out oxygen and allow you to handle the plutonium without getting radioactive particles of the metal on your skin. The coating would also absorb most of the radiation.

fact, it's the first, or lightest element. The tritium form of hydrogen is radioactive and is one of the important ingredients of the hydrogen bomb.

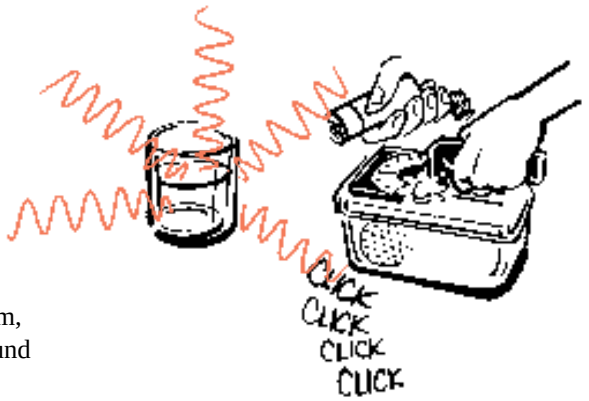
The liquid in the beaker is a dilute solution of sodium iodide. In this case, the iodine, called iodine-131, is radioactive. This type of iodine can be used for thyroid treatments. It's also of concern as a radiation hazard in nuclear power plant accidents or with fallout from atmospheric weapons testing.

Irene apologizes about the glassware—for safety purposes, she should be using unbreakable metal containers. You remind her that this is only a thought experiment, so it doesn't matter. She grumbles anyway, figuring she'll have to fill out a sheaf of imaginary safety report forms later.

Now, what physical evidence is there that these radioactive elements are emitting continuous streams of highly energetic ionizing radiation? Is there anything that you can see, hear, smell, or feel? After much inspection, you find no evidence. Then you pick up the plutonium—it's warm! This warmth is the only thing that seems unusual, but when you feel the jar of tritium and the beaker of solution, they're at room temperature.

Irene brings out a radiation detector, which immediately starts flashing and clicking, demonstrating that ionizing radiation is present. Presumably, the radiation has been present all this time, and the only hint was the warmth of the plutonium.

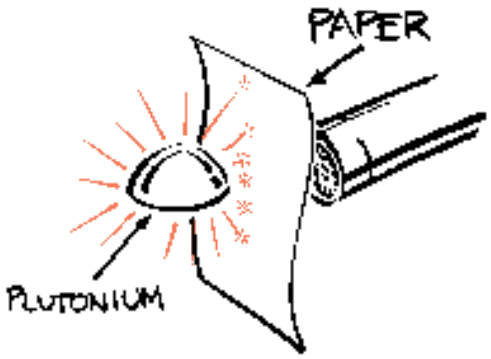
The invisibility of ionizing radiation is one of the reasons people fear it so much. You cannot sense ionizing radiation directly. You need instruments to detect it. Even the warmth you feel in the plutonium is an effect—the metal is being heated by its own radiation.



To assure yourself about the source of the radiation, you move around the room with the detector. The readings increase as you approach the iodine solution and drop off as you move away. Is it the only source? Why doesn't the same thing happen when you move toward the glass jar of tritium or the lump of metal?

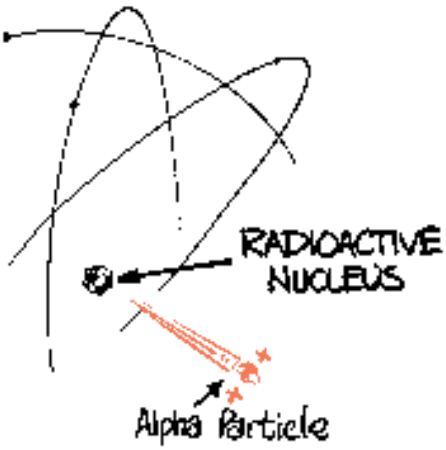
Then you happen to move the window of the detector right next to the plutonium, and the counts skyrocket! As you pull the counter back slowly, the buzzing sound holds steady until, just a few inches from the surface, the counts suddenly drop. There seems to be a limit to how far the radiation from plutonium can go. But up close it's very active.

You bring the detector back next to the plutonium, and Irene slips a piece of paper between the metal and the detector window. Again the counts drop precipitously. Most of the radiation from plutonium is stopped by paper!



You now realize that the glass jar may be blocking radiation from the tritium. Irene brings out a special detector called a tritium sniffer, similar to a Geiger-Müller counter except gas can flow directly through it. She releases some of the tritium gas into the counter, and this time there's a strong response.

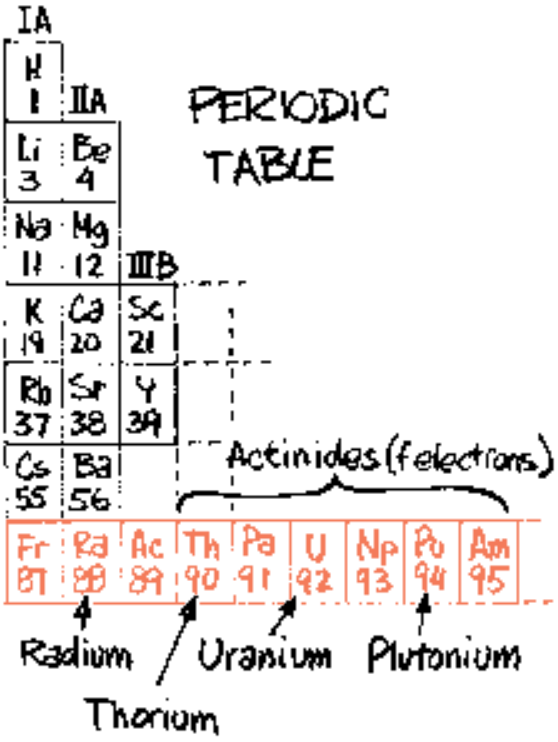
Apparently, these three materials emit different types of radiation because the emanations behave so differently. To understand what's happening we need to look more closely at the structure of the three radioactive atoms. We'll start with the plutonium.



The Alpha Emitters. As we pointed out earlier, atoms consist of a positively charged nucleus surrounded by a cloud of negatively charged electrons. One of the implications of this structure is a neat division between chemistry and nuclear physics. All chemistry is a direct consequence of the electrons on the outside. These light, speedy particles are the "hooks" that enable atoms to bind together and form molecules.

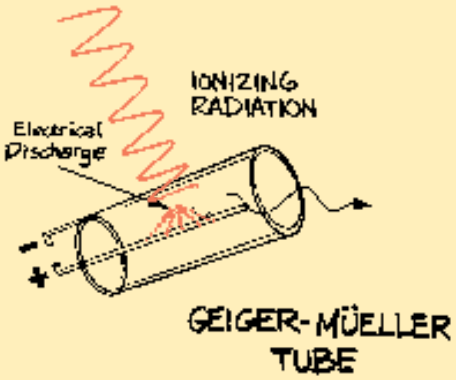
Radioactivity, on the other hand, comes from deep within the atom—it's the emission of radiation due to changes in the nucleus. Radioactive properties are nearly independent of chemical properties.

Many of the atoms that are radioactive—uranium, plutonium, thorium, radium, radon—are located at the bottom end of the periodic table. These are all heavy atoms. In fact, all the elements heavier than bismuth are radioactive. Have the nuclei of these atoms grown too big for their own good?



The Geiger-Müller Counter

A common radiation detector is the Geiger-Müller counter, which has a long, narrow tube containing a gas that's easily ionized. The tube has a wire down its center, and a voltage drop is created between the wire and the sides of the tube. Whenever radiation penetrates the tube and ionizes some of the gas, the voltage causes positive ions to be pulled toward the walls and negative electrons to accelerate toward the wire, creating an electrical discharge—a miniature lightning bolt. The resulting current pulse in the circuit is registered by the counter.

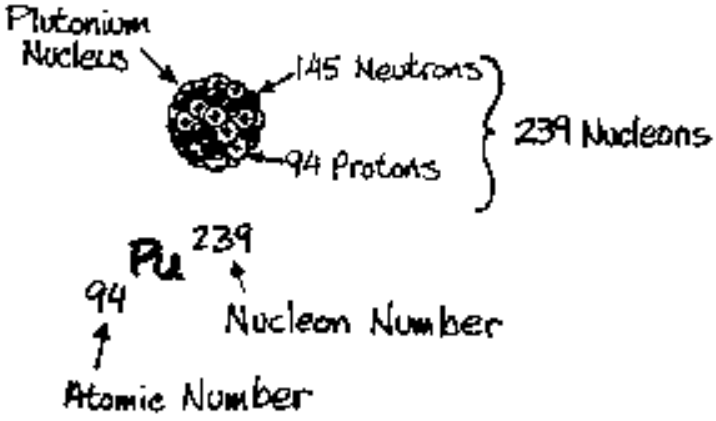


Sometimes radiation may not be counted by the detector because it's blocked by the wall of the tube or it passes through the tube without ionizing any of the gas. So to understand your measurements fully, you need to know the type of radiation you're trying to measure and the efficiency of the counter for detecting that radiation.

Still, a Geiger-Müller counter with a thin mica window on one end of the tube (to let some of the weakly penetrating radiations into the gas) is a good all-around tool for detecting most types of ionizing radiation. You can learn a lot about your environment and your own exposures taking measurements with a simple hand-held Geiger-Müller counter. There are several such counters available today in the $250 to $350 price range.

One of the favorite ways for these atoms to decay is by ejecting a charged particle from the nucleus called an *alpha particle*. Why do they do this? We'll need to examine nuclei and their forces before we can understand this type of radioactive decay.

If we start by looking closely at a plutonium atom, we'd see that it has 94 negatively charged electrons on the outside, balancing 94 positively charged protons in the small volume of the nucleus. The number of electrons in an atom is called the *atomic number* because it determines the atom's chemical properties and its place in the periodic table. Plutonium is the 94th element.

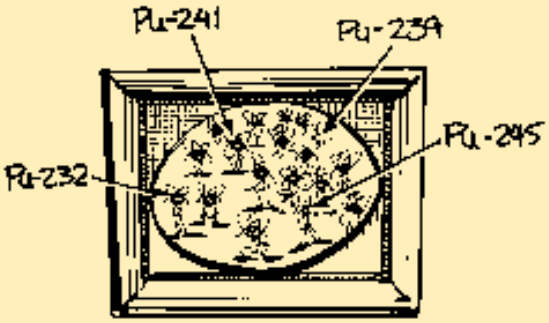


But that's not all. Besides the 94 protons in the nucleus, there's many of a second particle, called the *neutron*, squeezed in as well. The mass of the neutron is about the same as a proton (an atomic mass unit), and the proton and the neutron (called *nucleons*) constitute more than 99.95 per cent of the mass of any given atom. Looking again at the plutonium atom, we see that it has 145 neutrons, giving it a total of 239 nucleons (94 protons plus 145 neutrons). Thus, 239 is both the approximate atomic mass of plutonium and its *nucleon number*. We now know why the lump of metal is called plutonium-239.

Isotopes

If two atoms have the same number of protons, they have the same number of electrons, making them chemically identical, or the same element. But chemically identical atoms can have different numbers of neutrons. Changing the number of neutrons changes the nucleon number and the nuclear properties. Such atoms (with the same number of protons but different numbers of neutrons) are called *isotopes* of that element.

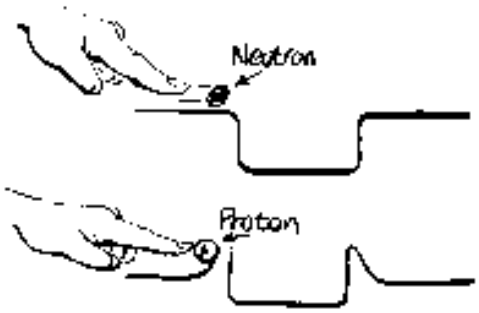
We identify different isotopes by appending the total number of nucleons to the name of the element, as we did when we called the metal plutonium-239. There is, in fact, a whole series of plutonium isotopes, ranging from plutonium-232 to plutonium-246. Each of these isotopes has 94 protons but different numbers of neutrons, ranging from 138 to 152. The isotope used in the atomic bombs, plutonium-239, was chosen because its particular mix of neutrons and protons give it nuclear properties suitable for a rapid and efficient—explosive!—release of its nuclear energy.



PLUTONIUM FAMILY PORTRAIT

To understand how the neutrons and protons are held together in the nucleus, we need to examine the forces between the particles. First, there are the electrical forces. We can experiment with these, for example, by rubbing a balloon against our hair—creating a slight imbalance of charge on the two materials—and then noticing that the balloon attracts our hair. Because of electrical forces, particles with opposite charge are attracted to each other, whereas those with the same charge are repelled from each other. Thus, a proton and an electron attract each other, whereas two protons or two electrons repel each other. Neutrons, with no charge, are unaffected by electrical forces. In fact, we can picture them helping to mediate the electrical forces trying to push the charged protons apart.

If there were only electrical forces, the protons would separate, each would attract an electron, there would be only one kind of atom, and chemistry would be very dull. Too dull in fact to sustain life. Nuclei as we know them are formed because of very strong nuclear forces that attract nucleons to one another.



The nuclear forces have a very short range. If you were able to push a neutron toward a nucleus you'd feel no force until you were very close to the nuclear surface, at which point strong nuclear forces would suck the neutron into the nucleus. The sensation would resemble pushing a marble along a level surface until it suddenly rolled into a deep basin.

If you were to do the same experiment with a proton, there'd be a major difference. This time the sensation would be more like pushing a marble up an incline that grew steadily steeper until the top where, once again, the marble would suddenly roll into a deep basin. In other words, you'd begin to feel electrical repulsion at very long range and the repulsion would increase in strength, making it more and more difficult to get the proton next to the nucleus. But once you did manage to get it there, attractive forces like those the neutron experienced, forces stronger than the electrical repulsion, would also suck the proton into the nucleus.

Such are the forces that hold nuclei together. Now we need to look at what makes the nuclei of large atoms fall apart, or decay. To do that requires an idea from quantum mechanics—the idea of tunneling. In our macroscopic world, an object rolling back and forth in a basin can't get out unless it has enough energy to roll up over the top edge. In the atomic world of quantum mechanics, a particle that doesn't have enough energy to get over the barrier can occasionally "tunnel" out through the sides, especially if the walls aren't too thick.

A nucleus resembles a basin with finite walls in the sense that the dominant force inside is attractive (the nuclear force holding the energetic nucleons together), but just outside the dominant force is repulsive (the electrical force that will expel particles that manage to break free). As discussed in more detail in "Alpha Decay of Heavy Nuclei," the heaviest nuclei have the thinnest barriers, making it more likely that particles can escape by tunneling.

Even so, individual nucleons can't escape because they have too little energy. But when a group of four nucleons, two protons and two neutrons, come together, the energy they gain from binding allows them to make it. This group of nucleons, called the alpha particle, is the most likely particle to tunnel out of a heavy nucleus. If we look at the periodic table, we see that an alpha particle is identical to the nucleus of a helium atom (atomic number 2), the lightest of the rare gases (or more exactly, it's the nucleus of helium-4, the most comon isotope of helium).

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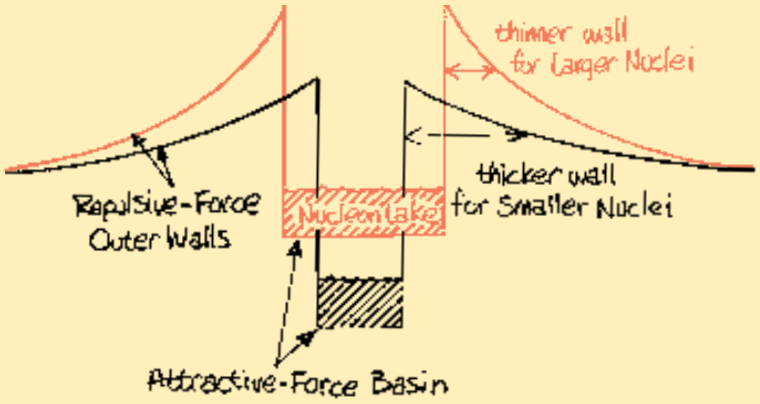
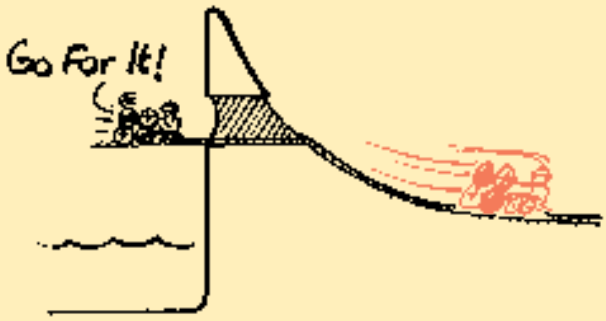
Alpha Decay of Heavy Nuclei



To understand in more detail why heavy nuclei undergo alpha decay in which an alpha particle "tunnels out," we need to discuss the characteristics of the forces inside nuclei. To start with, the volume of a nucleus is proportional to the number of nucleons it contains, just as a water drop has a volume proportional to the amount of water it contains. Although two nucleons attract one another very strongly when they get very close, at even shorter distances they repel even more strongly. This "repulsive core" keeps the density of nucleons from rising indefinitely. The repulsive core and the short range of nuclear forces means that a nucleon in the center of any but the smallest nuclei is attracted by about the same amount.

A useful analogy here is to think of the nucleus as the crater of a volcano with the basin and inner walls being the attractive potential of these nuclear forces and the outer walls being the repulsive potential of the electrical forces between protons. What happens to the shape of the volcano as we go to heavier atoms? Increasing the total number of nucleons makes the nucleus bigger and increases the diameter of the basin. Increasing the number of protons increases the charge, making the slope of the repulsive potential steeper—the flanks of the volcano are steeper and higher at a given radius. These effects combine to increase the height of the caldera rim and to make the walls thinner as you move below the rim. Also, the attractive force between nucleons is constant, so the drop from the rim to the crater floor stays constant.

Inside the crater, we may imagine a lava lake, representing the range of kinetic energies of the nucleons. In general, the top of the lava lake is *below* the level of the far away "plane," making tunneling impossible, or forbidden, for nucleons. However, every now and then, as the nucleons move about in the nucleus, they come together to form an alpha particle. The shape of the potential-energy volcano for an alpha particle is qualitatively the same as for individual nucleons. The major difference is that the binding energy gained in forming the alpha particle puts it at a level *above* the outside plane, and tunneling can take place.



As we already pointed out, the walls of heavy nuclei are thinner (for a given height above the floor) than the walls of light nuclei. Thinner walls makes tunneling more probable, so heavy nuclei decay frequently by ejection of an alpha particle, whereas light nuclei do not. When tunneling does occur and the alpha particle finds itself outside the walls, the repulsive electrical forces push it away from the nucleus (in our analogy, it careens down the side of the volcano). The released particles achieve high velocities and kinetic energies of several MeV. ■

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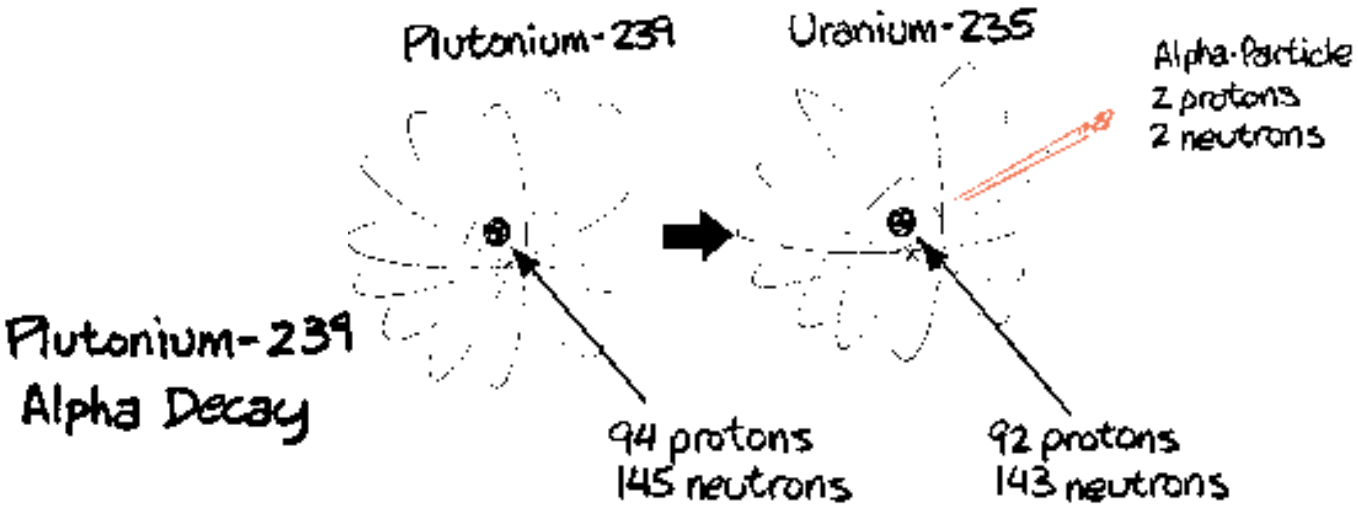
The alpha particles emitted by plutonium-239 all have essentially 5 MeV of kinetic energy, a typical energy for alpha decay. But as particles, they're relatively heavy, relatively slow, and possess a double charge, so they expend their energy quickly by creating a short, very dense trail of ion pairs. In air, they travel only an inch or two. This is why the detector in our experiment registered counts only when it was close to the lump of plutonium metal.

When alpha particles hit denser matter they stop almost dead in their tracks. They have such weak penetration abilities they can be blocked by a piece of paper or the dead, outer layers of our skin. While they are losing their energy, they each pick up two electrons, become neutral helium atoms, and float away.

Essentially all the radiation from our lump of plutonium consists of alpha particles. Each particle removes two protons from a nucleus, which means the atomic number of the atom is reduced to 92. Likewise, the alpha particle removes four nucleons, reducing the nucleon number to 235. Thus, when a plutonium atom emits an alpha particle, it becomes uranium-235, an isotope of the 92nd element in the periodic table.



Alpha particles, or alpha rays, are one of the primary types of radiation associated with radioactivity. They are the least penetrating but create dense ionization trails. As a result, the prime danger of an alpha emitter, such as plutonium, comes from having it inside your body. If you inhale or ingest plutonium, or have it pass into your blood stream through a puncture wound, much of the element can end up lodged in various organs, especially the lung, liver, and bones. The plutonium atoms, and their daughters, sit there, emitting alpha radiation and damaging the immediate surrounding tissue.

Of course, other alpha emitters, such as uranium and radium, are already peppering your insides. You take in these substances in the food you eat or the dust you inhale, but the amounts are small and minimal damage is done. In this vein, limits have been established, called *permissible body burdens*, for the people who work with plutonium and other radioactive materials. The idea is to remove people from such work before they've ingested amounts of these materials that have been shown to be dangerous.

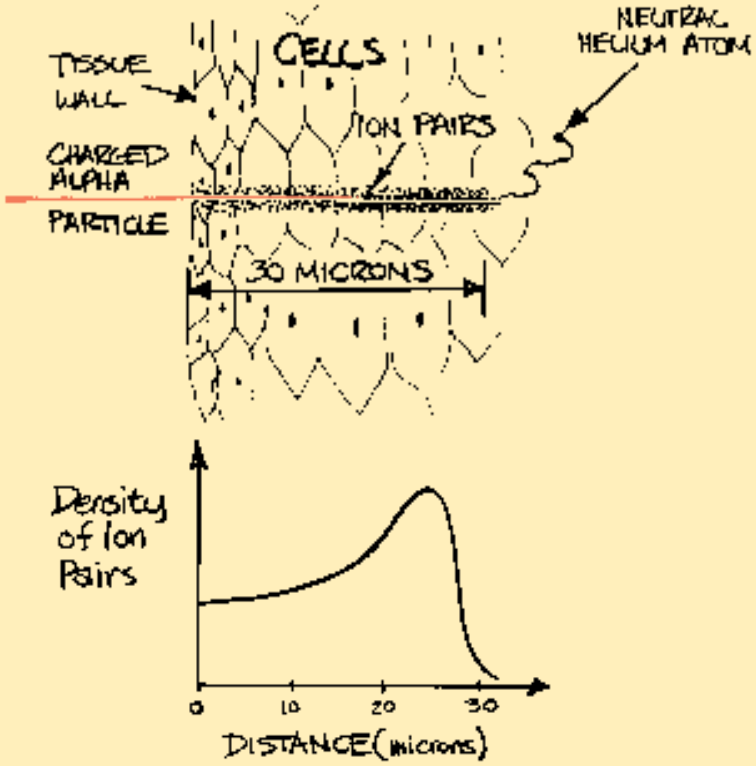
The Plutonium Alpha Particle

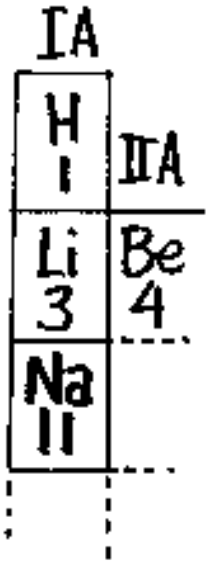
Initially, the alpha particles emitted by plutonium-239 have about 5 MeV of kinetic energy and are moving at a speed of about 1.5×10^7 meters per second (5 per cent of the speed of light). This relatively slow speed and the particle's double charge create a characteristic ionization trail that's short and thick. Usually, most of the alpha particles from a given radioactive material have about the same energy, so all the trails are essentially the same length.

In air, the 5-MeV alpha particles from plutonium-239 generate about 44,000 ion pairs per centimeter (centi = 10^{-2}). As a result, they travel 3.5 centimeters (1.4 inches) before their 5 MeV of energy is depleted, and they generate a total of about 150,000 ion pairs.

In denser matter, such as human tissue or paper, the path length of the 5-MeV alpha particles will only be 32 micrometers (micro = 10^{-6}). This distance is less than the thinnest part of the epidermis, the dead layer of external skin cells, and less than the 100-micrometer thickness of an average piece of paper.

With the shorter path length in dense matter, the density of ions pairs increases to 62,000,000 per centimeter, which is what makes alpha emitters dangerous when present in sufficient quantity. The damage is more of a shotgun blast than a rifle shot. ■

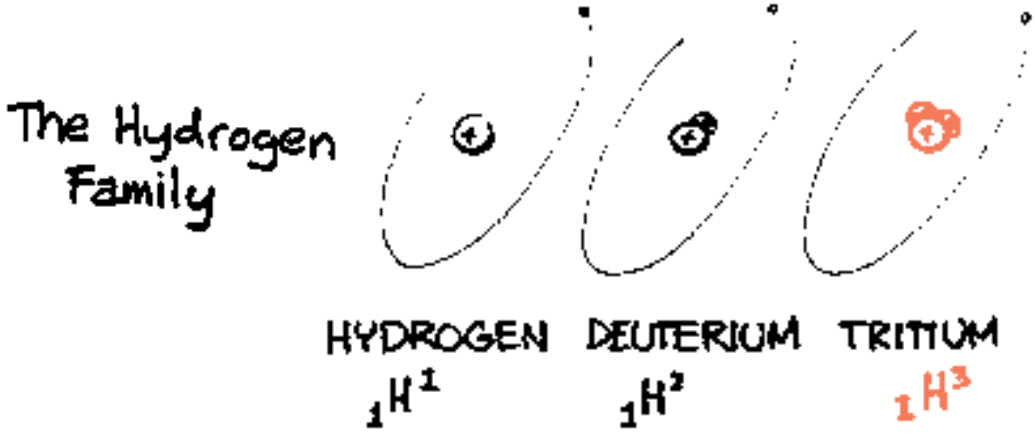




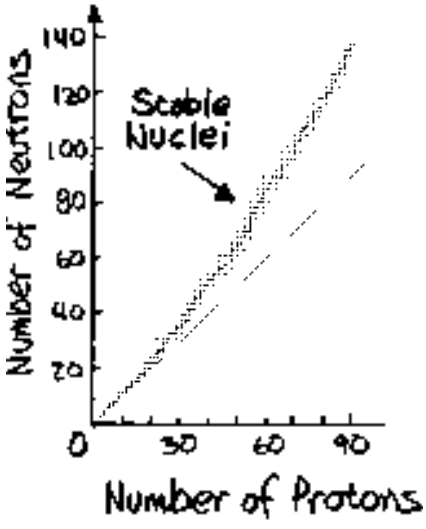
Beta Emitters. Now let's look at the tritium gas to see what's going on there. We're at the opposite end of the periodic table—the smallest atom—so it isn't radioactive because of its size! As it turns out, there's another reason—the ratio of neutrons to protons in the nucleus of particular isotopes can be out of balance.

Balance in the nucleus is determined by three things. First, the proton is more stable than the neutron. On that account, stable nuclei would have more protons than neutrons. Second, there's a quantum mechanical principle—called the exclusion principle—that requires identical particles to be in different states. Consequently, if you have more of one kind of nucleon than of the other, the excess of the more common kind end up in higher energy states. On that account, the most stable nuclei would have equal numbers of neutrons and protons. Third, the electrical forces repel protons and not neutrons, which favors neutrons over protons. The nucleus that's actually the most stable for a given element depends on a competition between these three effects.

Now let's examine hydrogen, which has three isotopes—hydrogen-1, hydrogen-2 (deuterium), and hydrogen-3 (tritium). The first two isotopes are stable (hydrogen-1 with a single proton and hydrogen-2 with a proton and a neutron), but the third isotope is radioactive. Why?



For nuclei with three nucleons, the fact that protons are more stable than neutrons is the key factor. Thus, tritium (2 neutrons and a proton) is not stable and is radioactive, whereas helium-3 (2 protons and a neutron) is stable. Hydrogen-1 and helium-3 are the only two nuclei where stability favors more protons than neutrons. All other stable isotopes have as many or more neutrons than protons because of the second and third effects. As the size of the nucleus grows, proportionately more neutrons are required as the third effect (electrical repulsion between protons) becomes dominant.



Nature has provided a way for nuclei such as tritium to change their charge without changing the number of nucleons, that is, without a large change in their mass. This process, called beta decay, can happen in two ways. In the case of tritium and other nuclei that have too many neutrons to be stable, a neutron decays to a proton while emitting an electron and another particle, called a neutrino.

The neutrino has no charge, negligible mass, and interacts with matter only through what's called the weak force, the force responsible for beta decay. In fact, the force is so weak that a neutrino passes through our radiation detector or our bodies with almost no chance of causing any ionization. Only the electron, or

Mass, Energy, and Stability

Why does the neutron decay into a proton rather than something else? First, the neutron is a bit heavier than the proton. Einstein's equivalence of mass and energy ($E = mc^2$) says that a heavier particle has more energy. Systems with higher energy tend to be unstable and decay to lower energy states by emitting photons or other particles that carry off the extra energy. However, such decays must still conserve energy, charge, and a few other things that remain constant in isolated systems. One of those things is a nuclear quantity called *baryon number*—which is one for nucleons but zero for lighter particles, such as electrons, photons, and neutrinos. Thus, ejection of a negative electron in beta decay means a plus charge must remain behind. In addition, the neutron decays into a proton rather than into gamma rays or neutrinos alone because the baryron number must be conserved.

beta ray, creates significant ionization in matter. Thus, when radioactive nuclei undergo beta decay, only the electron is detected and only the electron generates biological effects in our bodies.

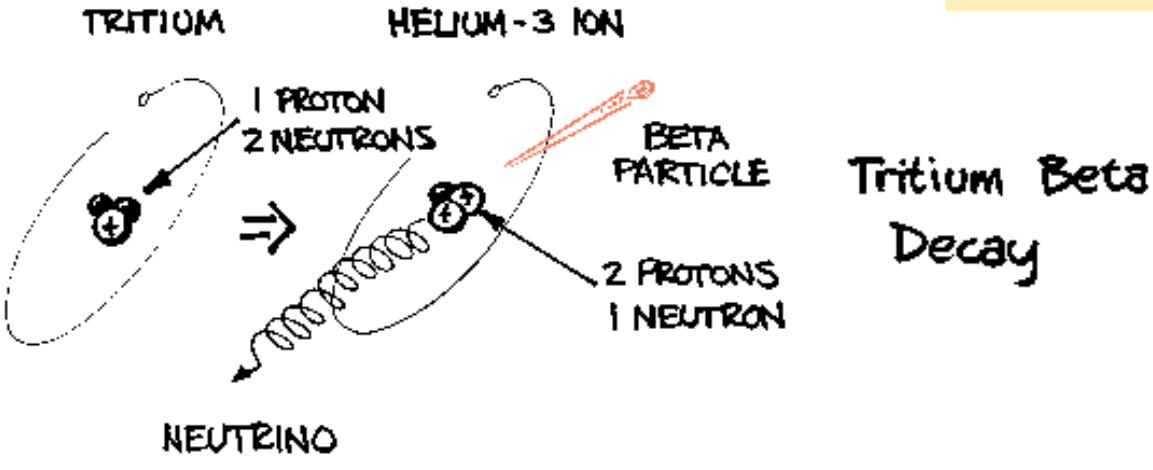
In another type of beta decay, a proton changes to a neutron while emitting a positron and a neutrino. The positron is the anti-particle of the electron and is just the same except that its charge is positive rather than negative. Beta decay with emission of an electron increases the atomic number by one; beta decay with emission of a positron *decreases* the atomic number by one.

In both types of beta decay, two particles are emitted, the electron (or positron) and the neutrino, and the available energy can be shared between them in a somewhat arbitrary way. As a result, beta particles emitted from a single source have a continuous distribution of energies rather than all the particles having essentially the same energy, as is the case for alpha rays.

Typical energies for beta particles are hundreds of keVs (a factor of ten lower than for alpha particles), although some radioisotopes emit beta particles with energies (several MeV) that range higher than alpha particles. However, the fact that electrons are almost 8000 times lighter than alpha particles means that the beta particles travel much faster.

Electron Capture

Another process that reduces the number of protons in the nucleus is one in which a proton captures one of the electrons surrounding the nucleus, turns into a neutron, and emits a neutrino. This process is called electron capture and is related to beta decay because it involves the weak force and the same four particles, the electron, neutron, proton, and neutrino.



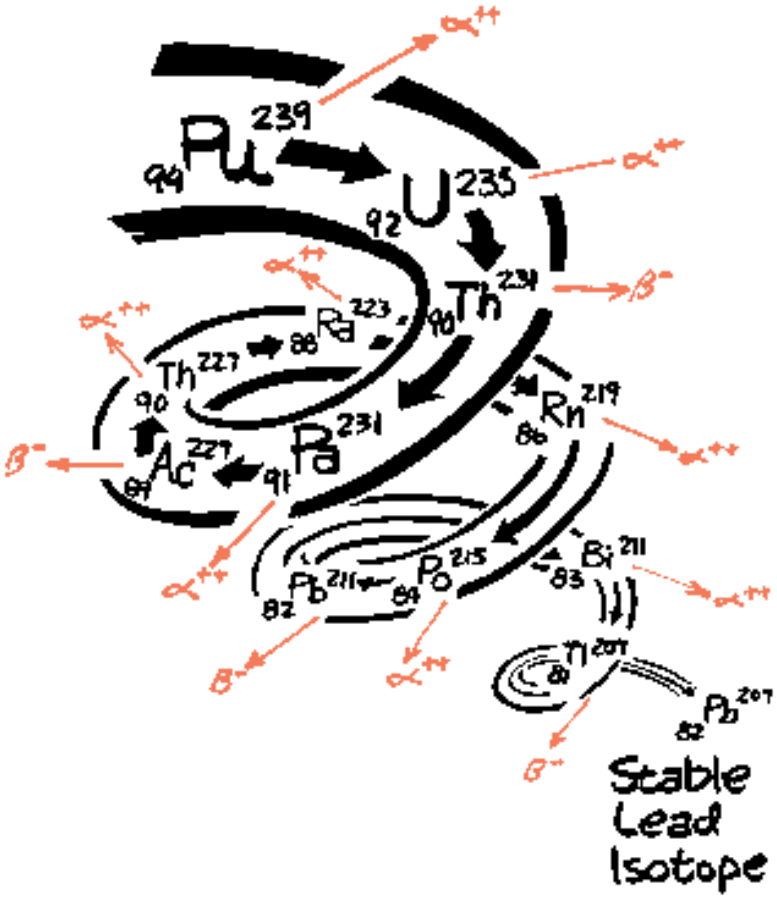
The beta particles ejected in the tritium decay have the lowest energy (an average of 5 keV) of any beta decay. This low energy is why the beta rays from the tritium gas did not even penetrate the glass walls of our container. On the average, the tritium beta particle travels a shorter distance in water or tissue than the plutonium-239 alpha particle. We'll meet stronger beta rays in our next example.

The Tritium Beta Particle

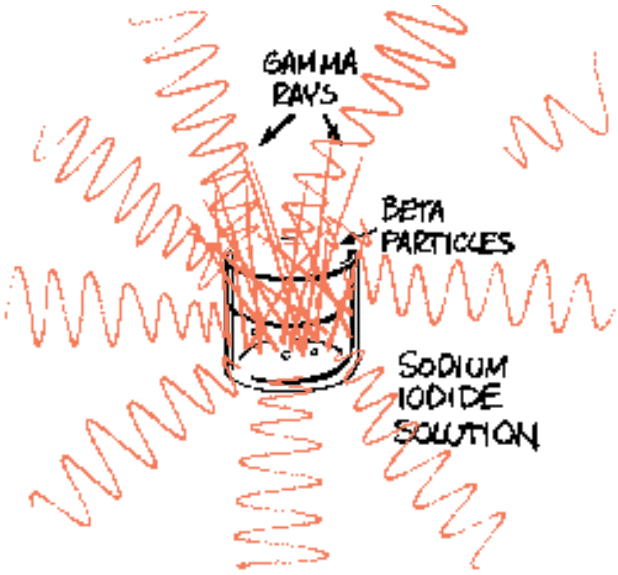
The beta particle emitted by tritium atoms has an average energy of 5 keV (and a maximum of 18 keV), a thousand times less energy than the 5 MeV for the plutonium alpha particle. In fact, this beta particle is so low in energy it travels much less than half a centimeter in air, and it won't penetrate mylar, glass, or the thin window on the Geiger-Müller counter. It takes a special detector—the tritium sniffer—just to record its presence.

The tritium beta is neither a shotgun blast nor a rifle shot; rather it's a bee-bee from an air gun. An average beta particle from tritium would, at the most, generate around 150 ion pairs in water. Of course, as with all radiation sources, tritium can be dangerous in the right place and at high enough concentrations. If tritium gets in the body, it can go everywhere (after all, it's hydrogen). Sufficient concentrations can then do immense damage throughout all the cells of the body.

Decay Chains. Now that we know about both alpha and beta decay and before we discuss the sodium-iodide solution that Irene put out for us, let's return briefly to the decay of heavy elements, such as plutonium. The isotope that results from a decay, called a *daughter*, does not necessarily have a stable nucleus. It may undergo a whole series of further decays, called a *decay chain*. The chain for plutonium, illustrated here, begins with two alpha decays but then includes a beta decay, another alpha decay, a beta decay, and so forth. The end result for plutonium, as well as for other heavy radioactive elements, is a stable isotope, usually of lead. But it can take billions of years for a radioactive atom at the top of a decay chain to undergo all the decays and reach its final stable configuration.



Radioisotopes. What can we say about the beaker of sodium-iodide solution? The solution was actually the most interesting because our detector was registering significant counts from the beaker even several feet away. What sort of radiation is the iodine giving off?



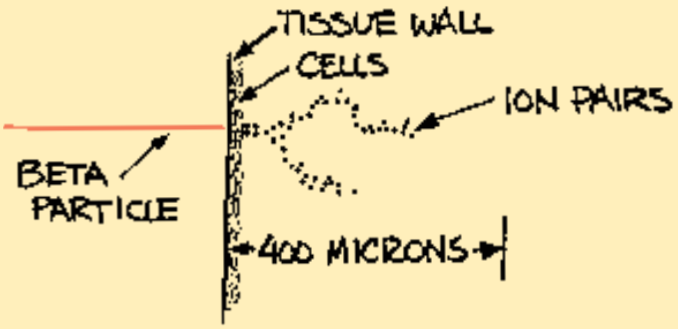
Every element in the periodic table can have a range of isotopes, some stable, others unstable and radioactive. The latter are called radioisotopes. Many of these radioisotopes emit more than one kind of radiation. Such is the case with iodine-131. In the periodic table, iodine is roughly halfway between plutonium and hydrogen—it's the 53rd element. All the natural iodine found in nature is iodine-127, which is stable and non-radioactive. The iodine-131 radioisotope has 4 more neutrons than iodine-127, and this excess makes it unstable. It has to be produced artificially—in nuclear reactors, in the explosions of nuclear weapons, or at accelerators.

With its extra neutrons, iodine-131 gains stability by emitting a beta particle. Once again, the decay converts a neutron to a proton, increasing the atomic number by one—the isotope changes to xenon-131. So far, this is similar to tritium, except the betas are more energetic and leave longer ionization tracks.

The Iodine-131 Beta Particle

Iodine-131 emits beta particles with energies up to 810 keV and an average energy of 180 keV, considerably more than the energy of the beta particles from tritium. The average iodine-131 beta particle is traveling very fast—67 per cent of the speed of light!—which is much more typical of beta particles.

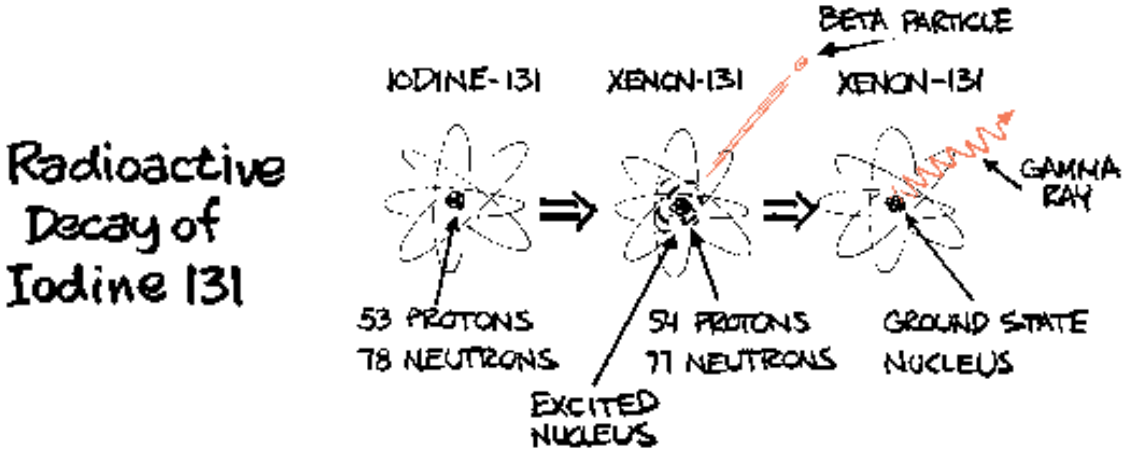
In air, the single charge and high speed of the average beta result in a sparse ionization track—about 250 ion pairs per centimeter (compared to 50,000 or so for an alpha particle), and the track is much straighter and longer (about 30 centimeters) than that from a tritium beta particle. In water or tissue, the density of ion pairs rises to 180,000 per centimeter, and the range drops to 0.04 centimeter, or 400 micrometers.



Thus, despite the higher energies, most of the betas never get out of the iodine solution or through the glass walls of the beaker. Some of the betas emitted at the water surface escape, traveling up to ten feet through the air. But placing an aluminum sheet that's 2 millimeters thick over the beaker will easily block all of them, even the most energetic.

The main threat from beta radiation occurs, once again, from ingestion. In fact, since iodine likes to concentrate in the thyroid, iodine-131 can be used to help kill cells in a hyperactive thyroid. With the beta particles traveling from 0.01 to 0.3 centimeter, the radiation is confined primarily to the thyroid, resulting in an efficient treatment of hyperthyroid disorder.

Another major difference between iodine-131 and tritium is that the beta decay of iodine-131 leaves the nucleus in an excited state. The newly formed xenon-131 atom has a balance of nucleons that make it stable, but the nucleus needs to rid itself of extra energy. Most of the time it does this by quickly emitting one or more gamma-ray photons. Photons have no charge and no mass, so after the gamma-ray emission, the xenon-131 remains just that—xenon-131. Except now it's happy and relaxed. In fact, xenon is one of the rare gases, so it diffuses out of the solution and floats away.



Almost all the radiation we measured in our thought experiment with the Geiger-Müller counter was gamma radiation from the iodine. Gamma rays are electromagnetic rather than charged-particle radiation, so they are highly penetrating. They pass through the solution, the glass beaker, the air, and our bodies.

Gamma rays are penetrating because, as we described earlier, photons lose energy randomly in "collisions" with atoms, knocking electrons free to create local regions of ionization. For a given thickness of material, only a fraction of the photons, and a smaller fraction of the energy, are absorbed. For example, a centimeter of water will scatter about 10 per cent of the incident photons from iodine-131, and in the process, absorb about 3 per cent of the incident energy. Doubling the thickness of water will scatter another 10 per cent of the remaining unscattered photons, but to calculate the absorbed energy, we'd have to take into account that 7 per cent of the incident energy is traveling through the water in the form of reduced-energy photons. In general, alpha and beta radiation have finite ranges; gamma radiation falls off continuously, never quite reaching zero.

The Gamma Rays of Iodine-131

We speak of the gamma rays of iodine-131 even though the real source of the gamma rays is the daughter nucleus, xenon-131. One or more gamma rays with energies ranging from 80 keV to 723 keV follow each beta decay. By far the most common gamma ray, accompanying 81 per cent of the decays, has an energy of 364 keV. Furthermore, the total gamma ray energy emitted (sometimes in the form of several gamma rays) is 364 keV in 89 per cent of the cases. To simplify our discussions, we will always speak as if all the decays of iodine-131 emit a single 364-keV photon.

In water or tissue, it takes 6.4 centimeters (2.5 inches) to reduce the intensity of 364-keV photons in half. Thus, although the beta radiation from iodine-131 in hyperthyroid treatments is limited to the thyroid, the gamma radiation deposits energy more diffusely throughout the body.

The following table summarizes information about the interaction with water of the three primary forms of ionizing radiation emitted by radioactive sources. We use

Alpha, Beta, and Gamma Radiation

Radioisotope	Radiation	Energy (MeV)	Range or Mean-Free Path in water or tissue (millimeters)
Uranium-238	Alpha	4.2	Range: 0.027
Polonium-210	Alpha	5.3	Range: 0.037
Carbon-14	Beta	0.154 maximum	Maximum range: 0.29
Phosphorous-32	Beta	1.71 maximum	Maximum range: 8
Iodine-125	Gamma	0.035	Average distance to collision: 33
Colbalt-60	Gamma	1.33	Average distance to collision: 164

other examples than the ones we've already discussed. In particular, alpha radiation produces short, dense ionization tracks; beta radiation produces sparse tracks that are longer; and the highly penetrating gamma radiation leaves scattered, local regions of ionization where the photons have knocked electrons free of their atoms. These local regions have the same type of ion density as the tracks from beta particles.

If the radiation source is external to the body, then only gamma radiation poses a threat. Alpha and beta radiation do not penetrate far enough to be very dangerous. However, if the alpha and beta sources have somehow been deposited in the body to become internal sources, they may be very dangerous.

Radiation Doses

Now you turn to your friend, Irene, and say, "This is more complicated than I thought. I'm beginning to realize why health physicists always seem to hedge when they're asked to explain how they calculate radiation doses. They *can't* give a simple answer."

"Exactly," Irene answers. "There are many factors that go into the calculation including the type of radiation emitted by the source and the circumstances of the exposure. Let's discuss these for our three radioactive materials."

The most important thing to know, of course, is how much energy carried by the ionizing radiation is actually deposited in your body, because biological damage increases with the energy absorbed by the cells. Thus, absorbed energy is the basis for several quantities that health physicists call *dose*.

When the tritium gas is inside the bottle, figuring the dose is easy—there's none! Likewise, as long as you keep the plutonium a few inches away, your dose from it is zero. (Actually, the plutonium is emitting a small amount of gamma and x radiation, but we'll ignore this.) The energy of the beta particles from the tritium is absorbed in the glass jar and the energy of the alpha particles from the plutonium is absorbed in air immediately surrounding the metal. (In both cases, much of the energy is absorbed in the materials themselves, and the radiation never escapes.)

If you hold the lump of plutonium in your hand, your body absorbs energy from the alphas—but the energy is deposited in dead skin tissue, where it's relatively harmless. If you kept the plutonium against your skin for a length of time, it would eventually lead to skin burns.

Now, say you lean over the beaker of sodium-iodide solution. What sort of exposure are you getting? Beta radiation would hit your face, but it only penetrates a short ways (about ten times farther than the plutonium alpha particles). And if you happen to be wearing glasses, the lenses would block the betas and none of the radiation would reach your eyes. At the same time, however, the gamma radiation is passing through the beaker, the table, your glasses, and exposing your entire body.

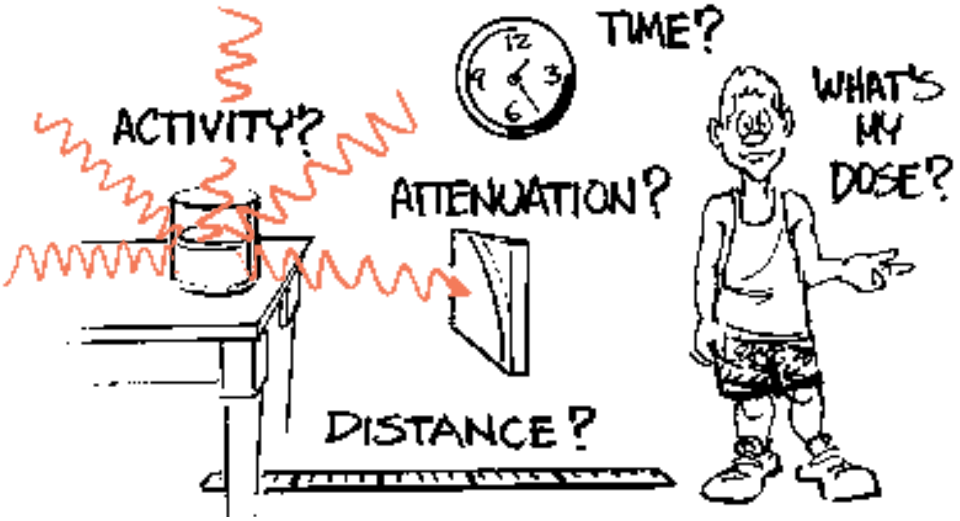
Of course, all this changes if the sources are internal. If you made water using tritium gas rather than hydrogen and then drank it, there'd be a beta dose everywhere, in all your organs and cells. In that case, it's the source that would have penetrated the body, not the radiation.

If you drank the sodium iodide solution, you'd need to calculate two doses. The first is a concentrated dose to the thyroid, because that's where the iodine ends up and deposits its beta rays. The second is a diffuse dose of gamma rays that travel out from the thyroid and deposit energy throughout the body (to be accurate, you should also add in doses from the small fraction of iodine outside the thyroid).

If you breathed plutonium dust, the particles would initially be deposited in your lungs. You would then need to know the eventual distribution of the plutonium, that is, what fraction ends up in each organ or tissue type and what fraction works its way out of your body. A significant fraction, for example, can be coughed up, swallowed, and passed on though the gastrointestinal tract. On the other hand, if the plutonium is in a soluble form, say a plutonium salt, it can move quickly to various organs, such as the bones, and be deposited there. Only with such information could you calculate an accurate dose.

Calculating the Dose. So far we've been talking qualitatively about whether the radiation ever reaches you and where it deposits its energy. But to calculate the size of the dose we first need to know the amount of energy emanating from the source. The amount of energy depends on two factors: the *activity* of the source, that is, the number of radiation particles being emitted each second, and the energy per particle. The product of these two factors is the power of the source, or the total energy being emitted per second.

How much of the emitted energy is finally deposited in your body depends on your distance from the source, the amount of time you're exposed to it, the attenuation of the radiation on its way to you by the air or by shielding, and the



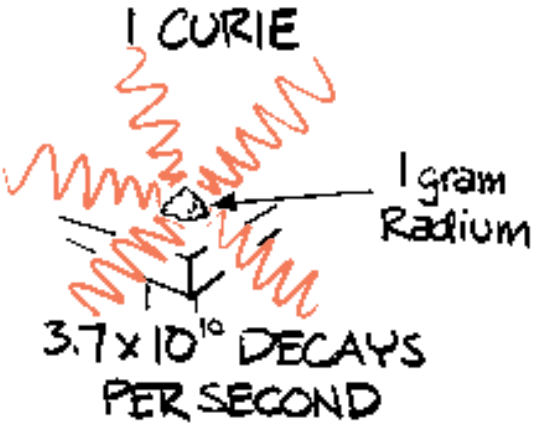
penetrating power of the radiation once it reaches you. For example, if you double how long you stand beside an external source with constant activity, you double your dose because twice as much energy gets deposited. Many of these factors can easily be overlooked in discussions of radiation exposures.

What about distance? Radiation from a localized source spreads outward as it travels. For example, the intensity of gamma or x radiation falls off with the inverse square of the distance. Absorption in air reduces the intensity still further, so doubling your distance from a gamma-ray source reduces your dose by a factor of more than four.

In the case of alpha and beta radiation, the range is what's important. Staying beyond this distance keeps the dose from those charged particles at zero. If you're within the range, you still need to subtract the energy lost to the air before the particles reach you as well as to account for any spreading of the beam.

Common Radiation Units. Irene suggests that to understand dose calculations you need to become familiar with several radiation units. The three most important are *activity*, *absorbed dose*, and *dose-equivalent*. We've already explained that activity, *A*, is a measure of the number of decays per second. The typical unit for activity is curies. The quantity that health physicists call the absorbed dose, *D*, is the energy absorbed per gram of tissue in the body, which is frequently given in a unit called the rad. Finally, the dose-equivalent, *H*, is the absorbed dose multiplied by a biological effectiveness factor and is typically expressed in rem. The most relevant quantity for determining an individual's risk from a radiation exposure is the dose-equivalent, *H*, but its calculation requires knowledge of the other two. We'll now explore these units more fully.

Activity. The activity, *A*, of a radioactive source is equal to the number of atoms decaying every second in the material. The more material that's present, the higher the activity because there are more atoms to decay and emit radiation. The higher the activity, the higher the dose you receive in a given amount of time.



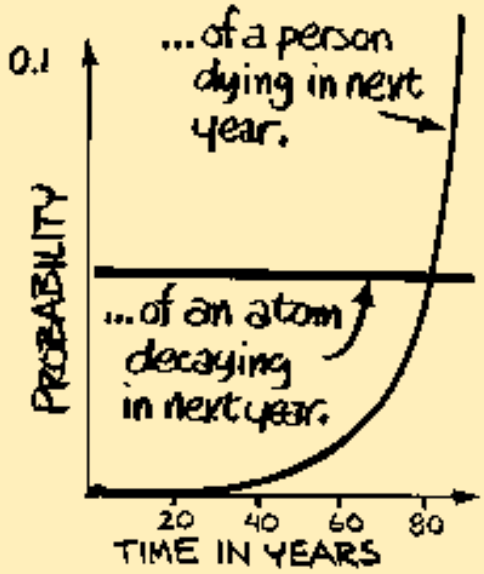
A common unit of activity is the curie, which is 3.7×10^{10} disintegrations, or radioactive decays, per second. The curie was originally defined in terms of radium, the second radioactive element discovered and isolated by Marie and Pierre Curie (the first was polonium). One gram of radium-226, the isotope the Curies had found, has an activity of 1 curie, that is, 3.7×10^{10} atoms decay per second. Since there are 2.7×10^{21} atoms of radium per gram, it takes a long time for the radium to disappear (11,000 years for more than 99 per cent to decay).

The *specific activity* is the number of curies *per gram* of material and measures the rate of decay in one material relative to rate of decay in radium (1 curie per gram). The specific activity of plutonium-239 is 0.06. In other words, plutonium-239 has 6 per cent as many decays per unit time as an equal mass of radium-226. We can thus calculate that one gram of plutonium-239 emits 2.2×10^9 alpha particles per second.

Two radioactive substances can have considerably different specific activities. An isotope with a very high specific activity, such as iodine-131, has a significant fraction of its atoms decaying every second. As a result, such isotopes don't hang around very long. We say they have short *half lives*.

Many of the radioactive sources discovered at the turn of the century—such as uranium and radium—have low specific activities and long half lives. Only a

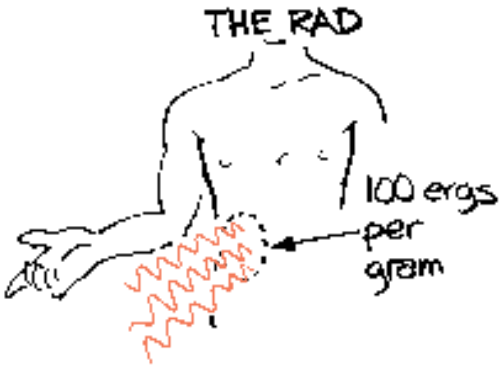
The Radioactive Half-Life



Biological life is a series of progressive stages from birth through aging to death. When you met Irene, you knew without asking that she wasn't two or even ten years old, and you probably could make a pretty good guess as to whether she was closer to 30 or 60. The life expectancy at birth in the U.S. is around 75 years, at age 75 it is around 11 more years, and hardly anyone lives to 150 years. The probability of death per year generally increases with age. Radioactivity is very different. There's no way to tell how long ago a radioactive atom was created. A nucleus of uranium-235 created yesterday by the decay of plutonium-239 is identical to one that has been on Earth since the planet was formed. One aspect of this indistinguishability is that the "life expectancies" are the same. So, if half of a set of identical nuclei decays in a set time, half of the remainder will decay in the next equal time interval, etc.

The time interval needed for half the atoms to decay is a commonly used parameter, called the half-life. For example, iodine-131 has a half-life of 8 days. If we start with, say, 10^{23} atoms of iodine-131, one-half (5×10^{22} atoms) will remain after 8 days, one-fourth (2.5×10^{22} atoms) after sixteen days, one-eighth (1.25×10^{22} atoms) after 24 days, and so forth. An important rule of thumb in radiation protection is that after seven half lives less than one per cent of the radioisotope will remain ($(1/2)^7 = 1/128$). Radioactive decay thus follows an exponential decay law:

$$N = N_o e^{-0.693\, t/T}$$



small fraction of the atoms actually decay every second, so those sources appear to have a constant activity. This is why the materials appeared to have been sources of endless energy and to have violated the conservation of energy laws.

Absorbed Dose. The absorbed dose, *D*, is the energy deposited in an organ or a mass of tissue *per unit mass* of irradiated tissue. A common unit for absorbed dose is the rad, which is 100 ergs per gram of material.

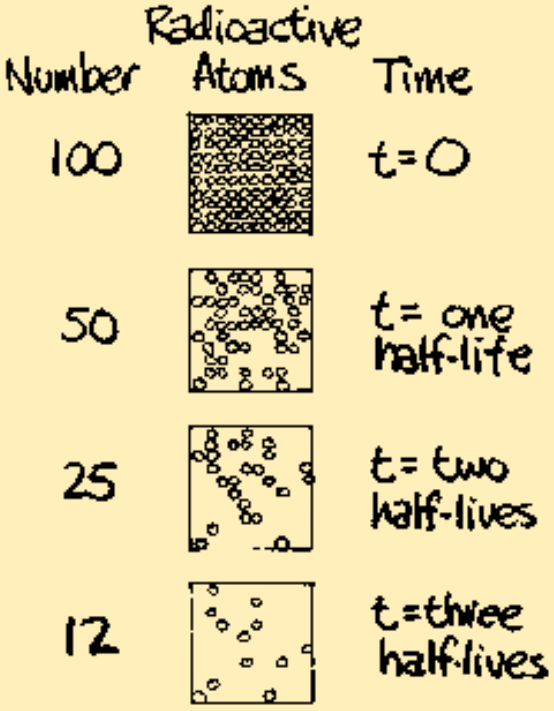
Note that absorbed dose is not the *total* energy deposited in an organism, organ, or mass of tissue. However, to calculate absorbed dose you usually calculate the total absorbed energy first. You use the activity of the source and the energy of the radiation to calculate the total amount of energy that arrives at the surface of your body (by taking into account such factors as the fraction of the radiation from the source that's moving in the right direction, the distance between the source and your body, the length of time for the exposure, and attenuation from any shielding or the air). You then use tissue absorption coefficients or particle ranges to calculate the total energy absorbed in the body.

where N_o is the initial number of atoms at time t 5 0, N is the remaining number of atoms at time t, and T is the half-life expressed in the same units as t.

We can use this formula to show, for example, that the fraction of plutonium-239 (with a half-life of 2.4×10^4 years) that remains after 8 days is N/N_o 5 0.9999994—only 6 atoms out of ten million have decayed! Quite a few less than the five million out of ten million for iodine-131.

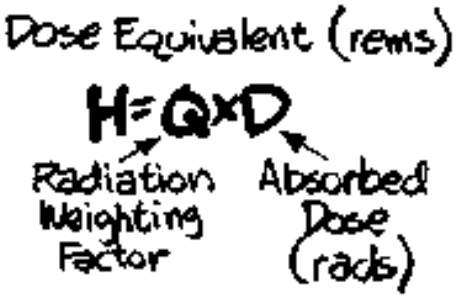
As these examples illustrate, the half-life of a radioisotope is an important indicator of the material's radiological activity—the shorter the half-life, the more atoms disintegrate per unit time. The specific activity (curies per gram) of a particular radioisotope is inversely proportionately to the isotope's half-life and its atomic weight. The half-life of iodine-131 is about 10^6 times shorter than that of plutonium-239, and each atom weighs about half as much. As a result, iodine-131 is 2×10^6 times more radioactive per gram. Let's hope our solution of radioactive sodium iodide was pretty dilute!

The first measurement of radioactive half-life was made by Rutherford in 1900, about four years after Becquerel discovered radioactivity. Rutherford measured the half-life of radon-220, or "thorium emanation," which is 55 seconds. With such a short half-life, the substance is quite active but also obviously disappears rapidly, in contrast to its original parent in the decay chain, thorium-232, with a half-life of 1.4×10^{14} years. ■



The last step is to calculate the absorbed energy per unit mass, which requires a decision on what mass of tissue to use—the mass of the whole body or just the mass of the irradiated tissue. When energy is deposited primarily in a single organ (such as the beta radiation of iodine-131 in the thyroid), one usually calculates the actual dose to that organ—after all, that's where the damage occurs. When energy is deposited throughout the body (such as from an external gamma-ray source), the mass of the whole body is obviously appropriate.

However, comparisons between different kinds of exposures are facilitated if the doses are all put on the same basis. To do this, organ-specific doses can be recalculated using the mass of the entire body to yield the *whole-body dose*. This dose is much lower than the organ-specific dose and, in one sense, is a rather artificial contrivance. In effect, we've spread the energy over the entire body. However, the adjusted value is more suitable as a measure of risk to the entire organism, and it can be added or compared to other whole-body doses.



Dose-equivalent. A key factor that the absorbed dose doesn't take into account is the density of the ionization created by the radiation. For example, alpha radiation leaves an ion track that's several hundred times more dense than that of a beta particle. This means that if an alpha particle and a beta particle penetrate tissue, the deposition of energy for the alpha particle is several hundred times more focused. The alpha won't cross through as many cells (possibly only one or two), but the effectiveness at creating lasting damage in the cells it does hit is higher per unit energy deposited. Generally, one rad of alpha radiation is about twenty times more effective at causing cellular damage—and thus cancer—than one rad of gamma or beta radiation.

Health physicists account for these differences using a *radiation-weighting factor*, *Q*, that represents the effectiveness of each type of radiation to cause biological damage. The factors are determined by measuring the occurrence of various biological effects for equal absorbed doses of different radiations.

The product of the radiation weighting factor and the dose ($Q \times D$) is a more direct measure of the biological risk and is called the dose-equivalent, *H*. The idea is that equal dose-equivalents generate equivalent amounts of biological damage. The common unit for dose-equivalent is the rem.

Looking at the table, you ask, "Why does gamma radiation have the same weighting factor as beta particles? After all, gamma radiation deposits its energy in a very diffuse manner."

What you say is correct. For example, less than half the energy of 5-MeV gamma-ray photons is absorbed as they pass horizontally through your torso. However, the energy that's deposited is from electrons that have been knocked loose. The ionization tracks generated at these points by the ejected electrons have the same ion density as beta particles, despite the fact the regions are scattered throughout the material. Thus, beta and gamma radiation delivering the same dose-equivalent create the same density of ionization in the cells per gram of tissue.

Radiation-Weighting Factors

Type of Radiation	Q
Alpha particles	20
Beta particles	1
Gamma radiation	1
Protons, Fast neutrons	20
Slow (thermal) neutrons	5

Irene shows you some calculations about possible doses a person might receive from the radioactive materials on the table. For example, a tenth of a microgram of plutonium-239 spread in a thin coating on your skin over an area about 5 centimeters in diameter would give a localized dose-equivalent to the skin tissue of about 3 millirem per second. After an hour, the total dose-equivalent would be 11 rem. It takes about 4000 rem of alpha radiation to the skin before you start to see hair falling out and more than 6000 rem before a skin burn appears.

If the same mass of iodine-131 (a tenth of a microgram) were present in the beaker (a very dilute solution) and you were standing so that your midsection was about a foot away, you'd receive a much smaller dose—an average of about 1.3 microrem per second—except now the entire body is exposed, not just a small amount of tissue in the palm of your hand. Your head and feet, which are furthermost from the beaker, will, of course, receive less than 1.3 microrem per second; your midsection will receive more. On the average, however, every gram of tissue in your body receives 1.3 microrem per second, not just a small amount of tissue in your hand as was the case for the plutonium.

These examples can help emphasize that the doses are based on energy per unit mass! The iodine-131 delivers a total energy to the body that's ten-thousand times more than the total energy from the plutonium-239. But the energy of the gamma

Important Units of Radiation and Dose

Basic Units

Type of Unit	Explanation	Older Unit	Newer SI Unit	Conversion
Activity, *A*	The number of radioactive decays per unit time occurring in a given source.	**curie (Ci)** 3.7 x 10^{10} decays per second	**becquerel (Bq)** 1 decay per second	1 Ci = 3.7 x 10^{10} Bq
Absorbed Dose, *D*	The energy absorbed from the radiation per unit mass of exposed tissue.	**rad** 100 ergs per gram	**gray (Gy)** 1 joule per kilogram	1 Gy = 100 rad
Dose-Equivalent, *H*	Absorbed dose weighted for the effectivness of the radiation for causing biological damage.	**rem** H (rems) = Q 3 D (rads) (Q = radiation-weighting factor)	**sievert (Sv)** H (Sv) = Q 3 D (Gy) (Q = radiation-weighting factor)	1 Sv = 100 rem

Other Derived Units

Type of Unit	Explanation	Equation
Effective Dose, H_E	A dose calculated for the whole body in which the dose-equivalents for various organs are weighted to account for different sensitivities of the organs to the radiation.	$H_E = \sum w_T H$, where w_T is the tissue-weighting factor and the summation is over all organs.
Whole-Body Dose, H_W	Dose-equivalent, H, for an exposure that irradiates the entire body uniformly, or the effective dose, H_E, when the exposure irradiates the body non-uniformly and different organs experience different doses.	$H_W = H$ (for uniform dose to body) $H_W = H_E$ (for non-uniform dose)
Collective Effective Dose, CED	A measure of total risk to an exposed population based on the average effective dose, $\langle H_E \rangle$, and the number of people being exposed.	CED = $\langle H_E \rangle N$, where N = number of people in the exposed population.

radiation is dispersed, and no one cell receives a large amount. The energy of the alpha radiation is concentrated, and each gram of irradiated tissue receives 100 times more energy from the plutonium than from the iodine-131. This fact, combined with the radiation-weighting factor of 20 for alpha particles, makes the dose-equivalent 2000 times larger for the alpha particles than for the gamma radiation.

It's the difference between focused and diffuse energy deposition. But that's an important difference when it comes to the effects of radiation damage on tissue and cells!

Irene's Calculations

Say you have 0.1 microgram of plutonium-239 coating the palm of your hand in a 5-centimeter diameter area. What dose do you receive from the 5-MeV alpha particles?

As a rough estimate, we assume that half the alpha radiation penetrates your hand and the other half goes into the air. Earlier, we'd shown that the activity of plutonium-239 is such that one gram of plutonium emits 2.2×10^9 alpha particles per second. Thus, from 10^{-7} gram, the skin would absorb the energy of 110 alpha particles per second, or (since there are 1.6×10^{-6} erg per MeV and 5 MeV per particle) about 0.0009 erg per second.

The alpha particles penetrate 30 micrometers into the skin, so the energy is deposited in a disc of tissue with a volume of about 0.06 cubic centimeter. Using a density for tissue of approximately 1 gram per cubic centimeter, we find that 0.015 erg per second are being absorbed by each gram of exposed skin tissue, which gives an absorbed dose rate of 1.5×10^{-4} rad per second in the skin tissue.

If we apply the radiation weighting factor for alpha particles of 20, we get a dose-equivalent rate of 3 millirem per second. If you go an hour before scrubbing off the plutonium, the dose-equivalent to the irradiated skin is 11 rem, not enough to cause observable skin damage.

What about the dose from the gamma rays of iodine-131? The activity of iodine-131 is 1.24×10^5 curies per gram, about two million times larger than that of plutonium. If there is 0.1 microgram of radioactive iodine in the solution, it will be emitting about 4.6×10^8 gamma rays in all directions every second. As we discussed earlier in the main article, we'll simplify by assuming each decay leads to a single 364-keV gamma-ray photon and calculate that there are 270 ergs per second of gamma-ray energy being emitted in all directions.

How much of this energy is absorbed in the body, say, of a six-foot, 180-pound person standing so his or her midsection is about one foot away? A bit of simplified geometry indicates that the body is intercepting about 6 per cent of the rays. A 364-keV gamma ray is attenuated, that is scatters, with a mean free path of about 10 centimeters in water, but only about a third of its energy is lost in this scatter. This begs for the use of the build-up factor defined earlier. However, for absorption in water at these energies, it's not too bad an approximation to assume that energy deposition is constant, 1/30th of the initial energy in each centimeter, or about 2/3rds of the energy in the 20-centimeter thickness of an average torso. Combining these numbers, we calculate that 11 ergs are being absorbed by the entire body every second.

Next, we divide by the mass of the body—180 pounds or 8.2×10^4 grams to arrive at about 1.3×10^{-4} erg per second per gram, or 1.3×10^{-6} rad per second. With a radiation-weighting factor of 1 for gamma rays, the body is receiving 1.3×10^{-6} rem per second as well. Standing next to the solution for an hour gives a whole-body dose equivalent of 5 millirem.

If we compare the two examples, the body receives about ten thousand times more total energy from iodine-131 than from plutonium. However, each *gram of skin tissue* irradiated by the plutonium absorbs about a hundred times more energy (0.015 erg per second) than that absorbed by each *gram of body tissue* from the iodine-131 (0.00013 erg per second). When the radiation-weighting factor of 20 for alpha particles (versus 1 for gamma rays) is included, the dose-equivalent rate to skin tissue from plutonium is about 2000 times higher than the dose-equivalent rate for the iodine-131. ■

$$\text{Absorbed Dose (rads)} = (\text{Activity}) \times (\text{Average Energy per Particle}) \times (\text{Time of Exposure}) \times (\text{Fraction of Energy Absorbed})$$

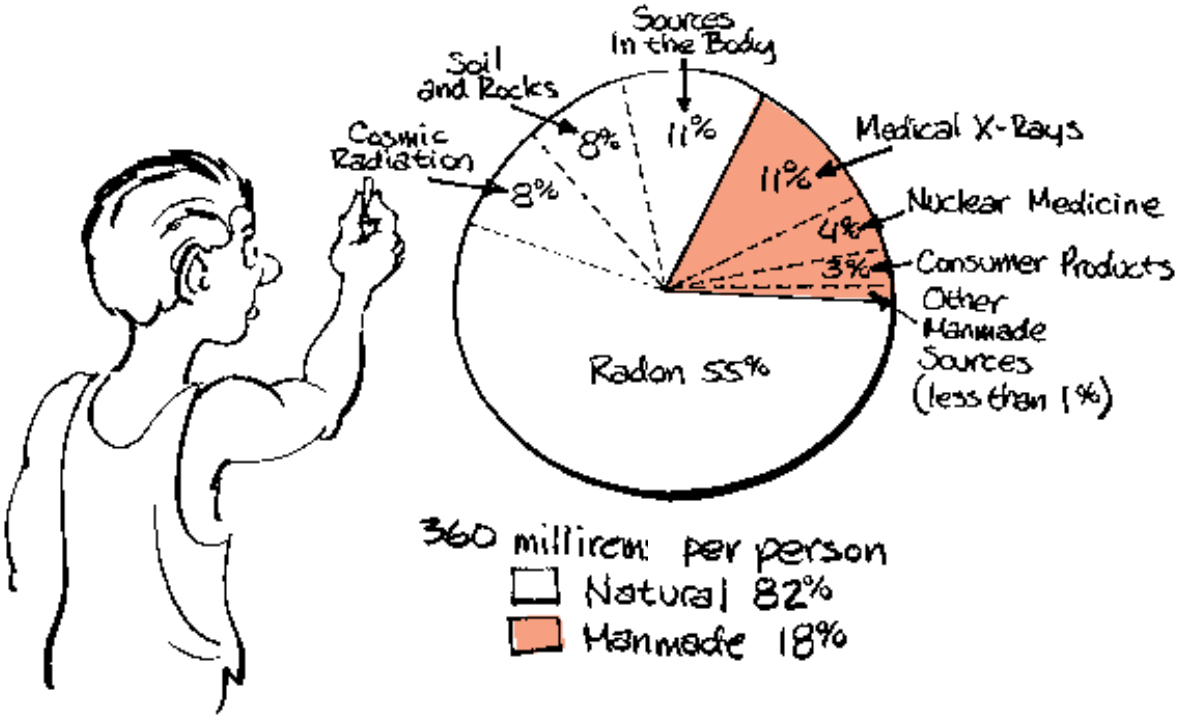
$$\text{Dose Equivalent (rems)} = (\text{Absorbed Dose (rads)}) \times (\text{Radiation Weighting Factor, Q})$$

Sources of Natural Background Radiation

"These numbers are all very nice," you say, "but I've nothing to compare them with."

Just then, Carl enters the room. "What you need is a tour of natural sources of ionizing radiation. If we look at the types of doses everyone is receiving every day, you'll have a much better feeling for what we're talking about."

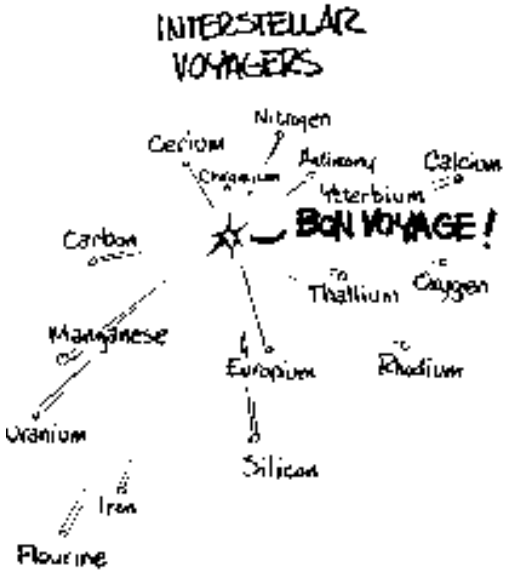
"To give you a reference point," says Irene, "the average person in the United States receives about 360 millirem of ionizing radiation every year. Eighty-two per cent of that—about 300 millirem per year—is from natural sources."



So the three of you grab radiation detectors and head outside to start measuring. Along the way, Carl and Irene discuss the major sources of natural background radiation. They explain that most people are not aware they're constantly being bombarded with ionizing radiation. This radiation is directed at us from the soil beneath our feet, from the heavens above our heads, and even from within our own bodies. Carl suggests we start with the star matter at our feet, and picks up a piece of granite rock to measure its activity.

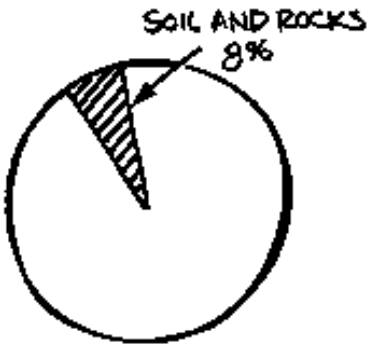
The Soil. Our planet was formed from a cloud of dust containing all the natural elements. Many of these, including a variety of radioisotopes, were trapped in the Earth's crust. Where did this cloud of debris come from?

Astronomers believe that the first stars were formed when only very light elements were present. In stars, many of the lighter elements are fused from hydrogen. Some of these fiery crucibles will become unstable and explode as supernovas, forming many of the other elements and spewing their material outward. New



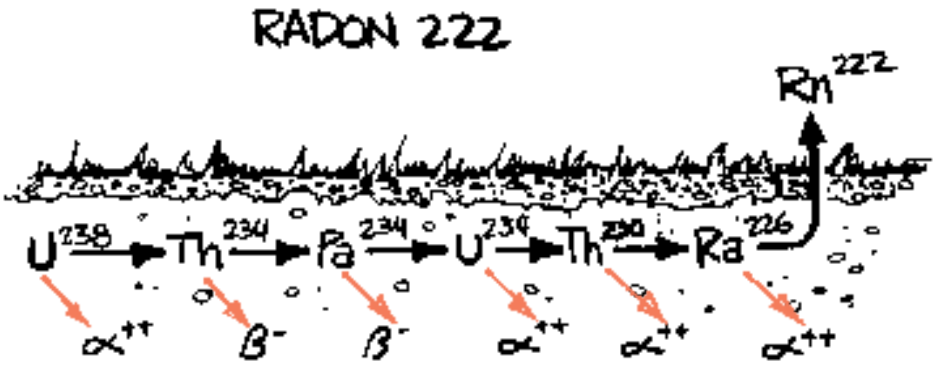
stars eventually form from these clouds and from additional hydrogen, but they now include the heavier elements produced by the previous generation of stars. As the stars form, they may leave behind some matter which coalesces into planets, which have all the elements necessary for life. We are the stuff of stars.

Initially, the ejected clouds of matter contain a broad distribution of stable and unstable isotopes, but the short-lived isotopes decay to stable daughters long before the matter condenses into a solar system. The isotopes with very long half lives, such as uranium-238 (4.5×10^9 years) and thorium-232 (1.4×10^{10} years), remain to become part of the Earth's crust. Uranium, thorium, and their daughters are especially plentiful in igneous rock, such as granite (about 4 parts per million uranium), as well as in bituminous shale (50 to 80 parts per million) and phosphate rock (20 to 30 parts per million). In Florida, the phosphate rock has uranium concentrations of about 120 parts per million! Thus, we breathe radioactive dust, we fertilize our gardens with radioactive materials, and we pour thousands of tons of radioactive atoms into the air every year from the smokestacks of coal-fired power plants.



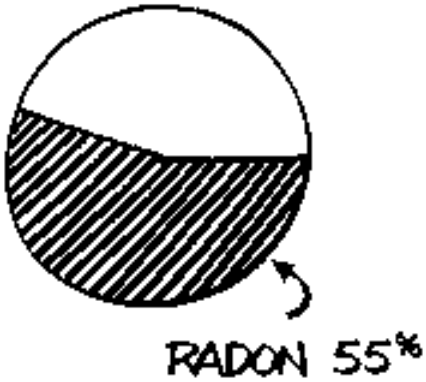
The average person receives an dose-equivalent of about 46 millirem per year from terrestrial gamma rays. This is only about 1.5 nanorem (nano = 10^{-9}) per second, 1000 times less per second than what we were receiving standing next to the iodine-131 solution. But we only stood next to the solution, say, for an hour (6 millirem total), whereas we receive the dose from the soil every second for most of our life. We can get away from it only on boats (although sea water is slightly radioactive also) or in airplanes (but then we get more cosmic rays) or in specially shielded rooms! The yearly accumulative dose-equivalent from the soil (46 millirem) is about nine times more than our one-hour exposure (6 millirem) from the iodine-131 solution.

Radon. Uranium and thorium both undergo a long chain of radioactive decays—the daughters are themselves unstable and continue releasing additional alpha, beta, and gamma radiation until a stable isotope of lead is finally reached. Uranium-238 undergoes eight alpha decays and six beta decays before it reaches the



stable lead-206 isotope. Thorium-232 undergoes six alpha decays and four beta decays before it reaches the stable lead-208 isotope.

Midway through the decay chains for uranium and thorium, radon isotopes are formed. Because this element is one of the rare gases, the type of radiation exposure changes from an external dose to a significant internal dose. Isotopes before radon on the decay chain remain in the soil. Radon, however, can diffuse out of the soil and accumulate in the air we breathe. The most common radon isotope—radon-222—is a member of the uranium-238 decay chain and has a half-life of 3.8 days. The radon isotopes in the other decay chains (thorium-232 and uranium-235) have short half-lives (55 and 4 seconds, respectively), so these radon isotopes typically decay before they can percolate out of the soil.



On the average, more than half of your total exposure to ionizing radiation is due to radon and its daughters (200 millirem per year). Radon itself is not the main culprit—if you breathe the gas in, you mostly just breathe it back out again. However, when the radon decays, the daughter atoms are charged and so stick to dust particles. These daughters can then be breathed in and deposited on the lungs. Once in the lungs, they continue down the decay chain, releasing alpha, beta, and gamma radiation to the tissue.

Water is another major source of radon. This source wasn't accounted for until recently, so the estimates of our average exposure to radon have increased. Water obtained from surface sources, such as lakes and reservoirs, is low in radon because very little of the gas remains dissolved. However, water pumped from wells can have relatively high concentrations of the gas that are released after the water comes from the tap. Your highest exposure to radon may actually come while you're taking a shower!

It's estimated that five to ten thousand cases of lung cancer annually are due to radon (6 to 12 per cent of the total number of cases). Many uncertainties make

Effective Dose, H_E: Weighting the Sensitivity of Organs

The average annual dose from radon is usually cited as 200 millirem (55 per cent of a person's average total dose) even though the actual dose-equivalent to lung tissue is estimated to be 2,400 millirem per year. What's going on here?

The 2,400-millirem dose-equivalent is a direct measure of potential damage to lung tissue. But what is the potential risk to the entire body? To calculate that type of dose, we need to account for the different sensitivities of organs or tissue types and we need to change the basis from an organ-specific dose to a whole-body dose.

A new factor, called the *tissue weighting factor* is applied. For lung tissue exposed to the radiation of radon daughters, this factor is estimated to be 0.08, a combination of the radiation sensitivity of lung tissue and the fraction of total body weight for lungs. Our new dose is then 2,400 x 0.08, or 200 millirem. When tissue weighting factors have been applied, the dose is called the *effective dose*, H_E, and it still has units of rem.

these estimates highly provisional, and a great deal of controversy surrounds the issue of radon. However, a linear relationship between radon exposure and incidence of lung cancer has been observed among uranium miners, where exposures to radon are hundreds of times greater than the average exposures in homes.

The propensity of the radon daughters to stick to a charged surface is so great that racquetballs and handballs have been found to acquire easily measurable radioactivity after being slammed around an enclosed court during a game. If you're not a handball or racquetball fan, a similar experiment is to blow up a balloon, charge its surface by rubbing it on a wool sweater or in your hair, and then walk around the room you want to sample for 10 minutes. Radon concentrations close to 4 picocuries per liter of air (the level at which the EPA recommends remedial action) increases the background counts on a simple Geiger-Müller counter held near the collapsed balloon by a factor of 10 or 20. You can even plot the decay rate and see the composite half-life for the radon daughters of about 45 minutes.

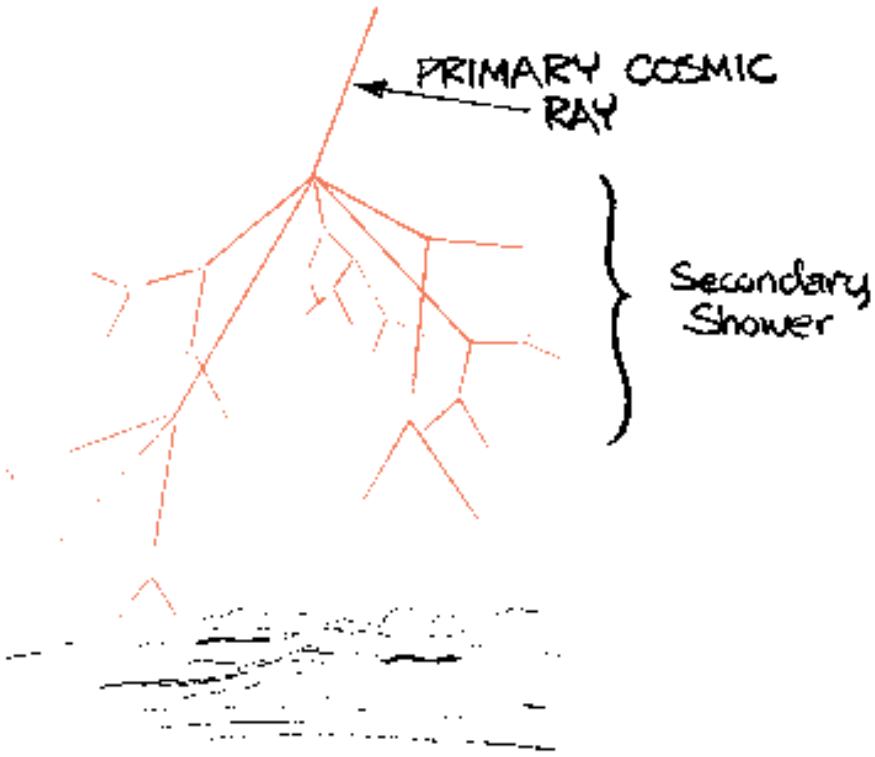
Home Radon Measurements

Many hardware stores carry radon measurement devices. These are usually of two types—charcoal canisters and alpha-track monitors. The charcoal canister is opened for several days, allowing the radon daughters to be absorbed on the charcoal. The canister is then sealed and returned to the lab, where the gamma radiation is measured. This type of device is especially good for initial screening tests, but atypical conditions during the measurement period could lead to an unrealistic value for the radon level.

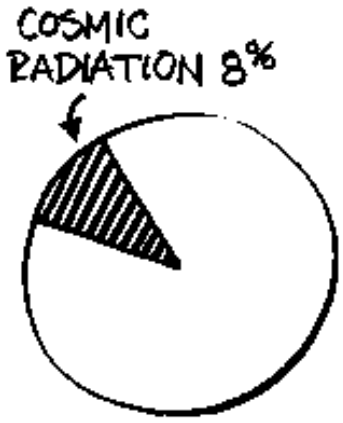
The alpha-track monitor provides a better measurement of average exposure because it can be hung on a wall for months before it's returned to the lab for analysis. The device is called an alpha-track monitor because the alpha radiation from the radon daughters creates damage tracks in a piece of plastic. An etching process at the laboratory makes these tracks visible so they can be counted. The density of tracks is a direct measure of the amount of daughters that had been deposited next to the plastic.

A more accurate way to measure radon levels is to take a series of measurements with EPA-approved radon devices. A series, or a long-term measurement, is necessary because there are many variables that influence radon levels, including the time of day, the season, the geology of the soil, home construction, barometric pressure, humidity, moisture in the soil, rate of ventilation in the home, and so forth. As a result of so many variables, two similar houses built on adjacent lots may show vastly different concentrations of radon.

Cosmic Radiation. The heavens contribute further to our background with *cosmic radiation*. In outer space, such radiation consists of the complete spectrum of photons from radio frequencies to ultra-high-energy gammas as well as high-energy particles (protons and other atoms stripped of their electrons). On their way to the moon, the Apollo astronauts literally "saw" this last type of cosmic radiation—when their eyes were closed, they would occasionally notice tiny flashes of light as energetic heavy nuclei hit their eyeball.



Cosmic radiation is constantly bombarding our atmosphere. This radiation has a very wide range of energies, but on the average, it's about 1000 times more energetic than that emitted by radioisotopes. Fortunately, the high-energy primary radiation is degraded by the upper atmosphere in collisions with atoms and molecules that generate a shower of lower-energy secondary radiation.

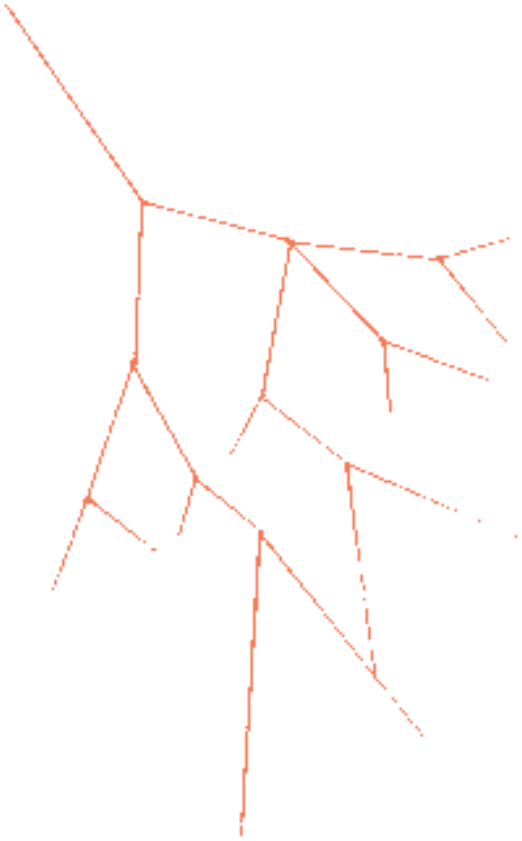


By the time the shower reaches the lower atmosphere, it has undergone many transformations and now consists of electrons, gamma rays, and more exotic but highly penetrating particles, some of which travel deep into the Earth. Roughly 20 particles per square centimeter arrive each second at the top of the atmosphere, but even with the many-particle showers occurring, only one particle per square centimeter per second remains at sea level.

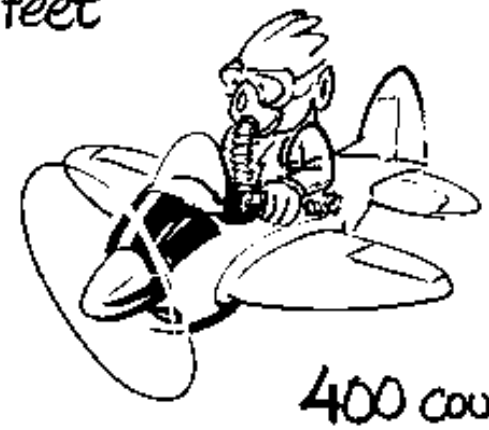
Occasionally, an ultra-high-energy cosmic ray hits the atmosphere, generating a shower of millions of particles that spreads over several square kilometers of the Earth's surface. The initial particles have energies up to 10^{13} times that of normal radioactivity, but they hit the upper atmosphere with a frequency much less than one per square kilometer per year.

On the average, your dose-equivalent from cosmic radiation is about 39 millirem per year. People living at sea level receive the least—26 millirem. People living in a mile-high city receive 55 millirem, adding about 7 percent to their total annual dose.

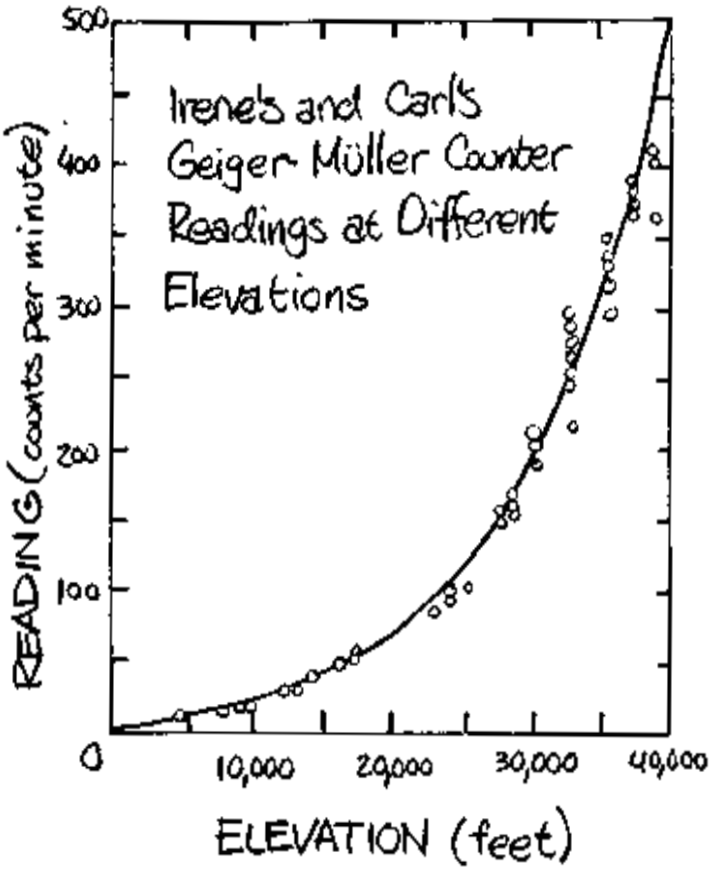
Traveling 2000 miles in a jet airliner, adds another 2 millirem. A Geiger-Müller counter that reads about 10 to 15 counts per minute at sea level, will record about 400 counts per minute at 40,000 feet. It has been estimated that airline pilots and crew members receive a higher occupational radiation exposure than x-ray technicians or nuclear power plant workers!



40,000 feet

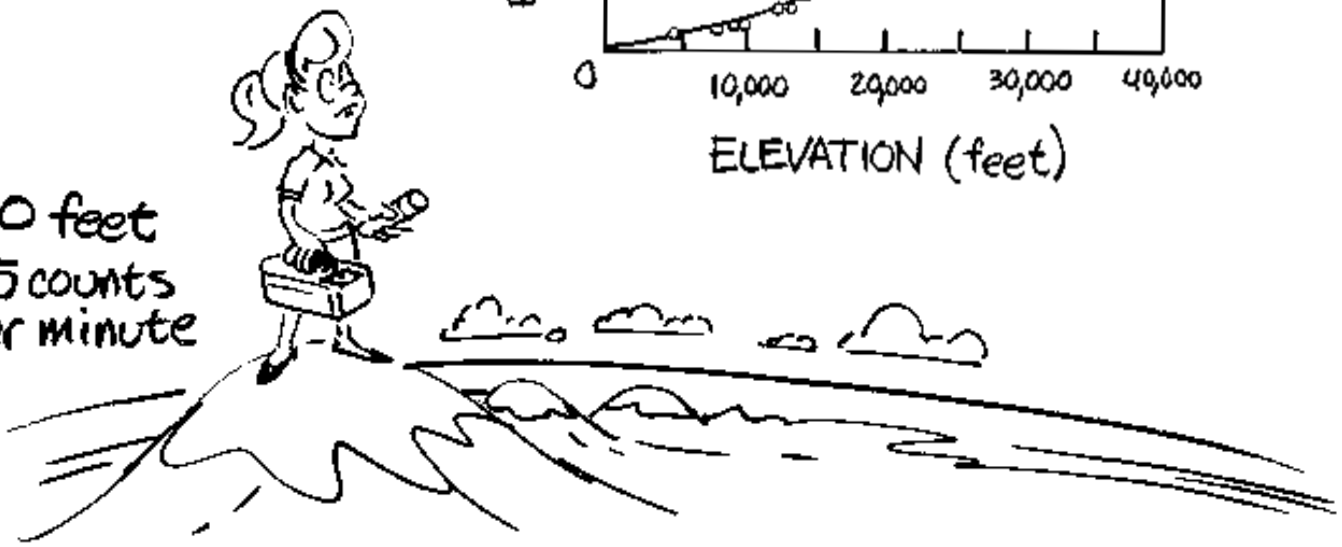


400 counts per minute

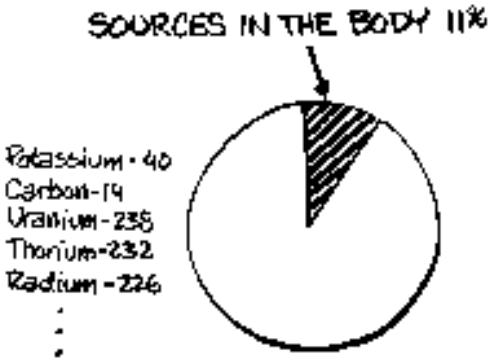


Geiger-Müller readings in counts per minute collected by Irene and Carl at various elevations while in a boat on a lake (lowest elevations), in a small plane with an altimeter (9000 to 17,000 feet), or during commercial flights while on business or vaction (above 20,000 feet) with the elevations announced by the pilot.

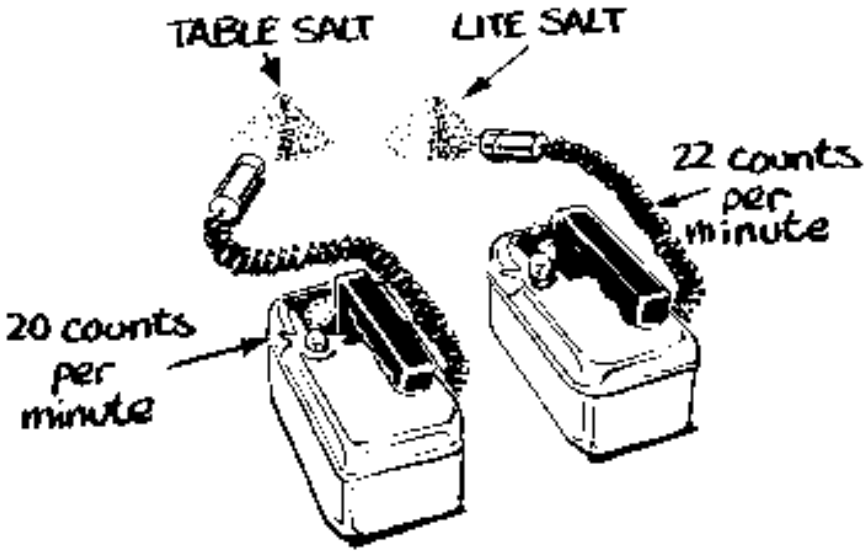
10,000 feet
25 counts per minute



Internal Exposures. Because we are the stuff of stars, we also have long-lived radioisotopes in our own bodies! In fact, about 11 per cent of our total annual dose of ionizing radiation is from internal exposures. This amounts to an effective dose of 39 millirem per year.



There are two main sources of these radioisotopes—long-lived primordial elements and radioisotopes generated by cosmic rays. The most important example of the first type is potassium-40, which has a half-life of 1.3×10^9 years. Potassium is a major element in the biochemistry of life and is distributed throughout our bodies, particularly in muscle. Potassium-40 constitutes only 117 parts per million of natural potassium, but this small amount is enough for a 70-kilogram person to have more than 4000 beta disintegrations occurring in his or her body every second! This isotope is by far the predominant radioactive component in normal foods and human tissues.



We also ingest uranium, radium, and thorium in the food we eat. For example, the skeleton of an average person is estimated to contain about 25 micrograms of uranium, which translates to about 0.3 disintegration per second (or one every three seconds). Thorium is the least active and least soluble of these three elements, so its contribution to our internal dose is small compared to uranium and radium.

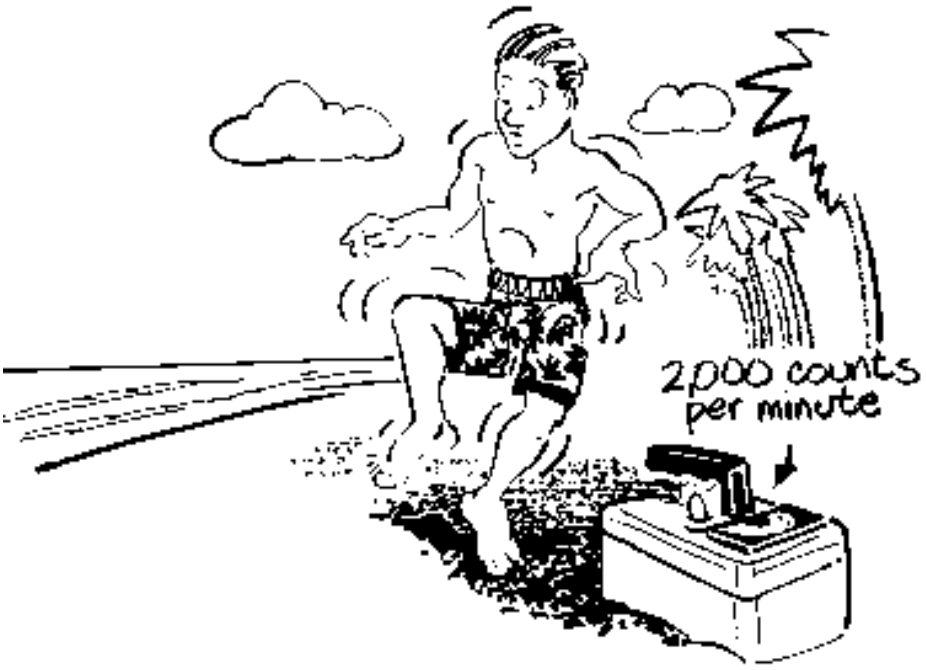
Radium-226 and its daughters are responsible for a major fraction of the internal dose we each receive. An isotope a third of the way down the uranium-238 decay chain just before radon, radium-226 is present in both soil and water. It's chemically similar to calcium and barium, so it passes easily into the food chain. Although most foods, especially cereals, have radium in them, brazil nuts, which concentrate barium, have been found to have radium concentrations a thousand times greater than those in the foods making up the average diet (although this sounds large, it's still hard to detect with an ordinary Geiger-Müller counter and is not a particularly good reason to stop eating brazil nuts).

Eighty percent of the radium that stays in the body ends up in the bone. It has been estimated that the average adult skeleton receives several disintegrations per second from radium and even more disintegrations per second from its daughters, all of which emit mainly alpha particles. The original estimates for the health hazards of plutonium were based on knowledge about the effects of radium, because it was suspected that plutonium would also migrate to the skeleton.

A radioisotope that's a product of cosmic radiation is carbon-14. This isotope is generated when a neutron collides with a nitrogen-14 atom in the atmosphere and a proton is ejected, converting the atom to carbon. Carbon-14 has a half-life of 5730 years and so can circulate through the atmosphere and become incorporated in growing plants, trees, and other life. Such incorporation stops when the organism dies. Measuring the remaining concentration of the isotope in organic debris is a standard method for determining the age of archeological discoveries when the age is of the order of hundreds to tens of thousands of years.

A typical adult has enough carbon-14 to have about 4000 beta decays per second, the same as potassium-40. However, in this case, the energy of the beta is very low (155 keV compared to the 1.31 MeV betas and 1.46 MeV gammas of potassium-40), so the ionization energy deposited in the tissue is about a factor of 8 less.

Variations in Background. The choice of where you live is a major factor in your day-to-day exposure to ionizing radiation. Living in the Rocky Mountain states, such as Colorado, Wyoming, or New Mexico, can more than double your average exposure from environmental sources over the national average. This increase is due to both the geology (adding 65 millirem per year) and the mile-high altitude of the region (adding 28 millirem per year of solar radiation). On the other hand, living in the gulf region, such as Texas and Louisiana, an area close to sea level with a sedimentary geology, can reduce your average exposure from the national average by 6 or more millirem per year.

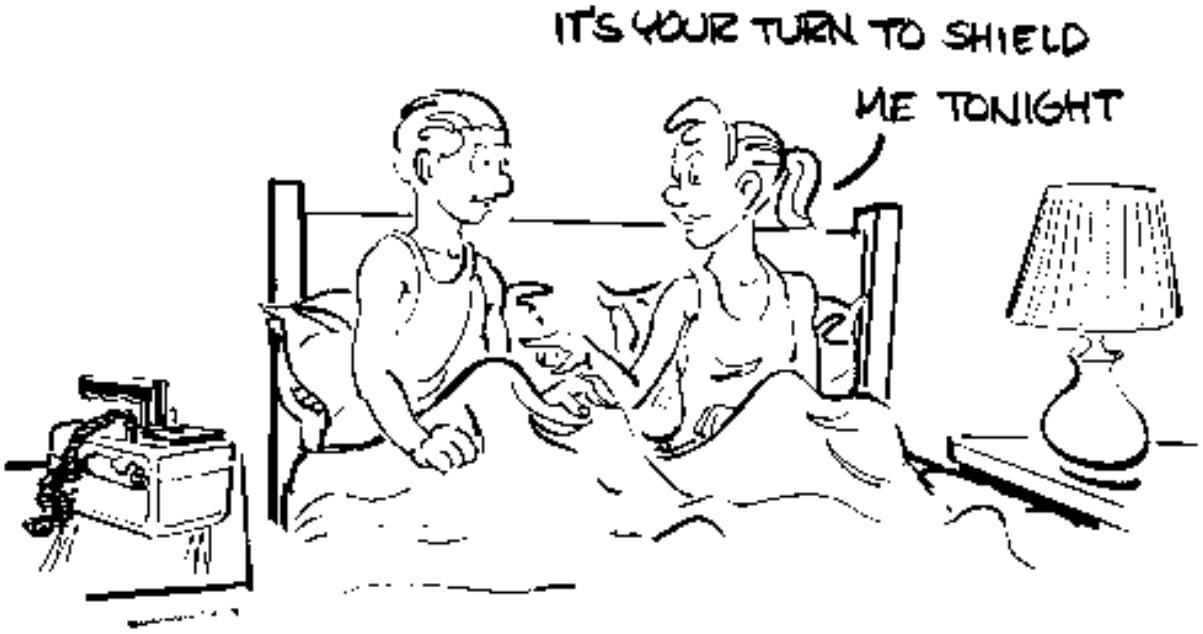


Several locations in the world are unique in having very high concentrations of thorium and thorium daughters in the soil that give rise to high external radiation exposures. For example, areas along the Brazilian coast and in the State of Kerala in India have monazite sands or soils containing thorium concentrations that can be as high as 10 per cent. Measurements on the black-sand beaches in Brazil, for example, show external dose rates that are a thousand times larger than the average terrestrial exposure (5 millirem per hour versus the normal 3 *micro*rem per hour).

People living in these areas do not, of course, spend most of their time directly on the beach but may, nevertheless, receive annual exposures higher than the maximum permissible occupational exposure to ionizing radiation in the United States (5 rem per year). Studies have tried to measure whether or not such continually high levels of radiation have caused detectable biological effects on populations in these areas, but so far they've been inconclusive.

Where's the best place to minimize the natural background radiation? One possibility is to live in a mine shaft that's been drilled into a thick layer of salt several thousand feet below the ground! The salt will contain very little uranium, and the earth will shield out most of the cosmic radiation. In this environment, a Geiger-Müller counter would record, say, about 2 counts per minute, rather than 10 to 20. However, only physicists trying to do experiments in an environment free of radiation, such as detecting the highly penetrating exotic particles in cosmic radiation, consider spending much time in such a habitat. If you continued eating normal food, you'd be the most radioactive object down there!

A tongue-in-cheek recommendation is that it's better for you and your companion to sleep in twin beds so as not to receive additional radiation from each other's bodies. However, at high elevations, it might be preferable to sleep close together so that your bodies provide a degree of mutual shielding from cosmic rays!



Man-Made Sources of Ionizing Radiation

"Well," you say, "What about our highly technological society? Aren't we adding all sorts of radiation sources?"

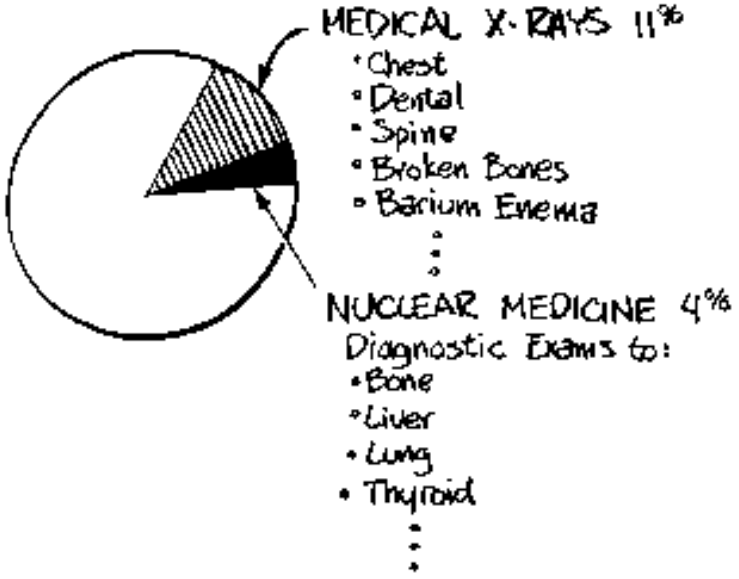
"Let's find out?" Irene says, and the three of you expand your search by exploring man-made sources of ionizing radiation. These sources include medical diagnostic procedures and treatments, consumer products, such as video displays and anti-static devices, life-style choices, such as airline travel and smoking, occupational exposures, such as mining and the nuclear-power industry, and world-wide exposures to the public, such as the fallout from atmospheric weapons testing (which peaked in the mid-sixties) and radiation leaks from nuclear facilities.

Medical Exposures. The greatest man-made exposures to average individuals are from medical procedures. For example, a typical diagnostic chest x ray increases a person's annual dose by about three per cent (10 millirem), a thyroid

scan using radioactive iodine may double the dose (adding another 300 or 400 millirem), and a dental x ray may only add 1 percent (1 millirem).

The purpose of diagnostic exposures is to see if a medical problem exists. As a result, there's a need to balance the potential benefit of learning about a serious but treatable problem against the damage that the radiation itself may do. The controversy over the use of x rays for detection of breast cancer in women, for example, is essentially a social exercise in deciding how to weigh the benefits against the costs. How often should such exams be given? At what age should they be started? What role should factors such as the latency period or the genetic predisposition to breast cancer play? The frequency of breast cancer in young women is so low that, for this age group, the risk of x rays generating damage or even the economic cost may outweigh the infrequent benefit of detecting an early tumor.

Advances in technology (such as more sensitive x-ray film) allow medical facilities to use lower exposures to gain the same information. Also, longer-lived radioisotopes that emit particle radiation are being replaced with shorter-lived radioisotopes that do not emit particle radiation. Iodine-131 has an 8-day half-life and emits beta particles, whereas iodine-123 has a 13-hour half-life and decays



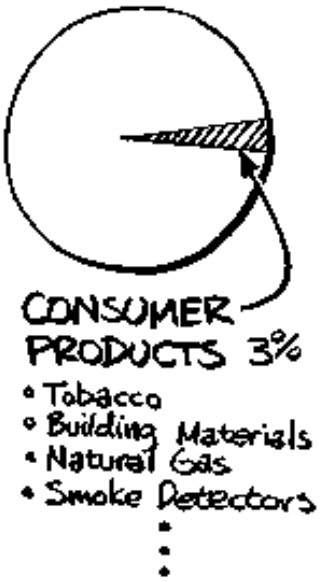
without emitting particle radiation, yet either can be used to examine the thyroid (if the patient is not so far from where the iodine-123 is produced that the isotope decays to too low an activity before it arrives).

In general, diagnostics that increase one's exposure to ionizing radiation by a fraction of the annual background appear to be a risk that the public finds acceptable. When other symptoms indicate the presence of a serious problem, higher exposures become acceptable.

Besides diagnostics, ionizing radiation can be used for medical treatment. Frequently, the purpose of the radiation is to kill a life-threatening cancerous growth, and exposure levels jump by orders of magnitude. Cancer patients undergoing radiotherapy receive many thousands of times their annual exposure to natural sources. Once again, though, advances in nuclear and accelerator technology are helping to make the radiation for certain therapies more site-specific, using the ionizing energy to kill the targeted cells with less collateral damage to healthy tissue.

Consumer Products. "What if I manage to stay out of my doctor's and dentist's offices?" you ask. "Where am I most likely to be exposed to ionizing radiation from man-made sources?"

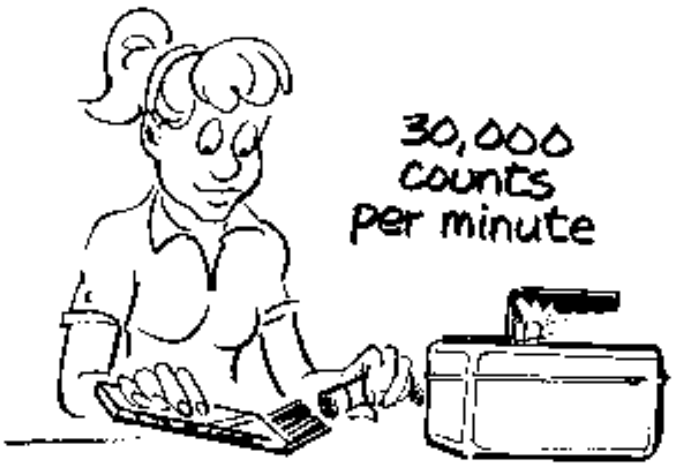
Carl answers that it depends on life style and choice of consumer products. He and Irene discuss several examples to show the wide range of possible sources.



Before and during World War II, radioluminous paint containing radium was used on gauges, markers, instrument dials, and clocks and watches to make the numbers and marks visible in the dark. After the war and into the seventies, millions of radioluminous timepieces were sold annually. Gradually, though, radium was replaced by other radioisotopes, such as tritium and promethium-147, both of which emit relatively low-energy betas that, unlike the gamma radiation of radium and its daughters, can be stopped by the watch or clock face. The average annual exposure to radioluminescent sources is now probably less than 10 microrem.

Many smoke detectors use an alpha source of americium-241 to detect smoke. How does this work? In the detector, a continuous current flow is created by using a voltage on a metal plate to accelerate and capture the alpha particles and the ions they create as they travel through the air. The distance between the source and the metal plate is about an inch, just at the edge of the normal range of the alpha particles. If smoke particles float into this stream, they alter the current flow, and the alarm goes off.

Is the smoke detector a significant source of radiation exposure to the public? The metal plate and the plastic case of the detector easily block the alpha rays and only a tiny amount of gamma radiation (from impurities and the neptunium daughters) escapes. Even with a radiation detector placed against the case of the smoke detector, radiation above normal background is difficult to detect. The main exposures from the americium-241 are to workers assembling the devices. Another concern, of course, is the possible leakage of the radioisotope into the environment when the detectors are discarded.



One of the most radioactive of consumer devices is the static eliminator, such as certain brushes used to clean negatives and CDs. These devices also take advantage of the ionizing power of alpha particles—in this case, reducing electrical-charge buildup. The brush is constructed so that the range of the alpha particles in air is about the distance from the source to the surface being cleaned. Generally, these devices use polonium-210 and are extremely active when you first buy them. However, the half-life of polonium-210 is only 138 days, so after seven half lives (2.5 years), the ionizing ability of the device will be a hundredth of what it was when purchased. If the brush has been used regularly for that long, the bristles will be dirty anyway.

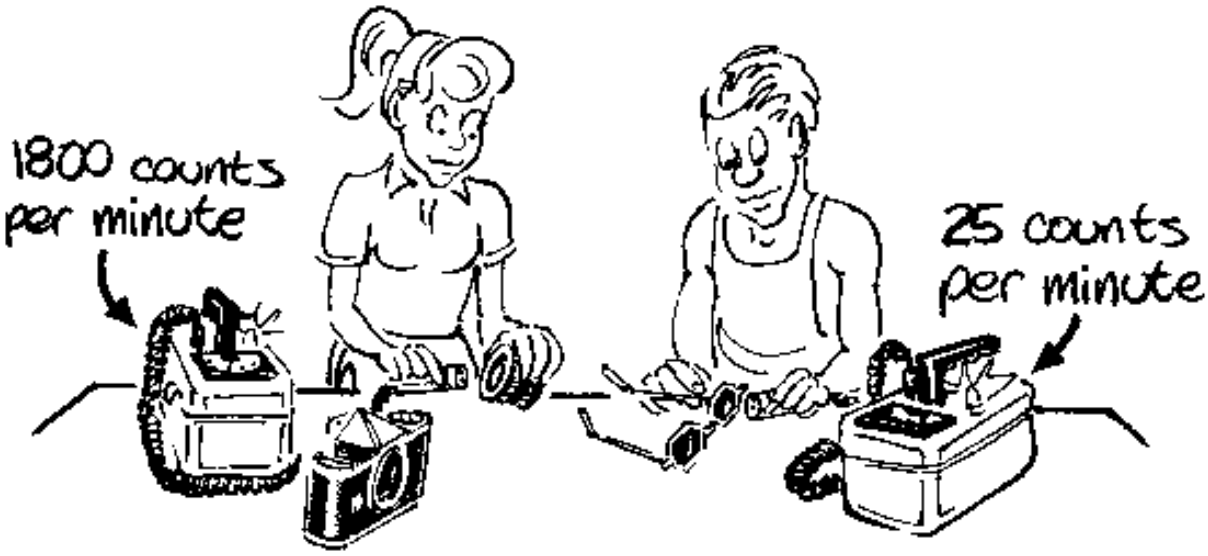
In past years, a source of ionizing radiation in the home was certain types of ceramic dinnerware. Manufacturers would mix uranium oxides or sodium uranite in their glazes to render colors of black, brown, green, and the spectrum from yellow to red. Such tableware can add tiny amounts to a person's annual exposure. More important, though, is ingestion of uranium if the glaze is cracked or hasn't been applied properly. Also, in some cases, the uranium can be leached from the glaze. The main hazard, however, is the chemical toxicity of the uranium (and lead) rather than the radiation. But it's interesting to check your ceramic dinnerware, such as the older, red-orange Fiestaware, with a Geiger-Müller counter to see if it's radioactive.

Experimenting with Alpha Sources

You can use the alpha source from a smoke detector or an anti-static brush to illustrate the limited range of alpha particles in air. Holding the source close to the mica window of a Geiger-Müller counter will give tens to hundreds of thousands of counts per minute and a sound that's close to a steady buzz.

As you move the source away from the window slowly, the buzz dcreases slightly because the beam of alpha particles is spreading. But at an inch or so from the tube, the buzz suddenly disappears. This drop in activity happens because you've reached the end of the range of the alpha particles—they're losing all their energy ionizing the air and no longer reach the counter.

Other surprising sources of small but steady exposures (tenths of a rem per year) to ionizing radiation are dental products and eyeglasses. Uranium has commonly been used in porcelain teeth and crowns to add whiteness and fluorescence—sparkling white! Certain ophthalmic glasses used for lenses and eyeglasses contain oxides of thorium and rare earths that make them radioactive. Rose-tinted glasses that have had thorium salts added as the tinting compound are especially bad. With increased regulation and the greater use of plastic lenses, this type of

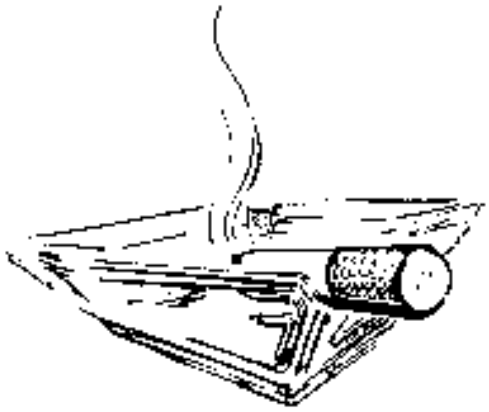


exposure to the public is being reduced. However, you may find that some of your camera lenses are radioactive because of thorium that has been added to increase the index of refraction.

Life Choices. Potentially one of the most serious radiation exposures for many people is cigarette smoking. The large tobacco leaf—like the absorbing surface of charcoal in a radon test device—provides an excellent surface for collecting the

long-lived daughters of airborne radon. As a result, tobacco has above-average concentrations of lead-210 and polonium-210. A 1987 report by the National Council on Radiation Protection and Measurements states that "tobacco products probably contribute the highest dose to the U.S. population of all consumer products."

Although external exposures to people from these radioisotopes is minute, smoking the tobacco creates large exposures to the lungs. The compounds of polonium-210 are generally volatile and are probably just breathed in and out. However, insoluble particles of lead-210 may concentrate in "hot spots" where the bronchi divide, leading to the growth there of the polonium-210 daughter and high local exposures. Small portions of the lungs receive annual dose equivalents that are huge (16,000 millirem) compared to the dose other cells in the body are getting from natural background radiation (360 millirem). This estimated dose equivalent is 8 times larger than that to lung cells from radon (2,400 millirem).

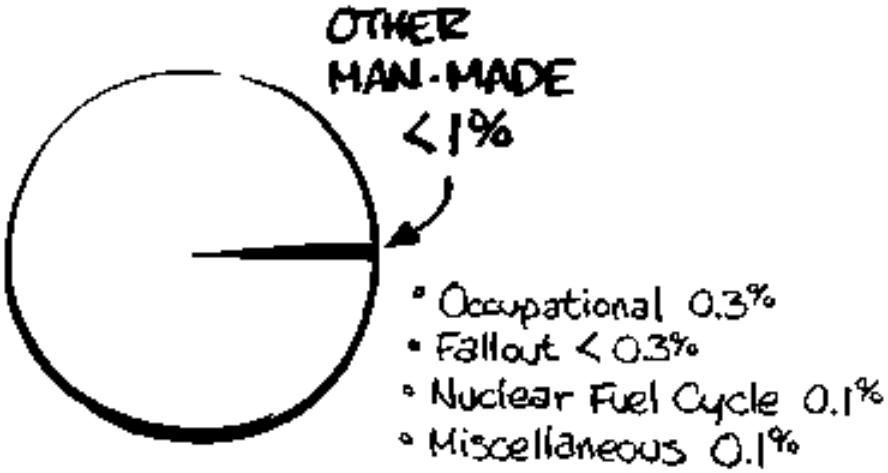


It's suspected that such radiation may be one of the major causes of lung cancer for smokers. In fact, certain studies of radon exposures show a synergistic relationship between smoking and radon—the combined risk appears to be greater than simply an additive effect of the two risks.

Another life choice that affects your annual exposure to ionizing radiation is the type of buildings you live and work in. For example, a masonry home, such as brick, stone, concrete, or adobe, can add another 2 per cent (7 millirem) to your annual exposure from radioisotopes in the building materials. This exposure is in addition to any effects the type of construction has on radon accumulation in the building.

Occupational Exposures. "But what about the people who have to work with this stuff?" you ask. "Aren't there problems for radiation workers?"

Indeed, one of the major ways people can be exposed to ionizing radiation at levels significant compared to the natural background is through the workplace. The medical application of x rays, industrial radiography, and work at nuclear power plants or for nuclear-weapons defense contractors obviously have the potential to expose workers to significant doses. Such occupations are carefully regulated and the workers are continuously or frequently monitored. Other workers, such as

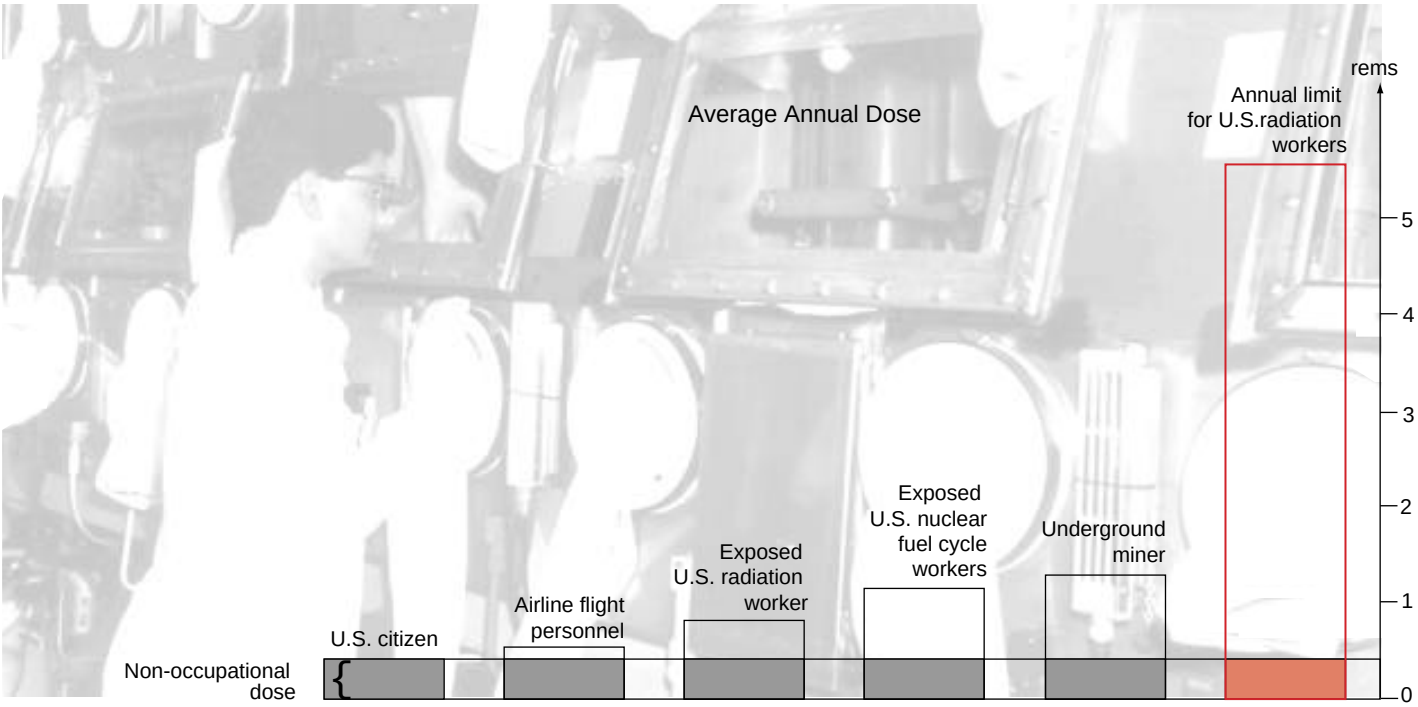


mining or airline personnel can also receive significant exposures.

The 1987 report by the National Council on Radiation Protection and Measurements estimates that about 1.6 million workers were potentially exposed occupationally to ionizing radiation in 1980, but only about half of those received measurable doses. The average effective dose to those in the latter group added about 60 per cent to their annual dose (210 millirem).

Exposures within certain groups were, of course, higher than the average. Exposed workers involved with the nuclear fuel cycle, on the average, added 600 millirem to their annual effective dose of ionizing radiation, almost tripling their total. The annual limit established by national standards for people in this group is 5 rem per year, 14 times larger than the national annual average.

Underground miners, on the average, tripled their annual effective doses (an addi-



tional 700 millirem), chiefly because of the alpha radiation of radon daughters. This type of exposure is minimized by using proper safeguards, such as adequate ventilation or filtered breathing devices. During World War II, such provisions were not used with the uranium miners in the southwest, resulting in high numbers of lung cancers among the miners.

Flight personnel on airlines flying at altitudes around 20,000 or 30,000 feet, receive, on the average, about 100 millirem per year (the same as ten diagnostic chest x rays, except the exposure during flight is to the whole body, not just the chest). This example illustrates the importance of the time of exposure, because everyone, including the passengers, receive only 0.2 millirem per hour, but the flight personnel are in the air about 500 hours a year.

Exposures to the General Public. "But how much of the radiation from these occupational sources leaks out to the public," you ask next.

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Splitting the Nucleus

The heaviest nuclei, those of plutonium and uranium for instance, may break into two large fragments, a process called *fission*. Sometimes fission may occur in the undisturbed nucleus (spontaneous fission), and sometimes energy has to be added to the nucleus, perhaps by the collision of a slow neutron (slow, or thermal fission) or perhaps by the collision of a more energetic neutron (fast neutron fission). Usually, several energetic neutrons fly out in addition to the two large fragments. If these neutrons collide with other unstable nuclei, further fissions can take place. Thus, each fission increases the number of neutrons available to generate more fissions, which is the basis of the chain reaction that powers nuclear reactors and the nuclear-fission bombs.

An example of a neutron-induced fission is:

$$ {}_0n^1 \; 1 \; {}_{92}U^{238} \rightarrow {}_{56}Ba^{139} \; 1 \; {}_{36}Kr^{97} \; 1 \; 3 \; {}_0n^1 $$

where the subscript on the left gives the atomic number, the superscript on the right is the nucleon number, and ${}_0n^1$ stands for a neutron. Note that the total number of protons (92) and the total nucleon number (239) is conserved in the reaction.

The two main fission fragments are typically unstable and, thus, subject to further decay and release of radiation. Neutron-induced fissioning of uranium or plutonium creates a large distribution of such fragments, typically ranging in nucleon number from 80 to 160. The most unstable of these decay rapidly. Others, including daughters of the short-lived fragments, are more stable with longer lives.

In any fission chain reaction, large numbers of neutrons are flying around. Because neutrons are neutral, they're not repelled by the nucleus and are frequently absorbed by the nuclei of other atoms, creating new radioisotopes. This process is called *neutron activation*. (It should be noted that when materials are exposed to alpha, beta, gamma, or x rays, any similar activation processes only occur at much, much lower levels. Thus, irradiating strawberries with gamma rays to kill bacteria does not make them radioactive.)

Much of the radioactive fallout of atmospheric weapons testing is a result of neutron activation of ground debris and materials in the air. Likewise, one of the main design considerations with nuclear reactors is to minimize production of radioisotopes by choosing structural materials and coolants that are low neutron absorbers. It's equally important to eliminate corrosion products and other impurities that can be activated as they circulate through the core.

The radioactive waste that the nuclear power industry is struggling to figure out how to store or eliminate consists of both fission fragments and neutron-activated radioisotopes. The main concern in accidental releases from reactors are the more volatile fission fragments present in the core. However, much of the neutron-activated material is present in aqueous waste, which can leak into the environment over long periods.

It's been estimated that on the first day of a nuclear power plant accident around 83 per cent of the dose received by people downwind is from iodine-131. The major contributor to the dose integrated over several years is from another radionuclide, cesium-137, which emits beta and gamma radiation and has a thirty-year half-life. ■

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"Actually, very little," Irene answers. "For example, it's estimated that the U.S. population receives only an average of about 0.4 millirem, or 0.1 per cent of their average total annual dose, from all operations related to nuclear power generation."

"From all operations?"

"Yes. That includes mining, milling, and enrichment of the ores, fabrication of fuel elements, releases by nuclear power plants, waste storage, and transportation. Of course, these numbers have been averaged over the entire U.S. population."

"What about someone living right next to one of the sites?"

The 1987 report by the National Council on Radiation Protection and Measurements estimates that the "maximally exposed individual member of the public" receives only 0.6 millirem per year from pressurized water reactors and 0.1 millirem per year from boiling water reactors, the two common types of reactors in the U.S. People living close to other types of operations can receive higher doses. For example, the maximum effective dose from airborne effluents might be 260 millirem per year from certain milling operations and 61 millirem from certain underground mining operations. In both cases, these numbers were based on the assumption that the exposures were at the maximum allowed levels. In practice, much lower exposures are usually experienced, and many operations have lower maximum values than the ones given here (some milling operations are as low as 0.4 millirem per year).

"That's fine for normal operations, but what if there's an accident?"

Certainly, the potential doses to the U.S. population from a major nuclear power plant accident could be very significant. The worst accident to date in the U.S. occurred at the Three Mile Island Nuclear Plant on March 28, 1979. The maximum individual effective dose to the public from that accident was less than 100 millirem, and the average dose to people living within a 10-mile radius of the plant was 8 millirem.

The Chernobyl accident in Russia on April 26, 1986, was much worse. Thirty-one people (firemen and workers at the plant, who received exposures up to 1600 rem) died from the accident, and 135,000 people in the region were permanently evacuated. Reports by the Russians to the International Atomic Energy Agency (IAEA) give the average dose to the evacuees as 12 rem—1500 times greater than the average dose to people around the Three Mile Island plant.

The distribution pattern of exposures around Chernobyl was very uneven, so that doses to the public ranged from 0.4 to 300 rem (which means some people received a dose of up to 800 times their annual background in only a few days!). A dose of 100 rem to an adult normally produces clinical signs of radiation sickness and requires hospitalization. These total doses included external gamma radiation, beta radiation to the skin, and internal doses to the thyroid from iodine-131.

In the first year after the accident, it has been estimated that residents of seven western European countries received doses that, for adults, ranged from 130 millirem in Switzerland to 2 millirem in southern England. Adults in Poland received up to 95 millirem.

Pripyat is now a radiation ghost town. Nearly 3 million acres of agricultural land

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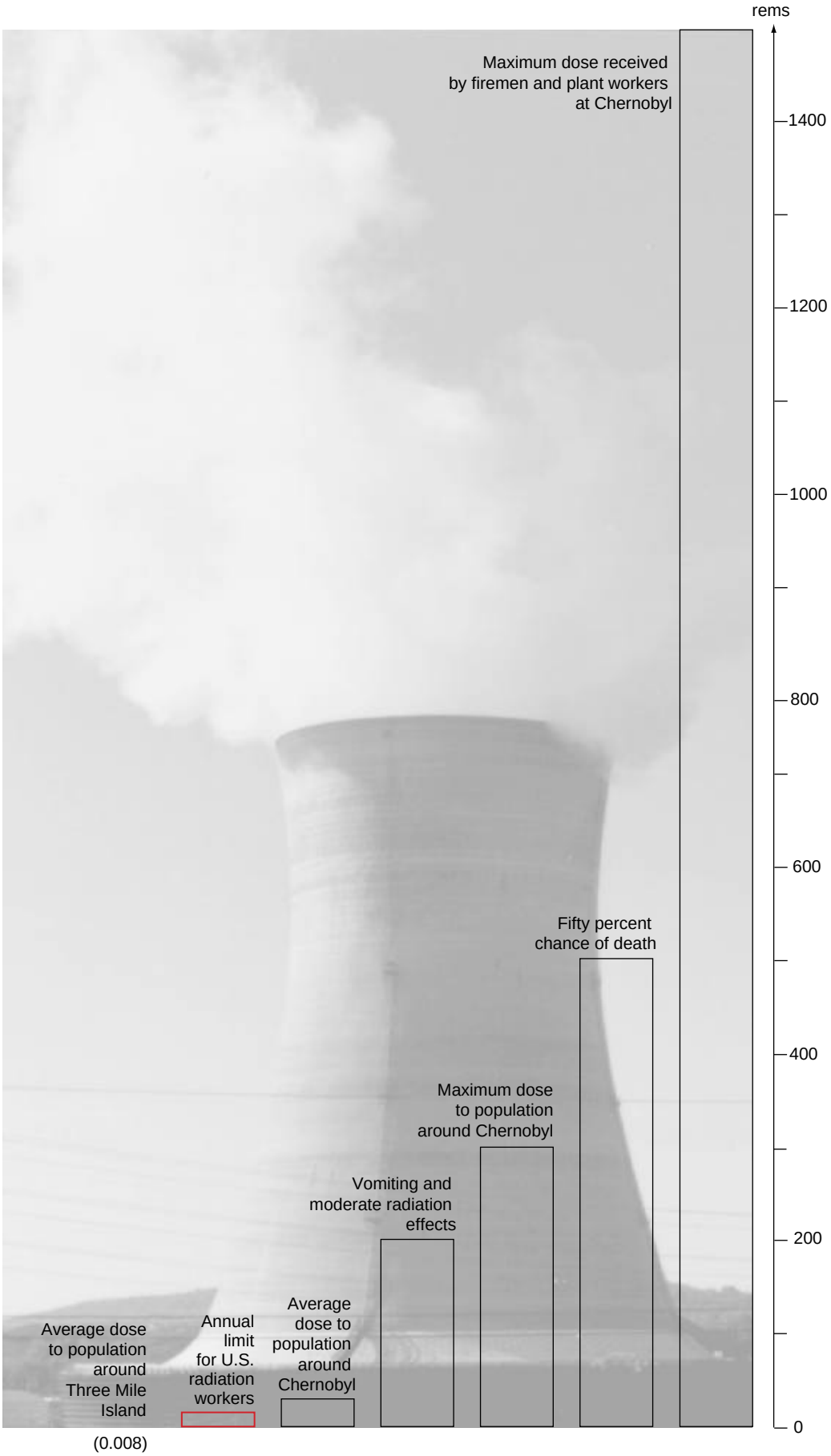
rems
Maximum dose received by firemen and plant workers at Chernobyl
1400
1200
1000
800
600
Fifty percent chance of death
400
Maximum dose to population around Chernobyl
Vomiting and moderate radiation effects
200
Average dose to population around Chernobyl
Annual limit for U.S. radiation workers
Average dose to population around Three Mile Island
(0.008)
0

The Collective Effective Dose: Looking at Populations

Absorbed dose, dose-equivalent, and effective dose all apply to individuals—or at the most, to an average individual. How does one estimate the risk of exposures to various populations?

To start with, we calculate the average effective dose for the people being exposed and then multiply by the number of people who have been exposed. The resulting value, the collective effective dose in units of person-rem (or person-sieverts), is a measure of the expected cancer risk in the exposed population.

Let's compare two drastically different exposures to see how this might work. The NCRP reported that in 1980 nuclear-fuel-cycle workers received an average effective dose of about 600 millirem. There were 91,000 people in the exposed group, so their collective effective dose was 54,600 person-rem. The NCRP also estimated that people using natural gas cooking ranges received (from radon in the gas) an average effective dose of about 0.37 millirem—1600 times lower per person than what the nuclear workers received. However, 125 million people were exposed to natural gas cooking ranges, so their collective effective dose was about 46,200 person-rem, almost the same as the nuclear workers. This means that about as many cancers should result from the use of natural gas for cooking as from workers involved with the nuclear fuel cycle.

Do you believe this? Remember, estimates enter the calculations in at least two places. First, radiation weighting factors are used so that the nuclear workers irradiated with neutron and gamma irradiation can be compared with people using gas ranges irradiated with the alpha and beta radiation of radon daughters. Second, tissue weighting factors are used to compare the whole-body irradiation of nuclear workers to the lung-tissue irradiation from deposited radon daughters.

A key assumption in all such calculations is that risk is linearly proportional to dose and independent of dose rate! Thus, high doses to a small group of people are assumed to lead to the same number of cancers as low doses to a proportionately larger group of people. Likewise, a one-rem dose from a short, single exposure is assumed to create the same harm as a one-rem dose from a slow, continuous exposure.

Now what is the increased risk to the entire U.S. population of people cooking with natural gas or of other people working in nuclear power plants? We divide the collective effective dose by the entire U.S. population (230 million in 1980) to obtain the average effective dose per capita. In other words, the dose has been spread out over the entire population.

With 54 per cent of the population cooking with gas, the annual doseis 0.2 millirem per person in the U.S. instead of the original 0.37 millirem per person exposed to gas-range cooking. With the nuclear workers, however, the annual dose is 0.2 millirem per person in the U.S. compared to the very large original dose per exposed worker of 600millirem.

In many ways, of course, the average effective dose per person in the U.S. is highly artificial, especially when the group of people actually exposed is small. But this dose is a measure of the expected increase in cancers in the U.S. due to the particular activity. Such a number is the basis of statements you may read in the newspaper (at least, it should be the basis) that cite the additional cases of cancer that may occur in the U.S. if, for example, the number of nuclear power plants is doubled.

Of course, the people most likely to contract those cancers are the individuals in the "exposed" population, and going further, those individuals within the group who received doses well above the group average. ■

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in the region have been lost for decades because of contamination with fission-product radioisotopes and plutonium. As this single accident shows, the potential damage from nuclear power plant accidents is very serious.

How Much Do I Get?

As our discussion of natural and man-made radiation sources makes evident, the types and amounts of exposures to ionizing radiation vary considerably from place to place, from person to person. The pie chart we've been using (page 29) summarizes the averages for people living in the United States based on the average annual effective doses.

As we've shown, doses from natural sources, including radon, account for 82 per cent of the average dose. Radon by itself, including radon in water pumped from underground, accounts for 55 per cent—the largest single factor. Cosmic and terrestrial sources each add another 8 per cent. Internal sources, such as potassium-40, make up the final 11 per cent for doses from natural sources.

Man-made sources account for 18 per cent of the dose, the largest being 11 per cent from medical x rays. Consumer products add another 3 per cent. Occupational exposures and exposures to the public from nuclear power plants and the fallout from weapons testing add less than 1 per cent.

Does our chart represent fair comparisons? For example, the internal dose and the medical x ray dose are both 11 per cent. You might say your own body is irradiating you from inside to the same extent that you're being irradiated from the outside by medical x rays. Of course, the internal dose is a slow, continuous bombardment; medical x rays are occasional, relatively intense doses. Furthermore, the dose given here is *averaged over the entire U.S. population*, an average based on the *collective effective dose* (see previous page). Clearly, actual individual doses may have large variations about this average. This is especially true for such exposures as medical x rays where many people have no x rays during the year and others may have several.

Why is such averaging useful? If the response to dose is linear, then the averages allocate the damage among the various sources, and suggest, for example that medial x rays and internal dose lead to the same number of cancers nationwide. It says nothing about individual risk, and it's certainly not correct if the dose response is nonlinear. Nevertheless, the average collective effective dose remains one of the more useful ways to draw risk comparisons between apples and oranges—or rather, between cosmic rays and thoriated camera lenses.

The table that follows (next page) is an attempt to help readers make a more satisfactory assessment of their own annual radiation doses. Remember, the average annual dose of ionizing radiation per person in the United States is about 360 millirem per year.

As you can see, we live in a sea of ionizing radiation, most of which has been here from the birth of the planet. Man's ability to manipulate radioactive materials and to create new sources of radiation is adding to the amount of ionizing radiation we receive each year.

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Personal Radiation Dose Chart

(*Adapted from Personal Radiation Dose, American Nuclear Society, 1990 with further data from NCRP Report No. 93 and NCRP Report No. 95.*)

Estimate your average annual effective dose in millirem by adding the numbers in the right column, including the numbers you choose for each category with a blank space.

Where you live:

Cosmic radiation at sea level						26
For your elevation in feet:						
500-1000 ft:	2	1000-2000 ft:	5	2000-3000 ft:	9	
3000-4000 ft:	15	4000-5000 ft:	21	50000-6000 ft:	29	
6000-7000 ft:	40	7000-8000 ft:	53	8000-9000 ft:	70	
9000-10,000 ft:	107					____

Terrestrial:
Live in state bordering the Gulf or Atlantic from Texas east and north: 23
Live in Colorado Plateau or Rocky Mountain State: 90
Live anywhere else in the United States: 46 ____

Internal:
What you eat and drink 40
Radon: Insert a value equal to your average radon level (in picocuries per liter x 100) or use the U.S. average of 200 ____

Life Choices:

Live in a stone, brick, concrete, or adobe building: 7 ____
Live within 50 miles of a coal-fired electric utility plant: 0.03 ____
Live within 50 miles of a nuclear reactor: 0.01 ____
Jet airline travel - each 1000 miles traveled annually: 1 ____
Smoke cigarettes - multiply packs per day by 870 (high degree of uncertainty) ____
Use a typical distribution of modern consumer products (U.S. average): 10 ____
Cook and heat with natural gas: 2 ____
Work with commercial fertilizer products (e.g., farming): 1 ____

Medical Exposures:

Received a diagnostic x-ray (U.S. average): 40 ____
Received a thyroid scan: 590 ____
Wear a plutonium-powered cardiac pacemaker: 100 ____
Received other medical radiation exposure (ask physician): ____

Occupational:

If you work with radiation sources, add your annual dose in millirems, or select the 1980 average value for exposed workers in you occupation:

Air flight crew: 670	Nuclear fuel cycle: 600	Medicine: 150
Industry: 240	DOE Contractor: 180	Well logger: 420
Government: 120	U.S. Public Health Service: 47	
Open-pit uranium mining: 115	Underground mining: 700	____

Public Exposures from Nuclear Age:

Transportation of radioactive materials: 0.6
Fallout from atmospheric testing: 0.5 ____

Your Annual Effective Dose (millirem): Sum the numbers in the right column: _____
(U.S. Average: 360 millirem)

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Many of the new radiation sources are highly beneficial to man and society as sources of energy, as research tools, and as diagnostic and therapeutic tools for medicine, but each source presents additional risks as well. Other sources of ionizing radiation are an incidental result of our consumer goods and life styles.

For our society to use radiation wisely, it's necessary to understand the specific dangers of individual sources rather than to bring wholesale condemnation to ionizing radiation. Reaching such understanding certainly requires more effort, but in the long run, such effort will certainly serve our society. We will be much more capable of finding the most satisfactory balance between the risks and the benefits of ionizing radiation. ■

Acknowledgements

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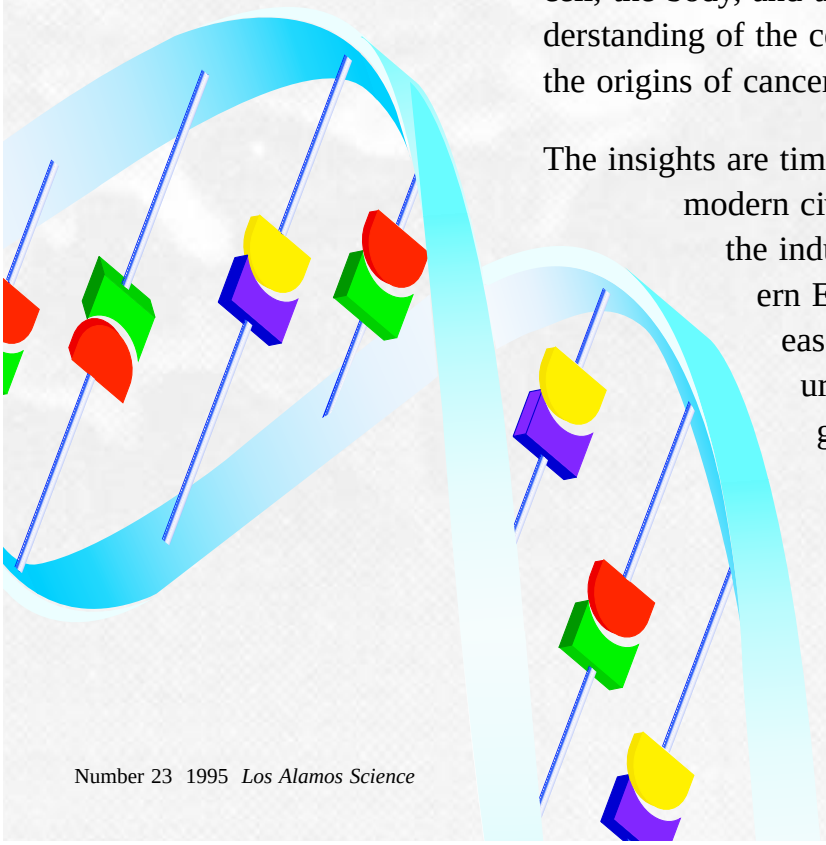
We have seen the enemy, and he is us!

—Churchy LeFemme, aka Walt Kelly

Radiation, Cell Cycle, and Cancer

Richard J. Reynolds and Jay A. Schecker

We live in remarkable times. The DNA within our cells—the entire human genome—is steadfastly being mapped and deciphered. That work combined with new results from molecular and cellular biology are enabling researchers to reconstruct the inner workings of cells in unprecedented detail. We are beginning to build a holistic framework for understanding the human organism, one that integrates the distinct yet interrelated roles of DNA, genes, the cell, the body, and the environment. With it comes a better understanding of the cellular origins of many diseases, including the origins of cancer.



The insights are timely. Cancer is one of the great scourges of modern civilization, for roughly one in five people in the industrialized nations of North America, western Europe, and Asia will die of it. It is a disease of the cell that develops because of failures in the mechanisms that regulate cell growth. An individual cell multiplies without restraint until it and its progeny eventually overwhelm tissues and organs. What initiates this process and how it progresses

has been the subject of theoretical and experimental investigation almost since the start of medical research. It has led to the identification of various cancer-causing substances, or *carcinogens*, in our diet and within our environment.

Ionizing radiation* is one of those carcinogens, and its ability to induce cancer is not in doubt. The tragic experiences of the radium-dial painters during the early part of this century and the sobering epidemiological studies of the atomic-bomb survivors of Hiroshima and Nagasaki bear witness to the fact that ionizing radiation can instigate a variety of cancer types. The bomb survivors, for example, display a small but statistically significant increase in the level of several cancers, including leukemia, breast, thyroid, and skin cancer. Radiation and cancer definitely correlate.

How does ionizing radiation cause cancer? How can a brief interaction with invisible particles smaller than an atom or the transient passage of massless electromagnetic waves cause a smoothly functioning, exceptionally well-organized cell to spiral chaotically out of control? Our cells for the most part are stable and predictable entities, yet exposing them to levels of radiation well below the lethal dose can induce behavior that will eventually lead to the death of an entire organism. How does this happen?

Answering these questions has proven to be extraordinarily difficult. Even today, the causes of cancer and the many ways the disease can progress are not completely understood. In the absence of a complete understanding, it has not been possible to determine the exact role that ionizing radiation plays in cancer induction. Nevertheless, a basic understanding does exist. Ionizing radiation can damage the DNA of chromosomes and potentially mutate the genes that reside on those chromosomes. Because genes ultimately dictate cell function and behavior, ionizing radiation, through its capacity to induce genetic mutations, can bring about a change in the basic nature of the cell. The cell becomes *transformed*, meaning that it is aberrant and is slowly evolving into a cancerous state.

Although this picture is correct, it is somewhat superficial. It does not take into account the rate of DNA damage or the particular type of damage that ionizing radiation induces, nor does it account for the powerful DNA repair mechanisms that help maintain the genome. It does not reveal that healthy cells have "defenses," or cellular responses, that can limit excess proliferation and prevent cancer from developing. Augmenting the basic picture and elucidating what is known specifically about radiation and *oncogenesis* (the causes of tumor formation) is the main objective of this primer. In attaining that goal, we will spend a considerable amount of time building concepts and vocabulary, beginning with *genes* and *gene expression*. We will relate gene expression to cell function and then expand upon the nature of cell regulatory processes. We will learn that once a cell has become transformed by some random, initial event, its progression towards cancer will be driven by the abnormal behavior or removal of specific, critical proteins. We will learn that within that set of "cancer-causing" genes, some are specifically correlated with DNA damage induced by ionizing radiation.

*We will restrict our attention to *ionizing raditation* in this primer, that is, only nuclear emissions and x rays. Effects due to lower-energy electromagnetic radiations, such as ultraviolet radiation and emissions from power lines, will not be considered.

Genes and Gene Expression

We are what we are because of our genes. This notion, along with the realization that DNA is the molecular carrier of heredity, are two of the seminal discoveries of modern science. It has been discovered that a gene is composed of a specific DNA sequence, and gene sequences are distributed throughout our chromosomes (see "DNA, Genes, and Protein Synthesis"). Each chromosome is a single, long DNA molecule that is woven around a complex protein structure. Every person inherits a set of 23 chromosomes from each parent, and for every chromosome passed to us by our mother, there is a corresponding chromosome contributed to us by our father. The 46 chromosomes that compose the human genome can be arranged into 22 pairs of matching, or *homologous*, chromosomes, plus one pair of sex chromosomes—the X and Y chromosomes. Females possess an XX pair, whereas males possess an XY pair (Figure 1). Because each chromosome in a homologous pair contains the same set of genes, our cells have two copies, or *alleles*, of every gene. The DNA sequences of two alleles are usually very similar but not identical—each contains information from one of the two parents. What happens when a cell makes use of dissimilar gene copies?

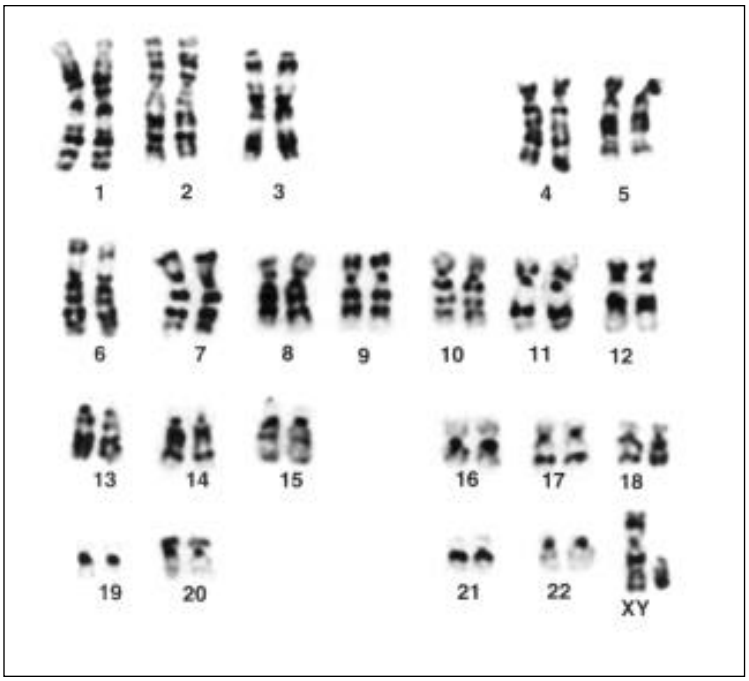


Figure 1. The Human Genome
The human chromosomes in this photograph were arranged to show the 22 pairs of homologous chromosomes, plus the one pair of sex chromosomes (lower right). The original photo was taken when the chromosomes had assumed their most condensed state. (For most of the life of a cell, a chromosome is in a very loose, threadlike form.) The chromosomes shown above were treated with a dye (Giemsa stain) that preferentially stains certain regions and thereby produces the unique banding patterns that are used to identify each chromosome. Because the two sex chromosomes are different (X and Y), or not homologous, the genome shown is that of a male, namely the well-known cytogeneticist T. C. Hsu of the University of Texas System Cancer Center. (Photo courtesy of T. C. Hsu.)

This question relates to gene expression, which was first systematically investigated by Gregor Johann Mendel (1822-1884), the "father" of modern genetics. Over the course of eight years, Mendel manipulated the breeding of several purebred strains of garden pea plants. He noted the manifestation of certain characteristics of the plants, say flower color or pea texture, and how often those traits appeared in each successive generation. From his observations, he was able to deduce the statistical laws of inheritance, using as a hypothesis the existence of two inherited "units" for each trait. (Mendel's units of heredity are what we now call genes. He used the word "Merkmale" to describe the units of heredity. The word gene was coined by the Dutch botanist Wilhelm Ludwig Johannsen (1857-1927).) Mendel was also able to deduce when certain traits would be observed, or expressed.

Take for example the trait flower color. Mendel found that a pea plant has a "gene" that dictates flower color, and that the gene has two "alleles," one for violet flowers and one for white flowers. He also found that the violet allele had a *dominant* mode of gene expression, that is, only one violet allele had to be present for the flowers to be violet. In contrast, the white allele had a *recessive* mode of expression, that is, both flower-color alleles had to be white for the flowers to be white.

Mendel's basic concepts about gene expression have been greatly expanded. The term "gene expression" is now used to describe the manifestation of traits at the molecular and cellular level. Expression begins with the processes of gene *transcription* and *translation* in which the DNA sequence that makes up a gene is used as a template to synthesize a protein (see "DNA, Genes, and Protein Synthesis"). That protein then produces certain observable characteristics in the cell. Thus a gene is said to be "expressed" when the protein that it specifies is actually synthesized and functioning in the cell.

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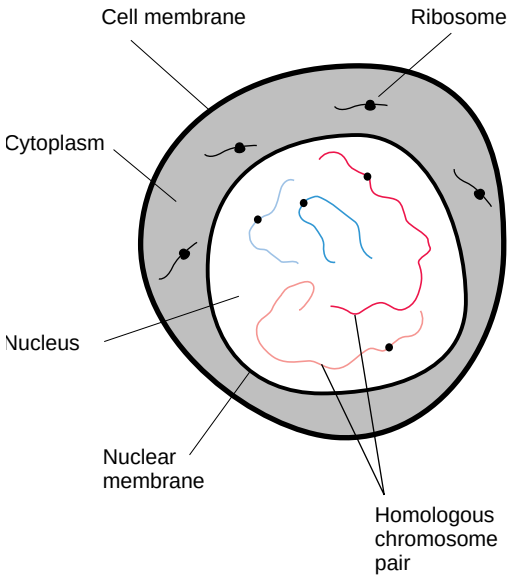
DNA, Genes, and Protein Synthesis

The cell is a marvelous ensemble of proteins, organic molecules, and organelles. Although it is on the order of ten microns or so in diameter, a cell is an incredible chemical factory with the capability to synthesize more than 10,000 different proteins and enzymes and the ability to oversee thousands of simultaneous chemical reactions. Figure A is a simple depiction of a mammalian cell in which we've selectively drawn only a few basic components (not to scale). The cell boundary is defined by an outer, bilayer lipid membrane. The cell interior is filled with an aqueous colloidal fluid called the cytoplasm. Floating within the cytoplasm are thousands of proteins and large, macromolecular structures. We've indicated a ribosome, which is a protein complex required for the synthesis of proteins. We've also conspicuously highlighted the cell nucleus, which houses all of the nuclear DNA (our genome).

Figure A. Basic Components of the Cell



If the DNA molecules found in a human cell were laid end to end and stretched out, the resulting line, though only 2 billionths of a meter wide, would be about two meters long, or about 200,000 times longer than the cell itself. Therefore, our DNA is packaged into dense constructs called chromosomes, each of which consists of a single, linear DNA molecule containing millions of base pairs. The DNA is twisted and packed around proteins called histones, and that structure is itself twisted into a secondary packing structure. There are at least four levels of twisting and packing, but the degree of packing and the chromosome appearance can vary, depending upon both transcriptional activity (described below) and the stage of the cell's reproductive cycle.

Human beings have a total of 46 chromosomes. Two of those chromosomes, called X and Y, determine the sex of the person. All males have an XY combination, whereas all females carry an XX combination. The other 44 chromosomes can be grouped into 22 pairs of “homologous" chromosomes. The individual members of each pair are very similar, but one is inherited from the mother and the other is inherited from the father (see Figure A and main article). For simplicity, we have depicted only four chromosomes, representing two homologous pairs.

As shown in Figure B, the double-stranded DNA that makes up a chromosome consists of two single-stranded molecules that are intertwined to form a double helix. The backbone of each single strand is a long chain consisting of repeating sugar-phosphate subunits. The sugars appear as pentagon-shaped rings in Figure B. (DNA is an acronym for deoxyribose nucleic acid. Deoxyribose is the particular type of sugar.) The sugar portion contains five carbon atoms, labeled 1' to 5', and the backbone is constructed by linking, through a phosphodiester bond, the 5' carbon of one sugar to the 3' carbon of the next. Because of the asymmetry in the phosphodiester linkage, the *phosphodiester backbone*, as it is often called, can be assigned an orientation, either 5' to 3' or 3' to 5'. The two strands of the DNA double helix actually have opposite orientations. One strand can be said to move “up,” whereas the other moves “down.” Many proteins that interact with DNA are sensitive to this orientation and can distinguish one strand from the other.

Attached to each sugar unit is one of four different nucleic acid bases: adenine (A), cytosine (C), guanine (G), and thymine (T). The bases can be further classified as purines (A and G) or pyrimidines (C and T). In forming the double helix, the bases will line up between the two DNA backbones, a base in one strand pairing with an opposing base in the complementary strand. The base pairs are chemically linked by hydrogen bonds. In the standard Watson-Crick base pairing, each pair must be

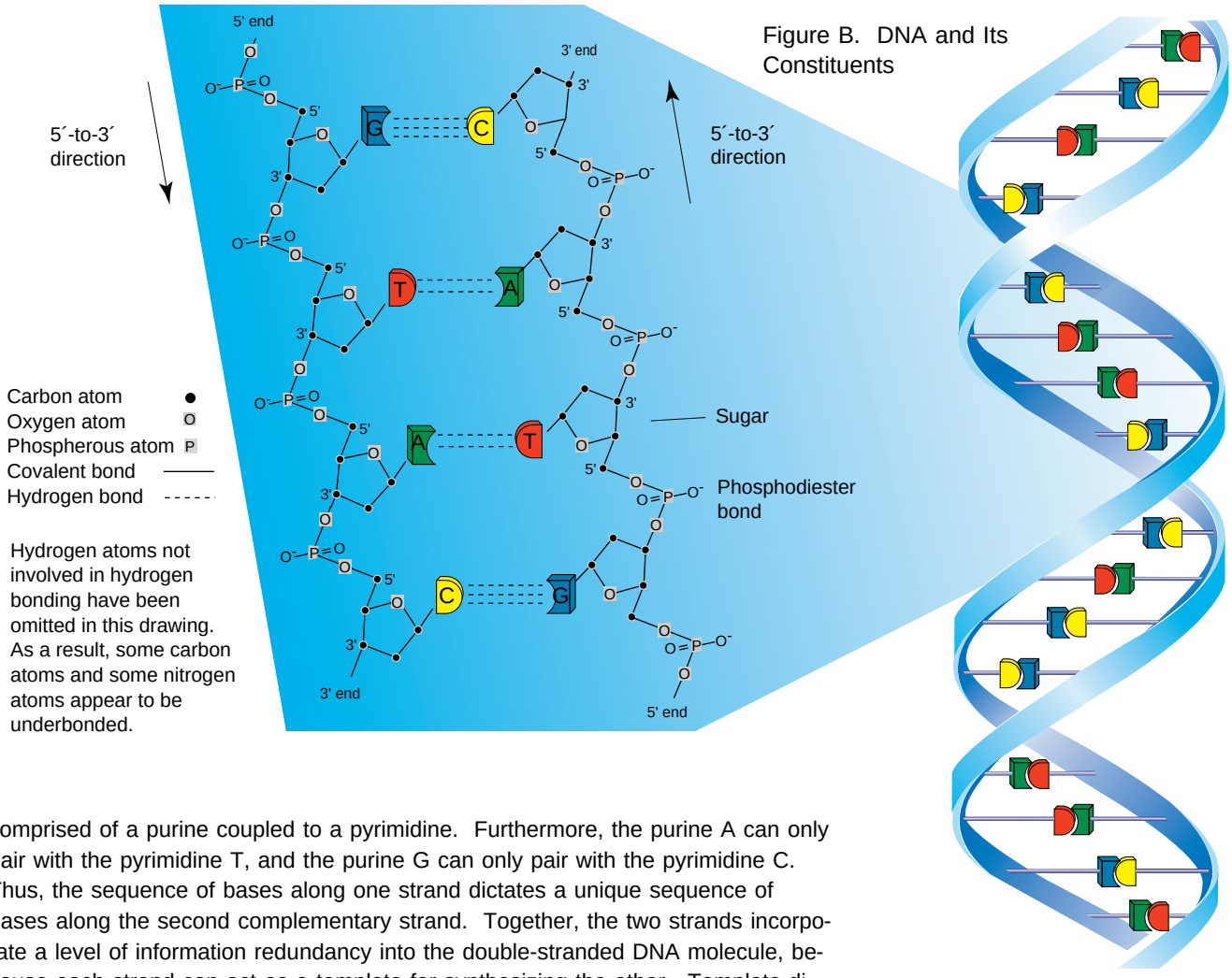


Figure B. DNA and Its Constituents

comprised of a purine coupled to a pyrimidine. Furthermore, the purine A can only pair with the pyrimidine T, and the purine G can only pair with the pyrimidine C. Thus, the sequence of bases along one strand dictates a unique sequence of bases along the second complementary strand. Together, the two strands incorporate a level of information redundancy into the double-stranded DNA molecule, because each strand can act as a template for synthesizing the other. Template-directed copying of each DNA strand is called replication.

The information encoded within the DNA molecule enables the cell to synthesize proteins. A gene, depicted schematically in Figure C, is that segment of DNA that codes for a single protein, and our genome contains roughly 50,000 to 100,000 genes dispersed among the 46 chromosomes. Because the overwhelming majority of cell processes are carried out by proteins, a cell goes to great lengths to ensure that the integrity of the base sequence is maintained. This is the primary role of DNA repair mechanisms (see “DNA Repair” on page 78).

To translate the information encoded by DNA into a protein product, the cell must go through a multistep process. First, the coding region of a gene is read, or transcribed, into a copy of the DNA sequence. The copy takes the form of a molecule of RNA, which is similar, with a few differences, to a single-strand of DNA. After some processing, the RNA will leave the nucleus and enter the cell's cytoplasm. The information contained in the RNA will be translated by a ribosome, a large macromolecule that guides the assembly of amino acids into the protein product.

Gene segments range from thousands to millions of base pairs in length. Therefore, Figure C depicts the DNA as a solid bar containing different subregions. We have indicated the coding region, which contains the actual sequence used for protein synthesis, and two regulatory DNA sequences that are used to control the

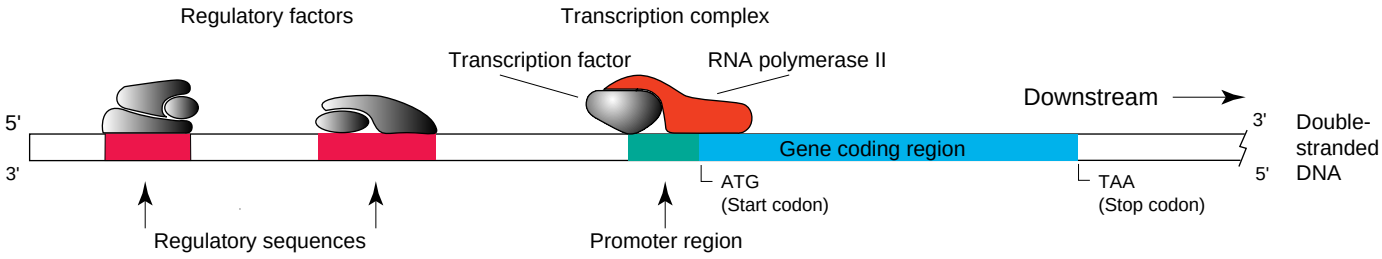


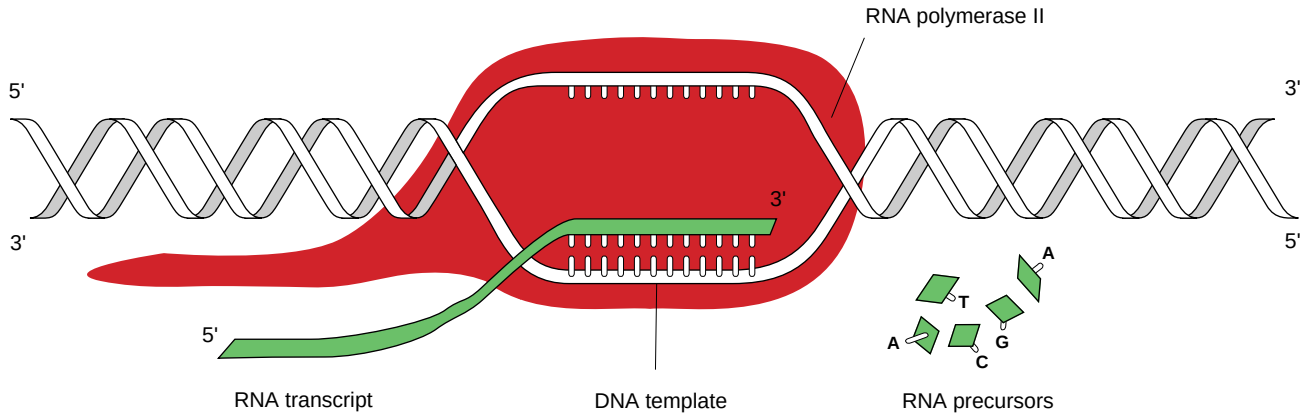
Figure C. Gene Structure and Transcription

rate and frequency of transcription. The double helix is actually a fairly open structure that permits access to the chemical groups of the DNA bases. Proteins called *regulatory factors* will recognize these groups and selectively bind to specific DNA sequences. By physically distorting the helix (bending and folding the DNA strands) or by promoting protein-protein interactions, the regulatory factors can either facilitate or inhibit transcription. The regulatory regions may be far removed from the coding region and may even be located "downstream."

Transcription of the DNA sequence into an RNA copy is initiated at the promoter region, which also contains a specific DNA sequence (TATA) that is recognized by a *transcription factor*. This factor is a protein that binds to the DNA and initiates the self-assembly of a transcription complex consisting of perhaps 10 or more proteins, including RNA polymerase II (RNA Pol II). The RNA Pol II complex will transcribe the DNA coding sequence. Thus, the initial step in creating a protein is tied to the presence (or sometimes the absence) of transcription factors and regulatory proteins. That is one way the cell has of regulating the expression of a gene.

As depicted in Figure D, RNA Pol II instigates the unwinding of the DNA double helix, which enables it to "read" and transcribe one of the two DNA strands. Because of the Watson-Crick base-pairing rules, the RNA molecule that is produced contains all of the information that was originally encoded in the DNA strand. As RNA Pol II moves along, the relaxed strands of previously transcribed DNA sections rewind. After the gene has been completely transcribed, RNA Pol II will leave the DNA and some processing of the RNA molecule occurs. The resulting RNA strand (now called messenger RNA, or mRNA) leaves the cell nucleus and will be used as the template for protein synthesis.

Figure D. Transcription of DNA to RNA



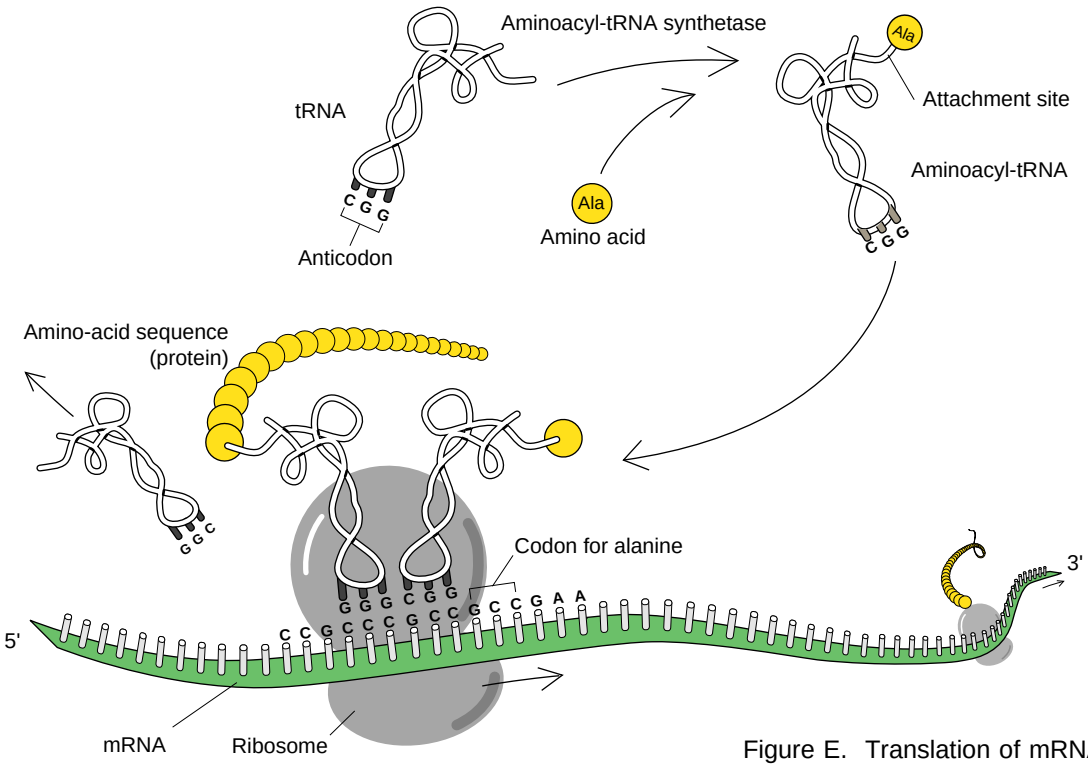


Figure E. Translation of mRNA to Protein

The process of converting the mRNA template into an actual protein is called translation, as shown in Figure E. Translation takes place at the ribosome. The sequence of RNA bases contained in the mRNA transcript is interpreted as a series of "words," or codons, consisting of three consecutive RNA bases. With some exceptions, each codon corresponds to a specific amino acid. These are the small molecules from which proteins are constructed. For example, the DNA base sequence GCC codes for the amino acid alanine. The exceptions are three *stop* codons (TAA, TAG, TGA) that are used as punctuation and indicate the termination of an amino-acid sequence.

A molecule called transfer RNA (tRNA) is the actual link between a codon and an amino acid. One end of the tRNA has an "anticodon" that pairs according to Watson-Crick rules with a codon in the mRNA template. The other end of the tRNA is bound to an amino acid that corresponds to that codon in the mRNA template. The top of Figure E shows the reaction that places the correct amino acid onto the corresponding tRNA. That reaction is catalyzed by a family of specific enzymes called the aminoacyl-tRNA synthetases. The ribosome facilitates the pairing of the anticodon region of a tRNA molecule to the mRNA codon and catalyzes the transfer of the amino acid to the growing protein chain. The ribosome steps along the mRNA molecule, adding an amino acid to the chain at each step, until it reaches a stop codon. At that point, the protein product is finished, and the ribosome detaches. Numerous ribosomes will often attach to the same mRNA, so that many copies of the same protein are produced for each DNA transcription event. It is clear, then, that DNA plays a critical role in protein synthesis. A single gene can get transcribed many times, and each time it is transcribed, many identical proteins are produced. If a gene coding for a major regulatory protein becomes mutated, then that single mutation can mean the difference between a normal and a dysfunctional cell. ■

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But a question remains. We have approximately 50,000 to 100,000 genes. Does every cell make use of all the genes that are encoded in its genome? The answer is no, and the reason has to do with a much more fundamental concept of gene expression—the notion of regulation. A gene embodies not only DNA sequences that code directly for protein construction but also regulatory sequences that control various aspects of the transcription process. Regulatory sequences include the *promoter* region, where transcription is initiated, and regions that control the rate and frequency of transcription. Those regulatory regions are recognized by *regulatory factors*, which are a class of proteins that bind to certain DNA sequences and either directly or indirectly (by attracting other proteins) inhibit or enhance transcription.

Therefore, the mere presence of a gene within our genome does not guarantee that it will be expressed. Instead, the production of a protein from the gene is dependent upon a very complicated relationship between DNA, regulatory proteins, and protein synthesis. In fact, the cell has at least six levels of control on gene expression, beginning with regulation of the promoter region and ending with the breakdown and removal of the protein product. Once produced, however, many proteins must first be activated by other proteins, form a complex, or both, before being able to play a part in cell processes. Protein activation and participation in protein complexes are but two examples of how a gene product can be regulated. The expression of a particular gene and the behavior of its protein product can therefore change due to a number of factors. Abnormal behavior can certainly be the direct result of a DNA mutation, but it may be expressed through a type of domino effect that links the action of one protein to the function of another.

Cell Differentiation

Cancer is a disease of cells, and human beings have lots of them. We are composed of approximately 10^{13} to 10^{14} individual cells, most of which are not identical. Instead, they have differentiated into roughly 350 types. Differentiation means that a cell has become specialized in function and structure and has compromised its independence and some of its capabilities in favor of being a cooperative member of a tissue and organism. Our cells, for the most part, are immobile, and therefore, the specialized cells in any given tissue depend heavily on other tissues to provide nutrients and basic resources, to remove waste, to create environmental stability, and to provide protection.

This interdependence is distinct from a single-cell organism. A free living cell is self-sufficient and behaves in a manner that best aids its own survival. Certainly, one survival mechanism is proliferative advantage. For example, the rod-shaped bacteria *Escherichia coli* can divide and produce two new bacteria every 30 minutes. In principle, then, *E. coli* has the reproductive capacity to produce well over 200 trillion progeny in just 24 hours!*

Clearly, the differentiated cells of a multicellular organism cannot exhibit this type of proliferative behavior, nor can they be insensitive to the needs of other cells. Instead, everything about a differentiated cell, including when it reproduces, its shape and size, and the chemicals and proteins it synthesizes, is essentially determined by the needs of the tissue and the organism of which that cell is a part. Ex-

*This number is a theoretical extrapolation. The actual number of bacteria that would be generated is limited by the availability of resources and by the necessity to remove heat and waste by-products.

erting its influence through a multitude of intricate, intercellular controls, the body ensures that the behavior of individual cells is directed towards sustaining the overall health of the organism. This paradigm of specialization is obviously a successful one that imparts survivability to all the cells of the body and to the entire organism.

How do cells differentiate? The process is only beginning to be understood. It is not simply that each specialized cell has a different set of genes, because all the cells of the body are genetic clones and possess the same genome. Nor does differentiation result from a change in the information content of the DNA or the amount of DNA present. Rather, specialization comes about because only a particular set of genes are expressed. Those expressed genes determine if the cell will be a nerve cell or a skin cell, if it is mobile within tissue (such as a macrophage), or if it grows slowly or rapidly. In one sense, the genome is analogous to a library that contains books on all subjects. When we wish to specialize our area of interest, we select from the library only those books that are appropriate for our needs and leave the other books undisturbed.

An *epigenetic* change within the genome—one that modifies gene expression without changing the information content of the DNA—appears to be the mode by which cells differentiate. Many differentiated cells pass their traits on to their progeny; that is, a liver cell begets a liver cell, which implies that the epigenetic changes to the genome are conferred to daughter cells. The transmission is believed to happen through a chemical modification of DNA sequences known as methylation. The methylation patterns are maintained during DNA replication, but the way in which they are originally established and the way they become modified is not fully understood.

However, not all cells are descendants of fully differentiated cells. Instead, the specialized cells of many tissues and organs originate from a class of relatively undifferentiated cells called *stem cells*. The successive progeny of stem cells display increasing degrees of specialization, and that process may continue for several cell generations. The stem cells are highly unusual. Their specific role in the tissue is to renew lost or damaged cells, but at the same time, they must maintain their own population. As illustrated in Figure 2, stem cells have the peculiar property of generating dissimilar progeny. One of the cells that is produced remains a stem cell, whereas the other cell begins to specialize in response to external signals. Those signals evidently help trigger the epigenetic changes. But each type of stem cell is slightly different, and the pathway of specialization that their progeny follow is also distinct. Thus, basal cells are ultimately the source of epithelial cells (those cells that make up the skin layers and the lining of the intestinal and respiratory tracts), whereas the hemopoietic stem cells are the precursors of about ten or more different cell types that make up the blood and the immune system.

As the progenitor of many tissue cells, the stem cells perform a function that highly differentiated cells have relinquished, namely repeated cell division. The terminally differentiated cells of the skin or the hemopoietic system are so specialized that they rarely divide. Stem cells renew those nondividing cells, and therefore, the role of the stem cells within the scheme of the organism is that of proliferation. Unlike *E. coli*, however, the reproductive potential of a stem cell is strictly regulated (as it is for all other types of cells). Cells will only multiply as a consequence of having received numerous extracellular signals. Growth factors, or *mitogens*, are positive regulators that stimulate proliferation. Other signals will inhibit growth and are considered to be negative regulators. Normally, cellular

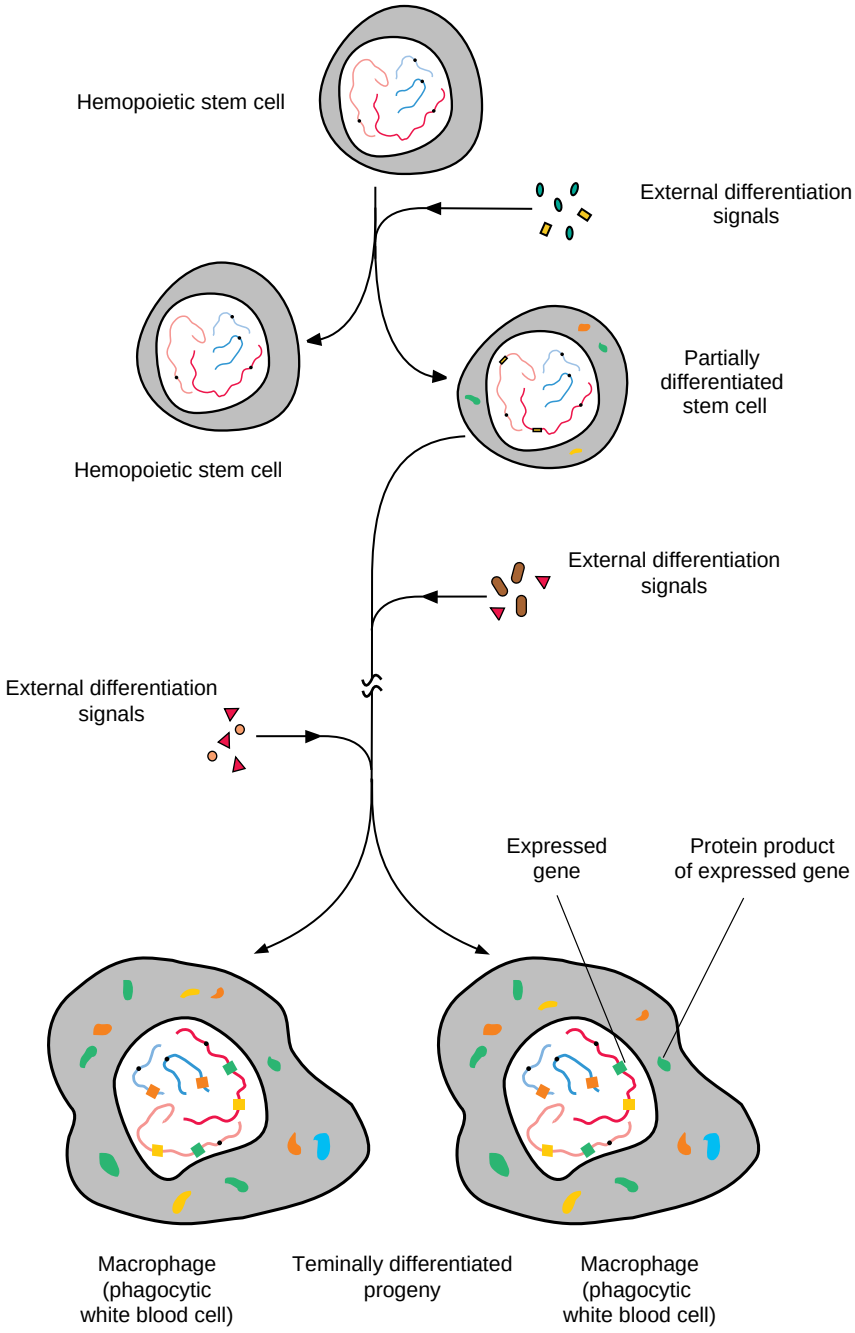


Figure 2. Cell Differentiation and Stem Cells

The hemopoietic stem cells are responsible for generating about a dozen different types of cells, including the various kinds of blood cells and the cell types that make up the immune system. The figure illustrates the generation of a highly specialized cell, the macrophage (a cell that lives within tissue and is descended from a white blood cell), from a relatively undifferentiated stem cell. The process of differentiation takes place over several cell generations, and it occurs because of the expression of different genes. When a stem cell divides into two cells, one of them will remain a stem cell. The other, in response to external signals, begins to specialize. This daughter expresses new genes (colored segments on the chromosomes) that are transcribed and translated into proteins (colored shapes in the cytoplasm). The new proteins modify the cell's function and appearance. The process of specialization continues through several more generations until finally a cell type reaches a terminal stage of differentiation. If a macrophage divides, both of its progeny will remain as macrophages. Because stem cells and their partially differentiated progeny divide frequently, cancers often emerge from those cell types.

proliferation is controlled by the cell's interpretation and response to these reciprocal types of regulation.

One of the major differences between a normal cell and a cancer cell is that the latter responds in an unbalanced manner to regulatory signals and proliferates at inappropriate times. A precancerous, or *neoplastic* cell, might undergo changes in the way it responds to regulatory signals, and it might divide independently of the needs of the tissue. If the modified behavior results in a proliferative advantage for a cell line, the uncontrolled growth can ultimately lead to the disruption of tissue function. Because stem cells are the most rapidly and frequently dividing cells in our body, they are in one sense "primed" to express proliferative advantages. Most cancers originate from the various types of stem cells or from the partially

differentiated progeny of stem cells. Because different sets of genes are expressed in those stem cell variants, the cancers that develop also differ from each other. They might present different characteristics and have altogether different consequences.

Proteins and Signal Transduction

We have stressed that cancer is a distortion of cell behavior and that a cancer cell differs from a normal cell largely because of malfunctions in processes that control cellular proliferation. From a mechanistic point of view, this translates into the failure of proteins to properly regulate what is called the *cell cycle*, which is the sequence of stages that a cell passes though when it undergoes reproduction. But the initiation and regulation of the cell cycle cannot be appreciated without a better understanding of how proteins work and how they can act as catalysts.

A protein consists of a chain of amino acids strung together like beads on a string. There are 20 common amino acids, which are distinguished from each other by a unique chemical side chain that is attached to a "core" carbon atom. Interactions between the various side chains will fold a protein molecule into a convoluted, three-dimensional shape. That shape is a critical feature that is central to a protein's function, for it affects the accessibility and position of individual amino acids. Typically, most of the protein merely serves as a means to configure a small subset of amino acids into a uniquely contoured region. That region, which is often in the form of a cavity or small protrusion, is called a *binding site.* Because of its unique shape, and because the amino acids that compose it have specific sizes, affinities, and chemical properties, the binding site allows only a select group of *target molecules*, called *ligands,* to interact and bind to the protein at that area. A ligand can be any type of ion or organic molecule, including proteins.

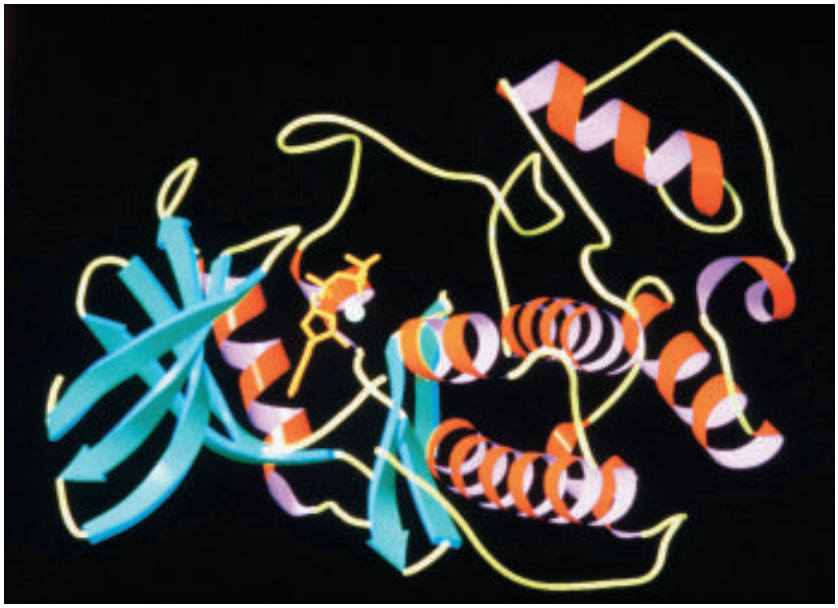


Figure 3. Cdk2 Protein

The cyclin-dependent kinases, or Cdk, are a major class of regulatory proteins of the cell cycle. This representation of Cdk2 shows, not atomic detail, but the amino-acid chain as a continuous ribbon. That depiction gives a feel for the protein's three-dimensional structure, which can provide insight into the protein's function. The catalytic binding site of the Cdk lies at the center of the protein. The cofactor, a molecule of ATP (yellow pentagon with branches), already lies within that binding pocket. A ligand will also bind to that site, and one of the phosphate groups making up ATP will be transferred to the ligand, thus bringing about its modification. Photo courtesy of Prof. Sung-Hou Kim, UC Berkeley. Reprinted with permission from *Nature* 363: 595-602 (© 1993, Macmillan Magazines Limited).

The binding site of a protein can simply allow the protein to adhere to its target molecule. For example, the binding site of a regulatory factor has an affinity for the exposed chemical groups of specific DNA sequences and thereby enables the factor to bind selectively to those particular segments of DNA. But a binding site often plays another, more ubiquitous role. It can hold a ligand within close proximity to another small molecule (a cofactor) for the sole purpose of facilitating, or catalyzing, a chemical reaction between those two molecules. Any protein catalyst is called an *enzyme.* Figure 3 is a computer-generated rendering of an enzyme, in this case, the protein Cdk2. This protein is one of several that are at the heart of cell-cycle regulation. Cdk2 is shown holding a molecule of ATP (the cofactor) within its binding site. ATP contains three phosphate groups, and Cdk2 will catalyze the transfer of one of those phosphate groups to a ligand that binds to Cdk2. The transfer and covalent attachment of a phosphate group to a target protein is called *phosphorylation,* and the enzymes that catalyze phosphorylation are called *kinases.* Thus Cdk2 is an example of a kinase.

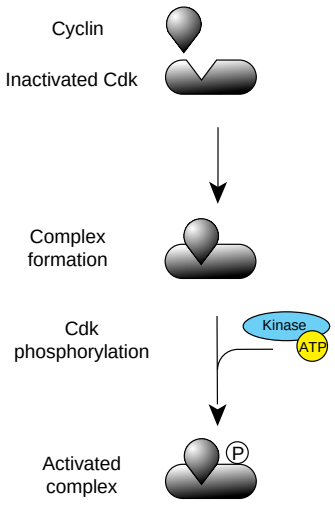


Figure 4. Activation of a Cyclin-Cdk Complex

The Cdk protein has a potential kinase activity that enables it to phosphorylate other proteins. To become an active kinase, the Cdk protein must first complex with a cyclin molecule. The binding initiates a structural change that enhances accessibility to the Cdk binding site and to the ATP cofactor that lies within that site. Once the complex has formed, activation still requires that the Cdk protein itself become phosphorylated. Cdk activity may also be regulated through phosphorylation at yet another site (not shown in the figure). Activation would then require removal of the inhibitory phosphate (dephosphorylation). The three separate steps of complex formation, phosphorylation, and dephosphorylation are the means by which Cdk is regulated. In reference to Figure 3, the cyclin binds to the Cdk along the blue ribbon area on the left side of the image.

Phosphorylation is a very common means of activating (or inhibiting) the function of a protein. Kinases, therefore, can play a regulatory role within the cell by helping to turn target proteins functionally on or off. The kinase itself may be regulated in that some type of protein interaction is required to activate its enzymatic capability. For example, Cdk2 is a *c*yclin-*d*ependent *k*inase, which means it must couple to a cyclin protein before it can catalyze phophorylation. (The cyclin family of proteins, like the Cdk, are major components of cell-cycle regulation. The cyclins will be discussed in the following section.) The joining with a cyclin modifies the Cdk protein and allows access to the Cdk's binding site (also called its binding pocket). But complex formation with a cyclin is only a required first step in activating the kinase activity of a Cdk. The states of phosphorylation at two distinct sites are also involved. The phophate group at one site keeps the binding pocket "open," whereas the phosphate group at the other site is an inhibitor of the Cdk's kinase activity. Thus, Cdk activation requires cyclin binding, phosphorylation at one site, and the absence of a phosphate group at a second site. A cyclin-Cdk complex and its activation are illustrated in Figure 4.

Proteins play equally important roles in the link between extracellular conditions and the cell-cycle control elements. When a cell initiates a new reproductive cycle, it is usually in response to external growth signals. These signals are relayed into the nucleus through a chain of interacting proteins that form a *signal transduction cascade.* The chain will convert the growth stimulus, which may be in the form of a hormone or a mitogen, into an action that is carried out by the cell. Often, this action is manifested through the transcription and expression of specific genes. Figure 5 shows a simplified version of one such cascade, in which a cell in a tissue has been stimulated to grow by a mitogenic signal. The mitogen may have been excreted into the extracellular medium by other cells of the tissue or else may have been released from distant organs and transported to the tissue by way of the circulatory system. In either case, the signaling molecule will bind to protein structures embedded in the cell membrane called receptors.

A fairly common class of receptors, the tyrosine kinase-linked receptors, exert their influence through the phosphorylation of specific tyrosine amino acids on target proteins. These receptors have two functional regions. One region protrudes through the cell membrane and is exposed to the extracellular medium, whereas the other remains inside the cell's cytoplasm and carries a latent kinase activity. Once a mitogen has bound to the receptor, the cytosolic (or intracellular) part of the receptor becomes enzymatically active. It will phosphorylate its target, which will then go on to activate additional proteins.

What follows is a deliciously complicated series of chemical reactions—a multiplexed chain of events mediated principally by phosphorylation events—that will sequentially activate (or inhibit) subsequent proteins in the cascade. In our figure, we've indicated one such protein, pRas, which is a participant in many different cascades and is important for the induction of several types of cancer. What is important for our discussion now, however, is that our representative cascade terminates in the cell nucleus. There, the activation of one or more transcription factors will stimulate the transcription of their respective target genes. The proteins produced from those genes will then effect some sort of trait, which in our example would be the formation of protein complexes that herald the start of a new reproductive cycle.

A similar chain of events can occur when the cell intercepts an inhibitory signal, one that prevents growth and cell division. That signal might initiate a signal-

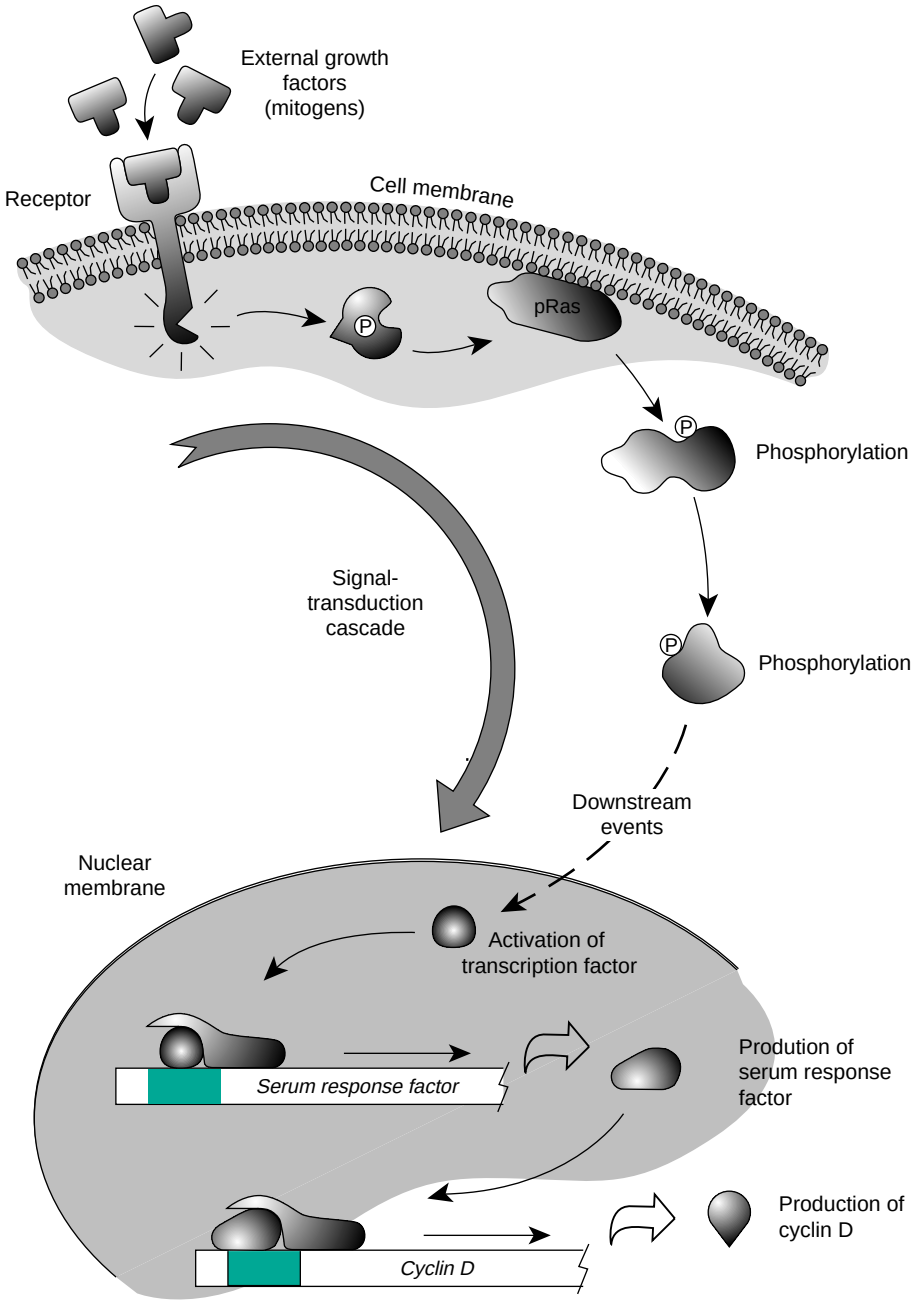


Figure 5. Signal-Transduction Cascade

Signal-transduction cascades relay external signals from the tissue or from other parts of the body into the cell. The one we've shown here is representative of a cascade that might stimulate an epithelial cell to grow and divide. The cascade starts with the binding of a signaling molecule, in this case a mitogen, to the extracellular part of a receptor. The part of the receptor that lies inside the cell then becomes enzymatically active and can initiate a cascade of protein phosphorylation events. In this diagram, the signal passes through pRas, a critical enzyme that is involved in many cascades. The message continues to be propagated by other proteins until it is eventually relayed into the cell nucleus. There a transcription factor becomes activated that will initiate the production of other transcription factors. We've indicated the production of serum response factor, which can then go on to help transcribe the cyclin-D gene. As a major regulatory protein of the cell cycle, the presence of cyclin-D protein within the nucleus is necessary to initiate cell division. Although the signaling pathways may proceed through any of several routes, often those different routes are channeled through one or two critical proteins. Improper expression of those proteins can therefore lead to an abnormal response to external signals and erratic cell behavior.

transduction cascade that could conclude in any number of ways, such as the blocking of a second cascade that is transmitting a positive growth signal. The cascade might terminate by blocking the transcription of a positively regulated gene. It might result in the production of a protein that will ultimately carry out some regulatory function through a direct interaction with another protein. Although the surface receptors, specific proteins, and endpoints of various cascades may all be different, most pathways use similar mechanisms to transmit signals from the external environment to some intracellular target.

Figure 5 and our description greatly understates the complexity of signal transduction. It is a far more intricate process than we have indicated, with many enzymes often participating in multiple pathways. A particular enzyme may be positively regulated in one pathway and thus help stimulate growth, whereas it may be negatively regulated in another pathway. Proteins can be activated not only by the addition of phosphate groups but also by their removal. A protein may further be inhibited by either of those methods. The cell employs all mechanisms, and it is not unusual to find several different modes of activation or inhibition acting within the same protein. The complexity of the cascades and the myriad interconnections are, in one sense, both an asset and a liability. Like a massive government bureaucracy, the redundancy tends to make a cascade fairly robust and insensitive to minor breakdowns. There is almost always a way to get around a dysfunctional part of the system. Likewise, however, it also means that there are many ways in which the system can break down.

The Cell Cycle and Basic Cell-Cycle Control

Both the body and the tissue tell the cell when to begin a new cell cycle. They do so through various growth-stimulating factors that instigate signal-transduction cascades. The cascades relay the information into the cell body or into the cell nucleus where processes that help coordinate and carry out cell division will be initiated. Coordination is essential because cellular reproduction is an enormous undertaking. The entire volume of the cell must double so that cells can divide repeatedly without decreasing in size, and all cellular substructures and organelles must be reproduced. The cell's genome must be exactly duplicated, which, for a human cell, entails the faithful replication of some 6 billion nucleic-acid bases and the synthesis of 46 new chromosomes. Eventually, new nuclear and cellular membranes must form as the parent cell cleaves itself in half.

Cell growth takes place more or less continuously as the cell cycle progresses. The overall protein and organelle content of the cell also tends to increase at a fairly uniform rate. In contrast to that continuous and nondistinct growth are the discrete events of DNA replication, chromosome separation, and the actual division of the cell. Those events occur at particular times and permit the cell cycle to be partitioned into four phases. As illustrated in Figure 6, those phases are termed G_1, S, G_2, and M. Newly generated cells are born into G_1 phase, and it is there that slowly dividing cells will typically spend the majority of their lives. In particular, a nondividing cell may enter a resting state often referred to as G_0. During G_0, the cell-cycle machinery is partially dismantled, and the cell may acquire specialized characteristics or may differentiate. Under the proper conditions, a G_0 cell can re-enter G_1 and, thus, continue cycling.

During S phase (for DNA synthesis), DNA replication duplicates the entire

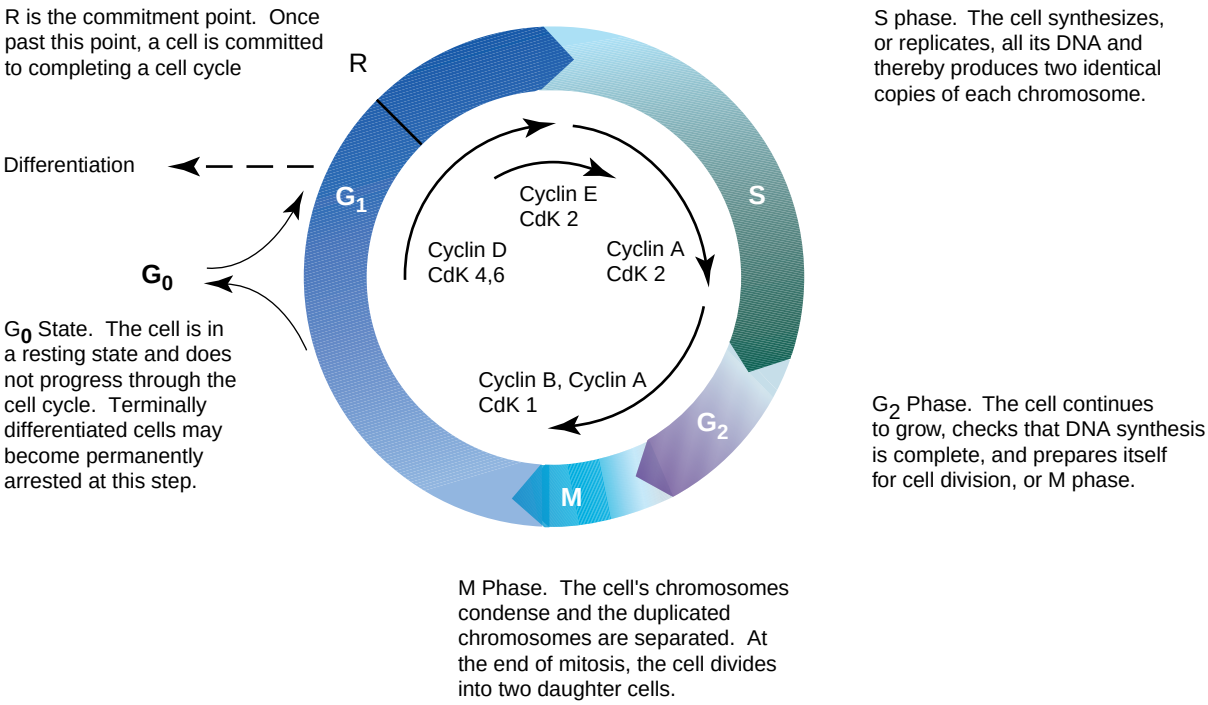


Figure 6. The Cell Cycle

The stages of cell division are collectively called the cell cycle. A newly created cell is "born" into G_1 phase. Cell differentiation will emerge from G_1 phase. Also from G_1, a cell can enter a nonreproductive state, called G_0, from which it will perform its usual functions. When new cell growth is called for, the cell will re-enter G_1 to begin a new cell cycle. The cell will begin to produce cyclin D and cyclin E and form active cyclin-Cdk complexes. Those will help advance the cell to S phase. The various activated cyclin-Cdk complexes that will regulate the progression of the cell cycle from one phase to the next are indicated in the center of the diagram. The cycle is completed after M phase with the cell dividing into two new cells.

genome and produces two copies of each chromosome. During G_2 phase, the cell continues to grow as it prepares for mitosis, or division of the cell nucleus. During the cell-division, or M (for mitotic), phase, the duplicated chromosomes will condense to their most compact form, align themselves along a central axis, and split into single chromosomes, which are then segregated to opposite sides of the cell. Next, new nuclear membranes form, creating two nuclei, and at the end of M phase, the cell divides into two cells. Each new cell is complete, and each has received an entire copy of the genome. The steps involved in mitosis are illustrated in Figure 7. If these steps are not carried out in a proper, sequential fashion, or if DNA replication or other cellular activities are not duly coordinated, one, or possibly both, daughter cells may be born incomplete. By necessity then, the entire cell-division process is extremely well regulated. That regulation is carried out by a series of protein-protein interactions and protein modifications.

Starting within the G_1 phase, and then again at distinct times during the cell cycle, the concentrations of specific cyclins increase within the nucleus. These cyclins associate with an appropriate Cdk to form a cyclin-Cdk complex. Recall that complex formation is a necessary step in the ability of a Cdk to act as a kinase (Figure 4) and that by controlling phosphorylation, kinases can regulate other proteins. Cyclin-Cdk complexes are the main control elements that regulate the progression and activity of each phase of the cell cycle.

Cyclins are actually a family of closely related proteins, and to date, eight general types, cyclin A through H, have been identified. (Some types—for example, cyclin D—are themselves families consisting of several related proteins.) With the important exception of cyclin D, each type of cyclin is synthesized during a unique and relatively discrete period of the cell cycle. Each is also degraded at a second, relatively discrete point. The cyclin concentration, therefore, varies over time, and as it changes, new cyclin-Cdk complexes are formed, thereby activating the Cdk. Each time a different kinase becomes active, the cell moves through a given phase or initiates some process, as indicated in the center of Figure 6. For example, cyclin-D-Cdk4, cyclin-D-Cdk6, and cyclin-E-Cdk2 all control the pro-

M phase

Prophase. The chromosomes condense into microscopically visible threads. Microtubules radiating from the two centrosomes collectively compose the mitotic spindle.

Prometaphase. The centrosomes migrate to opposite sides of the cell. The nuclear membrane disintegrates so that the microtubules can bind to each chromosome at the centromere.

Metaphase. The chromosomes have assumed their most condensed state. The X shape is a result of the two identical chromosomes being joined at the centromere. Each chromosome is aligned along the midplane of the cell.

Anaphase. The bond joining the chromosome breaks, and each moves towards opposite sides of the cell. The cell begins to elongate and narrow at the midplane.

Telophase. A new nuclear membrane forms around each segregated set of chromosomes, the chromosomes begin to decondense, and the cell begins to divide.

G_1 phase. The cell has cleaved into two cells. The chromosomes decondense to their normal extended state for the resumption of normal cell activities.

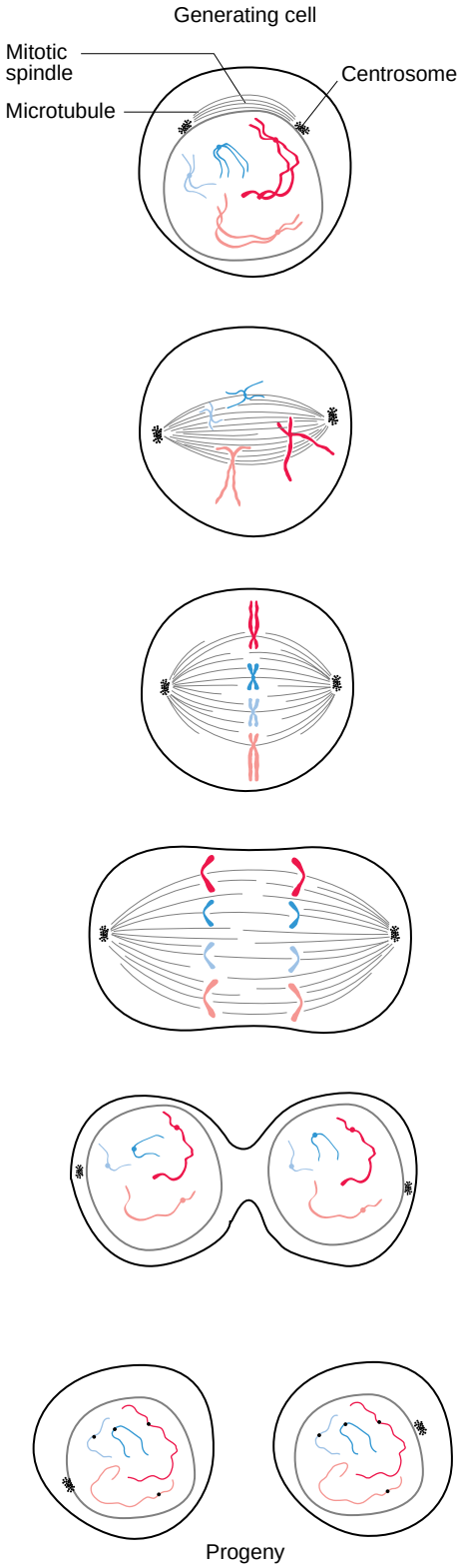


Figure 7. Mitosis and the Birth of Cells

Mitosis is the process whereby a nucleated cell segregates, partitions its already duplicated genome, and divides in two. The result is a set of chromosomes, identical to those initially possessed by the generating cell, being transmitted to each of the progeny cells.

gression of the cell cycle through G_1 and the transition into S phase, whereas cyclin-A-Cdk2 is necessary for progress through S phase. Typically, a phase or process will end when the cyclin is degraded. (In mitogenically stimulated cells the regulation of cyclin D comes about through the control over its subcellular localization and degradation rate.)

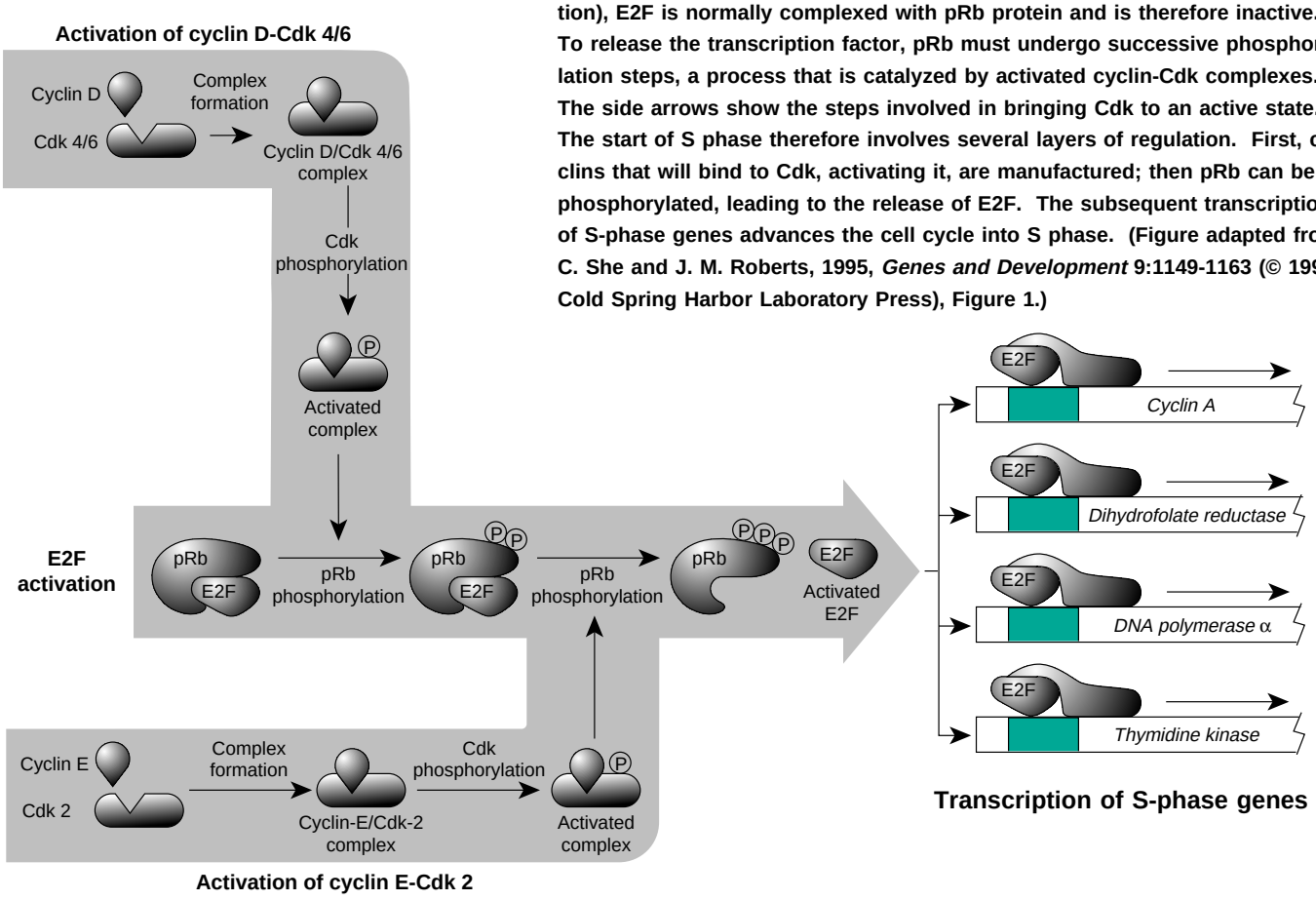
It has been learned that many of the proteins that operate within G_1 phase facilitate cancer development when they fail to function properly. We will therefore describe the G_1-to-S-phase transition in some detail. Also, many cellular responses to DNA damage are triggered from a point in G_1 called the G_1 checkpoint, and thus a section describing checkpoint control will follow. Although necessarily simplified, our description highlights those elements that are important for our later discussion of radiation-induced DNA damage and oncogenesis.

A new cell cycle and the progression through G_1 into S begins when a cell is stimulated to divide by mitogenic signals. Among other things, this initiates the positive regulation, or enhanced transcription, of cyclin D and cyclin E. Loosely associated with this transcriptional activity is a point in G_1 called R (for restriction point). Prior to R, cell-cycle progression remains sensitive to a variety of negative regulatory signals that can counter the effects of mitogenic signals. The cell can either return to G_0 or else begin to differentiate. Once past R, however, the cell is committed to continuing with the rest of the cycle.

Much of the metabolic activity that occurs during G_1 is directed towards preparing the cell for S phase. It is during S phase that the entire genome is duplicated, and so a substantial number of proteins and nucleotide precursors must be synthesized. The start of S phase, therefore, involves a significant amount of transcriptional activity, much of which is promoted by a transcription factor called E2F. (E2F is actually a family of transcription factors, E2F-1, E2F-2, and so on. Our discussion will be limited to E2F-1) If E2F is available, transcription and, hence, S phase can begin. But the availability of

Figure 8. G1-to-S Phase Transition

DNA replication requires the production of numerous proteins, including thymidylate synthetase, which is necessary for producing nucleotides, DNA polymerase α, which is needed to replicate DNA, and cyclin A, which will regulate processes occurring during S phase. Collectively, we've called the genes that produce those proteins S-phase genes. We've shown the regulation of a key step involved in the transcripton of S-phase genes: the release of the transcription factor E2F. As the central arrow indicates (E2F activation), E2F is normally complexed with pRb protein and is therefore inactive. To release the transcription factor, pRb must undergo successive phosphorylation steps, a process that is catalyzed by activated cyclin-Cdk complexes. The side arrows show the steps involved in bringing Cdk to an active state. The start of S phase therefore involves several layers of regulation. First, cyclins that will bind to Cdk, activating it, are manufactured; then pRb can be phosphorylated, leading to the release of E2F. The subsequent transcription of S-phase genes advances the cell cycle into S phase. (Figure adapted from C. She and J. M. Roberts, 1995, *Genes and Development* 9:1149-1163 (© 1995, Cold Spring Harbor Laboratory Press), Figure 1.)



E2F is carefully regulated by several mechanisms. Early in G_1 phase, E2F is bound to and inactivated by a protein called pRb. This inactivation prevents the premature transcription of S-phase genes. As illustrated in Figure 8, E2F is released only after pRb undergoes a structural modification caused by a series of phosphorylation events that are mediated by none other than the activated cyclin-Cdk complexes discussed earlier.

In fact, the cyclins may be considered the ultimate regulators of the transition from G_1 to S phase. Without them, Cdk would not become active, and the release of E2F from pRb would not occur. Conversely, if the cyclins were overexpressed or overly active, they could phosphorylate pRb prematurely and cause the early release of E2F and an abnormal progression through G_1 into S phase. The entire chain of events involving the cyclins D and E, the Cdk's, pRb, and E2F must function properly to regulate the transcription and expression of S-phase genes. If mutations to the genes that produce those proteins cause some of them to malfunction, the cell cycle may be compromised or it may simply break down. Thus, we have returned to our basic picture. Gene mutations that affect the function of certain proteins can lead to erratic or even deranged cell growth and cell behavior.

All other phases of the cell cycle behave in a manner similar to the G_1-to-S-phase transition. They are controlled by cyclin-Cdk complexes that, once formed, are able to activate proteins that can initiate a chain of subsequent events. The chores of a specific phase get carried out, and the cell advances to the next stage of its reproductive cycle. But the cell is not a simple, rigidly behaving automaton. The progression of the cell cycle and the advancement to each new phase can be regulated in response to environmental signals or internal triggers. The entire reproductive process can even be arrested. The decision to suspend cell-cycle progression is made at what are called the *cell-cycle checkpoints.*

Checkpoints and the G_1-Checkpoint Response

The only goal of cell division is to generate two viable cells, each inheriting an exact replica of the parent cell's genome. Given the potential consequences of transmitting incorrect genetic information, it should not be surprising to find that the status of the cell's DNA is internally monitored at the various checkpoints located within each phase of the cell cycle. If abnormalities in DNA structure or conditions that might affect DNA integrity are detected, then a checkpoint may slow the cell-cycle progression so as to allow time for the damage to be repaired. Through checkpoint control, the cell can prevent complications that result from attempts to replicate or segregate damaged DNA, and a cell can thereby minimize the consequences of the initial damage. Alternatively, a checkpoint may also respond to external signals, thus permitting the cell to halt reproduction if, for example, it detects that the tissue is not providing a favorable environment.

Checkpoints in G_1 and throughout S phase safeguard against damage in the DNA template. The G_1 checkpoint also controls the entry into S phase. A checkpoint in G_2 monitors the completion of DNA replication and the absence of chromosome damage, and it regulates the entry into M phase. A final checkpoint in M phase arrests mitosis if chromosomes are not properly aligned along the mitotic spindle (Figure 7: Mitosis). Thus, each checkpoint monitors different aspects of DNA replication and chromosome segregation, and each regulates a different phase of the cell cycle. Each is also sensitive to various environmental influences. As a DNA damaging agent, ionizing radiation triggers checkpoints in G_1, S, and G_2. But all of the checkpoints save G_1 are located beyond R, the cell-cycle commitment point. They can, therefore, only suspend the cycle's progression, without stopping it. Only the G_1 checkpoint can permanently bring the cell cycle to a halt.

Thus, the G_1 checkpoint seems to play the most important role in cell-cycle decision making. It is at the G_1 checkpoint that a cell can respond in any of several ways, depending on the nature of the damage or the environmental trigger. One response is to enter an arrested state that, like the G_2 arrest, suspends the reproductive cycle. Another cell response is *apoptosis.* This is in reality cellular suicide, or a metabolically activated form of cell death. Apoptosis can apparently be triggered from almost any phase of the cell cycle and by a variety of signals. It is a process that leads to the rapid elimination of the affected cell. Apoptosis appears to respond to the abnormal accumulation of cells that is characteristic of malignantly transformed cells and, thus, might help limit excess proliferation. It is further thought to respond to the loss of genetic integrity and to serve as a means of eliminating cells that have sustained unusually high levels of DNA damage.

A third cellular response is called *cell senescence,* which refers to a permanent quiescent state that is triggered after a cell has undergone a finite number of divi-

sions. The entire cell line simply stops dividing. First observed in cell cultures of human-skin fibroblasts, it is generally believed that this phenomenon applies to cells under normal physiological conditions as well. Senescence can be thought of as an internal constraint on the life-span of a cell line. By limiting the total number of cell doublings and hence the number of progeny, cell senescence will also constrain the effects that any individual cell can exert on the rest of the tissue.

These three cellular endpoints—the G_1 arrest, apoptosis, and cell senescence (see "Apoptosis" and "Senescence and Immortality")—can be viewed as defense mechanisms that are summoned to prevent the propagation of an altered cell. The first two are invoked in response to a broad range of insults, from DNA damage to nutritional deprivation, whereas senescence is more of a fail-safe method for limiting an excessive number of cell divisions. However, some cell types, especially those that are not prone to apoptosis, appear to become prematurely senescent following exposure to ionizing radiation. Those cells seem to use senescence more as a defensive response. Figure 9 summarizes the points just made concerning checkpoints and the G_1-checkpoint responses.

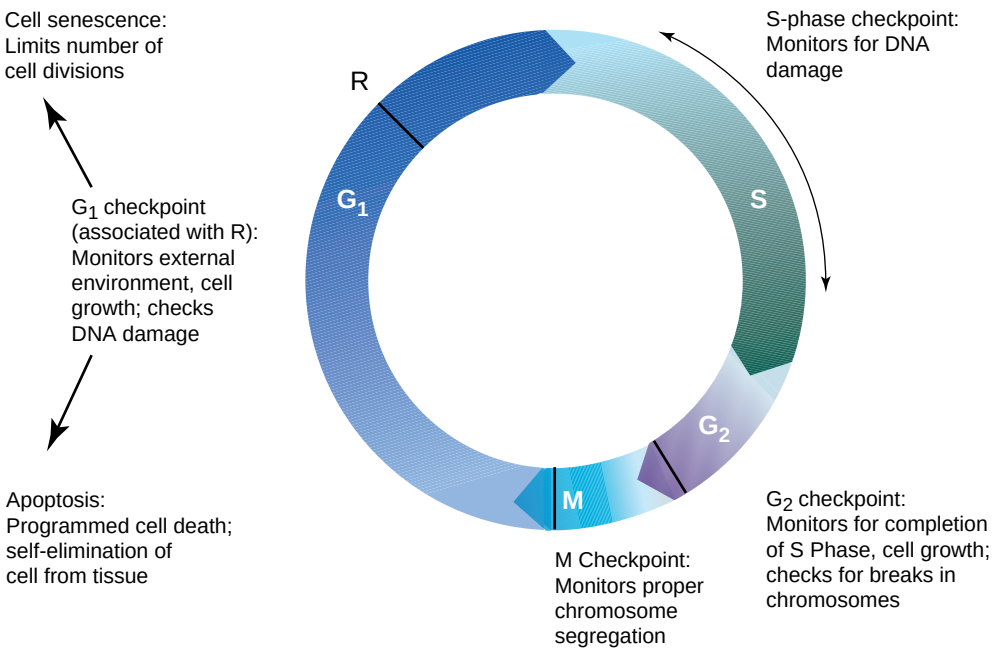


Figure 9. Cell-Cycle Defenses against DNA Damage

Checkpoints regulate the progression of the cell cycle. Both the G_1 and G_2 checkpoints are sensitive to environmental signals, such as nutritional status or tissue requirements, and will suspend the advancement to the next phase if DNA damage or a chromosome abnormality is detected. Faced with DNA damage, the G_1 checkpoint can trigger a cell-cycle arrest. It can also trigger an apoptotic response, which is a form of cell death. An excessive number of transits through the cell cycle can trigger cell senescence, which is thought to arise from the G_1 checkpoint. The checkpoint in M phase is triggered by faulty chromosome segregation, which is a severe breakdown of normal mitosis. The cell typically dies before passing this abnormality onto its progeny.

Each of those responses involves a critical protein called p53. This protein is a *transactivating* protein, which means that it initiates the transcription of other genes. In the case of the G_1 arrest, p53 will induce the production of negative regulators that inactivate G_1-cyclin-Cdk complexes. As stressed in the previous section, those complexes are the major control proteins of the cell cycle, and their deactivation prevents a cell from advancing to the ensuing phase. Specifically, the G_1 arrest is actuated by preventing the cyclin-D and cyclin-E complexes from interacting with the E2F-activation pathway. As in most cell processes, this happens in a somewhat convoluted manner.

DNA damage triggers a G_1 arrest through its effects on the stability of p53 protein. Under normal conditions, p53 is synthesized continuously throughout the cell cycle. Its concentration is controlled by its relatively rapid rate of degradation. In the presence of DNA damage, however, the protein is modified in a manner that makes it more resistant to degradation. This has the net effect of increasing its overall concentration and, thus, increasing its transactivating potential. The exact steps involved in going from DNA damage to this structural modification are presently unknown, although one possible mechanism is presented in "DNA Repair" on page 78.

The stabilized p53 protein is a positive regulator for the transcription of several

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Apoptosis

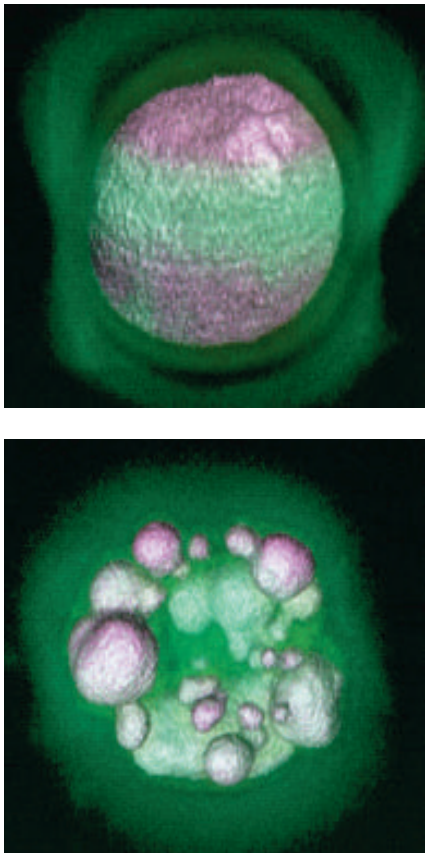


Figure 1. Apoptotic Nucleus
A DNA-binding fluorochrome was used to stain the cell's chromosomes, and a series of optical images, using a fluorescence, laser-scanning confocal microscope, were taken at different depths within the cell. The images were then used to reconstruct a three-dimensional image of the chromosomes within the nucleus. The top figure of a normal human lymphocyte shows that the chromosomes are uniformly distributed throughout the roughly spherical nuclear volume. The bottom picture shows an apoptotic cell. The chromosomes and the nucleus have fragmented and collapsed into small vessicles (apoptotic bodies). The cell will induce its own death by attracting a macrophage that will engulf and destroy the cell. (Photos courtesy of B. L. Marrone, Los Alamos National Laboratory.)

Apoptosis is a metabolically triggered form of cell death that is defined by progressive, cytologically observable changes in cell structure. It can occur in any one of several different situations, including the normal developmental process of eliminating unwanted tissue, such as webbing between fingers and toes, the physiological response to excess cellular division (hyperplasia), and the suicidal response to excessive damage to cellular DNA. Apoptosis also appears to respond to the abnormal accumulation of cells characteristic of malignantly transformed cells and may be inactivated in tumorigenic cells. Each of these individual processes meets the cytological criteria for apoptosis, and as a group, they appear to share biochemical features. To what extent they are actually mediated by the same or similar molecular processes, however, remains unclear.

The induction of apoptosis by DNA-damaging agents shares many features with the induction of G_1 arrest (see main article). Not only are both triggered by DNA damage, but both also appear to depend upon the transactivation of the *p21* and *gadd45* genes by the p53 protein. Apoptosis and G_1 arrest are mutually exclusive responses. The exact mechanisms regulating which response actually takes place have not been elucidated, but it is believed to depend, at least in part, upon the ratio of p21 to Gadd45 proteins. Irradiation of mitogenically stimulated cells favors the induction of G1 arrest over apoptosis. Irradiation of unstimulated cells favors apoptosis. Mitogenic signals are positive regulators of p21 synthesis but have no effect on the synthesis of Gadd45 and, therefore, act to increase the p21 to Gadd45 ratio. The p53 protein, the levels of which rise in response to p53 stabilization in irradiated cells, probably induces both p21 and Gadd45 to similar extents. It is therefore believed that mitogenic signals act through their influence on the levels of p21 and that a high p21 to Gadd45 ratio favors G_1 arrest over apoptosis, whereas a low ratio favors apoptosis.

Apoptosis is also responsive to a second set of regulatory proteins, Bcl-2 and Bax. As with p21 and Gadd45, the ratio of Bcl-2 to Bax seems to be important. In this case, Bcl-2 acts to inhibit apoptosis. However, Bcl-2 can become complexed with Bax, and in this form, it is no longer able to inhibit apoptosis. What controls the relative levels of Bax and Bcl-2? Both Bax and Bcl-2 are regulated at the transcriptional level by p53. The p53 protein stimulates the transcription of the *bax* gene while it represses synthesis of the *bcl-2* gene. Under normal conditions, Bcl-2 is continuously present and apoptosis is repressed. When p53 concentrations increase, as they do after cellular exposure to ionizing radiation, then the concentration of Bax increases relative to Bcl-2, and apoptosis is favored.

At this time, the relationship between regulation by p21-Gadd45 and Bcl-2-Bax systems is unclear. It is not known if these are sequential switches in a common pathway or if they represent parallel responses. Furthermore, it is not known if these switches are in some way linked to each other or if they are regulated by systems that are totally independent of each other. But it is clear that apoptosis is an important response for cells that have sustained DNA damage and, in this role, may act to eliminate severely damaged cells. It is also clear that apoptosis is important for maintaining the appropriate density of cells, such as B-lymphocytes, and that a breakdown in this process initiates a hyperplastic state that can progress into leukemia. ■

Senescence and Immortalization

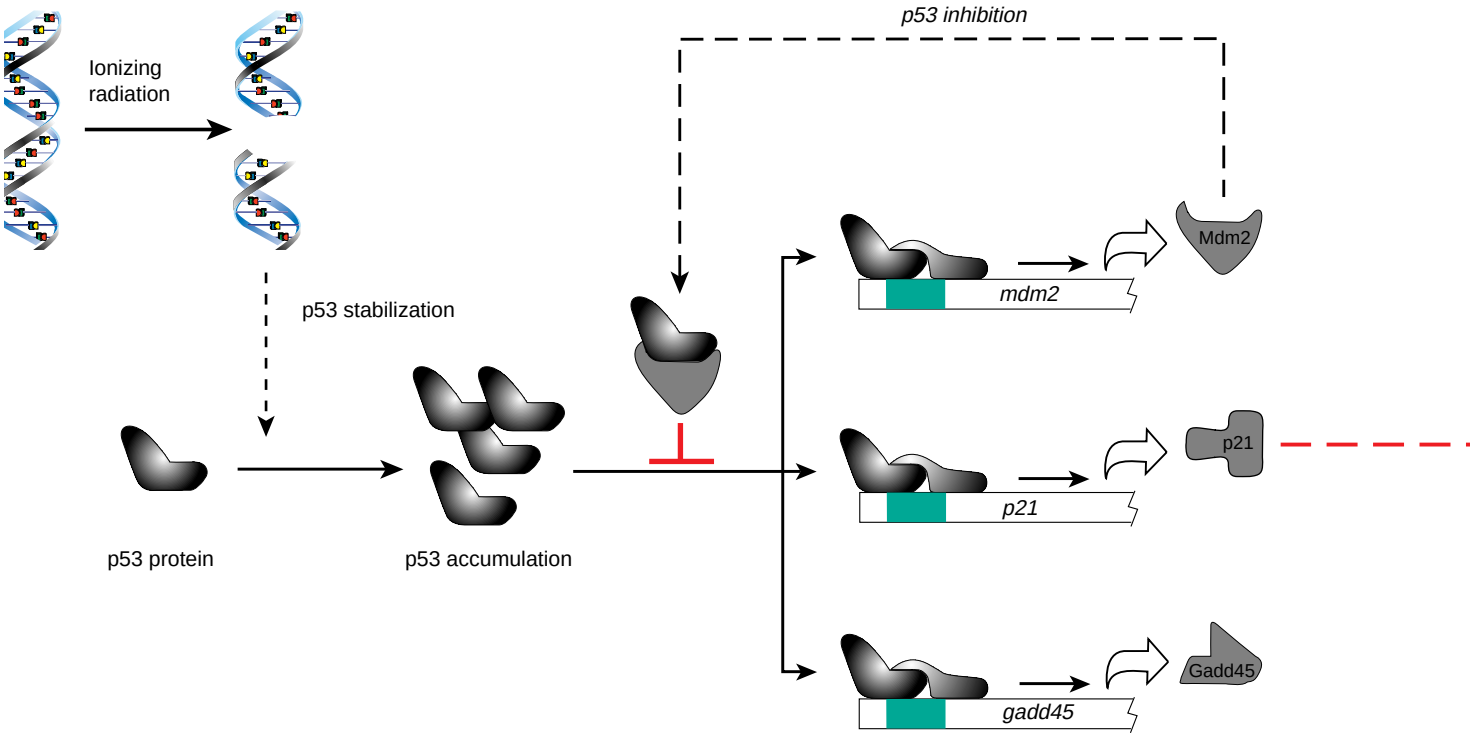
Senescence is a nonproliferative state that normal cells grown in culture will enter after a finite number of cell doublings. Senescent cells will no longer enter S phase, even under mitogenic stimulation, and they will no longer undergo cell division. Cells can be transformed such that senescence is abrogated and the number of cell doublings is extended. This extended life-span is usually accompanied by an escalating accumulation of chromosomal aberrations with each new cell division and an increased likelihood of cell death. Eventually, at a stage termed crisis, nearly all cells die. Under the appropriate conditions, however, a few transformed cells survive crisis and divide indefinitely. These cells acquire immortality. It is believed that to generate life-threatening tumors, a tumor cell must first escape the proliferative controls imposed by senescence and then must acquire immortality.

Table 1. Similarities Between G1 Arrest and Cell Senecence

	G1 arrest	Cell Senescence
Can enter S-phase?	yes	no
DNA content	diploid	diploid
Gene Expression		
cyclin D1	high	high
cyclin E	high	high
Cdk activity	low	low
p21	elevated	elevated
pRb	hypo-p	hypo-p
cyclin A	absent	absent
cyclin B	absent	absent
cdc2	absent	absent
metabolically active	yes	yes

In many ways, senescent cells resemble cells arrested at the G_1 checkpoint (Table 1). This suggests that the mechanisms mediating these two cellular responses may also be similar. A model has been proposed in which senescence is viewed as a specialized form of the G_1 checkpoint response, only triggered by a naturally occurring chromosome instability. Each end of chromosomal DNA terminates in a specialized repeating structure, the telomere. In normal cells, the number of repeats forming a telomere gradually decreases with each population doubling. Maintenance of telomere length would normally be the responsibility of an enzyme called telomerase, but the synthesis of telomerase is apparently terminated early in embryonic development. Thus, the absence of telomerase activity in adult cells results in the gradual erosion of telomere length.

It has been proposed that, at some point, one or more telomeres become too short to perform their normal function of masking DNA termini. Unmasked termini may be recognized as DNA lesions and trigger a G_1 arrest. This is the senescent state. It has been demonstrated, however, that transformed cells with inactive forms of p53 lose the ability to initiate a G_1-checkpoint response (which is also required for the maintenance of the senescent state) and would, therefore, be expected to continue cell-cycle progression even in the presence of DNA damage. Those cells, by continuing their proliferation, would further reduce the telomere length of their chromosomes and accumulate additional DNA damage in the form of nonfunctional telomere units. This predicted accumulation of DNA damage is consistent with the increasing amounts of genomic instability associated with extended life-span proliferation. Protection from the continued loss of telomere function and the resulting accumulation of DNA damage is provided by the restoration of telomerase activity. This is apparently a rare event that may arise as a result of the genomic instability manifested during extended life-span proliferation. The restoration of telomerase activity would lead to restoration of missing telomeres and to the stabilization of telomere length during DNA replication. With the loss of checkpoint controls and the restoration of telomere stability, crisis would be avoided, and the surviving cells would presumably be able to grow indefinitely and, therefore, be immortal. ■



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genes, including the *p21* gene.* The *p21* gene is an important player in checkpoint responses, and the central role of this protein can be appreciated from the variety of ways in which the gene encoding this protein has been cloned. For example, *p21* has been cloned as *cip1* (for *c*yclin-dependent-kinase *i*nhibiting *p*rotein 1) by a group that was seeking negative regulators of cyclin-dependent kinases. It was also cloned as *waf1* (an acronym for *w*ild-type p53-*a*ctivated *f*actor 1) by a second group of investigators that was looking for genes that might be responsive to changes in p53 levels. Finally, *p21* was cloned as *sdi1* (which stands for *s*cenescent-cell *d*erived *i*nhibitor 1) by a third group that was attempting to isolate genes that mediated the cell-senescence response. It is now known that each of these genes codes for the same 21-kilodalton protein, referred to simply as p21.** That protein binds to and is a negative regulator of several G_1 proteins, including cyclin-D-Cdk and cyclin-E-Cdk2 complexes.

As illustrated in Figure 10, the p21 protein blocks the kinase activity of the cyclin-Cdk complex. It does so through a protein-protein interaction, although the exact mechanism is not known. (Other than p21, a class of proteins called the cyclin-dependent kinase inhibitors (CKI's) can regulate the activity of a cyclin-Cdk complex. This interaction is not shown in the figure. The p21 protein is also considered to be a CKI.) The end result is that the cyclin-Cdk complexes are prevented from phosphorylating pRb, and thus, the E2F transcription factor is not released. The S-phase proteins necessary for the G_1-to-S transition are not synthesized, and the cell cycle cannot advance into S phase. Instead, the cell remains in an arrested state in G_1.

*We will designate the name of a gene in italics, and the protein product of that gene in normal type; for example, *p21* gene and p21 protein.

**The full name is $p21^{cip1/waf1/sdi1}$; throughout this article, it will be shortened to *p21*.

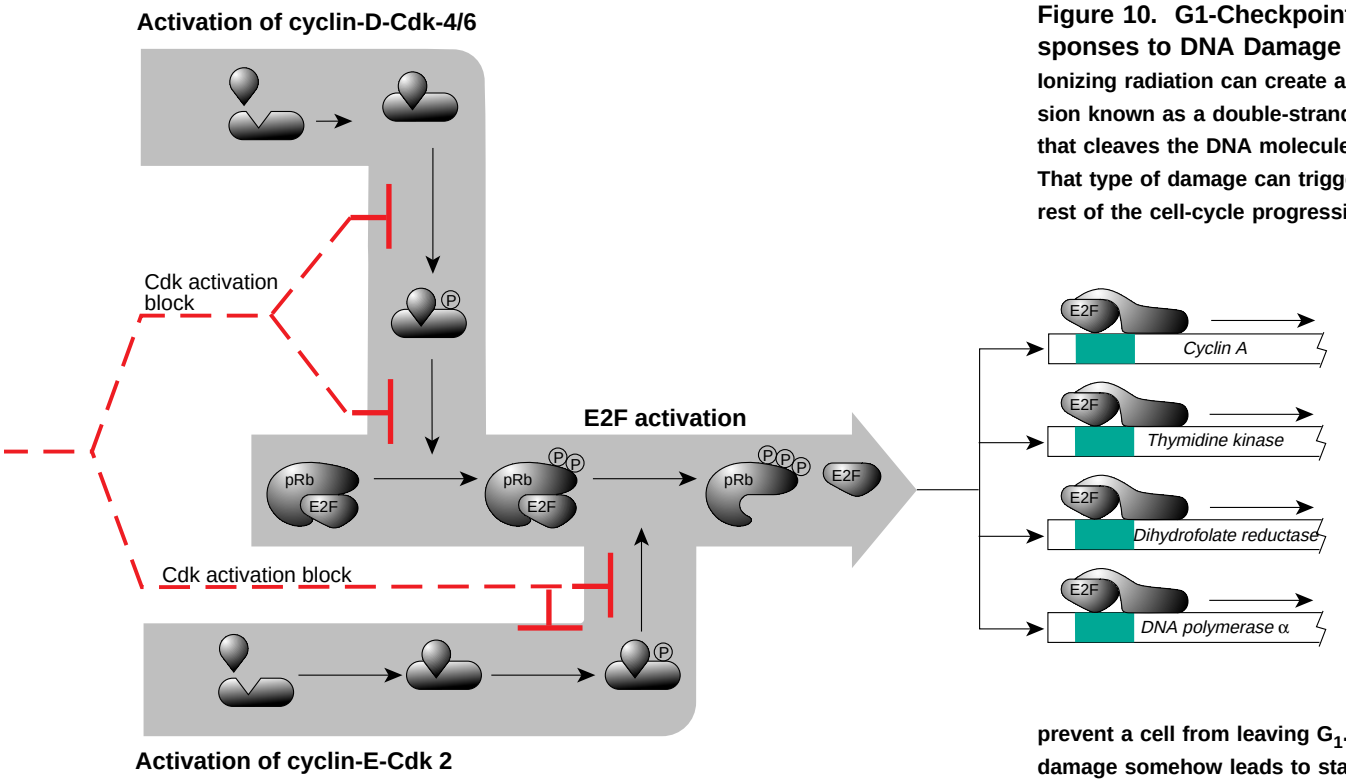


Figure 10. G1-Checkpoint Responses to DNA Damage

Ionizing radiation can create a DNA lesion known as a double-strand break that cleaves the DNA molecule in two. That type of damage can trigger an arrest of the cell-cycle progression and prevent a cell from leaving G_1. The damage somehow leads to stabilization and accumulation of p53 protein (the steps leading to p53 stabilization are not known). The p53 protein promotes transcription of several genes, including the three shown here. The p21 protein is the key protein involved in the arrest. It can block the kinase activity of cyclin-Cdk complexes. Those enzymes are no longer able to phosphorylate pRb, and the crucial transcription factor (E2F) that will transcribe S-phase genes is not released. The cell cannot begin S phase and remains in an arrested state within G_1. The p53 protein also initiates transcription of the *mdm2* gene which produces a protein that can inhibit the transcriptional activity of p53. Thus, the *mdm2* gene becomes part of a negative feedback loop that limits the duration of the G_1 arrest. The third gene shown here to be transcribed by p53 is *gadd45.* In conjunction with p21, the protein product of this gene helps to trigger the apoptotic response. Whether DNA damage results in a G*1* arrest or apoptosis depends in large part upon other factors. In either case, by triggering one of these two responses, the cell minimizes the potential consequences of attempting to replicate a damaged genome.

Figure 10 also shows that the stabilized p53 protein induces the expression of at least two more genes. Gadd45 protein is believed to play a role in the G_1 checkpoint and apoptotic responses to DNA damage. In particular, the relative concentrations of Gadd45 to p21 protein might be important in determining which response is triggered (see "Apoptosis"). Another interesting pathway in the figure involves the protein product of the third gene transcribed, Mdm2. It acts to block the ability of p53 to transactivate its normal target genes. By negatively regulating its own enhancer, Mdm2 effectively establishes a negative feedback loop on the entire transactivation pathway. That is one established way that the G_1 arrest itself is regulated and controlled, and it is potentially the means by which the cell will shut off the blocking mechanism so that it can continue with a new cell cycle.

Once again, a mutation in any of the genes involved in the G_1 checkpoint, including *p53, p21,* and *mdm2,* could result in abnormal cell-cycle regulation. In fact, the importance of a mutated p53 in carcinogenesis is underscored by the fact that more than fifty per cent of human tumors have cells containing mutations in this protein. But it must be noted that the checkpoints, by providing time to repair corrupted DNA, also help maintain the fidelity of the genome. Thus, a mutation that inactivates p53 may allow some cells to advance into S phase and replicate DNA even in the presence of DNA damage. That damage can potentially lead to more mutations that can then be passed to the cell's progeny. A *genomic instability*, or progressive accumulation of chromosome abnormalities, is very characteristic of cancer cells. So is a variability in chromosome number, which would indicate a breakdown in either chromosome segregation controls (G_2 or M-phase checkpoint responsibility) or possibly a dysfunction in DNA-replication controls. A cell that incorrectly expresses some of its cell-cycle regulatory proteins therefore establishes within itself a positively reinforced mechanism that is destined to bring about the improper expression of even more genes. The slightly transformed, aberrant cell can become the seed of cancer within our bodies.

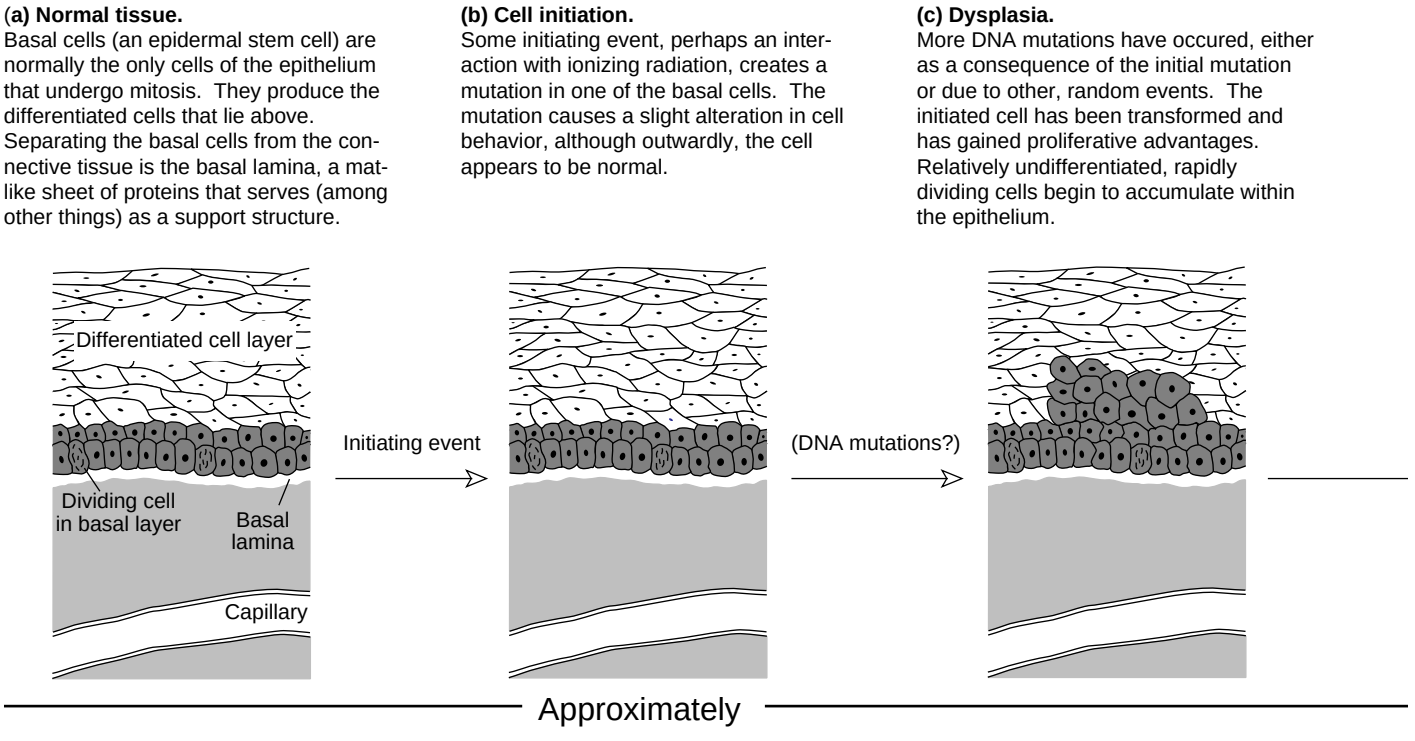
Cancer

Cancer is a gross distortion of cell behavior caused by numerous gene mutations and numerous abnormalities in the production and functioning of proteins. The specific abnormalities vary greatly, depending on the type of cancer as well as the type of tissue from which the cancer originated. Thus, there is not a single description of cancer or oncogenesis, because cancer is not a single disease. It is really a class of diseases all pertaining to unlimited cell growth that is potentially fatal to the organism. Broadly speaking though, carcinomas are cancers of epithelial cells, sarcomas are cancers of connective tissue or muscle cells, and leukemias are cancers of the blood and lymph systems. In the normal human population, over 90 per cent of all human cancers are carcinomas.

A substantial body of evidence now suggests that cancer initiates from a single cell that has been transformed due to a particular change in its DNA. Some event, such as exposure to radiation or exposure to a chemical carcinogen, creates a change in the genome. This may be a DNA mutation, or an epigenetic modification. Then, either through direct action or indirectly through a complex web of interacting proteins, the mutation changes the overall expression of some of the cell's genes. The cell continues to function, albeit slightly differently. Typically, the initial behavioral modification may be difficult to detect, but the functional change is passed on to future cell generations.

In general, a precancerous, transformed cell progresses through the characteristic stages and changes that are discussed in Figure 11. In comparison with a normal cell, a neoplastic cell is hyperresponsive to growth factors, underresponsive to growth inhibitors, and has an increase in metabolic transport capabilities. A cancer cell tends to have an irregular shape, an abnormally appearing nucleus, is more mobile, is invasive, and generally shows a genomic instability. Thus, cancer cells

Figure 11. Cancer Progression
This series of drawings depicts several stages typical of a cancer that initiates in an epithelial layer (such as cervical or colon cancer). (Figure adapted with permission from Alberts, et al., 1994, *Molecular Biology of the Cell*, third edition, New York and London: Garland Publishing, Inc., Figures 24-10 and 24-16.)



look different, grow excessively, and behave abnormally. The time scale needed to accumulate sufficient genetic damage to produce these derangements in cellular traits is typically decades, but for certain leukemias, it may be as short as a few years.

An autonomously growing, solid mass of cells like that shown in Figure 11d is called a tumor, or a neoplasm. (Not all neoplasias form tumors. Leukemias are a result of an unregulated increase in white blood cells, but these cells continue to circulate as individual cells within our bodies.) By necessity, a tumor requires an enhanced blood supply to provide nutrients and to remove waste. Called angiogenesis, tumor cells will help stimulate the production of blood vessels that help the neoplasm grow. By the time it is visible to the naked eye, a tumor may consist of over a billion cells, both normal and transformed.

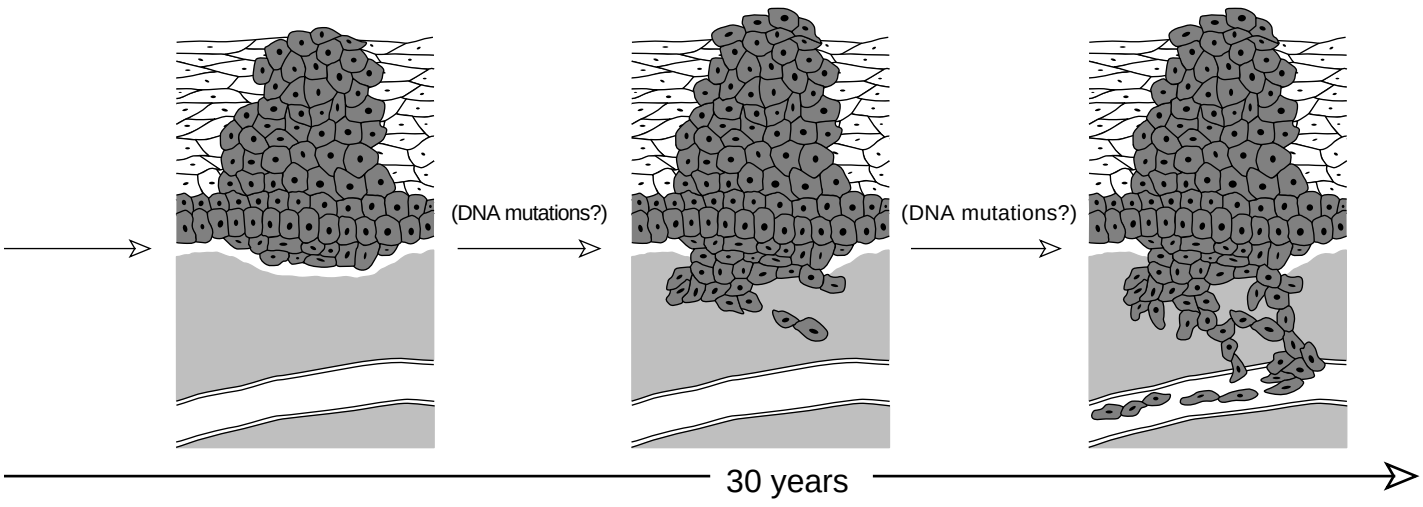
But a tumor is not necessarily cancerous. Cell senescence may still limit the proliferative potential of each cell and, thus limit, the size of the growing cell mass. In that case, the mass may have little physiological effect. A tumor may also be *benign*, which simply means that the neoplasm remains as a well defined cluster that does not spread into neighboring cells. Benign tumors in humans can often be identified and removed surgically with generally favorable results.

To be diagnosed as cancer, a tumor must become *malignant* (Figure 11e). It must gain the capacity to invade the surrounding tissue. This necessitates that individual cells acquire the ability to destroy or disrupt the proteins responsible for holding adjacent cells together. The disruption of intercellular adhesion enables invasive tumor cells to insert themselves between cells in the surrounding tissue and to migrate. Those cells can then disperse themselves throughout healthy tissue and form new growths.

(d) Benign tumor
More changes within the genome of the proliferating cell line leads to full tumor development. All layers of the epithelium contain undifferentiated cells.

(e) Malignant tumor
The tumor breaks through the basal lamina. This increased mobility and invasive property is characteristic of the malignant tumor. The cells are typically irregularly shaped, with an enlarged and irregularly shaped nucleus, have a noticeable genomic instability, and the cell line is immortal.

(f) Tumor metatasizes
Cancer cells break through the wall of a lymphatic vessel or blood capillary. The cells can now migrate throughout the body and potentially seed new tumors in different organs.



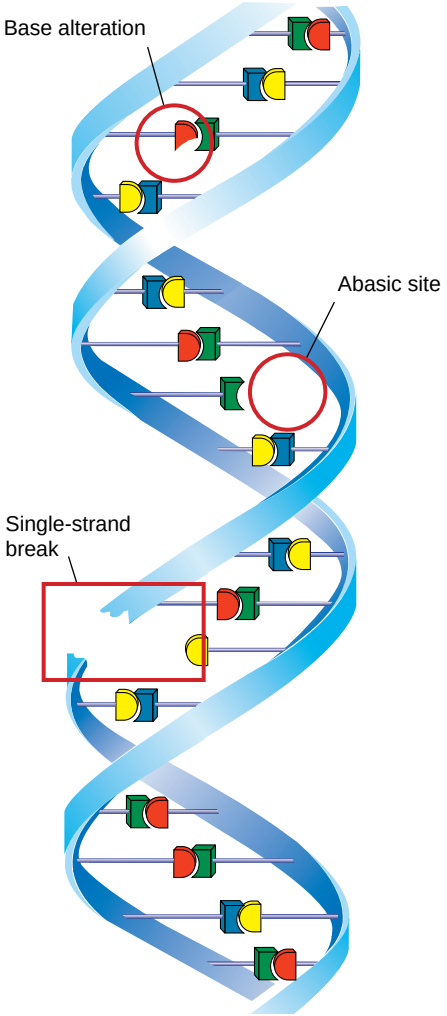


Figure 12. DNA Damage I: Base Alterations and Single-Strand Breaks

DNA bases consist of either one or two ring-like structures that contain both nitrogen and carbon atoms. A base alteration occurs when additional bonds between atoms are formed or broken or new chemical groups attach to the base. All of those situations result in a modified base structure that must be repaired. An abasic site occurs when a base separates from the sugar, leaving behind an unpaired base. Single-strand breaks in the phosphodiester backbone arise largely from hydroxyl radical attack at sugar units comprising the backbone. A gap opens in the normally intact DNA. All three of these general types of lesions are repaired with only a slight risk of genetic change.

The disease develops. Plagued with many growing tumors that are difficult to eradicate, the tissue gradually loses its ability to carry out its normal functions. Its resources are diverted to feed the growing cancer. The cancer may metastasize (Figure 11f), which means that the tumor cells will leave the original tissue, travel by way of the circulatory or lymph system, and invade other organs. As it spreads throughout the body, the tumor can invade and destroy tissue until one or more organs becomes so compromised that death ensues.

Radiation and DNA damage

This primer is about radiation and how radiation can act as a carcinogen to induce cancer. So far, we have only hinted at that relationship by stating that ionizing radiation can damage DNA and that DNA damage can lead to cancer. In reality, those are two separate statements and two separate research areas that must be linked together. Establishing that link, however, has plagued researchers for decades. The remainder of this primer will examine each piece and discuss what is currently known about the link.

Radiation is everywhere. It's invisible and penetrating. Radiation emanates from the soil, seeps as radon into the basements of our homes, and can be a product of the atomic bomb. Much is often assumed about exposing our bodies to radiation, but what *does* happen when an ionizing particle or photon passes through our cells? The radiation deposits energy in that aqueous environment and so creates reactive chemical species. In particular, radiation will produce a highly reactive species known as the hydroxyl free radical ($OH^{\bullet}$). This radical can easily break chemical bonds. An attack on the sugar to which a nucleic-acid base is attached can result in a single-strand break because all or nearly all of the sugar is typically lost. In that case, the break is actually a one-base-wide gap in the DNA backbone. Ionizing radiation can also cause simple modifications to individual DNA bases, creating numerous types of *base alterations.* An entire base can also become separated from the sugar, creating what is called an *abasic site*. Figure 12 illustrates some of the above mentioned DNA lesions.

Although ionizing radiation can lead to the creation of single-strand breaks, the rate at which it does so is negligible compared to a cell's normal metabolic processes. The latter produces copious amounts of hydroxyl radicals. It is estimated that for every single-strand break induced by background radiation, there are about ten million breaks induced by radicals generated during normal cellular metabolism. However, even though the total rate of single-strand breaks from such processes is high, the consequences of single-strand breaks are usually minimal. A cell possesses efficient and accurate mechanisms for rapidly repairing single-strand breaks (see "DNA Repair"). The repair makes use of the information redundancy built into the double-stranded DNA molecule and uses the undamaged complementary strand to restore the DNA to its original state. The vast majority of single-strand breaks are repaired without loss of information and with only a slight risk of genetic mutation. Although single-strand breaks might be lethal lesions to a cell if they are present during DNA replication, the result of DNA repair is that those particular circumstances are typically avoided.

Base alterations and abasic sites, on the other hand, can result in single base changes to the DNA strand known as point mutations. Damaged bases must be repaired, because they might possess altered or ambiguous Watson-Crick pairing properties. As for an abasic site, the DNA structure is compromised due to the in-

ability to form hydrogen bonds between the complementary DNA strands. In both cases, however, the DNA backbone is intact, and during S phase, DNA replication past those lesions will be attempted. The lesions can cause the replication to be error prone, potentially resulting in changes in the nucleotide sequence of the newly synthesized strand. Because the change in base sequence can affect the amino-acid structure and, hence, the protein structure, point mutations might alter the activity or regulation of the gene's protein product. Like single-strand break damage, however, generation of base alterations and abasic sites within the genome are dominated by processes other than ionizing radiation, and the repair of those lesions is similarly rapid and efficient. Probably as a consequence of that repair, ionizing radiation is a relatively poor inducer of point mutations compared with most chemical carcinogens.

Although single-strand breaks, abasic sites, and base alterations are induced by both ionizing radiation and normal metabolic processes, one particularly dangerous type of DNA lesion, the *double-strand break*, is induced preferentially by ionizing radiation. This is due to the manner in which radiation creates radical species within the cell, versus that of metabolic processes. Normal metabolism generates radicals one at a time and at essentially random locations throughout the cell volume. DNA lesions resulting from metabolically derived radicals, therefore, tend to occur at relatively isolated positions along the DNA molecule. Ionizing radiation, in contrast, deposits energy unevenly along the narrow track that is traversed by the ionizing photon or particle. As a result, many radical species are formed in a relatively limited area and tend to form clusters of radicals. If a radical cluster of this type envelops a DNA molecule, then multiple independent lesions might be induced within a localized region of the DNA and both DNA strands might become damaged, broken, or both. Not surprisingly, ionizing radiation can induce very complex lesions comprised of abasic sites and base alterations in addition to strand breaks, as illustrated in Figure 13.

The probability of a double-strand break occurring in any given cell is actually quite low. Thermal diffusion and chemical annihilation will quickly reduce the free-radical density within a radiation track. It has been estimated from Monte Carlo simulations that if the track passes at a distance greater than 2 nanometers from the DNA strand, the probability for DNA damage is slight. It has been estimated from cell-culture studies that approximately twenty to forty double-strand breaks occur per genome at 100 rad of exposure. At that rate, exposures equivalent to ordinary background radiation (typically about 0.3 rad per year) should produce only one double-strand break per ten cells per year!

A double-strand break is usually a mess, and repairing it can be problematic. Even a fairly clean double-strand break, wherein the two backbones are broken directly opposite from each other, results in at least a one-base-pair deletion and a disruption of the linkage between the two DNA segments. The passage of densely ionizing particles, such as alpha particles or neutrons, may break several proximal DNA molecules and cause base damage within each strand that can span several nanometers, or fifteen to twenty base pairs. Not surprisingly, the damaged bases are often excised as the free DNA ends are made ready for repair. The excision permanently removes bases. Simple rejoining of the exposed DNA ends is probably the major mechanism for the repair of double-strand breaks, but this mechanism would result in a loss of genetic information. Remarkably, another mechanism, called *homologous recombination*, exists within the cell that can restore missing information while repairing double-strand breaks discussed in detail in "DNA Repair"). At present, it is not clear what fraction of double-strand breaks

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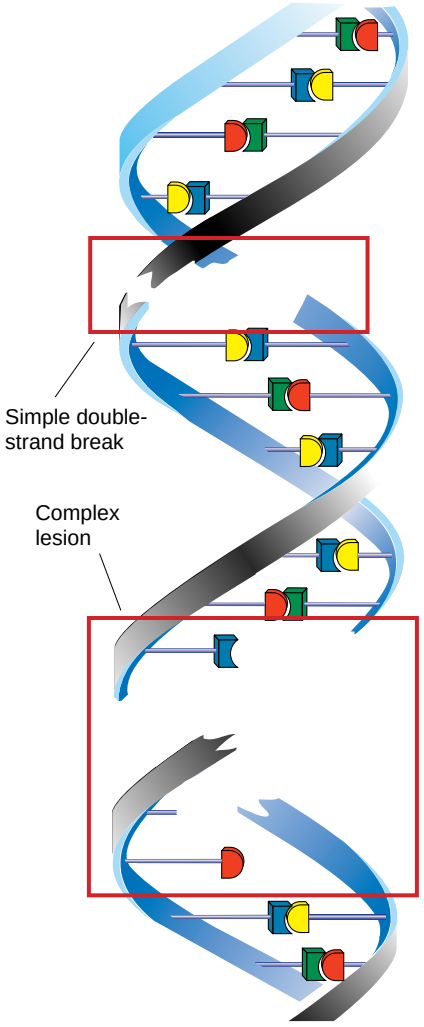


Figure 13. DNA Damage II: Double-Strand Breaks

Double-strand breaks result from two single-strand breaks that are induced at closely opposed positions in the complementary strands. Simple double-strand breaks (upper red box) can often be repaired by a simple end-joining procedure. Ionizing radiation often induces a complex lesion (lower red box) with base alterations and base deletions accompanying the breaks.

DNA Repair

Ionizing radiation induces four major types of DNA lesions. These are nucleic-acid base alterations, abasic sites, single-strand breaks, and double-strand breaks. Severe DNA damage might involve combinations of all three different lesions.

Most DNA base alterations are repaired by an enzymatic mechanism referred to as base-excision repair. This is a generalized repair mechanism that fixes many of the base alterations that are induced by ionizing radiation. The steps are outlined in Figure 1. Briefly, the damaged base and its associated sugar are removed from the DNA helix in a two-step process that leaves a one-base deletion. The missing base is replaced, using the undamaged complementary strand to ensure that the gap is filled with the correct base. Abasic sites are repaired in a similar manner. Repair of both base alterations and abasic sites by base excision restores the original nucleotide sequence.

Figure 1. Base-Excision Repair

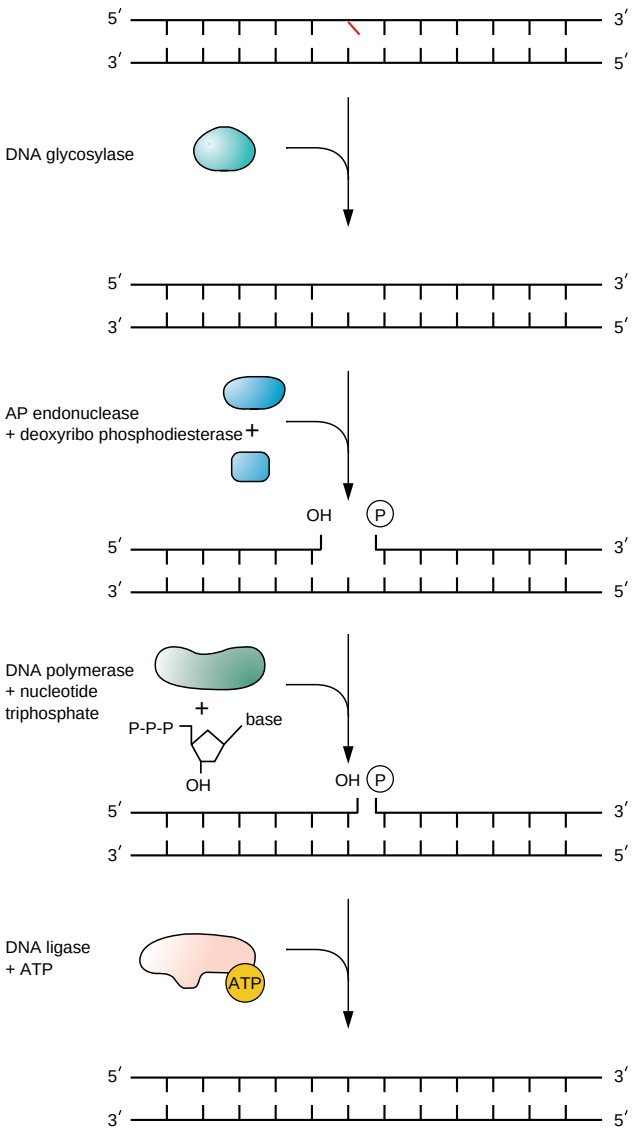
An altered base (slanted red line) results in a minor disruption of the DNA structure.

The lesion is recognized by a class of enzymes known as DNA glycosylases, which release the damaged base, leaving behind an abasic site.

An incision is made to the 5'-side of the abasic site by an AP-endonuclease and the remaining sugar is released by a deoxyribo phosphodiesterase.

The resulting one-base gap is filled by a DNA polymerase. Watson-Crick base pairing will dictate which base is used for the repair. The polymerase leaves a nick in the DNA backbone.

The repair is completed when a DNA ligase seals the nick. The DNA has been repaired with no loss of genetic information.



Single-strand breaks, which are lesions in the DNA backbone, frequently result from hydroxyl radical ($OH^{\bullet}$) attack on the deoxyribose sugar unit. The radical attack initiates the rupture of the sugar unit, leading to the release of the attached nucleic-acid base and most of the sugar unit from the DNA molecule. The result is a small, single-strand deletion, which is also repaired in a manner similar to base-excision repair. An exonuclease removes any sugar remnants, along with the phosphate group on the 5' side of the sugar. The resulting gap is filled by a DNA polymerase, again using the complementary strand as a template, and closure of the remaining single-strand nick is catalyzed by a DNA ligase.

Because there is an intact complementary DNA strand that is used in both base-excision repair and single-strand-break repair, these lesions pose little or no risk of permanent genetic change. This is not the case with double-strand breaks, which can be thought of as individual single-strand breaks that occur in opposite strands and within several bases of each other. The DNA molecule is completely broken in two. This type of damage usually results from severe insult to the DNA and is sometimes accompanied by significant base alterations in both strands. Thus, there may be no complementary strand immediately available with which to initiate repair.

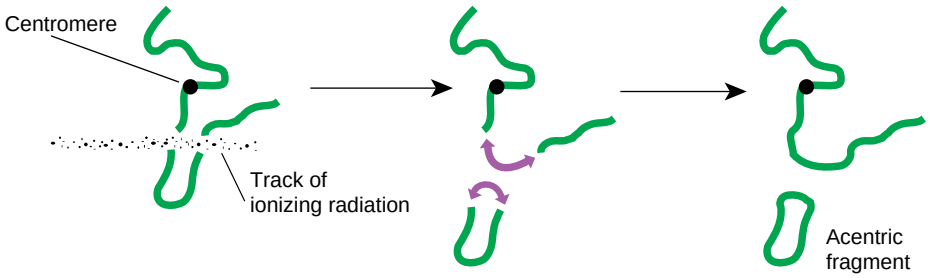
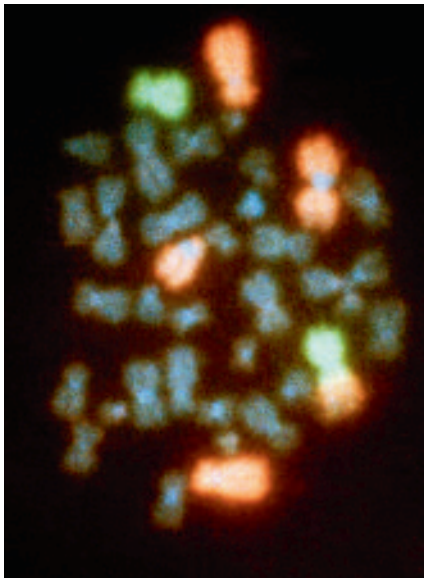


Figure 2.
Chromosome Deletions
Chromosomal deletions can arise if two double-strand breaks occur within the same chromosome, creating a DNA molecule that is broken into three pieces. If two of the end pieces are rejoined, such that the middle section of DNA is unattached, it is no longer associated with a centromere. This free floating piece, called an acentric fragment, may be lost during mitosis.

Double-strand breaks are often rapidly repaired by the simple mechanism of joining free ends, and this is likely to be a significant source of DNA mutations. In nonhomologous recombination, the free ends of broken DNA molecules are brought together and joined without reference to an intact partner. There are several mechanisms by which this can occur, the simplest employing a DNA ligase that ligates the two ends together. DNA topoisomerases I and II have also been identified as mediating the untemplated fusion of two DNA molecules. Although these mechanisms serve to rescue parts of a broken chromosome, they do so at the risk of introducing mutational changes and random genetic rearrangements.

Because end-joining reactions do not employ templates to guide the rejoining process, there is no means to replace missing information. Recall that each single-strand break is actually a one-base deletion. Joining the free ends of two single-strand breaks that are immediately opposite each other (creating a very simple type of double-strand break) will still result in the deletion of one entire base pair, and the formation of a deletion mutation. Furthermore, without a template, simple end-joining cannot even ensure that the ends being joined were from the same initial break. A chromosome deletion can occur if two or more double-strand breaks occur within the same chromosome, as illustrated in Figure 2. Because this deleted section is not associated with a centromere, the section (called an acentric fragment) is often lost when chromosomes are segregated during mitosis. This deprives a cell of a fraction of its genetic heritage.

A direct interaction between ionizing radiation and a cell's genome, however, can produce many proximal double-strand breaks. Joining of unrelated ends from



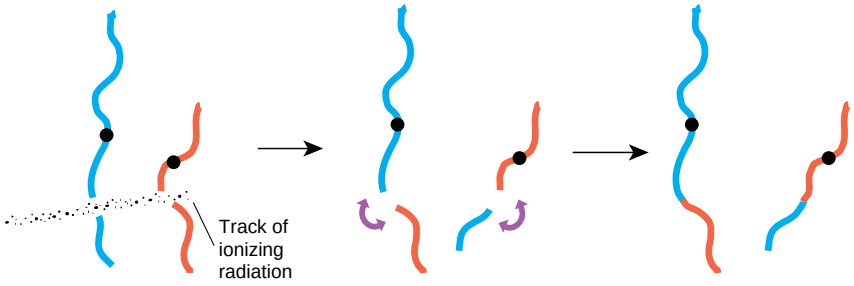


Figure 3. Chromosomal Translocation

A translocation occurs when large sections of genetic material are swapped between two or more chromosomes. In the illustration on the upper right, ionizing radiation creates double-strand breaks in two different chromosomes. The ends interchange when they are spliced back together.

The photo directly above of metaphase chromosomes from a human lymphocye shows a translocation between chromosome 1 and chromosome 8. Three chromosome pairs (1, 4, and 8) were labeled with colored markers that are specific for certain chromosomes. The two orange-colored chromosomes at the top of the photo are both chromosome 4. Chromosome 1 also appears orange. Chromosome 8 is marked with green. The orange-green chromosome is a translocation. A portion of chromosome 1 (center of photo) apparently became reattached to chromosome 8. It is not clear whether chromosome 8 remained intact or whether a portion was lost because of the translocation. (Photo courtesy of L. Gayle Littlefield, Ph.D, Oak Ridge Institute for Science and Education)

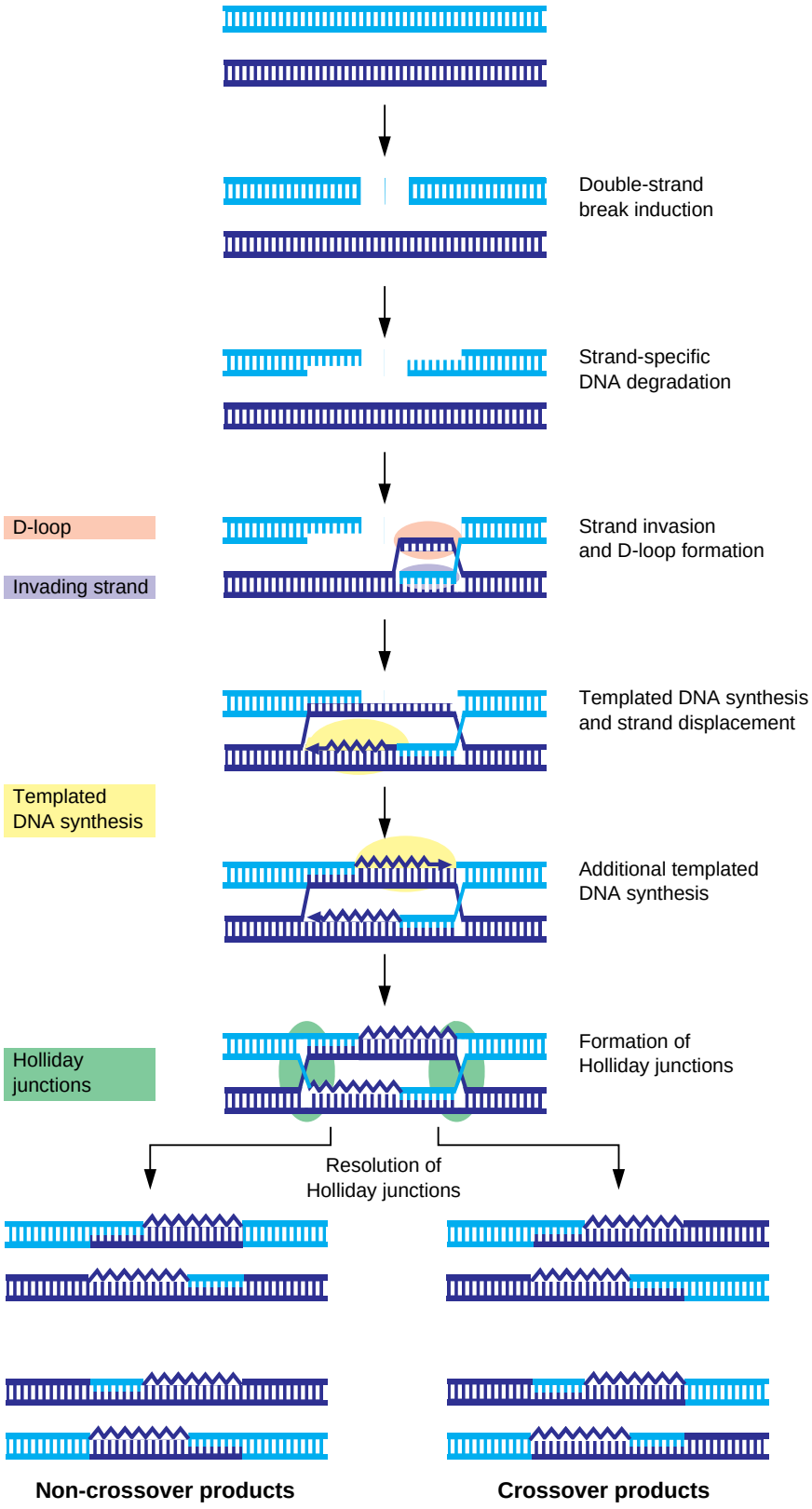
breaks in different molecules can result in genetic recombination, which is expressed at the chromosome level as chromosomal rearrangements and translocations. Figure 3 shows one such translocation.

Remarkably, there is a mechanism that is thought to be active in human cells that allows for the restoration of missing information. Called homologous recombination, it requires that a second, intact version of the DNA sequence be present in the cell. This can potentially be found on a homologous chromosome. The intact version is used as a template on which the fragments of the broken DNA molecule can be aligned in proper register. Figure 4 describes homologous recombination.

Recently, V(D)J recombination, which is the process that mediates the development of antibodies as part of the normal immune response, has been linked with the repair of double-strand breaks in DNA molecules. As such, it may provide an intriguing possible link between ionizing-radiation-induced DNA damage, p53 stabilization, and cell-cycle control.

An antibody "gene" is assembled from three different genetic elements, referred to as the variable (V), diversity (D) and joining (J) regions. Constructing the gene requires that V, D, and J sequences be selected from the collection of those available and that the selected sequences be joined to form the final antibody gene. The V(D)J-recombination system does this by inducing its own double-strand breaks and providing for their subsequent repair. Several different components of the V(D)J recombinase (the collection of proteins that mediate V(D)J recombination) have been identified and partially characterized. Two enzymes, RAG1 (*r*ecombination *a*ctivating *g*ene 1) and RAG2, are necessary and probably sufficient for introducing the site-specific cleavages. The resulting double-strand breaks are then bound by a complex of a least three proteins, including pKu70, pKu80 and p350, which is a DNA-dependent protein kinase (DNA-PK). The p350 protein expresses the kinase activity only when it is part of the pKu complex that is bound to a DNA end.

What is intriguing is that p53 is known to also bind to the DNA termini created by double-strand breaks and that p350 is capable of phosphorylating p53 in cell systems. It is speculated that the phosphorylation by DNA-PK is the mechanism by which p53 becomes stabilized and that this is the direct link between double-strand breaks and p53 stabilization that triggers the G_1 checkpoint (see main article) Recent findings have demonstrated that the V(D)J recombinase does participate in the repair of double-strand breaks induced by ionizing radiation and that this process contributes to the normal cellular resistance to the lethal effects of ionizing radiation. But it has not been proven that V(D)J recombinase directly helps induce the G_1 checkpoint nor that the particular site phosphorylated by p350 leads to an increase in p53 stability. ■



Adapted from Terry L. Orr-Weaver and Jack W. Szostak, 1985, Fungal recombination, *Microbiological Reviews* 49: 33-58.

Figure 4. Homologous Recombination

Homologous recombination requires two regions of identical or nearly identical DNA sequence. (In this diagram, two homologous DNA segments are indicated as separate molecules, but they might also be separate regions of the same molecule.)

The introduction of a DNA double-strand break into one of the two regions of homology provides the starting point for homologous recombination.

Unprotected ends generated by the double-strand break provide sites for strand-specific exonucleolytic degradation and the generation of protruding single-strand ends.

Invasion of the second DNA molecule by a protruding end can result in base pairing between the invading strand and a complementary sequence. The invading strand then serves as a primer for the initiation of DNA synthesis along the complementary strand of the intact molecule. Displacement of the second strand of the intact molecule (the D-loop) provides a single-strand region that can pair with the remaining end of the damaged molecule.

DNA synthesis proceeds along the displaced D-loop strand. Again, missing information is restored. This stage of the repair leaves two single-strand nicks.

Two cross-strand structures (Holliday junctions) form when residual single-strand nicks are sealed by a polynucleotide ligase.

Each Holliday junction can be resolved in two possible ways, resulting in four general types of recombination products. Two of these products retain flanking regions from the same parental molecule and are therefore noncrossover products. The other possible products are comprised of flanking regions from different parental molecules and are therefore crossover products. No matter which of these products is formed, missing DNA sequences have been replaced and the double-strand break sealed.

continued from page 77

are repaired using this mechanism. It is known, however, that ionizing radiation induces many deletion mutations and that these mutations probably arise during the repair of the double-strand breaks.

Because the repair of a double-strand break is generally nonspecific, free ends that arise from multiple breaks in chromosomes can get mixed and spliced back together arbitrarily. The result is a chromosomal rearrangement. These rearrangements include *chromosome deletions*, in which an entire section of a chromosome is spliced out, or a *translocation*, in which a piece of one chromosome is reattached to another chromosome. Chromosomal rearrangements that result in large DNA deletions, multiple translocations, or incomplete or distorted chromosomes are frequently fatal to a cell line. A surprising number of such aberrations, however, are not fatal. Stable translocations that don't result in cell death are readily found within the cells of healthy people, as well as in the cells of an irradiated population. Almost fifty years after the exposure, stable translocations can still be observed in the atomic-bomb survivors of Hiroshima and Nagasaki.

Oncogenes and Tumor-Suppressor Genes

The correlation of specifically mutated genes with specific cancers and the identification of two major classes of "cancer-causing" genes represent major breakthroughs in cancer research. One gene type, the *oncogenes*, are activated by the mutation or amplification of normal genes (called *proto-oncogenes*). Oncogene activation can be thought of as a gain of gene function, in that the overexpression or dysregulation of those mutated genes helps promote cell transformation. Due to this gain of function, oncogenes act in a dominant fashion, and expression of the transforming trait requires only one abnormal allele to effect change. Mutations in *tumor-suppressor genes*, on the other hand, are recessive in nature. Both alleles must be mutated or eliminated to disrupt cell functioning. Tumor suppressors normally act in a manner that regulates or impedes progression through the cell cycle, and it is the absence of that regulation that allows tumor development. The presence of either normal allele would result in the production of functional proteins, and therefore, both alleles must be inactivated. The inactivation of both alleles represents a loss of gene function. These concepts are illustrated in Figure 14. Due to the redundancy of cell-cycle regulatory processes, however, cancer development typically requires more than just the activation of one oncogene or the inactivation of one pair of tumor-suppressor genes. If one were to analyze the genome of a typical cancer cell, one would probably discover multiple mutational changes and find a complex mixture of oncogene activation and tumor-suppressor inactivation.

Many proto-oncogenes are part of regulatory pathways and exert their influence through the phosphorylation of target proteins, the formation of protein-protein complexes, or the regulation of transcriptional activity of target genes. Tellingly, most proto-oncogenes participate in the regulation of cellular proliferation or progression through the cell cycle. As previously mentioned, a disruption of those regulatory processes can result in abnormal proliferation and cell transformation.

Proto-oncogenes become oncogenes through the induction of one of several different genetic events, including DNA point mutations. For example, the *ras* gene is a proto-oncogene that is frequently made oncogenic by point mutations. The protein product of *ras* is pRas, the protein mentioned earlier as part of a signal transduction cascade (see Figure 5). A single point mutation at a critical site in *ras*

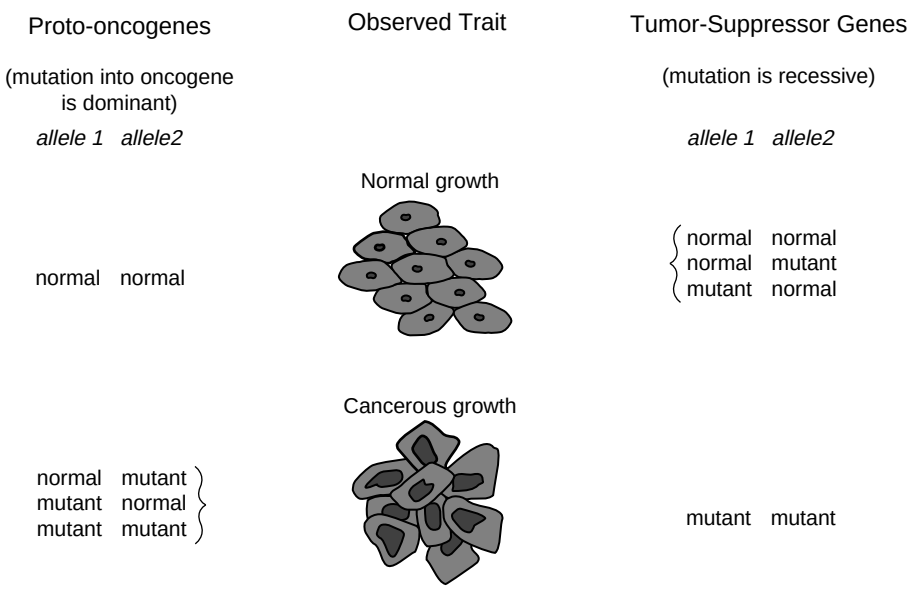


Figure 14. Proto-Oncogenes and Tumor-Suppressor Gene Action
The mutation of a proto-oncogene into an active oncogene represents a gain of gene function. The abnormal gene behaves in a dominant fashion and, therefore, only one of the two alleles normally present need be mutated (or overexpressed) to promote abnormal cellular proliferation. The mutant forms of tumor-suppressor genes represent a loss of function and are, therefore, recessive to the normal allele. Because the mutant forms are recessive, both alleles of tumor-suppressor genes must be inactivated by mutational changes.

may be sufficient to produce an abnormally fuctioning pRas protein that is always in an enzymatically active state. It no longer requires an activating signal to phosphorylate other proteins in the pathway. The entire cascade behaves erratically and continually sends a growth stimulatory signal to the nucleus. The cell either responds abnormally or else counteracts the signal via negative regulatory proteins. The *ras* oncogene is found to be mutated in about thirty per cent of all human cancers, including bladder and colon cancer.

Oncogenes may also be activated through a variety of cytogenetic events, such as large chromosome deletions, inversions, and translocations. Deletions result from the removal and loss of DNA segments, whereas inversions are the result of a DNA segment that has been removed from the chromosome and then reinserted at the same postion but in the opposite orientation. A translocation occurs when a section of one chromosome becomes reattached to a breakpoint in a second chromosome. Each of those processes results in the movement of large DNA segments, which may include a gene, from one position in the genome to a second position. If the breakpoints occur at the appropriate positions, the rearrangement can link a proto-oncogene to the distal end of another actively transcribed gene. In this way, transcription of the proto-oncogene can come under the control of a different and potentially more active gene. As an alternative scenario, the fusion protein may have altered properties, such as increased stability or resistance to negative effectors.

An example of oncogene activation through a translocation is the *bcl-2* proto-oncogene on the long arm of chromosome 18, which can become fused with the immunoglobulin heavy-chain (Ig H-chain) locus on the long arm of chromosome 14. This translocation is frequently associated with human B-cell lymphomas and has been identified in up to 85 per cent of the cases examined. A B cell, or B lymphocyte, is a type of white blood cell that is important for immune responses. The translocation positions the *bcl-2* gene downstream of the Ig H-chain promoter, which results in enhanced transcription of *bcl-2* and an overexpression of the Bcl-2 protein in B cells. This appears to prevent the B cells from undergoing apoptosis. At nominal Bcl-2 protein levels, external signals such as high cell densities

will trigger an apoptotic response in some cells. The B-cell population will be stabilized due to an equilibrium between cellular reproduction and apoptotic death. Cells that overexpress Bcl-2, however, become abnormally resistant to apoptosis and exhibit an extended life-span. The continued proliferation of B lymphocytes in the absence of appropriate cell death results in clonal expansion and an abnormal accumulation of cells that is ultimately recognized as leukemia.

Oncogene activation can be achieved by another process known as *gene amplification.* That phenomenon occurs when a region of DNA is replicated many more times than other regions of the cell's genome. Prior to gene amplification, a cell might contain anywhere between one and four copies of a given gene. After gene amplification, a gene might have hundreds or even thousands of copies per cell. If each amplified gene were transcribed at the same rate as its unamplified precursor, the encoded protein would be overexpressed in proportion to the increased representation of the gene. The cyclin-D1 oncogene was recognized as an amplified gene associated with parathyroid cancer. Cyclin-D1 protein was previously discussed in the context of regulating the E2F-activation pathway, and it is one of the major cell-cycle control proteins. Excess cyclin D1 is known to hasten the progression from G_1 to S phase and to reduce the influence of negative effectors on cell-cycle control. Under those circumstances, cellular proliferation is favored and a tumor can result.

But the regulation of cell reproduction is a result of a balance between positive and negative effectors. As outlined above, oncogenes are positive regulators that tend to stimulate cell growth (or to protect cells from apoptotic death). The tumor-suppressor genes act in a complementary fashion. Their normal role in cell regulation is to inhibit cell growth, and their protein products act as brakes on the cell cycle. The presence of any functional product, therefore, tends to limit cell growth and to suppress tumor formation. As a corollary, the complete absence of the gene (that is, loss of both alleles) enhances cell transformation and fosters neoplastic development.

Mutational inactivation of tumor-suppressor genes occurs by many of the same mechanisms that activate oncogenes, as well as additional mechanisms that result in a loss of function. Tumor-suppressor genes may be inactivated through the induction of point mutations, chromosome rearrangements, or the loss of part or all of a chromosome. Large deletions can eliminate the gene from the genome entirely or else remove so much genetic material that the protein product is not functional. But it is not required that the protein disappear altogether from the cellular pathways. The growth inhibitory function merely has to be compromised. Thus, single point mutations within a critical binding site can prevent the protein from functioning properly. The normal inhibitory function of the tumor-suppressor gene can then become inactivated.

The p53 gene, which was discussed earlier in connection with G_1 checkpoint regulation and apoptosis and which may also be involved directly in DNA repair, is the most notorious tumor-suppressor gene found to date. It is apparently mutated in one way or another in over fifty per cent of all human cancers. In the majority of cases examined, the inactivating mutations were found to be point mutations. The p53 protein contains a site-specific DNA binding region, the so-called *core domain.* The core domain specifies the sequence for a stretch of 190 amino acids, which are critical for the sequence-specific binding and transactivation properties of p53. Mutations at positions throughout this core domain have been found to correlate with human cancer.

Table 1. Some Oncogenes and Tumor-Suppressor Genes Active in the Cell Cycle

Oncogene	Activation	Human Cancer
cyclin A	disruption by viral infection	hepatocarcinoma
cyclin D	inversion	B-cell lymphomas
cyclin D	translocation	B-cell lymphomas
cyclin D	gene amplification	breast (~20%), gastric, esophageal carcinomas, parathyroid adenomas
bcl-2	translocation	B-cell lymphoma (85%)
E2F	overexpression	Cell culture and animal model systems
cdk6	overexpression	osteosarcoma
cdk4	gene amplification	sarcomas
mdm-2	gene amplification	soft-tissue sarcomas, metastatic osteosarcomas, malignant gliomas
ras	point mutation	~10% of all human cancers, including colorectal cancer (~30%), lung (~20%) pancreatic cancer (70-80%)
p53	point mutations (deletion mutations) (chromosome loss) (chromosomal rearrangement)	~50% of all human cancers, including breast, colon, liver, and lung
rb	deletion mutations chromosome loss (point mutations)	retinoblastoma (~100%) osteosarcoma

More than 70 oncogenes and about a dozen tumor-suppressor genes have now been identified within the cell. A partial listing of genes identified as oncogenes or tumor suppressors and discussed in this article is given in Table 1. These genes are "built" into our genomes and cannot be eliminated because they are so intimately tied to the proper functioning of the cell. For example, the *rb* gene, whose protein product, pRb, is essential in regulating the E2F transcription factor, is a well-known tumor-suppressor gene. A mutation of *rb* can lead to retinoblastoma, a rare cancer of the retina that typically shows up in childhood. Just as *rb* is central to the cell cycle, so is E2F, which is known to be an oncogene from cellular and animal studies. Those and all other oncogenes or tumor suppressors have been identified as such *precisely* because they are the genes that regulate cell behavior, and their improper expression, therefore, leads to neoplastic transformation. This lends itself to an interesting observation. Many "cancer-causing" genes specifically regulate cellular reproduction and thereby enable an organism to

maintain itself through growth and repair of tissue. Thus, cancer, which can bring about an organism's death, cannot be separated from those processes that help sustain an organism's life.

Ionizing Radiation and Cancer

Ionizing radiation can damage DNA, and that damage can lead to various changes in the genome, including gene mutations. From the point of view of the radiation biologist, the damage tends to be nonspecific. Genetic mutations appear in irradiated cells but with no apparent bias towards any particular gene. From the alternative perspective of the cancer researcher, specific oncogenes and tumor-suppressor genes have been correlated with specific cancers. Therefore, one concludes that genetic mutations do lead to cancer. Despite the apparent connection between the two viewpoints, there is still a crucial gap. Although many of the activating mutations in the genes *can* arise from interactions with ionizing radiation, we cannot in general state that they *did* arise as the result of a particular exposure. That is, it is usually not possible to say that radiation has induced a specific gene mutation and, further, that that specific mutation then results in a specific type of cancer.

There are several reasons for this lack of connectivity. The types of cancer normally found to be elevated in irradiated populations are also observed in nonirradiated populations. Frequently, the increased risk due to radiation exposure is small in comparison with the nominal risk. Therefore, one cannot deduce with any degree of certainty that a given cancer was due to a given exposure, as opposed to being the result of other factors. Furthermore, the development of cancer is a complex process, normally requiring multiple mutational changes that are accumulated over a period of many years. It is difficult to determine the order in which these changes arise. Establishing which of those genetic changes was the specific consequence of a radiation exposure that occurred many years prior to tumor formation is likewise very difficult. None-the-less, some correlations between radiation-induced DNA damage and cancer have been found.

One of the least ambiguous cases of a radiation-induced gene mutation concerns the *ret* oncogene. This oncogene has been associated with papillary adenocarcinomas of the thyroid, the predominant type of thyroid cancer found among the atomic-bomb survivors. The *ret* proto-oncogene is believed to encode a cell-surface receptor similar to those known to function in signal-transduction pathways. Since the *ret* proto-oncogene is known to be expressed more in fetal tissue than in adult tissue, it is hypothesized that the pathway is important for developmental growth and the maturation of tissue.

The oncogene was actually first recognized as a rearranged gene associated with thyroid cancer, and radiation-induced activation is thought to occur by this mechanism. The activating translocation occurs between a point within the *ret* gene, located on the long arm of chromosome 10, and a specific second locus, also on the long arm of chromosome 10. The ability of ionizing radiation to induce this specific rearrangement has been confirmed with cultured human cells. Moreover, in a recent study examining thyroid cancers in children from areas contaminated by the Chernobyl accident, this rearrangement of the *ret* oncogene was found in four out of a total of seven cancers examined, a remarkably high correlation.

Ionizing radiation is also believed to activate another oncogene, *bcr/abl*, through the induction of a specific translocation. The *c-abl* gene, located on chromosome 9, be-

comes fused with the *bcr* gene on chromosome 22. Each gene was originally located on one side of the breakpoint, and the fusion results in an abnormal, but still functioning, protein product. The *bcr/abl* oncogene has been strongly linked with a major form of radiation-induced B-cell leukemia called chronic myelogenous leukemia. Under normal conditions, the *abl* gene product is believed to act as a negative regulator of apoptosis in B lymphocytes. The *bcr/abl* fusion product becomes resistant to those signals that would normally override its protective influence. The increased resistance to apoptotic signals conferred by the *bcr/abl* oncogene leads to a clonal expansion and abnormal accumulation of the cells and, thus, to leukemia.

The only tumor-suppressor gene that is specifically correlated with radiation exposure is *rb*, which is a gene located on the short arm of chromosome 13. Mutations in both gene copies of *rb* are necessary to bring about retinoblastoma, which is a rare type of malignant cancer arising from the neural precursor cells in immature retinas. Retinoblastoma occurs in childhood and affects about one in every 20,000 children. Children that inherit only one defective *rb* gene have a predisposition for the disease. In the past, retinoblastomas were successfully treated by radiation therapy. Treatment with radiation, however, carries an increased risk of radiation-induced tumors when used to treat children with a familial defect in the retinoblastoma gene. Both primary and secondary retinoblastomas are characterized by the loss or inactivation of both rb alleles, and it is reasonable to assume that the increased risk observed with irradiated patients results from the inactivation of the normal *rb* allele.

Although many cancers have been correlated with ionizing-radiation exposure, the direct association with oncogenes or tumor-suppressor genes is frequently tenuous. Take as an example, lung cancer and the *p53* gene. Increased levels of lung cancers have been found in uranium miners exposed to radon gas. (Radon is a decay product of uranium, and so it will always be found in uranium mines.) Mutations of *p53* have been found in a number of those cancer cases. Most of those *p53* mutations are point mutations. We previously described how point mutations could arise from radiation-induced DNA base alterations, but we also indicated that radiation was not particularly good at creating that type of genetic change. Thus, correlating the *p53* mutations with radon is a little suspect. That suspicion should be coupled with research that indicates that *p53* inactivation seems to be a late-occurring mutation, that is, it appears in cells that have already been initiated and transformed. Late-appearing point mutations might be the result of some genomic instability that facilitates the accumulation of additonal mutations. Most of those mutations would be silent or have no effect on the cell. When a mutation appears in a critical gene, such as *p53*, the cell's transformation would get significantly advanced. Lastly, the uranium miners work in a hazardous enviroment and were exposed to elevated levels of silicates and diesel smoke. Many of them were also heavy cigarette smokers. Thus, in terms of epidemiology, this population is exposed to a complex mixture of carcinogens, and it cannot be concluded that ionizing radiation was the cause of the *p53* mutation in the lung cells of the uranium miners. It can only be stated that because of the exposure to elevated levels of radon gas and other environmental factors, uranium mine workers have an increased risk for developing lung cancer.

Conclusion

Ionizing radiation is a threat to human cells and ultimately to the entire organism. This threat begins with the induction of DNA damage, which may then be converted

into permanent genetic change. Ionizing radiation is an activator of onocogenes and an inactivator of tumor-suppressor genes. Oncogene activation promotes cellular proliferation, and the checks on this proliferation are removed through the inactivation of tumor suppressors. Together, these genetic events, when induced in cells that still grow and divide, can lead to unregulated cellular proliferation and cancer.

Yet, ionizing radiation doesn't seem to have *any* favored role in the induction of cancer; it is simply one of the many different types of carcinogens. The cancers that are strongly correlated with radiation exposure are also observed in "unirradiated" control populations. And although the data are still limited, radiation probably initiates cancer by mechanisms similar to those mediating the induction of "spontaneous" cancers and that are stimulated by other carcinogens. For example, activation of the *ret* proto-oncogene appears to be commonly associated with thyroid cancer in both irradiated and unirradiated populations. Activation of *abl* is commonly associated with B-cell lymphomas irrespective of radiation exposure. Most of the spontaneous and radiation-induced cancers in individuals with one normal and one mutant allele of rb probably involve inactivation of the remaining normal *rb* allele. Each of these genes is involved in the regulation of cellular proliferation, and similarities between spontaneous and radiation-induced cancers are striking.

Although radiation can induce DNA damage, human cells are not without their defenses. Many of the DNA lesions induced by ionizing radiation are similar or identical to those induced as a consequence of normal metabolic activity. DNA repair mechanisms can act to reduce the consequences of this damage. Most single-strand breaks and base alerations can be repaired perfectly. Even double-strand breaks are repaired so as to minimize genetic change. Simple end-joining reactions are optimized for retaining chromosomal linkage relationships and preserving the ability to segregate genetic information in a normal manner during mitosis. Homologous recombination can actually restore missing information (although this process is believed to mediate the repair of only a small fraction of double-strand breaks). Together these processes act to reduce the risk posed by the induction of DNA damage. But the damage induced by ionizing radiation poses more than one risk, and it should be remembered that the very process of DNA repair may actually create genetic alterations as part of an attempt to prevent cellular death.

Clearly, the induction of cancer is a complicated process, and our understanding of radiation's role in its induction is far from complete. But these are remarkable times. Research is progressing at an increasingly rapid pace, and amazing insights are reported daily. We have only recently begun to appreciate the remarkably active role that the cell plays in preventing the full development of cancer. Through cellular senescence and apoptosis, a cell effectively limits its own proliferative potential. How the cell triggers those responses and their contribution to the complexity of the cell cycle has only been gleaned within the past three or four years.

Current and future research into the cell cycle, the regulation of cellular proliferation, and the impact of radiation on these processes will undoubtly lead to additional insights. New proto-oncogenes and tumor suppressors will be discovered. Precise roles for known and soon-to-be-discovered genes will be defined. Our knowledge of DNA repair mechanisms and their contribution to genomic stability and genetic change in irradiated cells will be expanded. Each of these discoveries will move us closer to understanding the aberrations in cellular metabolism that enable the development of cancer. And each will advance us towards our goal of cancer prevention. In a few years, this primer will need to be rewritten. Perhaps then it will optimistically be called "Radiation, the Cell Cycle, and the Prevention of Cancer." ■

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Richard J. Reynolds earned an A.B. in microbiology from the University of California, Riverside, in 1969, and received his Ph.D. in Biomedical Sciences from the University of Tennessee Graduate School of Biomedical Sciences at Oak Ridge National Laboratory in 1976. He completed postdoctoral fellowships at the Medisch Biologisch Laboratorium, TNO, The Netherlands, and at the Department of Pathology, Stanford University. From 1980 through 1985, he served as a faculty member in the Department of Cancer Biology of Harvard University School of Public Health. Richard joined the Laboratory as a staff member in the Life Sciences Division in 1985. He has served as a scientific advisor to division management, a program coordinator for the Radiobiology Research Program of the Life Sciences Division, and maintained an active research program. His major research interests include the induction and repair of DNA lesions and the relationship of these processes to the genetic consequences of both ionizing and nonionizing radiations. He is best known for his studies on the induction, repair and biological significance of complex lesions resulting from localized damage in both DNA strands. Richard is a member of the American Society for Photobiology and the American Radiation Research Society.

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Radiation and Risk
a hard look at the data

Mario E. Schillaci

Radiation, and its effects on humans, may be the most studied, most regulated and most feared of the physical, chemical, and biological insults to which we are exposed. Ironically, it is also one of the most common. Every day, every minute of our lives, we are all subject to the constant bombardment of gamma rays, neutrons, and charged particles that are produced in our natural environment, even from radionuclides within our own bodies. This background environment of ionizing radiation is not a product of our modern world; rather, it has been present throughout human evolution.

It has been conjectured by some that, because biological organisms evolved in the presence of low levels of ionizing radiation, we and other life forms must have developed effective mechanisms to repair the damage caused by this exposure. Others contend that even the lowest levels of radiation have the potential to cause serious biological effects, such as cancer or genetic disease. In fact, no one knows for sure if low doses of ionizing radiation can produce serious biological effects in humans. What we do know is that high doses of radiation can produce such effects, and the risks can be quantified. From these known risks at high doses, one may estimate the risks associated with low doses, based on some procedure of extrapolation. Disagreement about such a procedure for extrapolating from high doses to the low doses that are of practical concern to radiation workers and the general public lies at the heart of much of the controversy surrounding potential human radiation effects. In the end, such extrapolations from high doses to low doses are based on theoretical biophysical considerations and convenience of application but not on hard human data. This article examines some of the issues involved in estimating risks of exposure to low levels of ionizing radiation.

The red circles in the photo at left graphically portray the rate of cancer mortality in the United States. On average, one in five people die of cancer, and one in five people in the photo are labeled at random with a red circle. The purple circles represent *excess* cancer deaths above the normal rate. The job of the radiation epidemiologist is to determine the number of *excess* cancer deaths among a group that has been exposed to radiation and then determine whether that number is *statistically significant.*

Because the rate at which radiation causes cancer is quite low, it is very difficult to detect statistically significant increases in cancer mortality caused by radiation unless the population is very large and the radiation doses are also fairly large. Consequently, risk estimates for radiation-induced cancer are based primarily on data from the Japanese atomic-bomb survivors.

What is the level of background radiation, and is there any evidence that it is harmful? The world-wide average annual whole-body effective dose to humans from natural sources of ionizing radiation is 238 millirem (see "Radiation Units"). Figure 1 shows the average contributions to the world-average annual dose per person from each of the major natural sources of ionizing radiation. The components that vary greatly, depending on location, are cosmic rays, terrestrial gamma rays, and radon. Variations of up to a factor of two are common, and up to a factor of ten are not that rare. In contrast, the dose associated with internal radiation varies much less from person to person, regardless of location. This dose is due mainly to potassium-40, which is a naturally occurring isotope of potassium, an essential chemical element that is ingested whenever we eat foods containing it.

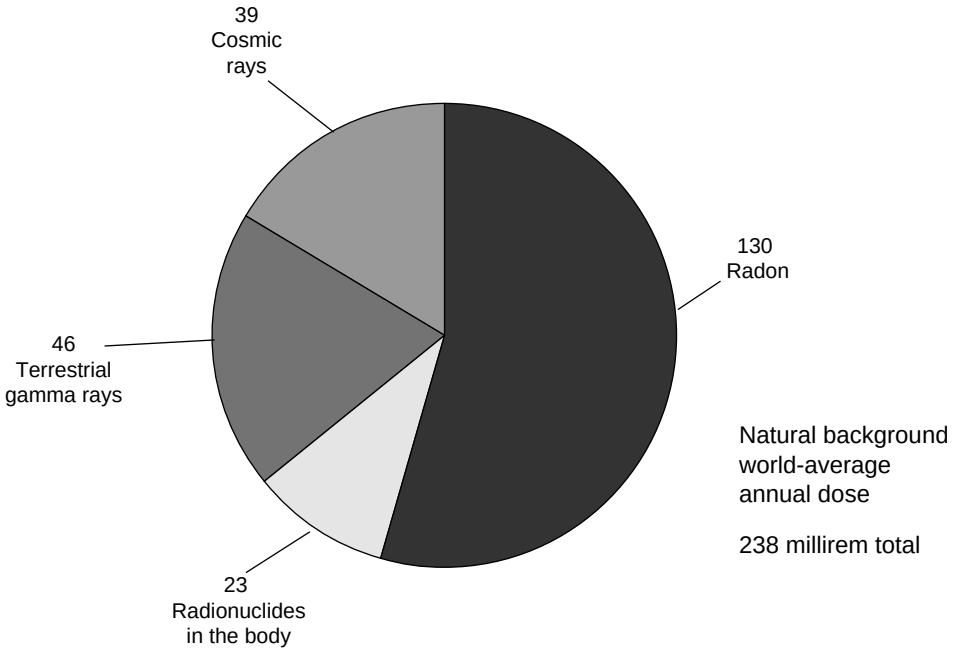

Figure 1. The Distribution of World-Average Annual Background Radiation
The pie chart shows the estimated number of millirem per year from the four major sources of background radiation. These estimates for world-wide averages were made by the United Nations Committee on the Effects of Atomic Radiation (UNSCEAR93). They differ somewhat from those shown for the average U.S. citizen (made by the National Council on Radiation Protection and Measurements) in "Ionizing Radiation—It's Everywhere!" page 29. Also, the total annual background dose quoted here, 238 millirem, does not include the average contribution of man-made sources to the public.

Radiation Units

For ionizing radiation, the unit of absorbed dose, the rad, corresponds to the deposition, via ionization and excitation processes, of 100 ergs of energy per gram of tissue. Some radiations are more effective, per unit of energy deposited, at producing biological damage than others. To account for these differences, the absorbed dose (in rad) is multiplied by a quality factor to obtain the dose-equivalent, which is expressed in rem (roentgen-equivalent-man); one millirem (mrem) equals one-thousandth of a rem. The rad and the rem are being replaced internationally by a new pair of units, the gray (Gy) and the sievert (Sv). The unit of absorbed dose, the gray, corresponds to one joule of energy deposited per kilogram of tissue, so one Gy equals 100 rad. The sievert is the corresponding unit of dose-equivalent; one Sv equals 100 rem.

Is there a correlation between cancer incidence or mortality and exposure to background radiation? It is known, both from animal experiments and human exposures to high levels of radiation, that ionizing radiation can induce some cancers; however, epidemiological studies generally have failed to find a statistically significant correlation between cancer mortality and levels of background radiation (see "Epidemiology and Statistical Significance"). A few studies claim to find a negative correlation, which means that some areas with higher than average levels of background radiation have lower than average levels of cancer mortality. Some researchers have concluded from these studies, together with cellular studies, that small amounts of radiation may induce an adaptive response that serves to protect humans from diseases such as cancer (this effect is also known as radiation hormesis). However, such negative correlations of disease with radiation dose may be caused by confounding factors not properly accounted for in the epidemiological studies. Adaptive responses to low doses of radiation have definitely been observed in experiments with human cells *in vitro*; however, the jury is still out regarding the existence of adaptive responses in humans at the clinical level (UNSCEAR94, Annex B). In summary, no convincing evidence exists that natural background radiation is harmful.

Experiments at low doses using animals are useful. However, because the effects of radiation vary widely from one species to another, animal data alone cannot be reliably used to predict ef-

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Epidemiology and Statistical Significance

Epidemiology, the statistical study of the occurrence of disease in populations, is the primary means of determining the relationship between radiation exposure and cancer risk. And yet such studies are no simple task. Their credibility is directly related to the strength of the numbers, or more technically, the statistical significance of the data. Using cancer as an example, we first explore the mathematical framework in which the significance of the data is evaluated.

Sample size and statistical significance

One in five Americans dies of cancer. But because cancer is a mysterious disease with a very complicated origin, it is impossible to predict exactly who the one in five will be. Because its occurrence is so unpredictable, the epidemiologist may simply assume that cancer strikes at random and that each of us has the same 20 per cent probability of dying of it. Such an assumption implies that any possible confounding factors are negligible and that known familial (genetic) factors are ignored. It is as if everyone's fate were determined as they walked in line past a giant barrel containing marbles in which one in five of them are blue. Each person blindly picks a marble out at random. If at your turn, a blue marble is picked, cancer will be your fate, otherwise, not. Now suppose that there is a population of 1000 whose fate was determined in the random manner just described. Should we expect that *exactly* 20 per cent, or 200, of the 1000 people will die of cancer? No. Although 200 is the most likely outcome, it is also likely that the outcome will be close, but not equal, to 200. Theoretically, any number of cancer deaths between zero and 1000 (or percentage between zero and 100) is possible, but the further away from 200, the less likely the result.

Epidemiologists treat cancer as a random event. It is as if everyone's fate regarding cancer were determined by whether or not he or she chose a blue marble from a giant barrel in which one out of five marbles were blue.

For a population of 1000, the probability of any given outcome lies on a bell-shaped curve, as shown in Figure 1. The curve is centered about 200, which is both the mean value (m) and the most probable number of cancer deaths for a population of 1000 chosen at random. The width of the curve is indicative of the range of likely outcomes and is characterized by a quantity called the standard deviation, s. In these types of studies, a useful approximation of the standard deviation is simply the square root of the mean, which in this case is about 14. As you can see from the graph, the vast majority of the possible outcomes (about 95 per cent) falls within the range of 172 and 228, or two standard deviations (28), around the mean. Therefore, although 200 is the most probable result, we would be

wrong to expect to always get *exactly* 200. Instead, we expect that, 95 per cent of the time, the result will fall within a range of two standard deviations on either side of the mean.

In epidemiological studies of radiation effects, the number of cancer deaths in the exposed population generally must be greater than about two standard deviations above the mean in the unexposed population for the result to be considered statistically significant. If the observed number is greater than the mean by more than two standard deviations, then the epidemiologists say they have determined a positive correlation between cancer deaths and radiation exposure. Similarly, a negative correlation is inferred if the observed number of cancer deaths is less than the expected number by more than two standard deviations.

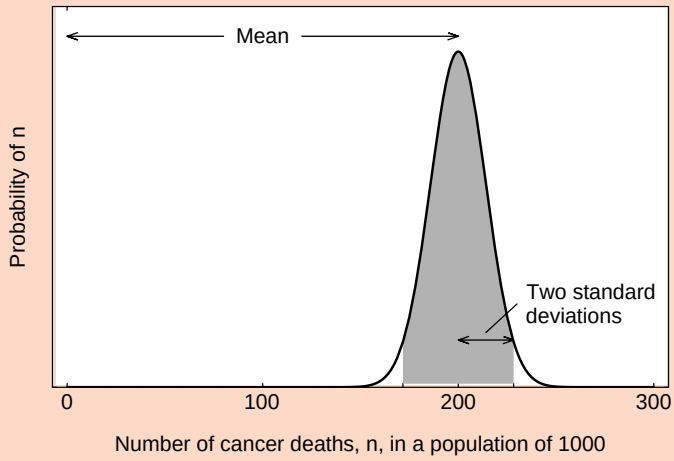

Figure 1. Fluctuations in the Number of Cancer Deaths

The probability of a certain number of random cancers occurring in a population of 1000 is represented by a bell curve centered about 200. The mean number and most probable number of cancer deaths is 200. The width of the curve is characterized by the standard deviation s, which is approximately equal to the square root of the mean, or 14. The shaded area under the curve between the values 200 1 2s and 200 2 2s is about 95 per cent of the total area, which means that in 95 out of 100 samples of 1000 people, the number of cancer deaths will fall between those two values. To find a statistically signifcant correlation between, say, radiation exposure and cancer, the number of cancer deaths would have to be greater than 200 1 2s.

The ability to distinguish excess cancer deaths due to radiation exposure from the expected ones improves markedly as the sample size increases. That's because the relative size of the standard deviation, s/*N*, decreases as the sample size, *N*, increases.

$$s/N = \sqrt{N}/N = 1/\sqrt{N}$$

Figure 2 illustrates this point. It shows the bell curve of Figure 1 for sample sizes of 1000 and 10,000, but this time the variable plotted on the horizontal axis is the fraction of the population that dies of cancer, rather than the absolute number of cancer deaths. Both curves are centered around the mean fraction of 0.20, but the widths of the curves, or the expected deviation from the mean, for the larger population is much smaller than that for the smaller population. Therefore, one has a much greater chance of detecting a statistically significant number of excess cancer deaths in a very large sample than in a small one.

Now that the statistical framework is defined, what's the next step for the cancer epidemiologist? Statistics on the "normal" cancer incidence and mortality must be obtained by studying the general population. (Incidence refers to the number of new cancers in a defined population per year, and mortality refers to the number of cancer deaths in a defined population per year.) The statistician is typically limited to vital statistics obtained from birth and death certificates kept by health departments at the federal, state, or county level. Age at death, number of deaths, and causes of death are the most important data used in determining specific mortality rates such as cancer death rates. In principle, one would like to check medical records against death certificates, but this is possible only with permission of the next of kin, because medical records are totally confidential.

In radiation studies, the epidemiologist collects data on an exposed population to see whether or not they exhibit an excess number of cancers compared with the number expected based on the mortality rates of a similar, but unexposed, population. As we've pointed out, statistically reliable results require large populations as well as accurate records of individual radiation exposures. Only a few identified exposed groups meet these requirements: the atomic-bomb survivors, patients that have received radiation for the diagnosis or treatment of various diseases, and nuclear workers.

Certain populations exposed to relatively high natural-background levels have been compared to those living in areas with more normal radiation levels, but in this case, only the average population doses are known, not the individual doses. In occupational studies, and especially in nuclear-industry studies, it is often the case that both the exposed and the unexposed populations are chosen from within the industry. That choice helps to insure lifestyle similarity and minimizes the so-called "healthy-worker effect," which is the built-in bias among the working population of having fewer diseases and a lower mortality rate than the general population.

The interpretation of epidemiological studies is another challenge. In a perfect world, one would be able to compare the rates of cancer incidence and cancer mortality in two populations whose members have identical cancer risks except for the fact that, in one, the members are exposed to radiation above the background level, and, in the other, they are not. In practice, members of the population differ in many factors affecting cancer risk including age, genetic predisposition, exposure to chemical carcinogens, and perhaps certain lifestyle factors such as smoking and socioeconomic level. A study must take into account any significant differences in these factors between the exposed and unexposed group. Another complication is that, within the exposed population, the cancer risk varies depending on the age at which one is exposed, the size of the dose, and the time since exposure. Consequently, one must have information on these three factors for all the members of the exposed population to assess the cancer incidence or mortality data properly. Moreover, because the latency time from exposure to detection may be 30 to 40 years for most cancers, both populations should be followed for the lifetimes of the subjects.

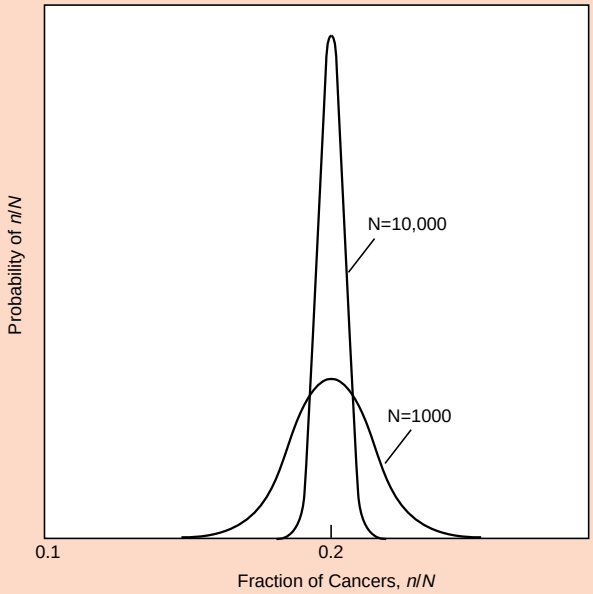

Figure 2. The Advantage of Large Sample Sizes

The two bell curves represent the probability for a given fraction of cancer deaths P(*n*/*N*) versus the fraction of cancer *n*/*N* deaths in a population of size *N*, where *N* equals 1000 and 10,000, respectively. The two curves are centered about the mean value of 0.2. Note that the width of the curve is much narrower for the larger population because, as *N* increases, the standard deviation of the fraction *n*/*N* decreases (approximately as 1/√*N*).

In general, epidemiological studies do not prove causation, rather they determine the correlation between two or more variables. A positive correlation suggests a link or association of some kind, the significance of which must be evaluated. In the worst case, the correlation may be due to a systematic bias in the study or to so-called "confounding factors" that were not explicitly included in the study, yet had a profound impact on the results. (For example, if bars were the only public places in which one were allowed to smoke, it would be incorrect to attribute all excess lung cancer among frequenters of bars to the intake of alcohol.) It's easy to be fooled—there are many kinds of hidden variables in the selection of the population, the gathering of the data, and the analytic procedures for interpretation that may bias the results of the study. Sir Bradford Hill, a well-known epidemiologist, listed nine factors that must be taken into account in evaluating the significance of data. Among them are the strength of the numbers themselves (Is the observed excess large or just marginally elevated? Is there a correlation between the size of the dose and the size of the excess?), the agreement between biological data and theory, and the consistency of the result with other studies done using different methodologies and different study groups. The epidemiological studies that address as many of these factors as possible, and then clearly lay out the statistical basis of their work for others to critique, are the studies that should be most trusted, discussed, and used to support conclusions about the effects of radiation. ■

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fects in humans. Therefore, those responsible for making recommendations regarding dose limits rely on human data whenever possible. Human data generally come from four sources: Japanese atomic-bomb survivors, radiation accidents, occupational exposures, and medical exposures.

All of the observed effects of ionizing radiation in humans occur at relatively high doses (that is, greater than about 20 rem). At the low doses that are of interest to radiation workers and the general public (that is, below a few rem), the epidemiological data are generally inconclusive, mainly because the change (up or down) in cancer mortality that might occur at such low doses is less than the variations that occur for all other reasons, both known and unknown. Consequently, the risks associated with low-dose exposures must be *hypothesized*. The conventional choice, considered prudently conservative, is a linear extrapolation, all the way down to zero dose, of the risks determined from observed effects at high doses. This prescription is termed the linear-dose-response, no-threshold (LNT) hypothesis.

Is such an extrapolation reasonable? Down to what level of dose? A rem? A millirem? A microrem? All the way down to zero rem? The answers to these questions are important for risk assessment. They are also important because they help shape the public perception of the dangers of ionizing radiation. Public perception, in turn, is driving the ever-increasing number and variety of laws, regulations, and guidelines dealing with ionizing radiation, all of which add considerably to the cost of doing business at a facility that handles nuclear materials. This cost, ultimately, is paid by our society.

The recent re-examinations of human radiation experiments that were carried out in the 1940s and 1950s have focused new attention on the possible biological effects of radiation. Actually, very little media attention focused on the health effects that resulted from these experiments, as this would have made very dull copy. In the interest of gaining a better perspective with which to evaluate the possible detrimental effects of those human radiation experiments, it is worthwhile to review what is known about the effects of ionizing radiation in humans, the dose levels at which these effects occur, and the risks deduced from these effects. The nature of the radiation protection standards derived from these high-dose risks by extrapolation to low doses is also of interest. More broadly, this review can help us to understand the significance of the levels of radiation that we ourselves might encounter and to evaluate the laws and standards that regulate our own exposures.

Radiation Effects in Humans

What are the biological effects in humans that result from exposure to ionizing radiation, and at what dose levels are these effects observed? In this section, we attempt to answer these questions by reviewing some exposures, both historical and current, that have resulted in observed effects. All the studies reported in this section are at dose levels above 10 rem; below this level, results are not statistically significant.

Radiation effects fall into two broad categories: deterministic and stochastic. At the cellular level, high doses of ionizing radiation can result in severe dysfunction, even death, of cells. At the organ level, if a sufficient number of cells are so affected, the function of the organ is impaired. Such effects are called "deterministic." Deterministic effects have definite threshold doses, which means that the effect is not seen until the absorbed dose is greater than a certain level. Once above that threshold level, the severity of the effect increases with dose. Also, deterministic effects are usually manifested soon after exposure. Examples of such effects include radiation skin burning, blood count effects, and cataracts.

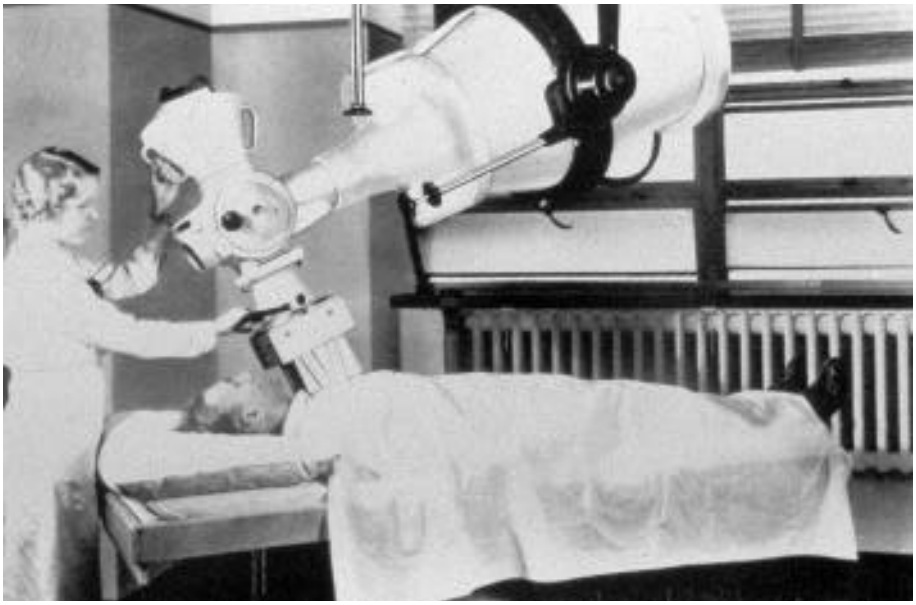
In contrast, stochastic effects are caused by more subtle radiation-induced cellular changes (usually DNA mutations) that are random in nature and have no threshold dose. The probability of such effects increases with dose, but the severity does not. Cancer is the only observed clinical manifestation of radiation-induced stochastic effects. Not only is the severity independent of dose, but also, there is a substantial delay between the time of exposure and the appearance of the cancer, ranging from several years for leukemia to decades for solid tumors. Cancer can result from some DNA changes in the somatic cells of the body, but radiation can also damage the germ cells (ova and sperm) to produce hereditary effects. These are also classified as stochastic; however, clinical manifestations of such effects have not been observed in humans at a statistically significant level.

Nuclear Accidents. During the first few decades of nuclear weapons development, several incidents occurred during which fissile material accidently came together in a critical configuration that produced, just briefly, an uncontrolled nuclear chain reaction (see "The Cecil Kelley Criticality Accident" on page 250). During these so-called critical excursions, workers received very high, sometimes fatal, whole-body doses of neutron and gamma radiation. High dose levels also have resulted from industrial radiation accidents and accidents involving improperly discarded or lost high-level radioactive sources (for example, medical sources used in radiation therapy). The Chernobyl accident resulted in high dose levels, particularly to reactor personnel and firemen; the Three-Mile Island accident did not result in high dose levels to anyone. From these experiences, together with high-dose animal experiments, an understanding has emerged of the biological effects of high-dose acute whole-

body exposure to ionizing radiation.

Acute radiation syndrome, the name given to the body's reaction to high-dose high-dose-rate exposures, involves three basic functional systems (the radiation-sensitive organ is given in parenthesis): the hematopoietic, or blood forming, system (bone marrow); the gastrointestinal system (epithelial lining of the small intestine); and the central nervous system (brain). Of the three, the hematopoietic system is the most sensitive to radiation, with syndrome and death thresholds of about 100 rad and 200 rad (whole-body effective dose), respectively. Irradiation causes the death of bone-marrow stem cells, which diminishes or stops the resupply of circulating red and white blood cells and other blood constituents. After about three weeks the reduction in blood supply causes immune deficiencies, infections and fever, bleeding, and even death unless the blood marrow has begun to regenerate. The earliest symptoms of fatigue, nausea, and vomiting probably involve all three functional systems. One measure of lethal dose is referred to as the LD50/60 dose, which is the acute dose that results in death within 60 days for 50 per cent of the exposed individuals. The LD50/60 in humans for hematopoietic syndrome is 300 to 350 rad (whole-body effective dose).

Radiotherapy for Cancer. Radiation therapy for the treatment of cancer is another context where both doses and dose rates are high, and the radiation effects are dramatic. The observable outcomes, both immediate and long-term, are an important source of information on radiation effects. The immediate effect at the cellular level is similar to that in acute radiation syndrome, namely the death of proliferating cells. The goal is to kill all of the malignant cells in a tumor, while sparing the surrounding healthy tissue. Dividing the total dose delivered into several smaller fractions preferentially spares normal tissues compared to the tumor. A typical treatment may involve up to about 6000 rad, fractionated into doses of 200 rad per day, five days per week, for 4 to 6 weeks.



X-ray machines of the type shown here (200-300 kilovolt) were the workhorses of radiation therapy from the 1930s through the 1960s. Damage to the patient's skin often limited the ability to treat deep lesions.

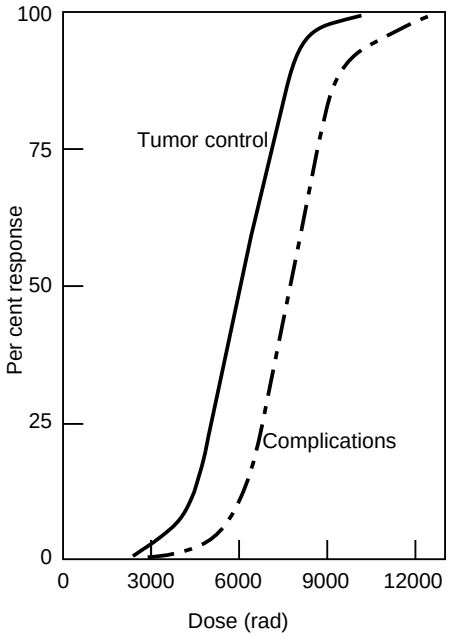


Figure 2. Effects of Radiotherapy
This graph of tumor-control rate and complication rate versus dose illustrates the delicate balance between tumor control and complications arising from radiotherapy. Increasing the treatment dose to improve the tumor-control rate leads to a higher rate of complications, whereas decreasing the dose to reduce complications results in a lower tumor-control rate. (Reproduced with permission from M. R. Raju, 1980, *Heavy Particle Radiotherapy*, New York: Academic Press.)

In terms of the goal of local tumor control, radiation therapy is successful for about two-thirds of the patients treated. However, it is estimated that approximately 5 per cent of second cancers that develop following radiation therapy are caused by the radiation delivered in therapy. As shown in Figure 2, there is a delicate trade-off between controlling the tumor and causing complications in nearby tissues. Although it is possible to reduce the rate of complications by lowering the treatment dose, this may be achievable only at the expense of decreasing the rate of control of the initial tumor.

Some individuals are particularly sus-

ceptible to radiation-induced cellular damage because they have inherited a deficiency in a mechanism that either signals or performs DNA repair. Individuals with such hereditary genetic disorders have an increased sensitivity to radiation. One of the best studied repair disorders is ataxia-telangiectasia (AT), a deficiency in cell-cycle checkpoint response to DNA damage (see "Radiation, Cell Cycle, and Cancer"). At the clinical level, patients with AT display progressive neurological and immune disorders. In addition, they are much more susceptible to developing certain cancers and, also, can develop devastating necrosis of normal tissues as a result of radiation therapy. AT is a recessive disorder, which means that both copies of the relevant gene must be defective for the disease to be manifested. Cultured cells from AT patients are about 3 times as sensitive to x-ray-induced cell death as are control cells. This increased sensitivity to radiation may not be restricted to patients with a manifest disease. There has been some suspicion that AT heterozygotes (defect on only one copy of the gene) also are at increased risk of developing cancer, both with and without medical exposures to radiation, but studies with cultured cells show only a small increase in radiation sensitivity. It is estimated that AT heterozygotes represent 1 to 3 per cent of the general population and 9 to 18 per cent of all breast cancers in young women.

Mass chest screening for tuberculosis was common during much of the century. Full-sized films were often used, but here the fluorescent image was reduced to a 100 millimeter format. The "portable" appartus shown was transported from site to site.

Historical Medical Exposures. During the decades from 1930 to 1960, the widespread use of radiation for the diagnosis and treatment of disease led, in a number of cases, to the unexpected induction of primary cancers. Epidemiological data have been collected from several of the exposed groups (UNSCEAR94, Annex A). Although the data are not sufficiently detailed to predict the quantitative increase of cancer risk with dose, they do demonstrate that doses in the hundreds, even tens, of rem have resulted in statistically significant increases in cancer mortality. The data also illustrate the many different types of cancer that can be induced by radiation exposure. For each study presented below, we show in parenthesis, if known, the *mean* organ dose for the group being discussed. We state these mean-dose figures to indicate the magnitudes of doses given that resulted in statistically observable effects; they are not intended to be interpreted as threshold values for those effects.

The following four studies all involve the use of large x-ray doses for diagnosis or treatment:

• More than 14,000 persons in Great Britain (1935-1954) were given x rays to treat ankylosing spondylitis, a disease of the spine. Cancers for which significant excess mortality was later found include: leukemia (380 rem), non-Hodgkin's lymphoma (380 rem), esophagus (400 rem), lung (180 rem), bone (300 rem), female breast (50 rem), and brain (140 rem).

• A study of about 19,000 female tuberculosis patients in Canada (1930-1952) who received multiple diagnostic chest-x-ray fluoroscopies found significant excess mortality for breast cancer (40 rem). A similar study of about 2600 female tuberculosis patients in Massachusetts (1925-1954) also found significant excess incidence of breast cancer (80 rem).

• About 11,000 children in Israel (1948-1960) and 2200 in New York (1940-1959) with tinea capitis (ringworm of the scalp) were treated by x-ray epilation, resulting in significant excess cancers of the brain (150 rem), thyroid (10 rem), and skin (non-melanoma) (450-680 rem).

• A study of more than 2600 persons in Rochester (1926-1957), who were exposed in infancy to x rays for the treatment of enlarged thymuses, showed a very significant increase in thyroid cancer (140 rem) and female breast cancer (80 rem).

From these studies, it would appear that the thyroid is a relatively radiosensitive organ, with a dose of the order of 10 rem sufficient to produce cancer in some cases. A similar conclusion applies to the female breast, for which a dose of the order of 40 rem seems sufficient to produce cancer in some cases.

Measuring Risk

Several definitions of risk are commonly used in epidemiology. For example, let us suppose that we are interested in the cancer mortality risk associated with an exposure to some dose of radiation. The *relative risk* (*RR*) is defined as the ratio of the observed number of cancer deaths *(O)* in the study population to the expected number (*E*) for a similar, but unexposed, population ($RR = O/E$). By similar, we mean similar in age and sex distributions, economic status, life style, and habits. The *excess relative risk (ERR)* is defined as the ratio of the excess number of cancer deaths *(O-E)* to the expected number *(E):*

$$ERR = (O - E)/E = (O/E) - 1 = RR - 1.$$

Note that the absolute excess *rate* of radiation-induced cancer mortality is obtained by multiplying *ERR* by the expected *rate* of cancer deaths for an unexposed population. Risk factors, or coefficients, are derived by dividing the risks defined above by the dose received.

We illustrate these concepts by a fictional example. Suppose a population of 1000 persons is exposed to an acute dose of 100 rem. And suppose that 220 are observed to die from various cancers, whereas the expected number is 200 (the expected rate is 200/1000 = 0.2). The relative risk and the excess relative risk are given by:

$$RR = 220/200 = 1.1,$$

$$ERR = 1.1 - 1 = 0.1.$$

The relative-risk factor and the excess-relative-risk factor are given by:

$$RR \text{ factor} = 1.1/(100 \text{ rem}) = 0.011 \text{ per rem, or } 1.1 \times 10^{-2} \text{ rem}^{-1}$$

$$ERR \text{ factor} = 0.1/(100 \text{ rem}) = 0.001 \text{ per rem, or } 10^{-3} \text{ rem}^{-1}.$$

Finally, the absolute excess cancer mortality rate is $ERR \times (0.2) = (0.1)(0.2) = 0.02$, and the corresponding factor is $0.02/(100 \text{ rem}) = 0.0002$ per rem, or 2×10^{-4} rem^{-1}. An additional point to be made for this example is that, at the 95 per cent confidence level, the excess deaths are not statistically significant, because the expected number of cancer deaths lies in the range of 172 to 228 (see "Epidemiology and Statistical Significance"). ■

However, in both instances, the dose quoted is the mean dose per patient treated, not the mean dose per cancer induced; so the association of the doses quoted with cancer induction is more suggestive than definitive. Of particular concern is the trend for increased radiosensitivity among younger patients. For several of the studies, the excess relative risk was found to increase with decreasing age at exposure, especially for breast cancer and thyroid cancer (see "Measuring Risk").

The potential carcinogenic effects of prenatal exposure to radiation are of importance because the developing fetus, who is experiencing rapid cell growth, may be more sensitive to radiation than are adults or children. Several studies have been made in the United States, the United Kingdom, and elsewhere of the possible association of childhood cancer with prenatal obstetric x-ray examinations. The relative risk estimate from all of these studies combined is about 1.4–that is, children irradiated *in utero* were found to have a 40 per cent higher incidence of cancer than unirradiated children. However, some researchers have expressed reservations about these results. One of the reservations is that the dose absorbed by the embryo or fetus is not very well known. Another is the surprising finding of the equality of relative risk for leukemia with that for solid tumors, which is not the case for postnatal exposures. Finally, among the Japanese atomic-bomb survivors, no association was found between childhood cancers and *in utero* exposures (mean uterine dose of 18 rad). As is often the case in epidemiology, these results seem to raise more questions than they resolve.

Another past medical practice that resulted in excess cancers was the injection of radium solutions for the treatment of various diseases. Radium is a naturally occurring radioactive element that was discovered by the Curies in 1898 and became widely taken for its alleged curative powers. When ingested or injected into the bloodstream, much of the radium is later deposited in the bone, where it and its radioactive daughter products bombard the surrounding bone tissues with radiation, most notably, alpha particles. Approximately 2000 persons in Germany (1944-1951) were treated for various diseases, including tuberculosis and ankylosing spondylitis, with multiple injections of radium-224 (physical half-life of 3.6 days) in the form of radium chloride. The resulting average skeletal dose was more than 400 rad, primarily from alpha particles, which are considered 20 times as damaging as x rays (1

rad absorbed dose of alpha radiation corresponds to 20 rem dose-equivalent). The subsequent incidence of bone sarcomas was found to be 280 times that expected from an unexposed population. Similar effects were observed in patients in the United States who were given radium-226 (1600-year half-life) and radium-228 (5.8-year half-life) before 1950.

Thorotrast, a colloidal solution of thorium dioxide, was used as an x-ray imaging contrast agent in several countries from the early 1930s to the early 1950s. It is deposited at several sites within the body, primarily in the liver and spleen.

Occupational Exposures. Before information about the potential dangers of radiation became well known and adequate measures were taken to control occupational exposures, high levels of exposure were fairly common and, in some cases, caused serious consequences for numerous workers. Perhaps, the most widespread serious biological effects from occupational exposure to radiation occurred among uranium miners. The miners inhaled radon and its decay products, most of which are alpha emitters, and suffered a greatly increased risk for lung cancer. Around the turn of the century, radon concentrations in the mines of central Europe were so high that about one-half of the miners died of lung cancer. A more recent comprehensive study of over 60,000 uranium miners from 11 locations throughout the world showed an 80 per cent increase in lung cancer deaths over what was expected, based on a comparison with over 7,000 unexposed miners. The uranium miners received an average exposure of 161.6 working-level-months.† Such an exposure results in a lung dose of almost 2700 rem, which corresponds to a whole-body effective dose of about 320 rem. This risk is not confined to uranium miners. For example, tin miners in China, who were also exposed to radon, suffered comparable excess lung cancer risk.

Table 1. Whole-Body Doses for Mayak Nuclear Weapons Facility Workers

	Worker Groups*			
	IA	**IIA**	**IB**	**IIB**
Average cumulative dose (rem)	122	49.2	245	71.6
Average annual dose (rem)	32.6	6.4	70.4	17.2
Per cent with greater than 100 rem per year	6.5	0.15	22.8	0.1

*Groups are defined in the text.

Natural thorium consists entirely of thorium-232, which has a very long half-life (greater than 10^{10} years), and many of its daughters are alpha emitters. It is estimated that an injection of 25 milliliters of Thorotrast delivered dose rates of alpha radiation of 1400 rem per year in the spleen, 500 rem per year in the liver, 320 rem per year in the endosteal layer of bone (inner surface surrounding the marrow), 260 rem per year in the bronchi, and 180 rem per year in the bone marrow. Not surprisingly, Thorotrast-treated patients suffered exceedingly high rates of liver cancer and leukemia, and statistically significant excess rates of several other types of cancer.

†A working-level is defined as a potential alpha-particle energy concentration of 1.3 3 10^8 MeV per cubic meter, which corresponds to an activity concentration for radon-222 in equilibrium with its daughters of 100 picocuries per liter of air. A working-level-month is defined as an exposure to one working-level for 170 hours, or one working month.

The occupational exposure that finally revealed the dangers of internal emitters was that of radium-dial painters, who were exposed to radium while painting luminous dials in the U.S. during the early decades of this century. The dial painters, most of whom were young women, would lick the ends of their paint brushes to get finer tips, thereby ingesting radium-226 and radium-228. Fatalities from severe anemia, resulting from exposure of blood-forming tissues to alpha particles, began to occur during the early 1920s among those with relatively large radium body burdens. Later, bone cancers began to appear among those with somewhat lower body burdens. A classic study of radium-induced cancers among the dial painters included more than 1500 females. Of the 154 subjects who received skeletal doses of greater than 20,000 rem, 62 subjects developed skeletal tumors (these 62 had a total of 65 head carcinomas and bone sarcomas combined). No skeletal tumors were observed in 1391 subjects who received skeletal doses less than 20,000 rem, which has been interpreted by some as evidence for a threshold—that is, a dose level below which no effect is observed.

This apparent threshold for radium-induced cancer seems to be contradicted by a study of a larger, but less homogeneous, population of more than 4000 subjects, including radium-dial painters, radium chemists, and patients who were therapeutically treated with radium in the U.S. before 1950. Of the more than 2400 persons for whom an estimate of skeletal dose was made, 66 bone sarcomas occurred, compared to fewer than 2 that would have occurred in an unex-

posed population. In addition, 35 sarcomas of the paranasal sinuses and mastoid air cells occurred, compared to fewer than 1 that would be expected for an unexposed population. The median cumulative skeletal dose at the time of tumor diagnosis was about 120,000 rem for the bone sarcomas. Three head-sinus carcinomas and three bone sarcomas (including a British dial painter) have occurred in individuals with skeletal doses of less than 24,000 rem, whereas only 0.2 would be expected for an unexposed population. For each type of cancer, the smallest cumulative skeletal dose was about 2000 rem (one case each), which is a factor of ten lower than the threshold value suggested by the study of dial painters alone. These results would seem to contradict the indication of a possible threshold skeletal dose of 20,000 rem, but the small number of cancers do not make a very convincing case. This larger study has the advantage of a larger population, whereas the study of dial painters involves a more homogeneous population.

Exposures in the U.S. nuclear industry and weapons laboratories have been controlled from the beginnings of the nuclear era in the early 1940s, in part as a result of the experience of the radium dial painters and the subsequent adherence to radiation protection standards. Consequently, the average annual exposures have been kept to a few rem or less, and the health effects, if any, are very difficult to detect through epidemiological studies.

We now know that the situation in the former Soviet Union was rather different. A study of workers at the Mayak nuclear-weapons facility in Russia documents that average cumulative exposures were in the range of hundreds of rem and that significant increases in cancer mortality resulted from those exposures. The dose data given in Table 1 have been compiled through 1989 and are organized according to, first, whether the workers started in the period 1948-1953 (I) or 1954-1958 (II), and second, whether they worked at the nuclear reactor (A) or the reprocessing plant (B). Statistically significant excess mortality risk for cancers of the hematopoietic and lymphatic systems, as well as all cancers combined, was found for group IB only. Apparently, during the early years of operation, chronic radiation sickness (chronic fatigue, depression, and an altered blood profile) was common, but rarely occurred in workers with less than 25 rem annual dose or 100 rem cumulative dose. Workers who exceeded both of these values had substantially higher cancer mortality than those who did not. The cancer mortality for those workers who did not exceed these values was similar to that of the general population. After 1968 in plant A, and 1974 in plant B, annual doses averaged over all workers were kept below 5 rem, which was the internationally recognized annual limit for individual radiation workers at that time.

X-ray fluoroscopy began around 1900. In this technique the x rays cause crystals on the screen of the instrument to fluoresce. The image is thus seen directly by the operator. Fluoroscopy was initially considered more effective than radiography because examinations could be conducted rapidly and without the use of expensive photographic plates. However, radiation damage to operators became well known even in the early years of the twentieth century.

Studies on health effects of radiation on radiologists and radiology technicians go back to the early use of x rays in medicine. British radiologists who began their professional work before 1921 had a 75 per cent higher cancer death rate than other medical practitioners. Cancers of the pancreas, lung, skin, and leukemia were significantly elevated. Doses received by those early workers are not possible to estimate, but whole-body doses of the order of 100 to 500 rad might have been accumulated by those entering the profession between 1920 and 1945. The cancer death rate for British radiologists who started in the profession after 1920 was not significantly elevated.

Until about 1950, radiologists in the U.S. were also observed to have excess cancer mortality, especially leukemia, lymphoma, and multiple myeloma, when compared with internists or other medical specialists who have less potential for radiation exposures. Both the British and U.S. studies show that, since adoption of radiation protection practices, any hazard attributable to radiation can no longer be demonstrated. Medical x-ray personnel in China and Japan during study periods of two to three decades before 1985 had increased relative risks for cancers of the esophagus, liver, skin, large intestine, central nervous system, and leukemia. In all studies, a consistent finding for medical x-ray workers in earlier periods, when they accumulated higher doses, is an increased risk for all cancers combined. However, the lack of dose measurements is a serious deficiency and limits the value of those studies for estimating radiation risk.

This abreviated survey of radiation effects in exposed populations suggests that acute radiation doses in the tens of rem range can result in an increased risk for some cancers, notably thyroid and female breast, and that the risk in-

creases with increasing dose for all cancers. The medical exposures were generally acute, whereas the occupational exposures were generally chronic. At high levels, both have been associated with elevated cancer incidence and mortality.

Risk Estimates Based on Japanese Atomic-Bomb Survivors

What is the cancer mortality risk per unit dose that is derived from observed effects of radiation in humans? In this section, we obtain quantitative cancer mortality risk factors for high-dose high-dose-rate exposures from an analysis of the most recent data for the Japanese atomic-bomb survivors (UNSCEAR94, Annex A). In addition, we examine non-carcinogenic prenatal effects in this group (UNSCEAR93, Annex H).

Atomic-Bomb Survivors. Perhaps, the best source of data on the radiation induction of cancer in humans is the Life-Span Study of survivors of the atomic bombings of Hiroshima and Nagasaki. The study involves a large homogeneous population, the subjects have been followed with great care for decades, and they represent all ages at time of exposure, both sexes, and a wide range of doses. The data on solid-tumor incidence cover the period from 1958 to 1987 and include about 80,000 individuals; the data on leukemia incidence and solid-tumor mortality cover the period from 1950 to 1987 and include about 86,000 individuals for each.

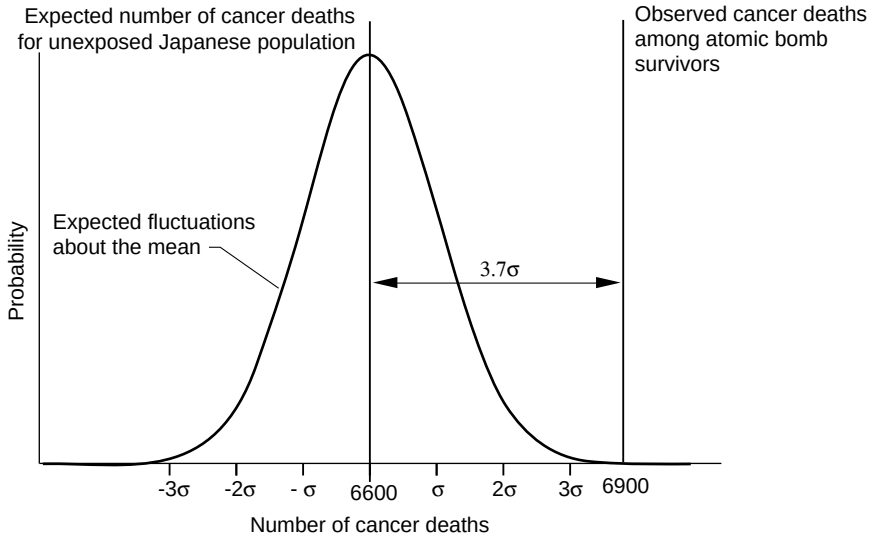


Figure 3. Excess Solid-Tumor Deaths among Atomic-Bomb Survivors
The observed number (6900) of solid-tumor deaths among Japanese atomic-bomb survivors (1950-1987) and the distribution of the expected number of such deaths, with a mean value of 6600. The observed number is 3.7 standard deviations from the mean, indicating that the number of excess cancer deaths is much greater than can be accounted for by fluctuations in the expected number. (Data from UNSCEAR94).

The 1985 total Japanese population is used as the basis for expected rates of mortality, cancer mortality, and cancer incidence, by age and sex, among an unexposed population. On the basis of these normal mortality rates in the atomic-bomb-survivor population, the number of solid-tumor deaths expected is about 6600, whereas the observed number is about 6900. As shown in Figure 3, this excess of 300 cancer deaths represents a statistically significant increase above the expected number, but the absolute number may seem surprisingly small to most members of the general public. Perhaps, this result, more than any other, provides a meaningful perspective for the public's anxieties regarding radiation, so it deserves emphasis. Of approximately 86,000 persons that survived exposure to atom-

ic bombings in 1945, only 300, or 0.35 per cent, are estimated to have died later (1950-1987) from radiation-induced solid cancers. In the leukemia incidence cohort, 75 persons, or 0.087 per cent, are estimated to have developed radiation-induced leukemia.

Table 2 lists those cancers for which statistically significant (90 per cent confidence) effects were seen for cancer mortality and for cancer incidence. Also given are the excess-relative-risk factors. Statistically significant effects were not seen, in either the incidence or mortality data, for cancers of the esophagus, bone and connective tissue, and brain and central nervous system. Also, statistically significant effects were not seen in the incidence data for non-Hodgkin's lymphoma. Unfortunately, an earlier analysis, which assumed that neutrons and gamma rays were equally effective for carcinogenic effects, had to be used for the leukemia and multiple myeloma mortality data, as these were not available in the most recent analysis, which assumed that

Table 2. Statistically Significant Radiation-Induced Cancers

Cancer Site	Excess-Relative-Risk Factor for Mortality* (rem^{-1})	Mortality Rate per 100,000 person-years†	
		male	female
leukemia	0.052	8.5	5.0
multiple myeloma	0.023	3.4	2.2
breast	0.018	0.2	27.2
bladder	0.012	5.8	1.6
lung	0.0076	73.0	30.9
colon	0.0047	23.3	15.6
liver	0.0044	3.6	1.7
stomach	0.0022	6.3	2.8

Cancer Site	Excess-Relative-Risk Factor for Incidence* (rem^{-1})	Incidence Rate per 100,000 person-years†	
thyroid	0.015	2.5	6.4
skin (non-melanoma)	0.0088	–unavailable–	

*Excess- relative-risk factors are calculated using a quality factor of 10 for neutrons, except for leukemia and multiple myeloma mortality, where a quality factor of unity is assumed.

†Normal age-adjusted cancer and incidence rates in the U.S. (1987-1991).

Table 3. Life-Span Study: Solid-Tumor Mortality (1950-1987)

Absorbed Dose (rad)	Mean Weighted Dose-Equivalent (rem)	Person Years	Number of Subjects	Observed Deaths	Expected Deaths
, 1	0	1,385,374	46,176	3,435	3,433
1-10	4	693,935	23,147	1,868	1,837
10-20	14	171,130	5,713	472	444
20-50	33	188,444	6,283	582	508
50-100	74	93,116	3,111	312	234
100-200	142	46,891	1,543	178	108
. 200	252	9,984	336	40	18

This table divides the exposed population into groups according to the dose received. The data in the first row, corresponding to absorbed doses of less than 1 rad, have been assigned a mean equivalent dose of zero rem. The first column gives the absorbed-dose intervals into which the data are organized, and these correlate with distance from the bomb blast. The second column gives the mean dose-equivalent (*D*) in rem received by each subpopulation. The third column gives the total number of person-years of follow-up (*PY*) for the subjects in each dose category. The fourth column gives the number of persons in each dose category. The next-to-last column gives the actual number of observed cancer deaths (*O*) in the time interval 1950-1987. The last column gives the number of cancer deaths expected (*E*) in each sub-population, based on a comparison of the age and sex distribution with an unexposed Japanese population.

neutrons were ten times as effective as gamma rays.

The solid-tumor mortality data for Japanese survivors are given in Table 3, grouped according to level of exposure, estimated from each subject's distance from the bomb blast. The data on doses are sufficiently consistent and the number of subjects in each dose interval is large enough to allow an estimate of the rate at which cancer mortality risk increases with radiation dose. This has been done by international bodies of experts in the fields of epidemiology and radiation protection.

With regard to hereditary health effects and prenatal carcinogenic effects, the numbers observed, even among this large cohort, are too small to be statistically significant. However, statistically significant noncarcinogenic prenatal deterministic effects have been observed. These effects include severe mental retardation, small head size, and low intelligence scores. For severe mental retardation, a sensitive period of 8 to 15 weeks after conception was identified. Radiation is thought to produce a dose-dependent loss of functional neuronal connections in the brain cortex, which is responsible for a downward shift of the bell-shaped Intelligence-Quotient (IQ) distribution. This downward shift is estimated to be about 30 IQ points per 100 rem, for exposures in the critical period of 8 to 15 weeks after conception. Severe mental retardation is clinically defined as more than two standard deviations (about 30 IQ points) below the average score of 100 IQ points, that is, below 70 IQ points. Based on these studies of the Japanese survivors, it is estimated that the radiation-induced shift in the IQ distribution, corresponding to a dose of 100 rem, would result in severe mental retardation in about 50 per cent of the prenatally exposed individuals. This effect is believed to have a threshold of about 10 rem.

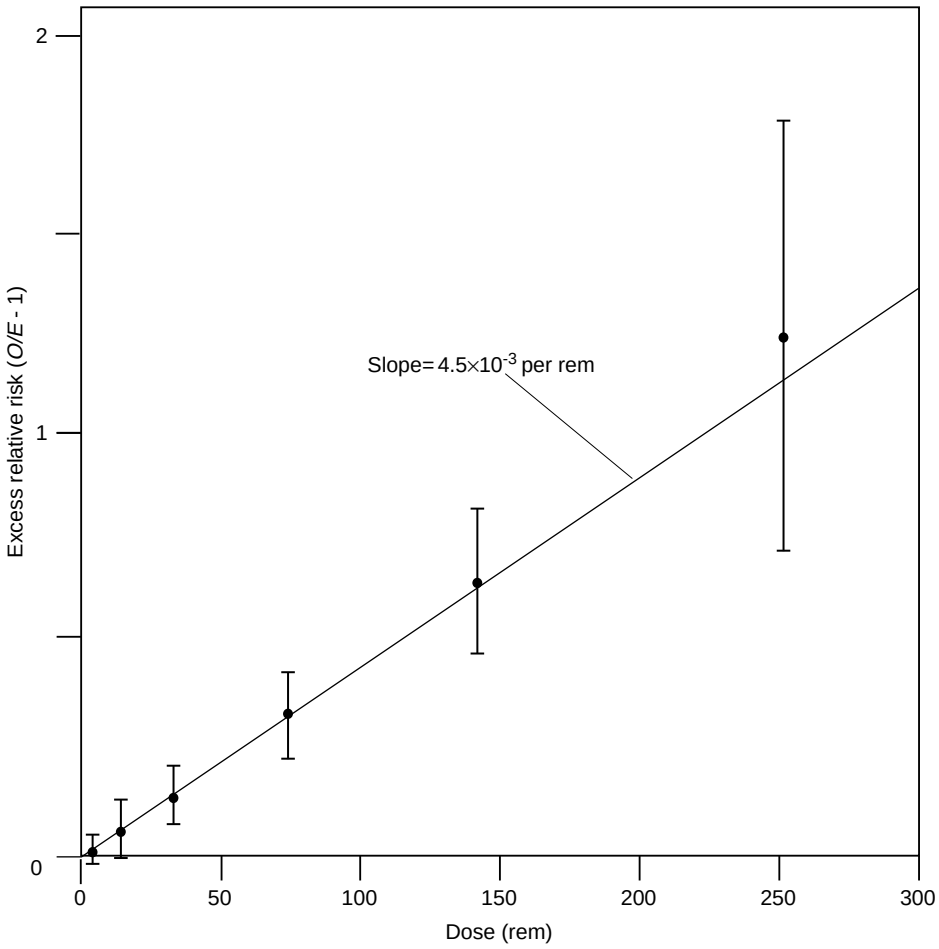


Figure 4. Excess Relative Risk for Solid-Tumor Mortality versus Dose for the Japanese Atomic-Bomb Survivors

This graph is a plot of the data in Table 3. The error bars correspond to plus and minus one standard deviation. A straight-line fit to the data yields the high-dose, high-dose-rate relative risk factor of 4.5 3 10^{-3} per rem. Note that the two data points below 20 rem, although lying on the striaght line, are also consistent with zero risk. (Data from UNSCEAR94.)

Risk Estimates for High Doses and High Dose-Rates. How should the cancer data be analyzed to determine the risks associated with radiation exposure? Let us do a simple, straightforward analysis of the solid-tumor mortality data in Table 3 to determine a risk factor corresponding to the acute high-dose exposure experienced by the Japanese survivors. Following current practice, we shall use the *excess-relative-risk* model (see "Measuring Risk"). We plot in Figure 4 the *ERR* for solid-tumor mortality versus dose (*D*) for each of the seven dose groups listed in Table 3. The error bars reflect the statistical uncertainty of each data point and are estimated assuming that the uncertainty in *O* (or *E*) is given by the square-root of *O* (or *E*); thus, they correspond to plus and minus one standard deviation (see "Statistical Significance").

The data in Figure 4 are fit nicely by a straight line with a slope of 4.5 3 10^{-3} per rem, which is the excess-relative-risk coefficient for solid-tumor cancer mortality. If we multiply this figure by the solid-tumor mortality rate in the general unexposed population, we can obtain the absolute rate of radiation-in-

duced cancer mortality per unit dose. In the Life-Span Study, the 1985 Japanese population and death rates are used as the unexposed population, from which is obtained the solid-tumor death rate of 24.3 per cent. Thus, we obtain the risk factor for radiation-induced solid-tumor mortality of 0.0011 per rem. If we include leukemia, the risk factor rises to 0.0012 per rem, which is the appropriate overall risk factor for high-dose high-dose-rate exposures. For example, if a population of 1000 persons is exposed to an acute whole-body radiation dose of 20 rem, we should expect, based on this analysis, 24 extra cancer deaths (1000 3 0.0012 per rem 3 20 rem) as a result of the exposure in addition to the 200 or so cancer deaths that might normally be expected. Stated differently, an individual exposed to an acute whole-body dose of 20 rem has about a 2.4 per cent chance of eventually dying from radiation-induced cancer. For comparison, an individual living in the U.S. has, on average, about a 1.5 per cent chance of dying in an automobile accident.

Referring to Figure 4, it will be noted that the solid-tumor data corresponding to doses below 20 rem (which is 84 times the average annual world-wide dose due to background radiation) are consistent with zero effect. If the error bars are extended to plus and minus two standard deviations, which corresponds to approximately a 95 per cent confidence interval, statistically significant effects are not seen below about 50 rem. Thus, the risk factor derived above may or may not apply to the low doses and low dose rates typically encountered by radiation workers and the general public. Nevertheless, an assumption of effects at low doses and low dose rates is prudent for establishing standards and guidelines for the protection of the health and safety of radiation workers and the general public.

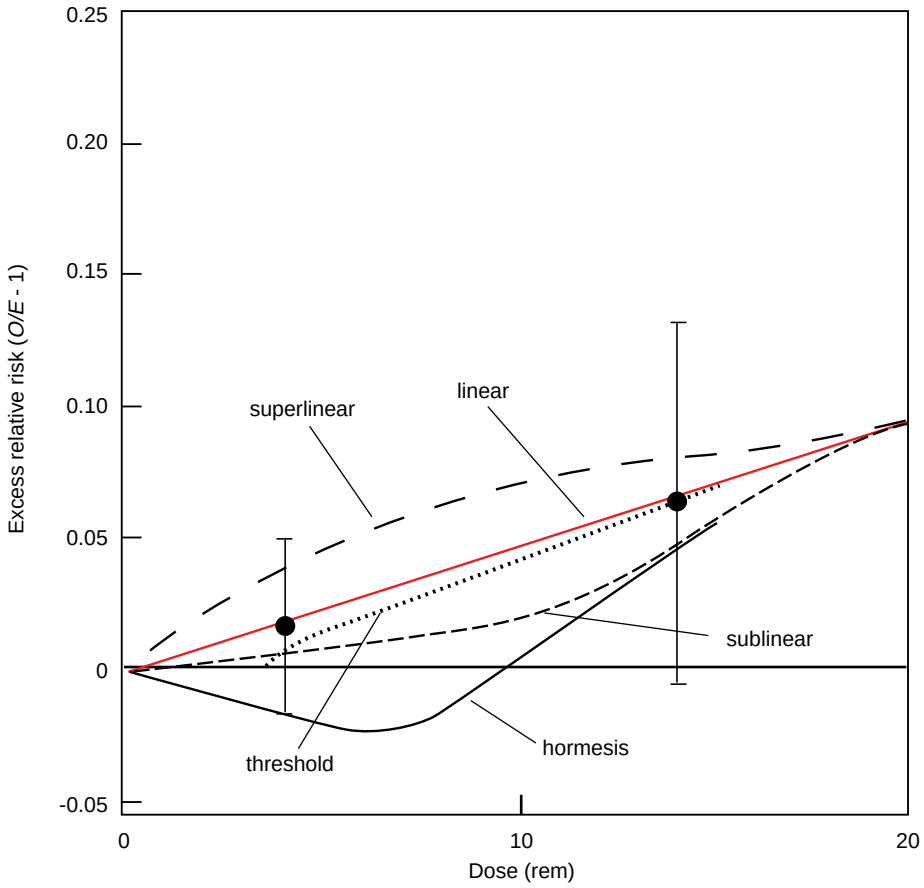


Figure 5. Extrapolation of High-Dose Data to Doses below 20 Rem
The low-dose data from Figure 4 with a straight-line extrapolation from the high-dose data, as well as other possible fits to the data, including (a) threshold/linear, (b) subliner, (c) superlinear, and (d) adaptive, or hormetic, response.

Extrapolating Risk Estimates to Low Doses of Radiation

Since the 1920s, when the risk of exposure to both internal and external radiation sources became apparent, official organizations have been established to recommend radiation protection standards. The most influential international organizations are the International Commission on Radiological Protection (ICRP) and the United Nations Committee on the Effects of Atomic Radiation (UNSCEAR), and in the U.S., the National Council on Radiation Protection and Measurements (NCRP). These organizations are charged with estimating the risks associated with exposure to low levels of radiation and recommending dose limits for radiation workers and the general public.

Risk Estimates for Low Doses. In the absence of convincing human data at the low doses and low dose rates that are of interest to radiation workers and the general public, the above-mentioned organizations have estimated the low-dose low-dose-rate risk principally by extrapolation of the risks obtained from the high-dose high-dose-rate atomic-bomb survivor data and other radiation effects studies. But what type of extrapolation is appropriate? The easiest choice (Figure 5) is to extrapolate the straight line drawn through the high-dose data in Figure 4 all the way down to zero. This choice, known as the linear-dose-response, no-

threshold (LNT) hypothesis, implies that the risk is proportional to dose all the way down to zero dose. This hypothesis further implies that the same number of excess cancers would arise from exposing 100 persons to 100 rem, or 10 thousand persons to 1 rem, or 10 million persons to 1 millirem (all doses are in addition to natural background). In the latter two cases, the predicted excess is well within the normal fluctuation of the expected number of cancer deaths for an unexposed population and, therefore, not identifiable as due to radiation exposure.

Figure 5 also shows some other possible choices for extrapolation from the high-dose data, namely: (a) threshold, where there is some value of dose below which there is no effect; (b) sublinear (dose exponent greater than 1), where the effect per unit dose at low doses is less than at high doses; (c) superlinear (dose exponent less than 1), where the effect per unit dose at low doses is greater than at high doses; and (d) adaptive response (radiation hormesis), where very low doses have a protective effect. The body of human exposure data, together with experimental animal data, do not allow the definite exclusion of any of the above possibilities; however, the results of most animal and cellular experiments favor either the LNT or sublinear hypotheses. Theoretical considerations involving the random nature of the fundamental damage processes in cellular DNA, as well as the fallibility of cellular repair mechanisms, also favor the LNT and sublinear hypotheses over the others. For the LNT hypothesis, the cell's repair effectiveness is assumed to be independent of dose. For many cellular experiments, the cell's repair effectiveness is seen to increase with decreasing dose, which is consistent with the sublinear hypothesis. In other words, the radiation becomes less effective per unit dose at low doses. Also, the cell's repair effectiveness is seen to increase with increasing time between doses, and with lower dose rates.

The radiation-protection community has adopted the LNT hypothesis as a conservative basis for estimating risk. However, they have chosen to modify risk estimates based on this hypothesis to take into account results from animal and cellular experiments indicating that low doses and low dose rates are less effective at causing biological damage. In particular, the risk factor for low doses (less than 20 rem) or low dose rates (less than 0.6 rem per hour) is set equal to one-half the risk factor for high doses (1.2×10^{-3} per rem) (see UNSCEAR 94). The risk factor for radiation-induced cancer mortality then becomes 6×10^{-4} per rem for the general population, which is within the range of uncertainty of the official NCRP and ICRP- recommended risk factor of 5×10^{-4} per rem. Because the working population does not include children, the risk factor for workers is set somewhat lower, at 4×10^{-4} per rem.

Thus, the risk factors for low-dose (less than 20 rem) or low-dose-rate (less than 0.6 rem per hour) radiation exposure that are generally used throughout the world today are 5×10^{-4} per rem for the general public and 4×10^{-4} per rem for workers. These factors are to be applied to exposures in excess of natural background levels. For example, a person living on the East Coast, with a natural background level of 200 millirem per year, who is occupationally exposed to a dose rate of 100 millirem per year for 40 years, has incurred an excess risk for cancer mortality of 0.16 per cent (4×10^{-4} per rem $\times$ 0.1 rem per year $\times$ 40 years $=$ 0.0016). Another person, living in Denver, with a natural background level of about 340 millirem per year, who receives no additional exposures, incurs no additional risk for cancer mortality. Thus, the person on the East Coast incurs a greater risk than the person in Denver, despite the fact that the person in Denver is receiving a higher total dose per year than the person on the East Coast. If this seems strange to the reader, you are not alone.

It should also be noted that radiation received from medical exposures is not included in records of occupational exposures.

What is the risk factor for radiation-induced hereditary effects? It is known that radiation can cause mutations in the DNA of germ cells (ova and sperm), and those changes can be propagated from one generation to the next. These radiation-induced mutations are similar to those that occur spontaneously. Are there clinical manifestations arising from radiation-induced mutations? Epidemiology has not detected statistically significant hereditary health effects of ionizing radiation in humans. Based on cellular and animal studies, statistically significant hereditary health effects in human populations at the dose levels usually experienced are not expected. Even among the Japanese atomic-bomb survivors, predicted hereditary health effects of their exposure to radiation would not appreciably increase the normal incidence of such effects that are due to all other causes.

Risk estimates, therefore, must be based largely on genetic studies of organisms and on cellular studies with radiation. Using two different methodologies, UNSCEAR estimates the risk in the reproductive segment of the population for serious effects in the two succeeding generations following exposure to be about 3×10^{-5} per rem. (Serious effects include stillbirths, major congenital defects, and cancer incidence before the age of twenty.) A risk value of 1.2×10^{-4} per rem is given for all generations after exposure.

Population studies show that diseases with an important genetic component occur in five to six per cent of live-born individuals. If all congenital anomalies are considered part of the genetic load, the percentage rises to about eight per cent. Thus, the additional genetic risk from low radiation doses is trivial compared with the genetic load carried in the general population.

Population Requirements of Low-Dose Studies

Statistically significant results showing a definite correlation (either positive or negative) between low-level exposures and excess cancers are very difficult to obtain, primarily because the risk factor for excess cancer mortality per unit dose is so small. Thus, for low doses, one needs to follow a very large population for several years for there to be a chance of detecting any correlation at all.

As an illustrative example of the statistical difficulties encountered at low doses, consider the problem of trying to correlate variations in cancer mortality with variations in doses from natural background radiation. Background doses vary by more than a factor of two, depending on location. Let us suppose that the actual number of radiation-induced cancer deaths varies as predicted by the linear-dose-response no-threshold hypothesis. Then, for a population of N persons, the number of excess cancer deaths is given by $(5 \times 10^{-4})DN$, where 5×10^{-4} rem^{-1} is the hypothetical cancer mortality risk factor for the general public and D is the dose in rem (above normal background). The expected number of cancers for an unirradiated population is $0.20\,N$, where 0.20 is the cancer mortality rate for the general population. The expected fluctuation in the number of expected cancer deaths is given by the standard deviation, $(0.20\,N)^{1/2}$. In order to be confident of the result, the number of excess cancer deaths should be more than two standard deviations; let us say three standard deviations. Thus, for the number of radiation-induced excess cancer deaths to be at least three times as great as the expected fluctuation in the number of cancer deaths in an unirradiated population, the following inequality must be satisfied:

$$(5 \times 10^{-4})DN \geq 3(0.20\,N)^{1/2},$$

which yields $N \geq 7.2 \times 10^6/D^2$. Therefore, to observe a change in cancer mortality due to an extra dose (from an elevated background level) of, say, 0.24 rem per year over a lifetime of 75 years, or 18 rem, requires a study population of more than 20,000 persons. A similar population is required for a control group, and both populations must be stable (that is, individuals remaining in the area). This simplified example assumes that everyone in the population receives a similar background dose, and it takes no account of possible confounding factors involving diet, habits (for example, smoking), physical activity, and so forth. Including all of these additional considerations may well double or triple the populations required, resulting in a very large, very expensive project that must last for several years. It is, therefore, not too surprising that few such studies are undertaken. ■

Another measure of the effectiveness of ionizing radiation in producing hereditary health effects is the dose required to double the normal incidence of the observed effect, which is estimated to be about 200 rem for the Japanese atomic-bomb survivors. The overall uncertainty in this estimate is considerable, but the figure is thought to be conservative. Applying a low-dose-rate factor of two for chronic exposures results in a minimal estimate of the doubling dose of 400 rem, which is about 1700 times the average annual dose from background radiation (UNSCEAR93).

Radiation Protection Standards. Both the ICRP and the NCRP have recommended upper limits on radiation exposure that are intended to prevent the occurrence of deterministic effects and to ensure acceptably low levels of risk for stochastic effects. Both organizations use the conservative LNT hypothesis to estimate risks for doses below the level of statistically significant data. This hypothesis is equivalent to a stochastic model of radiation effects. It should be emphasized that the cancer mortality risk factors (5×10^{-4} per rem for the general public, 4×10^{-4} per rem for workers) are often applied, especially for public exposures, at dose levels that are orders of magnitude smaller (that is, a few millirem) than those at which effects of ionizing radiation are actually observed in humans.

The annual dose limits recommended by the NCRP in 1993 (NCRP116) include, for occupational exposures, 5 rem for stochastic effects, and for nonstochastic effects, 15 rem for the lens of the eye, and 50 rem for all other organs. Also, the NCRP recommends that a worker's lifetime effective dose not exceed 1 rem multipied by the worker's age in years. Thus, for example, a worker who retires at an age of 65 years with a cumulative whole-body dose of 65 rem (which is relatively rare) has a hypothetical probability of 2.6 per cent (4×10^{-4} per rem $\times$ 65 rem $=$ 0.026) of dying from radiation-induced cancer. The probability of cancer mortality for the general population is about 20 per cent. For the general public, the NCRP recommends an annual limit of 0.1 rem for continuous or frequent exposure and 0.5 rem for infrequent exposure. Thus, a person exposed to 0.1 rem per year for 75 years has a hypothetical probability of about

0.4 per cent (5×10^{-4} per rem × 0.1 rem per year × 75 years = 0.00375) of dying from radiation-induced cancer. All exposures are considered to be in addition to background levels.

A more complete listing of the standards, together with the events and the philosophy that has guided their development, can be found in the article "A Brief History of Radiation Protection Standards."

Human Exposures to Low Doses of Radiation

In previous sections of this article, we described human exposures to radiation that resulted in observed effects, particularly cancer. Generally, the doses received in these cases were high. Most of these exposures occurred in the first half of this century, before the risks associated with radiation were well understood. What levels of radiation exposure are radiation workers and members of the public experiencing today, and what effects, if any, are observed? What are the risks associated with these exposures? In this section, we attempt to answer these questions by reviewing the dose data and epidemiological studies for environmental and diagnostic medical exposures of the general public and the occupational exposures for nuclear workers. We shall also apply the risk factors derived in the previous sections to determine the hypothetical risks for cancer mortality associated with these low-level exposures and compare the results with epidemiological data, where possible.

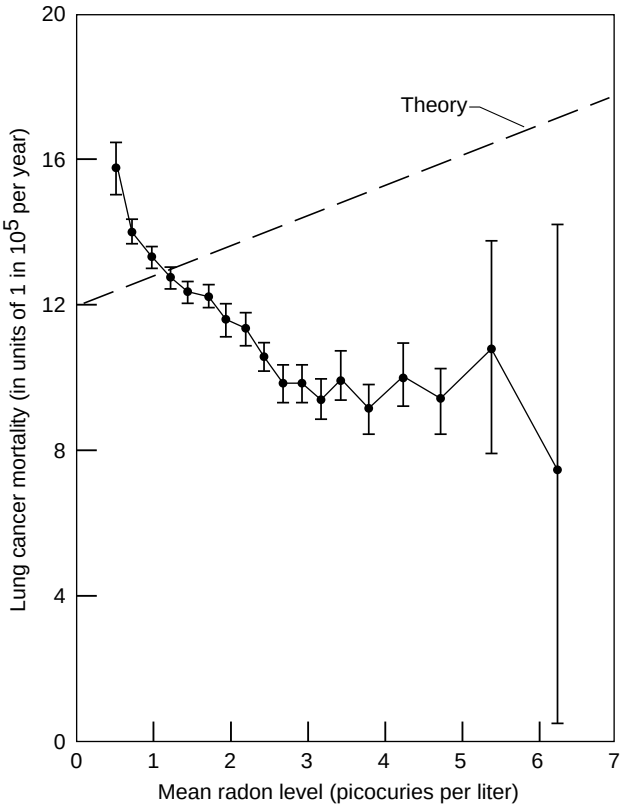


Figure 6. Is this Hormesis?
The graph shows lung cancer mortality versus mean radon concentration in lowest level of homes for 1,601 U.S. counties. Data are for females, and error bars correspond to plus and minus one standard deviation (the data for males are similar). The theory line is obtained by applying the linear-no threshold (LNT) hypothesis to higher-dose data for miners. The theoretical risk increases at a rate of 7.3 per cent per picocurie per liter, whereas the data show a decreasing risk with increasing radon concentration. Thus, the LNT hypothesis is contradicted by this study. (Reproduced from B. Cohen, 1995, *Health Physics* 68: 157-174.)

Environmental Exposures. As stated earlier, the world average annual effective dose from natural sources is about 240 millirem, with a little more than half due to radon and its decay products and 23 millirem from radionuclides within the body, particularly potassium-40. Cosmic rays and terrestrial gamma rays account for the remainder. No one knows what percentage of observed cancer deaths, if any, is due to exposure to background radiation. However, it is of some interest to determine the percentage obtained from a straightforward application of the risk factors for radiation-induced cancer mortality, even though the risk factors are meant to be applied to exposures in excess of natural background. This exposure (240 millirem per year), taken over a 75-year life span, would result, hypothetically, in an increased risk of cancer mortality of 0.9 per cent (5×10^{-4} per rem × 0.240 rem per year × 75 yrs = 0.009). Thus, according to the risk estimates extrapolated from high doses, background radiation may account for less than 5 per cent (0.009/0.20) of all cancer deaths.

If background radiation is responsible for some cancer deaths, then the considerable variability in background levels with location and altitude might result in observable variations in cancer mortality from one region to another. The magnitude of the variability of this natural background radiation is noteworthy. While cosmic radiation accounts for about 25 millirem per year at sea level, this rate is approximately doubled for the "mile-high" cities of Albuquerque and Denver, and approximately quadrupled for Quito, Ecuador, at 9350 feet, because of the decreased atmospheric shielding at higher altitudes.

Gamma rays resulting from the decay of radioactive nuclides in the soil and rocks accounts for 46 millirem of the world average annual dose. In the U.S., this contribution varies in the range of 15 to 150 millirem per year, with the East Coast and Gulf Coast regions generally at the lower end of the range, and the Central Rockies (Denver area) near the upper end of the range. In several locations of the world where deposits of thorium-rich monazite sands occur, notably the Ker-

ala Coast of India, dose rates of several hundred millirem per year are found for the terrestrial contribution.

Indoor radon represents the largest contribution to the average annual background dose, and it can vary by a factor of ten or more. Studies of U.S. homes have found a mean activity concentration in the ground floor (lowest livable area) of 1.25 picocuries per liter, which would correspond to an annual whole-body effective dose equivalent of about 400 millirem, if these areas were occupied 100 per cent of the time (or 40 millirem for 10 per cent occupancy). The activity concentration in approximately 6 per cent of U.S. homes exceeds 4 picocuries per liter, the level at which the U.S. Environmental Protection Agency recommends corrective action be taken.

Because background radiation levels vary so widely around the world, epidemiologists have looked for correlations between cancer rates and background dose. The effect of exposures to widely varying levels of background radiation are more likely to be observed with leukemia than most other cancers. This is because the radiosensitivity for leukemia is greater, the time interval between exposure and the onset of disease is less than for most other cancers, and the natural incidence of leukemia is extremely low. Also, the influence of other environmental risk factors is thought to be less for leukemia. Studies in the United States, Canada, France, Sweden, and China have failed to find a significant correlation between leukemia incidence and background radiation levels (see "Population Requirements of Low-Dose Studies").

Table 4. Medical Diagnostic Procedures

X-ray Examinations*

(1985-90) average annual total number of examinations	1200 per 1000 persons
(1985-90) average annual number of dental examinations	400 per 1000 persons
(1980) average annual effective dose per patient	50 millirem
(1980) annual collective effective dose	9.2×10^6 person-rem

Effective Doses from Diagnostic X-Ray Procedures†

lower GI tract	720 millirem
upper GI tract	410 millirem
angiography	680 millirem
urography	310 millirem
computed tomography	430 millirem
dental examinations	a few millirem

Nuclear Medicine Procedures*

(1985-90) average annual number of procedures	26 per 1000 persons
(1982) average annual effective dose per patient	500 millirem
(1982) annual collective dose	3.2×10^6 person-rem

Effective Doses from Diagnostic Nuclear-Medicine Procedures†

cardiovascular	1400 millirem
brain	870 millirem
bone	630 millirem
thyroid scan	380 millirem
thyroid uptake	250 millirem

*Data for the US.
†Data for a group of nations for which there is at least one physician per 1000 persons.

The Chinese study (1970-1985) in Yanjiang County, Guangdong Province, represents the most extensive study on the health effects of natural background radiation. This study, involving some 70,000 persons, took place in two neighboring regions in which a difference in annual dose of 200 to 300 millirem was associated with nearby deposits of monazite sands. Based on estimates from the Japanese Life-Span Study (omitting the dose-rate reduction factor), an excess risk for leukemia incidence of 27 per cent by age 50 years would be expected for the group with the higher annual dose. However, the leukemia mortality rate in this group was lower than in the control group (26 versus 33 deaths), though the difference was not statistically significant. One would conclude from this result that the risk factor based on extrapolation from the high-dose Japanese data overestimates the leukemia risk. However, an

increase in chromosome aberrations was seen in cells taken from the group receiving the higher annual dose compared to the control group.

Another possible correlation to look for is one between radon exposure and lung cancer. Figure 6 shows the results of a study of lung cancer mortality per county versus mean radon concentration per county for more than 1600 U.S. counties, representing almost 90 per cent of the U.S. population. The data show a *negative* correlation up to concentrations of at least 7 picocuries per liter. This result would seem to imply that up to dose-rate levels of 200 to 300 millirem per year (assuming 10 per cent occupancy) radon exposure has a hormetic effect, that is, radon exposure *decreases* the chance of lung cancer mortality. The LNT hypothesis, of course, predicts an *increasing* lung cancer mortality with increasing radon exposure. Of ten other studies in countries world-wide, two (Norway and Sweden) showed a significant positive correlation between lung cancer and radon concentration, two (France and United Kingdom) showed a significant negative correlation, five (Canada, China, Finland, Italy, and Japan) showed no significant correlation, and Denmark was found to have a higher lung-cancer rate than Sweden despite a lower mean radon concentration.

Table 5. Distribution of Cumulative Doses in IARC Study of Nuclear Workers

Dose Range (rem)	Fraction of Workers
0	0.11
0 - 1	0.49
1 - 5	0.20
5 - 50	0.19
50 - 100	0.009
.100	0.001

Diagnostic Medical Exposures. Medical diagnostic examinations represent the largest exposure of the general public to man-made radiation. Table 4 lists frequency and dose information for x-ray examinations and nuclear-medicine diagnostic procedures. Although individual doses are relatively small, the total annual collective dose equivalent from diagnostic x-ray and nuclear-medicine procedures in the U.S. is 1.24×10^7 person-rem, which is rather large. How many excess cancer deaths might be attributed to this collective medical exposure? Simply multiplying the collective dose by the risk factor for cancer mortality (5×10^{-4} per rem) yields 6200 hypothetical excess cancer deaths per year for the U.S., which is about 1 per cent of the total annual number (547,000) of cancer deaths and about 8 times the standard deviation (740) of this number. This crude estimate would seem to suggest that the number of hypothetical radiation-induced cancer deaths associated with diagnostic x-ray and nuclear-medicine procedures in the U.S. should be observable, if real. Interpretation of these data would be complicated by a number of confounding factors—for example, many persons exposed in diagnostic procedures have pre-existing disease, and up to one-half of the procedures take place in the last year of life. These confounding factors would diminish the significance of observed mortality statistics.

Nuclear Industry Exposures. The nuclear industry provides a setting in which the average exposures are above background, but are still relatively low, because of the adherence to radiation protection standards. Nuclear workers make an ideal group for studying the effects of low-level exposures in the few-rem range, because they are monitored regularly and records are easily available. In fact, several studies have been made of workers in nuclear energy and weapons facilities in the United Kingdom, United States, and Canada. Averages of individual cumulative doses for workers at these facilities were in the range of 0.8 to 12.4 rem, which, when

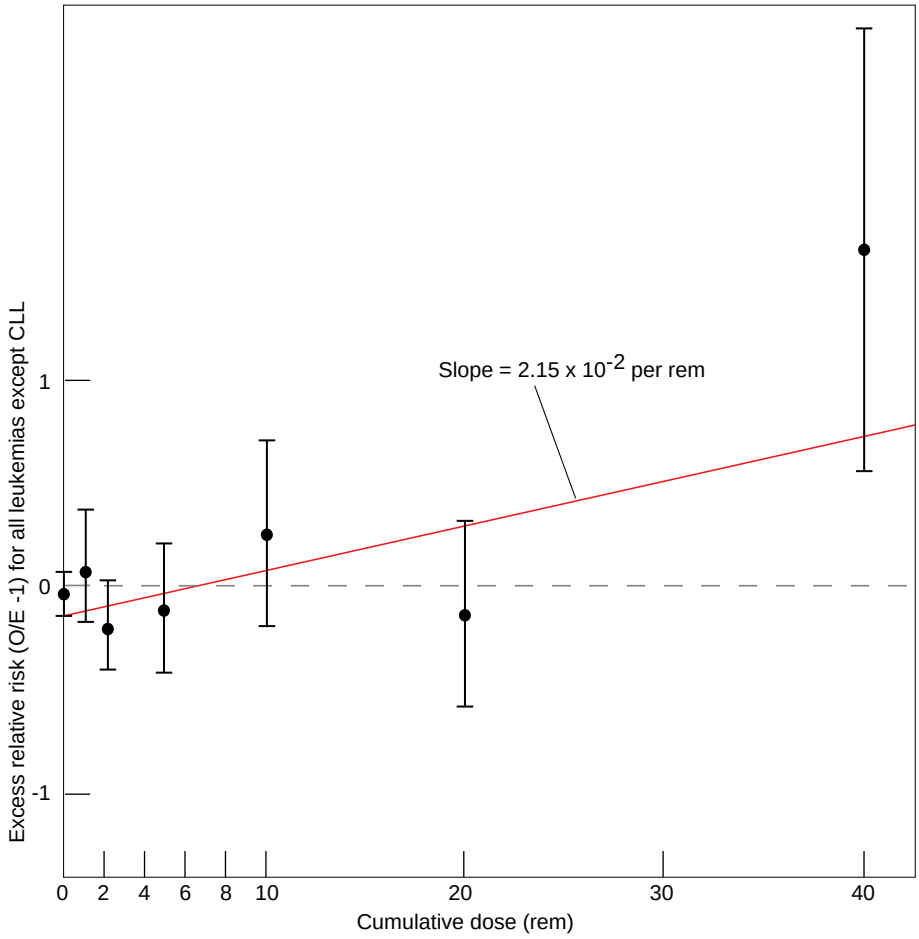


Figure 7. Nuclear Worker Data for Leukemia Risk

Excess relative risk for mortality for all leukemias, excluding chronic lymphocytic leukemia, versus cumlative dose for 96,000 nuclear industry workers in the United Kingdom, the United States, and Canada. The error bars correspond to plus and minus one standard deviation. Forcing a straight-line fit to all of the data yields a relative risk factor of 2.15 3 10^{22} per rem. However, if the highest-dose data point is excluded, the remaining data show no increase of risk with increasing dose. (Data from E. Cardis, et al., 1995, *Radiation Research* 142: 117-132.)

multiplied by the risk factor for workers of 4 3 10^{4} per rem, yield a hypothetical average risk range for radiation-induced cancer mortality of 0.03 per cent to 0.50 per cent. For all cancers taken together, there were no statistically significant excess risks of radiation-induced cancer found in any of the studies.

Looking at specific cancers, a significant excess risk (about 27 per cent) was found for lung cancer in workers at Oak Ridge plants, with the average individual cumulative dose a very low 1.7 rem. This dose yields a hypothetical risk for cancer mortality of 0.07 per cent. However, there is some indication that smoking may be a confounding factor in these results. At the Sellafield plant in the United Kingdom, the average individual cumulative dose was 12.4 rem, which yields a hypothetical cancer mortality risk of 0.5 per cent. A "significant trend" was reported for excess leukemia risk when exposures were lagged by 15 years to better align them in time with the appearance of the disease. However, it should be noted that there were 10 leukemia deaths overall at Sellafield, whereas 12 would have been expected if the radiation exposures posed no risk.

The International Agency for Research on Cancer (IARC) Study Group on Cancer Risk among Nuclear Industry Workers performed an independent study of the combined data, mentioned above, from the United Kingdom, United States, and Canada. This study, involving more than 95,000 individuals, is the most extensive study to date for cancer mortality risk associated with protracted exposure to low levels of radiation. The distribution of cumulative doses received by the study population, listed in Table 5, was rather skewed in that 60 per cent of the cohort received doses of 1 rem or less and only about 1 per cent received doses of 50 rem or more. All doses are assumed to be at low dose rates. Excluded from the study were 19 workers who received greater than 25 rem in a single year.

The excess relative risk (*ERR*) for all cancers, excluding leukemia, was reported to be negative at -7 3 10^{-4} per rem, with a 90-per-cent confidence interval from -39 3 10^{-4} to +30 3 10^{-4} per rem, which is consistent with zero risk. For leukemia, excluding chronic lymphocytic (CL) leukemia, which is thought not to be induced by radiation, the excess relative risk (*ERR*) was reported to be positive at 2.2 3 10^{-2} per rem, with a 90-per-cent confidence interval from 0.1 3 10^{-2} to 5.7 3 10^{-2} per rem, which is barely significant (the 95-per-cent confidence interval overlaps zero risk). Taking into account the range of uncertainties, the quoted results for non-CL leukemia are consistent with those obtained from a linear extrapolation of the high-dose, high-dose-rate data from the atomic-bomb survivors, and with a low-dose, low-dose-rate effectiveness multiplier of one-half, though the range of uncertainty of this multiplier is quite large (0.027-1.7).

Table 6. Plutonium Experiments in Humans (1945-1947)

Subject	Isotope	Intake (nCi)	Time (yrs)	Dose (rem)	LNT Probability (per cent)
CAL-I	Pu-238	3500	20.7	6400	,100.
	Pu-239	46			
CAL-II	Pu-239	169	0.698	13	0.65
CAL-III	Pu-238	51	45.0	155	7.7
CHI-I	Pu-239	400	0.438	19	1.0
CHI-II	Pu-239	5900	0.0465	29	1.5
CHI-III	Pu-239	5900	0.465	300	15.
HP-1	Pu-239	280	14.2	380	19.
HP-2	Pu-239	310	2.45	80	4.0
HP-3	Pu-239	300	37.2	880	44.
HP-4	Pu-239	300	1.42	46	2.3
HP-5	Pu-239	310	0.411	14	0.7
HP-6	Pu-239	330	38.3	990	50.
HP-7	Pu-239	390	0.715	30	1.5
HP-8	Pu-239	400	29.7	1000	50.
HP-9	Pu-239	390	1.25	52	2.6
HP-10	Pu-239	380	10.9	410	20.
HP-11	Pu-239	400	0.0164	0.6	0.03
HP-12	Pu-239	290	8.01	230	12.

The authors of this study give the relative risk (*RR*) for all leukemias except CL leukemia for 10-rem exposure as 1.22, which means that a person exposed to 10 rem of low-LET radiation over a working lifespan is 22 per cent more likely to die from non-CL leukemia than a similar, but unexposed worker. This statement would lead the casual reader to infer that the data at dose levels around 10 rem actually show an effect. However, an examination of the data presented for all non-CL leukemia mortality in 7 dose intervals, the last being greater than 40 rem, shows that for only the last dose interval is a positive effect observed (Figure 7). The risk factors quoted above are found by forcing a linear fit to all of the data; however, if the one data point for doses above 40 rem is excluded, the remaining 6 data points for doses below 40 rem show a flat response with dose (that is, no increasing risk with dose). The range of uncertainties in the final results would also seem to allow either a sublinear or superlinear dose response at low doses, in addition to the assumed linear response. This very large and careful study of nuclear workers does not provide a definitive resolution of the problem of determining the dose response at low doses (less than 20 rem). However, this study does provide valuable new information at low dose rates.

Human Radiation Experiments

Recently, a great deal of attention has been focused (for the third time) on human radiation experiments that were carried out in the United States. during the 1940s and 1950s. Most of the experiments in which Los Alamos were involved are discussed in part III of this volume. Here, we wish to examine the

doses received and the hypothetical risks associated with those experiments. The experiments include the plutonium-injection experiments and three series of tracer studies done at Los Alamos.

Plutonium Injections. Starting in April 1945 and continuing for a period of about two years, 16 persons were injected with plutonium-239, one person with plutonium-238, and one person with a plutonium-238/239 mixture (see Table 6). The subjects in the studies were patients at the following hospitals: Manhattan Engineer District Hospital in Oak Ridge (subject designated HP-12); Billings Hospital of the University of Chicago (CHI-I to III); University Hospital of the University of California, San Francisco (CAL-I to III); and Strong Memorial Hospital of the University of Rochester (HP-1 to 11). Both plutonium-238 and plutonium-239 are alpha emitters and are retained in the body for several decades. The amounts injected ranged from 100 to 5900 nanocuries. The purpose of these investigations was to determine the excretion rate of plutonium over time for known intakes. These data, together with extensive animal data, were critical for constructing models that were used to determine the plutonium intakes and consequent body burdens, based on excretion data, for workers in the nation's nuclear-weapons complex. It was not the purpose of the studies to observe radiation effects, as none were expected; nor were any observed. The subjects in the studies were chosen partly on the basis of expected short remaining life spans (less than 10 years), although about one-third lived much longer than expected. Whether the subjects were informed of the nature of the experiment and the potential hazards is a matter of some controversy. What is known is that at least one subject was not informed and at least one subject was informed. The issue of informed consent is an important one and is treated elsewhere (see "Ethical Harm" on page 280). Here, we wish to examine the doses received and the associated hypothetical risks of cancer mortality, based on the current risk factor (5×10^{-4} per rem) derived from the LNT hypothesis and the subsequent lifetimes of the subjects. It should be noted that the recommended limit for plutonium-239 in the body during most of the Manhattan Project was 5 micrograms (310 nanocuries). Around the time the injections were begun, a provisional limit of 1 microgram (62 nanocuries) was adopted. In 1950, the official limit was lowered to 0.5 microgram (31 nanocuries).

Let us derive the risks associated with the radiation exposures resulting from these plutonium injections by naively applying the hypothetical risk factor recommended for radiation protection applications. In Table 6, we give the relevant data for each of the subjects; the fourth column is the remaining lifetime from time of injection for each subject. The current radiation risk factor for cancer mortality is applied to the cumulative whole-body effective dose equivalent, which is given in the fifth column of Table 6. The hypothetical LNT probability that this dose could have induced death from cancer, given sufficient time, is given in the last column of Table 6. It should be pointed out that this procedure is meant to apply for relatively small probabilities, and it overestimates relatively large probabilities. Excess mortality probabilities of greater than 100 per cent are, therefore, excluded, as in the case of CAL-I. Most of the subjects did not live long enough for any possible plutonium-induced cancers to develop. For four of the subjects, who lived 20 years or more, the hypothetical probability for radiation-induced cancer mortality exceeded 40 per cent. However, none of the subjects died of causes that could be related to the plutonium injections. From these results, one might conclude that the risk factor overestimates the cancer mortality risk for internal exposures to plutonium. Although the number of cases is too small to be significant, this conclusion is consistent with the observed results for the radium-dial painters. In both cases, the doses were due to internal alpha emitters that deposit their radiation in bone. In general, the uncertainties associated with plutonium dosimetry are rather large. Even in these cases, in which the activities injected are known precisely, substantial uncertaintities in the resulting doses remain, primarily related to the activity distribution in the body and to the subsequent biological damage produced.

Tracer Studies: Radioiodine. During a period of almost two decades following World War II, 42 persons, including 8 children (under 10 yrs) and 6 teenagers, ingested iodine-131 and iodine-125 in studies at Los Alamos with the dual objectives of improving diagnostic techniques to detect thyroid disease and estimating doses due to ingestion of food containing radioiodine that came from the fallout of atmospheric nuclear-weapons tests. The volunteers in these studies comprised the researchers themselves, their children and their colleagues. The activities of the radioisotopes ingested by the adults were in the microcurie range, resulting in doses to the thyroid of a few rem and whole-body effective doses of about 100 millirem or less. The children ingested about 10 nanocuries of radioiodine, resulting in thyroid doses of 80 to 160 millirem, depending on age, and whole-body effective doses of about 5 millirem or less. For both adults and children, the whole-body dose was a small fraction of the annual background dose in Los Alamos. As a result of these studies, the doses received by patients diagnosed for thyroid disease using radioiodine were significantly reduced. Also, these studies enabled researchers to determine the doses associated with radioiodine in fallout from nuclear weapons tests.

Tritium. During the 1950s, three volunteers from Los Alamos ingested tritium in the activity range of 2.5 to 14 microcuries, resulting in whole-body ef-

fective doses of about 200 to 900 millirem, which corresponds to a maximum of about three times the annual background dose in Los Alamos. The volunteers were the researchers themselves. The tritium was ingested as HTO, which is distributed in the body in the same way as water. The biological half-life of HTO in the body is about 10 days. The purpose of these experiments was to study body water kinetics and to improve radiation dosimetry for tritium exposures.

Other Radionuclides. During the 1960s, several metabolic studies and studies with nuclear-medicine applications were carried out with volunteers at Los Alamos using a variety of radionuclides, including sodium-22, potassium-42, zinc-65, rubidium-86, cesium-134, and cesium-137. The activities administered were in the range of 0.1 to 1.4 microcuries, resulting in whole-body effective doses of 0.1 to 100 millirem, which correspond to small fractions of the annual background dose in Los Alamos.

Discussion and Conclusions

We have seen that biological effects in humans resulting from exposure to ionizing radiation have been observed with statistical significance in a large variety of situations. Very high doses lead to cell killing, which is an intended effect in radiation therapy in the treatment of cancer, and which has been seen in several accidental exposures, leading to acute radiation syndrome. Lower, but still high, doses were received in many medical and occupational exposures, mostly during the first half of this century, leading to the induction of several types of cancer. The Life-Span Study of the Japanese atomic-bomb survivors represents the most complete source of information on human exposure to ionizing radiation, with doses spanning the range from low to very high, and with several types of cancer induced. From these experiences, we know that radiation is relatively effective at inducing cancers of the thyroid and breast, as well as leukemia, and relatively ineffective for bone cancer and cancers of the brain and central nervous system. Our knowledge of clinically observable hereditary effects, on the other hand, is gained mostly from cellular and animal experiments, as no such effects have been observed in humans.

Based on the cancer-induction and mortality data obtained in the Life-Span Study of the Japanese atomic-bomb survivors, as well as data obtained from other studies, a linear dose-response relationship for ionizing radiation at doses above about 20 rem, delivered at a high dose rate, is well established. Quantitative risk factors are readily derived from these high-dose, high-dose-rate data. For the low-dose, low-dose-rate regime that is pertinent to radiation workers and the general public, the conservative *hypothesis* is made that these same risk factors apply all the way down to zero dose. The acknowledged diminished effect of ionizing radiation at low doses (less than 20 rem) or low dose rates (less than 0.6 rem/hr) is approximated by multiplying the risk factors obtained at high doses and high dose rates by one-half, resulting in a cancer mortality risk factor for the general public of 5×10^{-4} per rem (or 1 chance in 2000 per rem), and for occupational workers of 4×10^{-4} per rem (or 1 chance in 2500 per rem).

Below about 20 to 40 rem, most data on cancer induction and mortality in humans are inconclusive because of inadequate statistics. One human study at low doses reported here that seems to involve sufficient numbers for good statistics is the U.S. study that found a *decreasing* mean lung-cancer incidence rate with *increasing* mean indoor radon concentration on a county-by-county basis. However, when all studies of radon-induced lung cancer are considered together, the results are inconclusive. A second such study is the one dealing with background radiation due to monazite sands in Guangdong Province, China, which failed to find an increased leukemia risk, as predicted by the LNT hypothesis. A third study with the potential for good statistics is the study of nuclear workers in the United Kingdom, the United States, and Canada, which failed to find an increased risk for all cancers combined, excluding leukemia. A positive risk was reported for non-CL leukemia; however, an examination of the data shows that, below 40 rem, the data are consistent with no excess risk.

Epidemiological studies of cancer induction in humans exposed to low-LET radiation at low doses and low dose rates generally have low statistical power, and consequently, have been interpreted by some as being consistent with a linear extrapolation from the high-dose, high-dose-rate data, and by others as indicating no additional risk at low doses compared with the observed cancer incidence in the general population. Taking all of the studies together, one is forced to conclude that, at present, the low-dose response for cancer induction in humans cannot be determined with any reasonable degree of confidence.

Unless more studies with high statistical power become available to settle the question (see "Population Requirements of Low-Dose Studies"), the linear-dose-response, no-threshold hypothesis must be viewed as a prudent choice for estimating effects at doses below 20 rem. This is not to say that it is reasonable to regulate public exposures all the way down to zero dose. The hypothetical risk associated with the dose received by everyone from natural background radiation represents a small fraction of the sum of the real risks that all of us face in our daily lives. These real risks are associated with our jobs, our automobile use, our personal habits and tastes, and our leisure activities. The number of fatalities per year related to specific occupations, miles driven, smoking, alcohol consumption, bicycle

riding, hang-gliding, and so forth, are measured quantities; they are not hypothesized. It seems reasonable to this author to cut off our concern with the risks accompanying exposure to man-made radiation at some sensible fraction of the dose due to natural background radiation, since we all seem to accept with alacrity large variations in the natural background as we move from place to place. Within the context of the linear-dose-response, no-threshold hypothesis for extrapolating risks to low doses, there is no difference in collective cancer mortality risk between 1000 persons receiving 10 millirem and one person receiving 10 rem (assuming that all 1001 persons are "similar"). To this author, such a conclusion seems absurd.

We must choose, as a society, to begin to treat the risks associated with man-made radiation rationally or to continue to deal with these risks emotionally. Treating these risks rationally means placing them in perspective with all of the other risks that we willingly, perhaps reluctantly, accept. Continuing to deal with these risks emotionally rather than rationally means that we shall continue to waste societal resources that might be spent more constructively, and in some cases, continue to choose a greater risk over a lesser risk. Nowhere is this choice framed more sharply than in the issue of nuclear-power generation. We can continue to oppose nuclear generation in the hope of getting environmentally "friendly" non-nuclear options, such as solar, geothermal, or wind-driven power; but such a choice is, in reality, a choice for fossil-fuel generation, which is definitely not environmentally "friendly" (for example, smog, respiratory illnesses, and global warming all result from fossil-fuel generation). We can continue to insist that we be protected from every last "particle" of man-made radiation, in the expectation that the very high cost of such protection will be borne by someone else; but in fact, that cost is borne by our society and, ultimately, affects us all. We have the freedom to base our choices on reason or on emotion, but we are not immune from the consequences of our choices. ■

Further Readings

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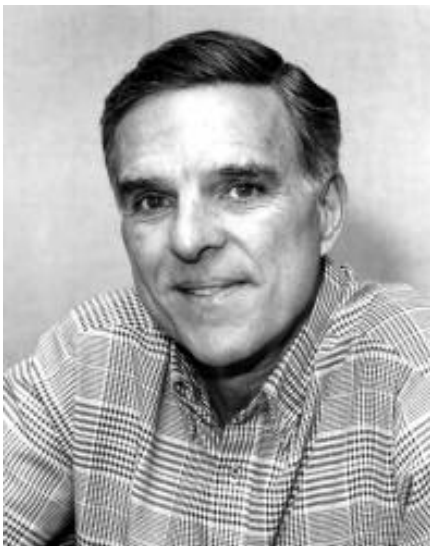


Mario E. Schillaci came to the Laboratory in 1967 as a postdoctoral fellow in the Theory Division. In 1970, he joined the Medium-Energy Physics Division where his principal interests included non-nuclear research applications of LAMPF beams. During his tenure with LAMPF, Mario completed investigations in several diverse fields including: radioisotope production, muon chemistry, muon spin rotation, pion channeling, the neutrino oscillation experiment (LSND), and pion radiotherapy, for which he helped develop codes for determining energy deposition in tissue from pion beams. In 1982, as an outgrowth of this collaboration, he joined a radiobiology research project headed by M. R. Raju, of Life Sciences Division, that studied mechanisms of biological damage in mammalian cells using ultrasoft x rays. Mario's interest in biological effects of radiation led him in 1993 to join the Dose Assessment Team (ESH-12) of the Environment, Safety, and Health Division. Mario was a member of the Human Studies Project Team that investigated the Laboratory's involvement in human radiation experiments. He received his B.S. in physics from Drexel University and earned his Ph.D. from Brandeis University in theoretical elementary particle physics.

A Brief History of Radiation

Health physics is concerned with protecting people from the harmful effects of ionizing radiation while allowing its beneficial use in medicine, science, and industry. Since the discovery of radiation and radioactivity 100 years ago, radiation protection standards and the philosophy governing those standards have evolved in somewhat discrete intervals. The changes have been driven by two factors—new information on the effects of radiation on biological systems and changing attitudes toward acceptable risk. The earliest limits were based on preventing the onset of such obvious effects as skin ulcerations that appeared after intense exposure to radiation fields. Later limits were based on preventing delayed effects such as cancer that had been observed in populations of people receiving high doses, particularly from medical exposures and from the atomic-bomb exposures in Hiroshima and Nagasaki.

During the evolution of standards, the general approach has been to rely on risk estimates that have little chance of underestimating the consequences of radiation exposure. It is important to realize that most of the effects observed in human populations have occurred at high doses and high dose rates. The information gathered from those populations must be scaled down to low doses and low dose rates to estimate the risks that occur in occupational settings.

Immediately after the discoveries of x rays in 1895 and radioactivity in 1896, x-ray devices and radioactive materials were applied in physics, chemistry, and medicine. In the very early days, the users of x rays were unaware that large radiation doses could cause serious biological effects. They also had no instruments to measure the strength of the radiation fields. Instead, the calibration of x-ray tubes were based on the amount of skin reddening (erythema) produced when the operator placed a hand directly in the x-ray beam. The doses needed to produce erythema are very high indeed—if the skin is exposed to 200-kilovolt x rays at a high dose rate of 30 rad per minute, then erythema appears after about 20 minutes (or 600 rad) of exposure, and moist desquamation (equivalent to a third-degree burn) occurs after about 110 minutes (or about 2000 rad) of exposure. (For comparison, recall from the primer "Ionizing Radiation—It's Everywhere!" that for x rays and gamma rays the rad, the unit of absorbed dose, is equal to the rem, the unit of dose-equivalent, and that the average annual background dose in the U.S. from natural and man-made sources is about 0.36 rem per year.)

Wilhelm Conrad Roentgen (above) discovered x rays in 1895 in Wurzburg, Germany. Also shown is his laboratory and a radiograph of a hand that he made in 1896 after his only public lecture on the discovery of x rays.

Protection Standards

William C. Inkret, Charles B. Meinhold, and John C. Taschner

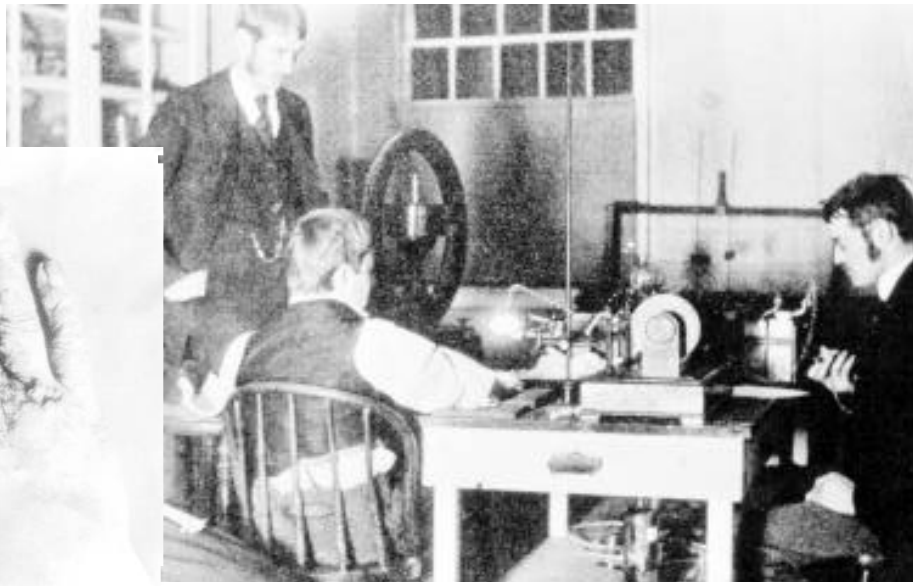
Early ignorance of the hazards of radiation resulted in numerous unexpected injuries to patients, physicians, and scientists, and as a result, some researchers took steps to publicize the hazards and set limits on exposure. In July 1896, only one month after the discovery of x rays, a severe case of x-ray-induced dermatitis was published, and in 1902, the first dose limit of about 10 rad per day (or 3000 rad per year), was recommended. The 10 rad-per-day limit was based not on biological data but rather on the lowest amount that could be easily detected, namely, the amount required to produce an observable exposure, or fogging, on a photographic plate. By 1903, animal studies had shown that x rays could produce cancer and kill living tissue and that the organs most vulnerable to radiation damage were the skin, the blood-forming organs, and the reproductive organs. Table 1 contains estimates of dose rates encountered by radiation workers in the early part of the 20th century.

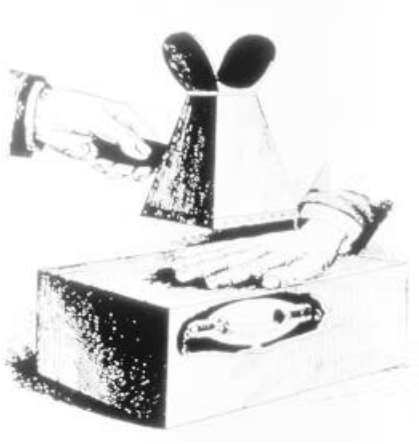
Antoine Henri Becquerel discovered radioactivity in 1896 in Paris. He is shown here in his laboratory.

In September 1924 at a meeting of the American Roentgen Ray Society, Arthur Mutscheller was the first person to recommend a "tolerance" dose rate for radiation workers, a dose rate that in his judgement could be tolerated indefinitely. He based his recommendation on observations of physicians and technicians who worked in shielded work areas. He estimated that the workers had received about one-tenth of an erythema dose per month (or about 60 rem per month) as measured by the x-ray-tube current and voltage, the filtration of the beam, the distance of the workers from the x-ray tube, and the exposure time. He also observed that none of the individuals had shown any signs of radiation injury. He concluded that the dose-rate levels in the shielded rooms were acceptable, but in proposing a tolerance dose, he applied a safety factor of ten and recommended that the tolerance limit be set at one-hun-

Table 1. Dose Rates for Radiation Workers in the Early Part of the 20th Century

Occupation	Approximate Dose Rate (rad min^{-1})
fluoroscopist	0.6 - 6 (hands) 0.006 - 0.06 (body)
x-ray therapy technician	0.006 (body)
radium therapist or technician	0.006 - 0.06 (body)





It was common for the hands of the early radiologists to receive exceptionally high radiation doses. The loss of fingers, as shown in the photograph above, was sometimes the result. Such conditions are ultimately caused by outright killing of many cells. In the case above, dermal basal cells and blood vessels were critically injured in the fingers, scar tissue probably plugged the blood vessels and stopped the flow of blood. The loss of blood supply ultimately led to the death of tissue in the fingers and the loss of those extremities.

dredth of an erythema dose per month (equivalent to about 70 rem per year). A tolerance dose was "assumed to be a radiation dose to which the body can be subjected without production of harmful effects." Mutscheller presented his recommendation in a paper entitled, "Physical Standards of Protection Against Roentgen Ray Dangers," which was published in 1925. Quite fortuitously, F. M. Sievert arrived at about the same limits using a similar approach.

In 1934, the U.S. Advisory Committee on X-ray and Radium Protection proposed the first formal standard for protecting people from radiation sources. By then the quantitative measurement of ionizing radiation had become standardized in units of roentgens,* and therefore, the recommended limit on dose rate was expressed as 0.1 roentgen per day. That value was in line with Mutscheller's recommendation of one-hundredth of an erythema dose per month, and in fact, the two tolerance limits differed only by a factor of two. Whether that difference was due to a rounding factor or a technical difference in the way the roentgen was measured in the U.S. versus Europe is open to interpretation.

It is worth emphasizing that those early limits on exposure to x rays were not arrived at through quantitative observation of biological changes but rather through a judgement call based on the absence of observed biological harm.

The dose limits for radiation sources outside of the body (external sources) were augmented in 1941 by a limit on the amount of radium a person could tolerate inside the body (radium tends to be retained by the body, and because of its long radioactive half-life, it thereby becomes a relatively constant internal source of radiation). The devastating experiences of the radium-dial painters and the origin of the radium standard are described in "Radium—The Benchmark for Internal Alpha Emitters" (see page 224). Decade-long clinical observations of twenty-seven persons who were exposed internally to radium, in combination with quantitative

*The roentgen, the first formal radiation unit, was adopted in 1928 and specifies the quantity of ionizing radiation in terms of the amount of electrostatic charge it produces passing through a volume of air. In particular, the Roentgen is defined as that amount of ionizing radiation that produces 1 electrostatic unit of negative charge in 0.00129 gram of air (1 cubic centimeter of air at standard temperature and pressure). For x rays, 1 rad = 1 rem = 0.96 roentgen.

measurements of their radium body burdens, were the basis for the radium standard. In particular, it appeared that the retention of 1.0 microgram or more was required to produce deleterious effects. Applying a safety factor of ten to that result, the committee members responsible for recommending a standard (many of whom had performed the clinical research on the radium patients) suggested that 0.1 microgram (or 0.1 microcurie) of radium would be an appropriate tolerance limit. Again, the ultimate criteria used was a judgement call: They all agreed that they would feel comfortable even if their own children had that amount in their bodies. That initial standard has essentially remained in effect up to the present.

In the 1930s, Robley D. Evans developed the first quantitative technique for making *in vivo* measurements of radium body burdens. Those measurements were the basis for the radium standard set in 1941.

In 1944, the radium standard was used as a basis for setting the first tolerance limit for internal retention of plutonium. A working-lifetime limit of 5 micrograms (0.3 microcuries) was proposed on the basis that plutonium was long-lived and would be a boneseeker like radium and that the alpha-particle emissions from 5 micrograms of plutonium would deposit ionizing energy at the same rate as the alpha emissions from the allowed 0.1 microgram of radium. In 1945, as a result of animals studies on the relative toxicity of plutonium and radium and on their relative distribution in the body, the Manhattan Engineer District reduced the plutonium limit a factor of 5 to 0.06 microcuries. The Hanford Site, where plutonium was being produced in reactors, reduced the limit even further to 0.03 microcuries. Although today's standards are expressed in terms of an annual inhalation limit rather than a maximum permissible body burden, the current limit recommended by the International Commission on Radiation Protection (ICRP) translates to a body burden that is about the same as the working-lifetime limit set at Hanford during World War II. The concern for limiting and monitoring intakes of radium and plutonium were the beginnings of the field of internal radiation dosimetry.

A great deal of research, particularly animal studies, on the biological effects of radiation were carried out during and immediately after World War II. In 1949 the United States, Canada, and Great Britain held a conference at Chalk River, Ontario, on permissible doses and then published the Tripartite report in which all radiation protection information that had been gathered was discussed and collated. A number of new concepts concerning the measurement of dose had been developed through animal studies. These included *absorbed dose* (measured in rad), *dose-equivalent* (measured in rem), *relative biological effectiveness* (RBE), which relates the rad to the rem for different types of radiations, the absorbed dose as a function of photon energy and depth in tissue (depth dose), the radiotoxicity of plutonium, and the concept of a reference anatomical human. The Tripartite report also recommended standards for internal and external radiation protection, including a plutonium body-burden limit of 0.03 microcuries, a limit on the bone-marrow dose of 300 millirem per week (about 15 rem per year), and a limit on the skin dose of 600 millirem per week (a factor of 2 lower than the value initially recommended by Mutscheller in his 1925 publication). With the exception of the plutonium limit, those values were adopted by the ICRP and the National Council on Radiation Protection and Measurements (NCRP, the new name for the old U.S. Advisory Committee) in 1953 and 1954, respectively. (The plutonium limit recommended by the ICRP was somewhat higher at 0.04 microcuries for the maximum permissible amount of plutonium-239 fixed in the body.)

During the 1950s, further reductions in the standards for external radiation were made as a result of studies on the survivors of the two nuclear weapons dropped on Japan and studies of survivors of high-dose medical procedures. In particular, an early analysis of data from the Japanese atomic-bomb survivors indicated an apparent change in the ratio of the number of males to females among infants born

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to survivors. At the same time, data from experiments on mammals and fruit flies demonstrated that genetic changes could be induced from very high radiation exposures. Thus, radiation-induced genetic effects became a dominant concern in the early 1950s and led to the first recommended standards for annual dose limits to the public. Later analyses indicated that the early assessment of the atomic-bomb survivors was incorrect, and to this day, radiation-induced genetic changes in humans have *never been observed*. Nevertheless, the fear of future genetic effects lingered on and probably inspired the creation of such science fiction characters as Godzilla, the Incredible Shrinking Man, Spiderman, the Incredible Hulk, and many others. The concern also led to a reduction in radiation protection standards.

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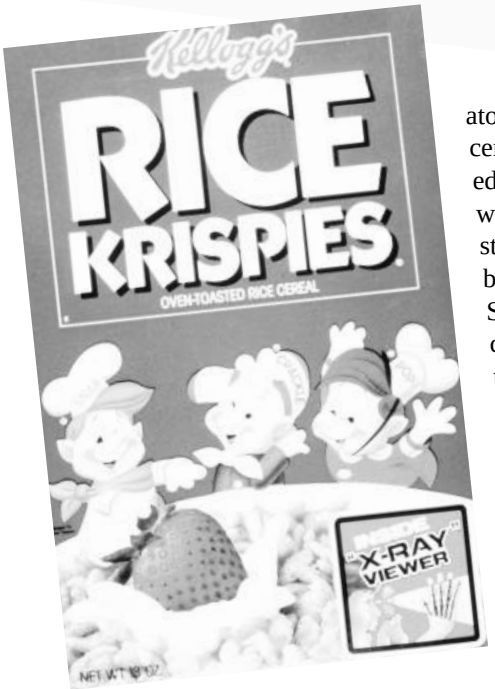
In 1957, the ICRP recommended an annual occupational dose limit of 5 rem per year, and in 1958 the NCRP recommended a life-time occupational dose limit of [(age in years − 18) × 5] rem, or a limit of 235 rem for someone who works from ages 18 to 65. The NCRP also recommended an annual limit to the public of 500 millirem per year. In 1960, the Federal Radiation Council recommended an annual limit of 500 millirem per year for an individual in the general public and a limit of 170 millirem per year as the average annual dose to a population group.



Radiation had a big impact on the popular imagination in the 1950s.

By 1961, it was generally understood that the risk of genetic effects had been overestimated in studies of the atomic-bomb survivors, but another risk was becoming apparent—studies of cancer incidence and mortality among the survivors were beginning to show elevated rates for leukemia. As time passed, elevated rates for solid-tumor cancers were also observed. Those findings as well as other studies led to the understanding that different cancers have different latency periods, or elapsed times, between irradiation of the individual and clinical observation of a malignancy. Solid tumors have latency periods of 25 to 40 years, and leukemia has a latency period of 2 to 25 years. The latency periods generally hold true irrespective of the particular agent that serves as the carcinogen.

The unmistakable appearance of an increased rate of cancer among the atomic-bomb survivors had a profound impact on the radiation protection community—it brought into focus the possibility that even low levels of exposure might induce cancers. Of course, the data regarding malignancies were obtained from populations receiving high doses at high dose rates. Risks estimates for low doses could only be made by extrapolating the high-dose data, and that procedure suggested that the cancer risks from low doses were small. Nevertheless, there were no data to suggest the existence of a threshold dose for radiogenic cancers, so the small risk per person at low doses had to be considered in relation to the large number of workers who were receiving those doses.

Those considerations resulted in a philosophical shift from mere compliance with dose limits and the avoidance of deterministic effects (such as cataracts and per-

manent damage to organs) to an emphasis on reducing overall cancer risks to working populations. The ICRP defined a system of dose control consisting of three parts: justification, optimization, and limitation. Justification requires that no new practice involving radiation shall be allowed unless its introduction produces a positive net benefit. Optimization requires that all doses shall be kept *as low as reasonably achievable* (ALARA) taking into account the relevant economic and social factors. Limitation requires that any individual dose not exceed limits set for appropriate circumstances. In today's applications of the dose-control concept, justification and optimization dominate. (More to the point, subjective judgements of regulators rather than the mathematics of optimization often drive the dose limits to lower and lower levels; economic factors are often ignored; and the net result is to make operations involving radiation and radioactive materials extremely expensive.)

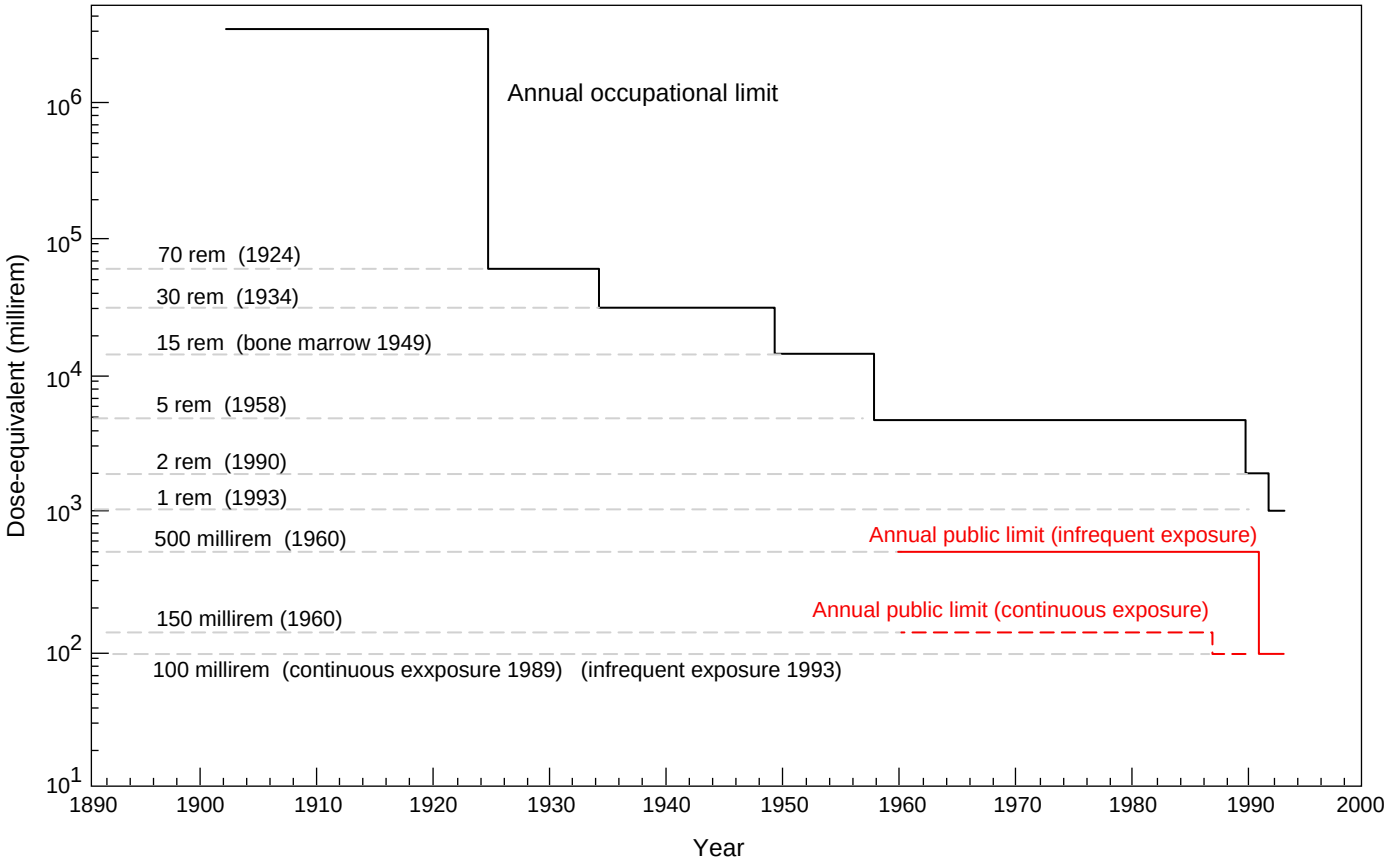


Figure 1. Radiation Dose Limits over the Past Century

This logarithmic plot of the recommended limits on annual exposures to radiation shows a continual decrease from the beginning of the century to the present. The 1993 NCRP recommendation for occupational dose limits allows for an average of about 1.5 rem per year over a working life from age 18 to age 65 (that is, a lifetime limit for an individual 65 years old is 65 rem; this dose distributed over a 47 year period yields about 1.5 rem per year). The ICRP does not recommend a lifetime dose limit; rather, an annual limit of 2 rem per year averaged over any 5-year period is recommended.

In 1977, the ICRP adopted a more formal risk-based approach to setting standards. That approach required that the average incremental risk of death from radiation exposure to workers in radiation industries be no larger than the average incremental risk of death from traumatic injuries to workers in "safe" industries. The incremental risk of death in safe industries is one in ten-thousand, or 10^{-4}, per year. Studies of the atomic-bomb survivors had shown that the risk coefficient for radiation-induced cancer mortality was about 10^{-4} per rem. Based on that risk coefficient, the ICRP recommended a maximum annual dose limit to a radiation worker of 5 rem per year. The 5-rem annual limit was set under the assumption that the

average dose would be less than 1 rem per year, and, thus, the average risk of death would be the same as for safe industries. Thus, the new 1977 limit was unchanged from the 1957 limit, but it was now justified in terms of a risk-based philosophy.

During the 1980s, estimates of the doses received by the atomic-bomb survivors were adjusted downward based on new estimates of the ratio of neutrons to gamma rays in the radiation produced by the bomb. Also, new data on cancer incidence and mortality among the survivors indicated higher rates for some cancers than previously thought. That meant the risk per unit dose, or the risk coefficient, was higher, and in fact, it was calculated to be 4×10^{-4} per rem. Based on that increase, the ICRP released a new set of international recommendations in 1990. They recommended limiting radiation exposure to 10 rem over any 5-year period and 5 rem in any one year. The public limit was set at a 100 millirem per year averaged over any 5-year period.

The 1993 NCRP limits on annual radiation doses relate both to stochastic effects, such as cancer and genetic effects, and to deterministic effects, such as cataracts or permanent damage to an organ. Stochastic effects, by definition, arise from random processes. The probability of their occurrence increases with increasing dose, but their severity does not. Moreover, there is no threshold dose below which the risk is zero. In contrast, there is a threshold dose for deterministic effects. That is, doses below the threshold will not kill enough cells to cause dysfunction in a tissue or organ.

The NCRP released its own new set of national recommendations in 1993. Those limits and the associated risks are listed in Table 2. They relate both to stochastic effects, such as cancer and genetic effects, and to deterministic effects. The present limits for deterministic effects are not much different than the first recommendations: 50 rem per year to any tissue or organ and 15 rem to the lens of the eye to avoid cataract formation. The recommended limits on whole-body doses for stochastic effects, first set at 5 rem per year in 1958, are now set at no more than 5 rem in any one year and a lifetime average of no more than 1.5 rem per year.

Table 2. Current Standards and Associated Estimates of Risk (NCRP Report Number 116, 1993)

Category	Annual Limit	Recommended Risk Coefficient	Estimated Risk at the Annual Limit
Occupational annual whole-body limit for stochastic effects	5 rem (stochastic)	4×10^{-4} rem^{-1} (for fatal cancer)	2 in 1,000 per year
		8×10^{-5} rem^{-1} (for severe genetic effects)	4 in 10,000 per year
Occupational lifetime limit	1 rem × age (years)	—	3 in 100 at age 70
Occupational annual limit for deterministic effects	15 rem to lens of eye 50 rem to any other organ or tissue system	—	no risk if limits not exceeded
Public annual whole body limit for continuous exposure	100 mrem	5×10^{-4} rem^{-1} (for fatal cancer)	1 in 10,000 per year
		1×10^{-4} rem^{-1} (for severe genetic effects)	1 in 100,000 per year
Public annual whole-body limit for infrequent exposure	500 mrem	1×10^{-4} rem^{-1}	1 in 10,000 per year
Negligible individual dose (annual whole-body dose per source or practice)	1 mrem	—	no discernable effects (5 in 10,000,000)

The current limits represent a culmination of intensive epidemiology and radiobiological research. However, there are still many open questions regarding the detailed mechanisms that cause biological effects. What are the relative risks of different types of radiations, acute versus chronic exposures, age of exposure, and chronic exposure to low doses? Those concerns dominate discussions on the future evolution of radiation protection standards. ■

Charles B. Meinhold has been the President of the National Council on Radiation Protection (NCRP) since 1991. He is also a Senior Scientist and Deputy Division Head of the Radiological Sciences Division at Brookhaven National Laboratory. Charle's field of expertise is the application of radiological physics and radiobiological data to radiation protection. He served as Chairman of NCRP Scientific Committee I on Basic Radiation Protection Criteria from 1988 to 1992 and was a co-author of the basic recommendations of the NCRP and ICRP. Charles has been a member of the International Commission of Radiological Protection (ICRP) Main Commission since 1978 and is presently its Vice Chairman. He was Chairman of Committee 2 on Basic Standards of the NCRP from 1985 to 1992. Charles is President of the International Radiation Protection Association (IRPA) and has been a member of the IRPA Executive Council since 1984. He has served on the oversight committees for Rocky Flats and for the Indian Point, Shorham, and Pilgrim nuclear power stations, and was appointed by the NRC to serve on the Blue Ribbon panel for Three Mile Island Unit 2. Charles has a B.S. in physics from Providence College and studied radiological physics at the University of Rochester under an AEC Fellowship. He is certified by the American Board of Health Physic, and is an Honorary Professor of the China Institute of Atomic Energy.

John C. Taschner joined the Laboratory in 1992 as a technical staff member in the Environment, Safety and Health Division (ESH-10) and is involved in radiological transportation accident exercise planning. In 1994, he joined the Laboratory's Human Studies Project Tea, and was the Project Leader for the RaLa/Bayo Canyon Project. Prior to coming to Los Alamos, John was Deputy Director of the Navy's Radiological Controls Program Office in Washington, D.C., and has held numerous key health physics management positions with the U.S. Navy and the U. S. Air Force. Over the past thirty years, John has served on several Radiation Protection Standards Committees. Since 1992, John has been the Vice Chairman of the American National Standards Institute's N43 Committee, which writes radiation safety standards for non-medical radiation producing equipment. He has been a member of the Health Physics Society since 1958 and is a member of the American Academy of Health Physics. John earned his M.S. in radiation biophysics from the University of Kansas in 1966 and, in 1973, received his certification in Health Physics by the American Board of Health Physics.

William C. Inkret See biography at the end of "On the Front Lines."

ON THE FRONT LINES

Plutonium workers past and present share their experiences

a roundtable organized by Bill Inkret and Guthrie Miller under the auspices of the Environmental Safety & Health Division

Plutonium metal is one of the major legacies of the Cold War—about 89 tons of it can presently be found in the pits of stockpiled nuclear weapons. The entire world ardently hopes that most of that nuclear fuel will be retired to some safe place in some benign form. A small fraction will inevitably continue to be used in the remaining nuclear stockpiles. Both aspects, retirement of the fuel and maintenance of the stockpile, require a place to handle plutonium and people who are willing and able to do the work safely.

Los Alamos was the place where, in 1944, reactor-produced plutonium in gram quantities was first fashioned into the pure metallic form needed to build an atomic bomb. Today the Laboratory remains one of the few places in the world where that very dangerous material can be handled safely. The town is also the present or former home of many men and women who worked with plutonium on a daily basis. Some of those people had accidents, and as a result, now carry in their bodies small quantities of plutonium.

For this issue of *Los Alamos Science*, which is dedicated to radiation protection and the story of the human radiation experiments, we asked a small group of past and present Laboratory employees to tell their stories of what it was and is like to work with plutonium. All of them have been involved in significant accidents or uncontrolled situations that led to significant internal exposure to plutonium. Some of their exposures are among the most serious that have occurred in the history of the Laboratory. Today, vastly improved working conditions have made accidents much less common than in the early days, but a small number of unlikely events are bound to happen even now. The personal experience of such events and their aftermath is presented in what follows.

Open hood in D-Building–1944

The participants represent all eras of the Laboratory from the Manhattan Project days to the present. A few are members of an informal group known as the UPPU club (translated as "You pee Pu!"), which was established at the Laboratory by Wright Langham in 1951. One had to have accumulated a significant plutonium body burden to qualify for voluntary membership. Those volunteers agreed to be monitored periodically and are being monitored to this day.

A plutonium body burden usually cannot be detected by an external radiation monitor because the alpha particles emitted by the plutonium are completely absorbed and never leave the body. The most reliable detection scheme is to measure the small fraction of that burden that is excreted in the urine daily. So starting in the forties, the urine of a plutonium worker was monitored on a regular basis. The amount measured in the urine is then related to the amount retained in the body using data and methods derived from a series of animal and human experiments. Wright Langham, who was responsible for the protection of workers during the early days at Los Alamos, was instrumental in the design and analysis of some of those experiments (see "The Plutonium Injection Experiments"). If urine assays and models like the Langham equation indicate that a worker has retained an amount near or above the limit set by radiation protection standards, then he or she is not allowed to work with plutonium again.

The roundtable was organized into several distinct parts. The participants were first asked to describe their personal experiences working with plutonium and their concerns about safety. That discussion illustrates the evolution of attitudes and practices from the Manhattan Project through to the present. For the second part, the participants were asked to describe the accidents that led to their intakes of plutonium. Next, they were given the opportunity to ask questions of the health experts that were present, and finally, they were asked to give their views of the plutonium injection experiments.

We want to thank them for sharing their feelings and experiences and for their essential contributions to the mission of the Laboratory.

The Participants

Here we introduce the ten men who agreed to share their stories of plutonium intakes. It is their belief that open communication will help the Laboratory, the community, and the whole of society to understand the human factors associated with managing our plutonium legacy.

These ten individuals are representative of a variety of plutonium intakes that have occurred in the history of the Laboratory. The magnitude of each individual's intake is expressed as the estimated committed effective dose-equivalent in rem, which is the dose that will be accumulated over a fifty-year period from the time of intake. These rem doses are divided into classes as follows: Class I: 10–30 rem, Class II: 30–100 rem, Class III: 100–300 rem, Class IV: 300–1000 rem.

Although the rem dose is meant to be a universal measure of the cancer risk from radiation exposure, the rem doses for plutonium accumulate slowly and may not have as large a cancer risk as an equal acute dose of gamma and x radiation. Therefore, the doses quoted here are most useful in comparing with other plutonium intakes.

To put these doses in perspective you may recall that the average background dose is about a third of a rem per year, or about 15 rem over a fifty-year period. Thus, for example, a person whose body burden of plutonium corresponds to a Class-I dose will receive a total radiation dose somewhat greater than background.

Ted Magel (Class III) and **Nick Dallas** (Class I) arrived at Los Alamos in early February 1944. They are credited with the first production of plutonium metal at Los Alamos. Ted received a puncture wound, and both Nick and Ted inhaled plutonium dust, which resulted in high nose counts. (Each nostril was swiped with moistened filter paper, which was put in an alpha counter to measure the amount of radioactivity in terms of counts per minute (cpm), or disintegrations per minute (dpm) when corrected for counter efficiency.)

Bill Gibson (Class III) came to Los Alamos in June of 1944 and worked in the plutonium recovery laboratory. From 1944 to 1945, Bill received exposures that resulted in four high nose counts (over 1000 cpm from one nostril, a level rarely seen in recent years) and one plutonium-contaminated wound, which was surgically excised. He was removed from plutonium work in 1954.

Ed Hammel (Class II) came to Los Alamos in June 1944 to replace Ted Magel as section leader for the plutonium metallurgy laboratory. The relatively primitive working conditions in D Building, as opposed to specific incidents, account for Ed's intake of plutonium.

Harold Archuleta (Class I), a lifelong resident of Espanola, came to work at the Laboratory's metal fabrication group in the plutonium research facility at DP site in 1958. In 1971, Harold suffered a plutonium-contaminated wound, which required excision, and in 1987, he inhaled plutonium dust, which resulted in a high nose count (over 1000 dpm from one nostril). Howard was removed from plutonium work in 1990 and retired from the Laboratory in 1993. He is now an escort for a Laboratory contractor.

Arthur Beaumont (Class III) arrived in Los Alamos in 1946 to work as the recreation director in Theater #2. In 1951, he began working at DP site on weapons components and later worked on the artificial heart program. Art's intakes occurred in the 1970s and involved both plutonium-239 and plutonium-238. Art was removed from plutonium work in August 1973.

Jose Gonzales (Class I) was born in El Rancho and spent summers on his father's homestead on Barranca Mesa in Los Alamos. In 1958, he began work at DP site as a radiation-protection technician. Jose relates numerous incidents in which intakes have occurred.

James Ledbetter (Class I), a native of Oklahoma, came to Los Alamos in 1969 and began working on plutonium heat sources for the Jupiter fly-by mission. Jim was one of the workers exposed in the infamous CMR-Building airborne plutonium accident of 1971 in which a malfunction of the ventilation system transported airborne plutonium out of the hot cell into the cold operations area.

Michael Martinez (Class I) began working in the metal production laboratory at TA-55 in 1980. TA-55 is the site of the state-of-the-art plutonium facility that was completed in 1978. John was involved in an airborne release of plutonium-239 in 1993. Michael was removed from plutonium work that same year.

Jerry Taylor (Class IV) began working at TA-55 in 1980. In April 1981, Jerry cut his left hand with a plutonium contaminated knife while working inside a glovebox. The wound was surgically excised twice, and chelation therapy was administered for a period of over one year. Jerry was removed from plutonium work and continued to work at the Laboratory until 1985.

Setting the Stage in Chicago

Ed Hammel: As background for this discussion, I'd like to read a paragraph from the diary of Glenn Seaborg. As most of you know, Seaborg, in collaboration with Art Wahl and Joseph Kennedy, was the first to isolate plutonium and to demonstrate that it was a new man-made element heavier than uranium. [*Trace quantities of the new element were made by placing samples of uranium in the Berkeley cyclotron and bombarding them with either neutrons or deuterons. When uranium-238 absorbs a neutron, it transforms into neptunium-239, which rapidly decays to plutonium-239, the isotope used in nuclear weapons.*] That work was done in 1941, two years after the discovery of nuclear fission and just as the possibility of making an atomic bomb was first being seriously considered by the United States following communications from Great Britain.

Ted Magel in 1944

By April 1942, the decision to build the bomb had been made, and Seaborg and his Berkeley colleagues had joined the Plutonium Project at the Metallurgical Laboratory [Met Lab] at the University of Chicago. They were charged with developing chemical methods for isolating and purifying reactor-produced plutonium. Nuclear reactors were still just a dream—Enrico Fermi was under the west stands of Stagg Field, the University of Chicago's athletic stadium, building the uranium pile in which he hoped to demonstrate the first self-sustaining nuclear chain reaction (he did not succeed until December 1942). Nevertheless, Arthur Compton, the initiator of the Plutonium Project, was fairly certain that uranium reactors like Fermi's could be used to manufacture the kilogram quantities of plutonium needed for a bomb.

In January 1944, accelerator-produced plutonium in milligram quantities was just becoming available to the Berkeley chemists, but gram quantities were soon to be delivered from the pilot production reactor in Clinton, Tennessee. On January 5, Glenn Seaborg wrote:

> *As I was making the rounds of the Laboratory rooms [at the Met Lab] this morning, I was suddenly struck by a disturbing vision. I pictured in my mind the expanded scale of work with solutions containing plutonium that will soon result from the large quantities of plutonium soon to be received from Clinton Laboratories. I visualized beakers of plutonium solutions throughout the laboratory rooms, and it struck me forcibly for the first time that plutonium handling will now no longer be confined to micro quantities manipulated by specially trained experts. Recalling the health problems incurred by workers in the radium dial-painting industry, I realized clearly that similar hazards face those of us working with alpha-particle-emitting plutonium-239. I was struck by the fact that despite the great care in planning by the Project medical people, no one has anticipated and made special provision for the wide-scale handling of alpha-active material which presents special hazards of ingestion. It became clear to me that our rather ordinary laboratory hoods are inadequate for this task and that rather extensive rebuilding of our laboratory facilities to emphasize adequate air flow and extraordinarily clean operations will be necessary. I am determined that none of the people for whom I am responsible shall be subjected to any avoidable dangers from handling alpha-active plutonium.*

That note was written nine months after the Los Alamos Laboratory (Site Y) was established and a month before any plutonium arrived at Los Alamos. From the Met Lab and other sources, we knew that we would be working with a very hazardous substance. But we had a tremendous job to do in terms of making this material into a metallic fuel for the bomb. Nobody had ever seen pure plutonium metal. Nobody knew any of its properties. Nobody knew its density, its melting point, or how hard or brittle it was. Nobody knew how to fabricate it. All we knew was that we had to do it. And we had to do it as carefully as we could.

Los Alamos Science: *Ted Magel, you were the first person to isolate*

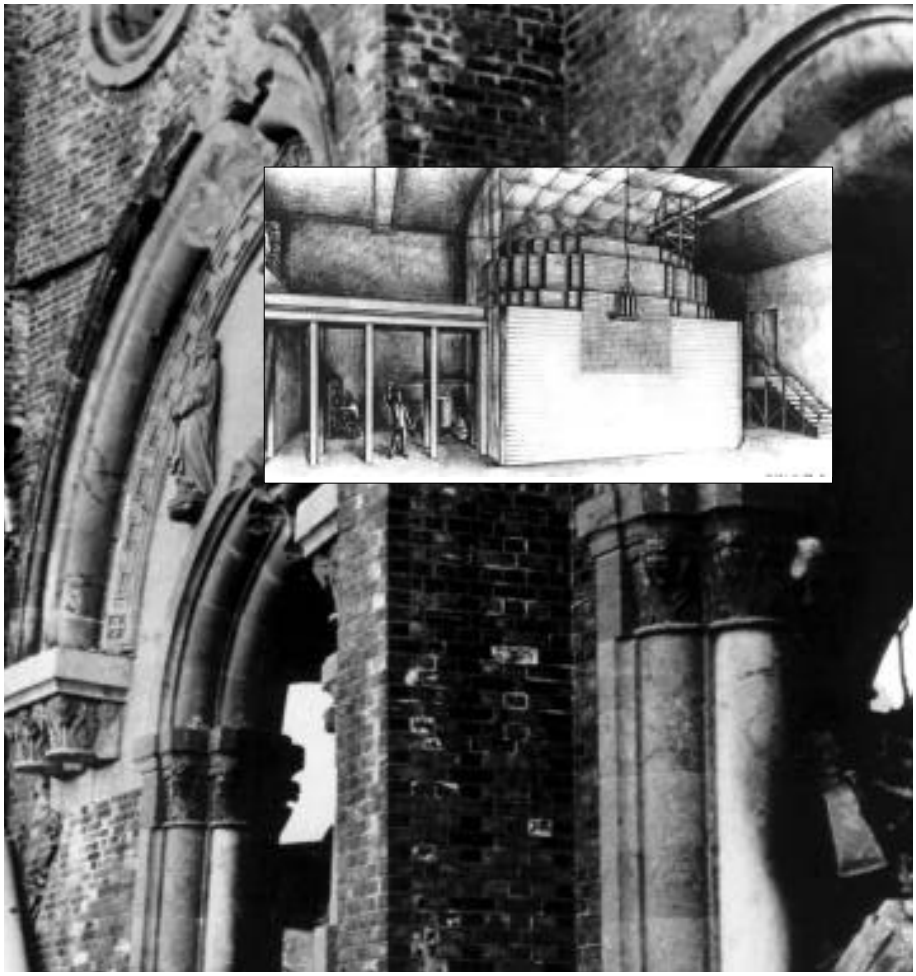
plutonium in a pure metallic form. Tell us how you came to work with plutonium in the first place.

Ted Magel: Well, I was actually at Berkeley when plutonium was discovered. I was doing my graduate work in chemistry under Professor G. M. Lewis, and Seaborg, Art Wahl, and Joseph Kennedy were just across the hall. I had no part in their discovery, but I knew about it. Then when Seaborg went to Chicago to set up the Met Lab, I was the fifth chemist that he asked to join him. At first, we were working with tracer amounts of plutonium—and finally with microgram amounts that could only be observed under the microscope.

Los Alamos Science: *What was the purpose of the work at the Met Lab?*

Ted Magel: The laboratory was called "The Metallurgical Laboratory" to disguise the real nature of our work. In actuality, we were developing chemical techniques for separating the plutonium that was going to be produced in a uranium pile. We worked with a big load of uranyl nitrate that had been bombarded with neutrons for weeks and weeks at the cyclotron at Washington University in St. Louis. That material was supposed to mock up the material that would eventually be sent from the Clinton reactor. We managed to precipitate out a plutonium compound from this big mixture; it was the first plutonium compound seen under the microscope.

For various professional reasons, I decided to leave Seaborg's chemistry group and work for Dr. Chipman. He had been brought out from MIT to head up some metallurgical operations needed for the plutonium-production system. In 1943, Chipman asked me to go over to Site B, an old brewery on the south side of Chicago near the University, and set up a group to work on techniques to produce plutonium metal from the very small quantities of plutonium compounds that would initially become available. Nick Dallas and I went to site B. I recall that we spent all of our efforts during 1943 on small-scale reduction techniques for making pure metal buttons.



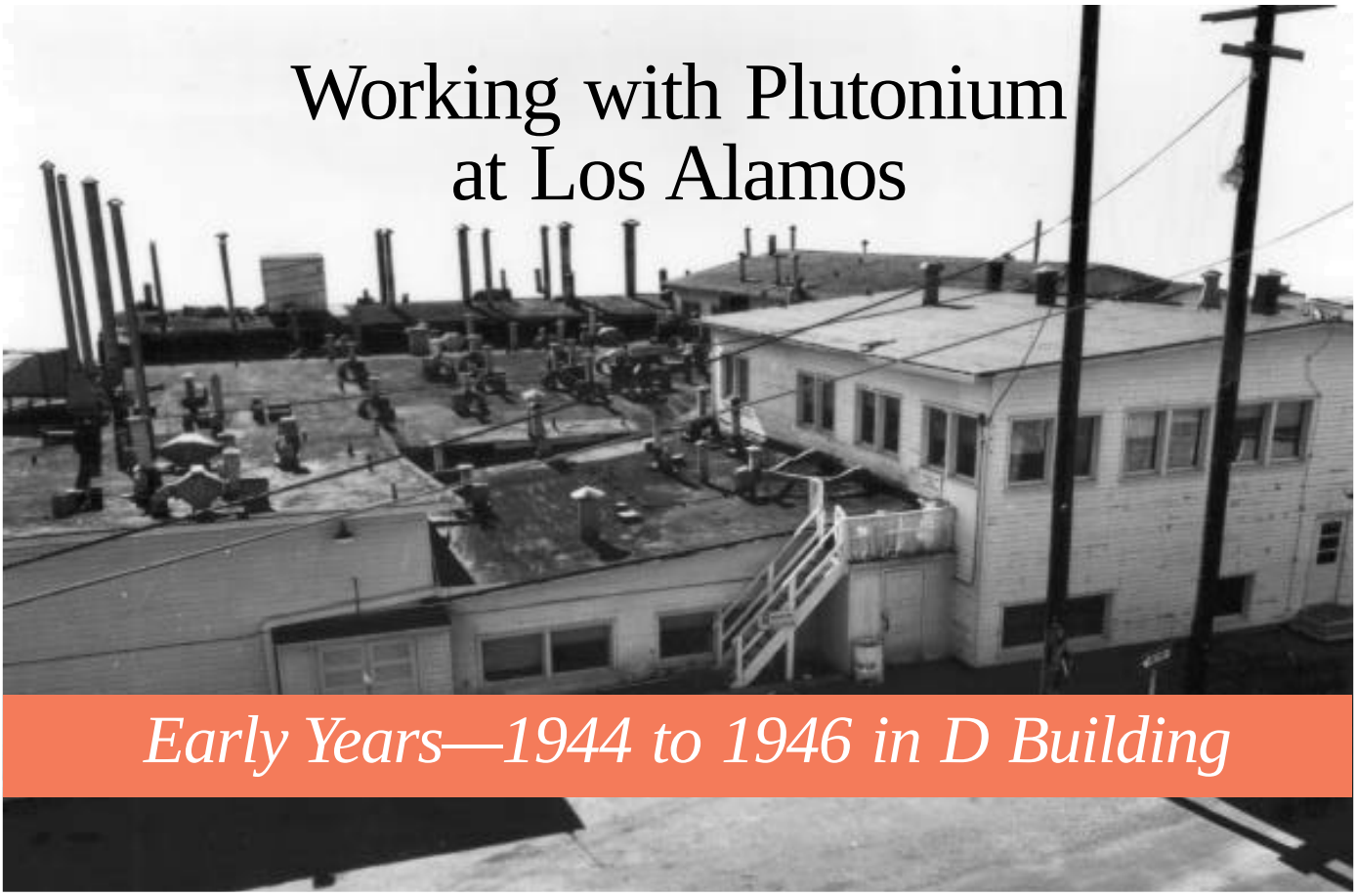
Inset: Fermi's pile under the stadium at Stagg Field, University of Chicago

There wasn't any plutonium around at that time, so we used stand-in elements like uranium, alloys of uranium, manganese, and so on. During that year Nick and I developed the hot-centrifuge procedure for making small-scale good-yield reductions of uranium fluoride to uranium metal.

Anyway, one night I was awakened by Chipman at about 11:00 o'clock and asked to go immediately to a meeting where they said, "We want you and Dallas to pack your things right now and go down to Los Alamos. They want to see if you can reduce uranium, and they want you to get ready to reduce plutonium on the one-gram scale." So we packed up our equipment and went to Los Alamos.

At that time, everybody was having trouble producing tiny quantities of uranium and plutonium metal using standard procedures. And the difficulty was pretty obvious. The smaller the quantity of material, the greater the surface effects that cause the metal to hang up on the walls of refractory crucibles. As a result, it's very difficult to get a good yield of solid, nonporous metal. But that was the goal, to make a solid button that could be used for measuring the bulk properties of the metallic phase.

Working with Plutonium at Los Alamos



Early Years—1944 to 1946 in D Building

All plutonium chemistry and metallurgy at Los Alamos was done in D Building, one of the most elaborate and costly structures at Site Y. It was designed to minimize contamination of plutonium by light-element dust particles in the air. According to official descriptions it had five miles of piping, a complex air-conditioning system with special provsions for air washing and electrostatic dust removal, very complex laboratories serviced with water, air, gas, and electricity, and "deluge shower baths" to wash off contamination.

Ted Magel: Nick and I arrived at Los Alamos about February 3, 1944 and went immediately to the metal-reduction area in D Building. Well, the place seemed like a morgue to us; everyone was quiet and working in isolation. I guess they were discouraged. Dick Baker was having a great deal of difficulty with his metal-reduction work, and morale was low. Nick and I quickly transformed the place and got everyone excited. Within a week, we had set up all the equipment that we'd brought with us from Chicago and were making 1-gram reductions of uranium in our hot centrifuge.

On March 2, the chemists gave us a 50-milligram quantity of plutonium fluoride to reduce to metal. That's a very small amount of material but that was all that was available. Nick and I worked with it, and in our second attempt at reduction, we were able to make a tiny coherent sphere of plutonium metal weighing 20 milligrams. That was a 40-per-cent yield, better than we expected after our first failure.

We continued to refine our methods and to wait, along with everyone else, for the arrival from the Clinton Laboratory of the first gram samples of plutonium. When they finally came, Eric Jette and Cyril Smith decreed that Dick Baker would get the first crack at a reduction, but Dick's stationary-bomb method yielded only a black cokey mass rather than a coherent button of plutonium metal. A few weeks later, a second sample became available, and this time, it was given to us.

Nick Dallas: Ted, you really should tell the whole circumstances of that reduction.

Ted Magel: The reduction of a gram quantity of plutonium was considered a very big deal because that amount of metal would allow much improved measurements of many crucial material properties. The reduction was supposed to take place on March 24, 1944, and General Groves and several top administrators had been specially invited to observe us as we did it.

Well, when does everything go wrong—when you have a whole lot of observers, right? So on the 23rd, I said to Nick,

Well when does everything go wrong—when you have a whole lot of observers, right? So on the 23rd, I said to Nick, "Let's go up to the lab and make the reduction tonight before all these people get here."

"Let's go up to the lab and make the reduction tonight before all these people get here." Nick agreed, and we carried out the reduction using the hot-centrifuge bomb method [*see "Plutonium metal—the first gram"*]. When it was done, we cut open the bomb, dropped the little button of plutonium metal in a glass vial and put it on Cyril Smith's desk with a note that read:

Here is your button of plutonium.
We have gone to Santa Fe for the day.

Everyone was pretty mad at us and claimed that we had contaminated the lathe and the back shop when we had opened the bomb to retrieve the plutonium button. I don't believe that we had, but I understood how they felt. In any case, once they had the button, they immediately started measurements of density and so forth. Also, Dick Baker continued his work on the stationary bomb and eventually developed excellent procedures for working with the larger quantities of plutonium that continued to arrive from the Clinton pile.

Nick Dallas: Ted, after we made the first button, I believe we started working on plutonium purification techniques.

Ted Magel: Right Nick. After about eight more 1-gram reductions, we went to work on developing ways to make super-pure plutonium. We needed to remove all light-element impurities. The worry was that alpha particles from the plutonium would hit light-elements and produce neutrons. The high neutron background would then cause the bomb to pre-initiate and fizzle before the critical mass was fully assembled.

Well, just as we were getting off the ground on light-element purification, it was discovered that plutonium from the production piles at Hanford would contain substantial quantities of plutonium-240, an isotope that produces neutrons as it undergoes spontaneous fission. Since plutonium-240 cannot be removed chemically, the gun method for assembling the plutonium bomb was abandoned and the project turned to the implosion method. That meant Dallas and I were no longer needed to make super-pure plutonium.

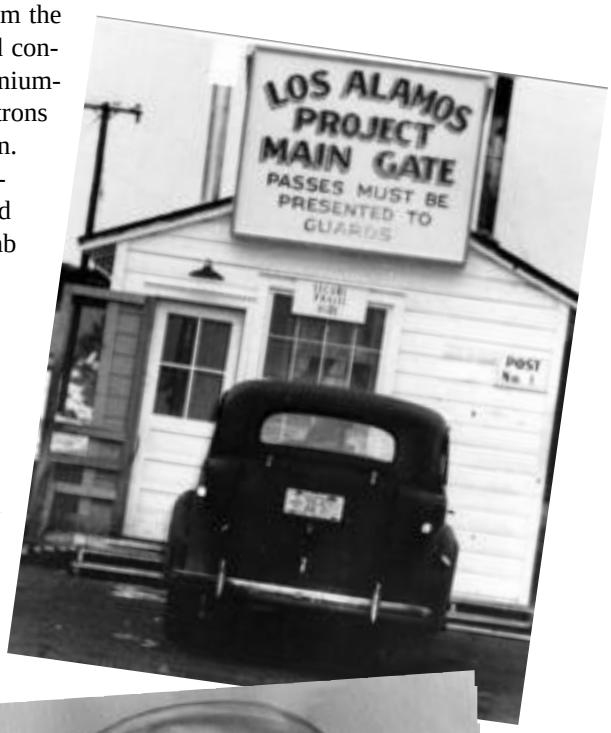
Oppenheimer told the chemists that we were welcome to stay and find jobs elsewhere in the Laboratory. Nick and I elected to leave. I think we were the first ones ever to leave Los Alamos and still remain on the Manhattan Project. We went to work for Dr. Chipman at MIT where we produced nonporous, highly sintered crucibles of pure magnesium-oxide—3 inches in diameter and about a foot high—for holding molten uranium and plutonium. And we shipped large numbers to Dick Baker's group out at Los Alamos.

Los Alamos Science: *Was the fact that you both had body burdens of plutonium one of the reasons for leaving?*

Ted Magel: Not at all. We did have a few mishaps with plutonium, and we were being monitored by Dr. Hemplemann and Wright Langham, but that's not the reason we left.

Los Alamos Science: *We'll want you to discuss the accidents in the second half of this discussion, but let's go back to Ed.*

Ed Hammel: I started work on the project in 1941 back in Princeton, on the heavy water part of the project.



Bill Gibson in 1944

Technical area around Ashley Pond

Ed Hammel in 1944

My wife had serious sinus problems, and someone told me that there was a place on the project out west where it was really dry. I managed to get transferred, and I arrived at Los Alamos at the end of June 1944. I was the replacement for Ted Magel in the plutonium metallurgy lab. My section got the reduced buttons from Baker and was responsible for remelting them, alloying them, and then casting them. We did that from June 1944 to the end of the war. I hadn't worked with radioactivity before I came to Los Alamos, and I learned shortly after arriving that Magel had received a large dose, but there was a job to be done.

Los Alamos Science: *Were you concerned about the health risks of working with plutonium?*

Ed Hammel: I think that everyone in D Building was aware of the risks. But there was a war going on. We didn't know exactly what was happening in Germany, but we knew their capabilities. We learned about the raid on the heavy water plant in Norway. We feared the worst, and I think that everyone working in D Building was primarily concerned with not being responsible for some stupid accident that would in any way delay completion of the overall operation.

Los Alamos Science: *What were the working conditions in D building? Were they very primitive in terms of containment of plutonium?*

Ed Hammel: We worked with wooden dry boxes, which were pretty primitive, and we worked in open hoods for some procedures. But we tried to be very careful. We wore respirators and special protective clothing, and nose counts were carried out for all personnel working with plutonium.

Los Alamos Science: *What is a nose count?*

Ed Hammel: Usually twice a day members of the health group would turn up to take nose swipes. They would swab the inside of the nostrils of each worker with a damp, rolled strip of filter paper that was attached to the end of a swab stick. After completing the collection, each nose swipe would be placed in an alpha counter to see if there was any radioactivity.

Los Alamos Science: *Bill Gibson, you were here about the same time as Ed. What was your experience?*

Bill Gibson: I came here the same month as Ed, June 1944, to work in the plutonium recovery lab. And like Ted Magel and Nick Dallas, I'm a member of what is called the UPPU club. All of us in that club got an appreciable amount of plutonium inside us during World War II. I won't say how much, and nobody was really sure until about 1954. By then, analytical techniques had improved to the point that inconsistencies in the analysis had been materially reduced and the data appeared to be more meaningful. I was taken off my job and not allowed to work with plutonium or put my hand in a glove box again.

And I began to think of the science fiction pieces that I'd seen in the Sunday newspapers and thought, "Oh my God, are we entering a new age?"

Los Alamos Science: *What did you think about this material at the time?*

Bill Gibson: I was in an Army combat unit at the time I was assigned to Los Alamos and I didn't have a clearance, so at first, I didn't know what I was working with. The characteristics of the material were reasonably close to uranium but not quite the same and not the same as any other element of the

periodic table. And I began to think of the science fiction pieces that I'd seen in the Sunday newspapers and thought, "Oh my God, are we entering a new age?" After a month, I received my clearance and was told what it was all about, including that I was working with a new man-made element plutonium. Of course, I knew about radioactivity, and I knew that in the old days the people who had painted the radium watch dials had suffered from radium poisoning and died some pretty terrible deaths. But Wright Langham was a very sharp man, and he cautioned us about the hazards of plutonium. He and Louis, Dr. Louis Hempelmann, kept pretty close watch over us.

But the conditions were primitive. Like Ed said, we worked in open hoods. There was a table with a glass top that resembled a slanting shelf, and we put our hand under the glass to work. We worked with all kinds of chemical residues and with all kinds of crucibles. We had to recover plutonium from almost every element in the periodic table. Sometimes things got pretty sloppy. As a matter of fact, the first eight grams that we worked with was called our jinx batch. After it had been ether-extracted and was in its purest form, one of my compatriots put it in a petri dish and put the petri dish in an oven to speed evaporation. When he tried to pull out the glass dish, the bottom fell out, and the whole thing, plutonium and all, went on the floor. We cleaned up the spill, it was about 8 milliliters of liquid, and got it almost to the final purification. That is, we had it in the centrifuge at the precipitation stage, and while it was whirling around like mad, one of the centrifuge cones broke, and the stuff came out all over the inside of the centrifuge and out through the ventilation of the centrifuge onto the floor. Again we cleaned it up, got it purified and sent it to the dry-chemistry operation where their controller got stuck, and the stuff burned to a cinder. So we had to start again for the fourth time. We finally did get out most of the eight grams and gave it back to the dry-chemistry section, who prepared it for metal reduction.
As I said, the conditions were not the very best. When we spilled the solution, we had to get down on our hands and knees and clean it up. But we were able to recover almost all of it, and that was what we were after.

Los Alamos Science: *Were you concerned about your own health when you were in these situations?*

Bill Gibson: The combat unit that I came from wound up in the Battle of the Bulge, so my philosophy was that if I died twenty years later from working with this stuff, I would be lucky compared to my compatriots who hadn't had the chance to live that long. My attitude was to be as careful as possible and to do the best I could as a soldier of the United States Army.

Ed Hammel: What was paramount in our minds was not the danger of radioactivity, but rather that this stuff was extremely valuable, at least 100 times more valuable than gold, and for gosh sakes, we better take care not to lose any of it.

Bill Gibson: We did try to protect ourselves from inhaling plutonium microparticles by wearing dust masks, the kind that miners use. But they weren't very effective. I don't think there were many days during World War II when I was without a positive nose count of between a few hundred and 20,000 disintegrations per minute.

Los Alamos Science: *Bill, we'll wait until our discussion of accidents and health consequences to hear more of your story. But now we turn to another period in the story of plutonium workers marked by the move to DP site and less primitive working conditions.*

Infirmary

Covered bridge across Trinity Drive connecting technical areas

Middle Years—1952 to 1978 at DP Site

By late 1944, the need for a safer and larger facility to handle fabrication and recovery of plutonium was evident. The site selected for the new complex, originally called "D Site," was on a mesa across from the modern-day airport and down about a mile from the original technical area of the Laboratory, which is now the center of the town. The new complex was officially named "DP Site" on March 16, 1945, to avoid any confusion with the existing "D" Building. Although many theories exist about the exact meaning of DP, the minutes of the Plant Building Committee, headed by J. E. Burke, suggest that P stood for Plant. (In a 1981 article, however, Burke stated that the P stood for polonium). The buildings at DP site are made of metal and were built with elaborate ventilation systems, closed hoods, and all kinds of features to keep exposures to a minimum. Operation began at the site in 1945.

Los Alamos Science: *Art, your experiences began in DP Site, didn't they?*

Art Beaumont: Yes. But I first came to the Santa Fe area back in 1946. I came to look up a gal I had met when I was with the 10th Mountain Division. We really hit it off, and I decided to stay. In April, I got a job up here on the mesa first with the U.S. Army Corps of Engineers, and then with the Zia Company, as recreation director of Theater Number 2. By July of that year, my wife and I were married. A bit later, I went back to school at the University of New Mexico and earned a masters degree in educational administration. Then, in May 1951, I was hired by the Laboratory. Although I didn't have a degree in chemistry, I had enough coursework in science that they hired me to work on the fabrication of plutonium parts for weapons.

Los Alamos Science: *What did you know about plutonium when you first started?*

Art Beaumont: I didn't know anything. I just walked down to Building 5 at DP Site and started to work. There was no education; I wasn't even sure what I was working with, to be very honest. There was a stainless steel glove box with weapons components, and one of the first things I did was use a piece of sandpaper to make a certain tolerance for a weapon item. It was really kind of amazing. I would be sanding away and all of a sudden I would see a little fire in front of me. Plutonium dust had accumulated and caught on fire. I would use graphite to put out the fire or just take a piece of sandpaper and smother it.

Los Alamos Science: *The plutonium would catch on fire?*

Art Beaumont: Yes, small pieces of dust with lots of surface area are pyrophoric; it starts burning by itself.

Los Alamos Science: *Were you concerned about the health hazards?*

Art Beaumont: Not at all. From Building 5, the fabrication unit, I went to Building 2, which was recovery, and

I worked there for a long time. We were like a family down there. Everybody cooperated with everybody. I worked with people like Dr. Baker, who everybody probably knows about, and it was just fun working with him. I had absolutely no fear of plutonium, but one afternoon about 3:30 P.M., I was asked to go to the administration building. There they told me, "You've reached the threshold of allowed plutonium in your body; we have to transfer you." I still have the letter from Dr. Baker that said I was being reassigned from DP West to DP East. Since that day, I've felt that if there was somebody like me, whose count was building up, the one thing the Laboratory could do would be to tell that person and give them a choice of being reassigned before they acquire their limit. Instead, out of the clear sky, I was told I had reached the threshold. I hope the Laboratory is doing things differently with the people who are working today.

Jose Gonzales: I understand what Art is saying. It's hard not knowing exactly what's going on. Back in the early days the Laboratory people would transport plutonium in convoys only fifteen feet from my kitchen door down the hill in El Rancho. I remember hearing those convoys passing our house at 1:00 A.M. in the morning. It would have been nice if they had told us what was in them. The family knew there was a secret project, but they didn't know anything else. My father had had a homestead on what is now called Barranca Mesa. It's the most northerly mesa in Los Alamos. In the early forties, the Federal Bureau of Investigation came to our home and condemned the property for war purposes. They gave us 30 days to move out, and that's when we went down to El Rancho. My father worked at D Building during the war and was there during the early stages of the plutonium work. He lived a happy life and died at the age of 85.

Los Alamos Science: *Jose, what made you decide to work at Los Alamos?*

Jose Gonzales: I had a business down in Pojoaque, and when it went down the tubes because the highway department was widening the road, I decided to apply to Los Alamos. That was 1958. Dr. Thomas Shipman in the Health Division called me for an interview and explained the field of radiation monitoring to me. He explained what my duties would be, and then I wound up being assigned to DP Site. There I had a chance to work with some of the pioneers in plutonium work—like Bill Gibson, Art Beaumont, and Bill Maraman. I felt comfortable from the start even though I didn't know exactly what was going on in the experiments. I guess what made me feel good was that I had the equipment to protect myself and to protect those people that were out there. A lot of elderly people of Spanish descent were working there as laborers, electricians, craftsmen, and so on, and I was able to communicate with them in Spanish.

Then just a month after I started work, there was a fatal accident. That sort of shook me up, but then I went to guys like Bill Gibson, Bill Maraman, and Dr. Shipman, and they were able to put me back on track. [*This fatal criticality accident in which Cecil Kelly was killed is one of three such accidents that have occurred at Los Alamos; the others took place in 1945 and 1946. A criticality incident, or the accidental initiation of a nuclear chain reaction, usually occurs by collecting a mass of fissile material into a small space. The nuclear chain reaction that results releases a lethal flood of gamma rays and neutrons.*] I learned from the experience that people can die from radiation—you can plan for a job for three weeks, and it only takes one second to mess it up. After that, I felt good because I understood even more why I was needed, and I liked being part of a supporting group. We were there to help in whatever manner we could. Safety was number one, and we always tried to be prepared.

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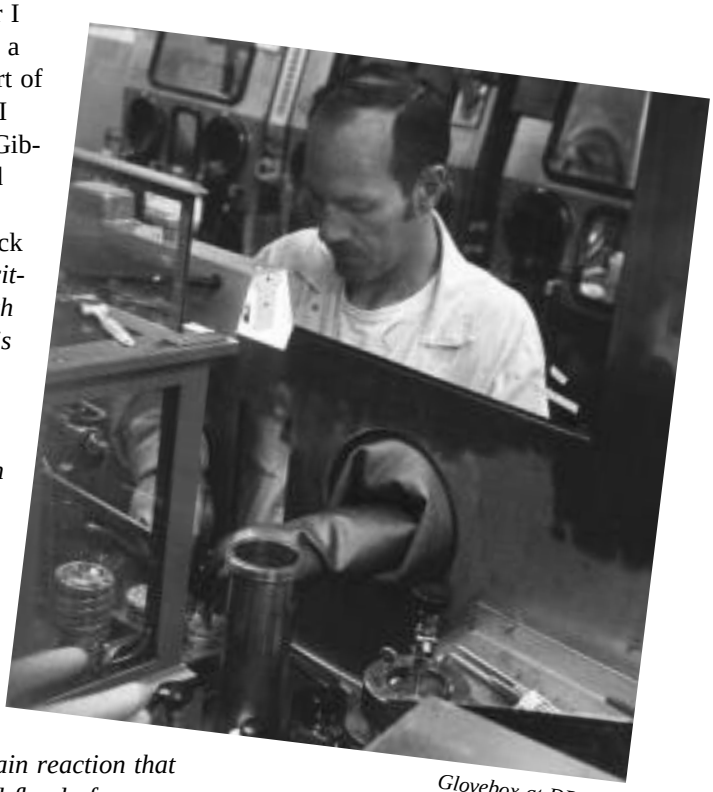

Glovebox at DP Site

Los Alamos Science: *What exactly was your job out there?*

Jose Gonzales: In my first years, I did routine radiation monitoring. I posted the dose rates, and I helped people with routine operations, like getting dressed in protective clothing and then changing back to their own clothes when they left the area. Also, I made sure the right equipment was there. Over the years, I worked in all the labs at DP Site. I assisted with the first batch of plutonium-238 that came there. It was going to be used as an energy source for a heart pacemaker. I also worked with the people who did metal reductions, turning compounds into pure metal. They worked in a long line of glove boxes called the MPL, the metal prep line. In 1978, when we were preparing to move to the new facility at TA-55, I was the only one left with any experience on that line. That's when Larry Mullins, Dana Christensen, and Art Morgan asked me to run the system. I was upgraded to a chemical technician, and I worked on that line for 13 years until I retired in 1991. I helped assemble the laser-reduction apparatus, and I made the first laser-reduction of plutonium. Conventional reductions took 18 to 20 minutes; the laser method reduced the time to 6 seconds and also reduced the neutron exposure. You know back in 1978 when I was upgraded, my first job was to help decommission the metal prep line before it was moved to TA-55. Now the Lab is about to decommission it again, and they have asked me to work as a consultant preparing a set of safety checks on their procedures for decommissioning. It feels good that I can still help.

Los Alamos Science: *Did you enjoy your work?*

Jose Gonzales: Yes, I did, but I enjoyed it most when we were back at DP Site. We all called each other by our first names; there was none of this mister stuff. We were one united family. When something happened, everyone went in as one unit to take care of it. Also, they gave me the opportunity to go out to the Nevada Test Site. I made about ten trips out there, and at one point, I worked on the Rover program, which was a program to develop a nuclear-powered rocket that could travel to Mars. I really enjoyed that experience. I worked for the Laboratory for 33 years, and I don't have any grudges against the Laboratory or the people I worked for or the people I worked with, and that makes me comfortable.

We all called each other by our first names; there was none of this mister stuff. We were one united family. When something happened, everyone went in as one unit to take care of it.

Los Alamos Science: *Jim Ledbetter, you also worked on the Rover program in the 1960s, didn't you?*

Jim Ledbetter: Yes, my first experience as a radiation worker was at the Nevada Test Site. I was employed as a technician in the Nuclear Rocket Development Program in the Advanced Space Program. President John F. Kennedy was the champion of that program. He wanted to promote research that would enable manned space missions to distances beyond the moon, more precisely, to Mars. My job was on the Rover reactor, which was to be used as the fuel source for the manned spacecraft. I was responsible for the mechanical arms that were used to disassemble the reactor parts and prepare them for diagnostic tests. The work involved very high radiation fields. All of us were very highly trained by outside contractors before we were pressed into service. I spent a

number of years out at the test site doing postmortem examinations on various reactor designs built by Los Alamos and Westinghouse.

Los Alamos Science: *Why did you come to Los Alamos?*

Jim Ledbetter: Following President Kennedy's death, subsequent administrations determined that there would be no mission to Mars in the foreseeable future, and in 1969, the Nuclear Rocket Research for the Advanced Space Program ended. At that time, I was offered a job at Los Alamos. It was similar to the past work in the Rover Program. I was involved in robotics and hot cells providing postmortem operations on experimental fuels and components for breeder reactors. We were a team of engineers, technicians, and scientists who, in a six-month period, developed the primary containment and the robotics to do the job.

In 1970, the Laboratory informed us that we were going to participate in an assessment of the heat source for the Jupiter fly-by experiment. The unit used plutonium-238 as the heat generating material and a thermocouple package from TRW to generate power for the on-board components. It was in this manner that signals would be transmitted back to earth. Our task was to disassemble two of the units so Los Alamos scientists and engineers could assess the performance and recover the components and materials.

Following receipt of the first unit and removal of the TRW thermocouple package, the hot-cell process began. We completely dismantled the plutonium heat sources and rewelded the components into tantalum containers. They were then removed from the hot cell and stored for reuse. The first disassembly went very smoothly with no malfunctions and no unusual occurrences. The process went very well even though a sense of urgency surrounded our efforts. The experiments were being pressed to meet NASA schedules, so we quickly prepared for the second disassembly. It was during the second disassembly that we encountered problems. Despite those problems, the people at Los Alamos persisted, and the NASA schedule for the fly-by was met. It was very rewarding to us that we could be involved and see success as the spacecraft transmitted data from Jupiter several years later. After the project, we were informed that the heat source had transmitted signals far beyond Jupiter, to distances as far away as Pluto. Its performance exceeded expectations and provided data for a much longer period.

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Los Alamos Science: *It sounds like the years at DP Site were a very expansive era in the history of the Laboratory. New energy sources, interplanetary space travel, all kinds of dreams were in the air. Now we'll go on to the opening of the modern facility at TA-55 and the practices and attitudes of today.*

Modern Times—1980 to the Present at TA-55

The modern plutonium facility at TA-55 was authorized in 1971 following a devastating fire at the Rocky Flats Plant in Colorado. The Los Alamos facility was designed to withstand all natural disasters, accidents, and terrorist activities, and to protect workers under unusual circumstances such as power failures. Its modular construction has permitted continual upgrades so that it remains a state-of-the-art facility to this day (see "The Modern Role of the Plutonium Facility").

Los Alamos Science: *Jerry Taylor, you worked at TA-55. What was it like when you first came to the job?*

Jerry Taylor: I was in awe when I first walked into TA-55. It was like entering the spacecraft in *2001 Space Odyssey*. There were all these stainless-steel valves and pipes everywhere. The whole facility was awesome.

Los Alamos Science: *You knew people who worked there, didn't you?*

Jerry Taylor: Yes. My uncle worked there, and his brother-in-law was a group leader. My father and some of my cousins also worked there. In fact, my grandparents had been in Los Alamos since 1943. My grandfather worked on the first bomb.

When I first started, I went to a safety course and learned about criticality and radiation hazards. I saw all the procedures we had to go through, all the safety precautions, all the monitoring to protect us. But it never scared me. I really enjoyed learning the work at TA-55. We got to go and see what they did in some of the other labs and down to the vaults where they store plutonium and all kinds of things containing plutonium. There are a few fuel rods down there in a pool of liquid, and they are the most beautiful aqua color I have ever seen.

It was really amazing to me that we could make this material. Lots of times, we started from contaminated trash, and all of a sudden, we ended with a piece of plutonium metal. I was always in awe of all of it. I enjoyed the work. It never did scare me until the day of the accident. But then it got to me, because I knew the health hazards. That was fourteen years ago, and I still worry to this day about what the long-term exposure to internal radiation

will do to me. I know Bill Gibson, I used to work with him. He had an exposure almost fifty years ago, and he's still around. And Art Beaumont is still here, even though he's been exposed. But I still have questions about it.

Los Alamos Science: *Did anyone else in your family ever have any internal exposures to plutonium?*

Jerry Taylor: My uncle had a very small exposure, but my dad never has. I don't know if my grandfather ever had one. He was a machinist up here. My family has worked here all these years, and I'm the only one that has a contamination besides my uncle, and I think his is very small.

Los Alamos Science: *How did you feel about the fact that plutonium is used to build bombs?*

Jerry Taylor: It never really bothered me. When scientists first came up with the bomb, there was a lot of dying going on in the war. The scientists, the bomb, they stopped the war, so I think it was a good thing. Plutonium is a dangerous material, and it can make a very dangerous weapon. I hope we won't have to see it used again. There is a lot of good work that goes along with the radiation work. I would love to work at the Lab again. There's a lot of neat stuff going on all the time. It's not boring.

Los Alamos Science: *Jerry, can you describe what it's like to work in a glove box at TA-55?*

Jerry Taylor: At first it's very awkward, it's like you don't have any hands. You keep dropping things. Once you get used to it though, it becomes pretty easy.

Bill Gibson: You certainly don't want to try to set your watch while you're working in the glove box. The gloves are inside the box and are attached to a pair of openings in the walls. You put on the gloves by putting your hands through the walls, so when you work in the box, your hands are always in the gloves. There's a big window in front of you to let you see what you're doing. The glove box is totally enclosed so nothing can escape. Not only that, any ventilation at all is inward since there's a slight negative pressure in the box.

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Jerry Taylor: It was hard at first to manipulate your hands while you're in those heavy gloves, but it soon became pretty easy, and I always enjoyed it. I wish I could have done more of it. It was a good experience except for the accident. After the accident, I wasn't allowed to do that kind of work anymore. The exposure was too big.

Los Alamos Science: *Michael Martinez, you have been working at TA-55 for a long time.*

Michael Martinez: Yes, I came to the Lab in 1980 and worked in the metal production room at TA-55. There you convert an oxide to a fluoride and then to a metal. Like Jerry was saying, it was very interesting when I first went in there. Everything—the pipes, the valves, you name it—it was all interesting. And it was hard to get your hands in the glove box at first. It was hard to do anything inside the glove box with leaded gloves. Once in a while, you would catch yourself grabbing your hand and trying to pull off the gloves. But of course you can't. You're taught how dangerous the material is, and you learn a lot of safety precautions. You know what you can do and what you can't do. It never did scare me; even after the incidents that gave me some exposure, I wasn't scared.

Los Alamos Science: *How did you end up working with plutonium?*

Michael Martinez: A friend of mine who was working with plutonium asked me if I would like to take a similar job. He wanted to know whether I would be scared, and I told him, "No." So I got the job. At first I didn't know much about radioactivity, but I learned as I went along. One October during the first three years of working there, I was pulled out of the plant to work on salt casting and other jobs, because I had already received the exposure that I was allowed for that year. When the next year started, I was allowed to go back into the plant and work with plutonium again. But now, after this last incident, I was told I would never be able to work with plutonium again.

Los Alamos Science: *What did you like about the plutonium work?*

Michael Martinez: I'm not happy about having to stop this work. Plutonium is what made us a free country. I'm proud that I worked with it, and I wish I could continue.

Los Alamos Science: *Do your family and friends share your feelings?*

Michael Martinez: They worry some about the dangers, but I tell them it was just as dangerous when I worked on cars. If I stick my arm in the fan, my arm is going to go. If I get under the

Of course incidents did happen and you dealt with them. If you tore a glove, you changed it. If the window cracked, it had to be changed. And sometimes you would get contaminated.

Safety excercise at TA-55

car and the jacks are not set right, the car is going to fall on me. Working with plutonium is the same. There are a lot of rules you have to obey, so you don't initiate a criticality accident. If you're going to be doing something, you do it safely. If you're not careful, something is bound to happen.

Los Alamos Science: *How frequently were you monitored for contamination?*

Michael Martinez: You're supposed to check yourself with a hand probe every time you pull your hands out of the glove box, and then again as you leave the room, you check your hands and your feet. Finally, before you leave PF4 (the plutonium area of TA-55), there's a monitor, a person, who checks you completely. Most of the time you're clean, but once in a while, you get a couple of clicks. You check your gloves—the surgical gloves that you wear under the big leaded gloves in the glove box. You can't see anything, but you know they're hot, they're contaminated with radioactivity. You call the monitor to see if you should change the gloves or whatever. It's kind of weird because you can't see anything, you can only hear the clicks.

Los Alamos Science: *Harold Archuleta, what was your experience in becoming a plutonium worker?*

Harold Archuleta: I came to work in 1967 at the old DP Site in group CMB-11. That was the metal-fabrication group where castings of various shapes and sizes were produced. I had to be highly trained because the work was totally hands-on. At first, I had to just watch; they wouldn't let me do anything for the longest time. Then I started making ingots. Later, I moved up to rods and then finally to hemi-shells. The hemi-shells had to be perfect. The group relocated to TA-55 in 1978. There I worked as head caster and tech supervisor. I was also responsible for training technicians as well as staff members, young and old. Just as I had been trained, I would always emphasize that safety was the number one priority. Of course incidents did happen, and you dealt with them. If you tore a glove, you changed it. If the window

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cracked, it had to be changed. And sometimes you would get contaminated.

The present facility is different from the old DP site. It's not like a family anymore where everyone cooperated and helped each other out.

Bill Gibson: There's a good reason for the change. When we were at DP Site we were a group of about 50 or 60 people. At TA-55, the group suddenly grew to about 300, and the only people you knew well were the people in your own area.

Los Alamos Science: *Were you proud of your work? Did you enjoy your job?*

Harold Archuleta: Overall, my job experience was a positive one. I enjoyed the research and production. We were in competition with Rocky Flats, and we would always come out ahead.

Accidents with Plutonium

In this part of the discussion the participants were asked to describe the accidents or incidents that led to their plutonium intakes.

Harold Archuleta: My first incident occurred after opening a freezer in the attic at DP West, Room 500. Plutonium was stored in freezers because the cold temperature keeps it from oxidizing. One particular Monday morning, I was given a casting ticket to retrieve plutonium buttons for casting. Upon opening the container, I noticed the buttons were oxidized. I then realized the freezer was not in operation. After reporting the problem, a nose count was taken immediately. A high count was found in both nostrils. Contamination was also found on my gloves. Shortly after this incident, Harold Ide who was in charge of H-1 contamination incidents, informed me that I was required to give fecal samples. I did so for a few months.

The second incident occurred while casting plutonium rods. During the filling of the molds, a slight overflow occurred, causing a sliver to form. While I was unloading the molds, I felt a pin prick on my right middle finger. I immediately stopped and reached over with my left hand and held the neoprene glove bringing my right hand out to the edge of the glove port opening. I called to a monitor who happened to be close by. He checked, and no contamination was found. But at the wound counter, it was found to be contaminated. I was taken to occupational medicine where I was told, "There are two things we can do. We can let you heal over, in which case you'll have a body burden, or we can take you over to the hospital and cut it out." I chose excision. At the hospital they gave me a shot and then they started to cut. I could see the blood run. They checked it with the wound counter, and it was still hot. They cut some more, and they kept cutting until it was below background on the instruments. Then they stitched it, about six or seven stitches on my finger. I was removed from plutonium work while I recuperated.

The third incident involved another nasal intake. I was changing a thermocouple tube in a pressurized furnace. Due to a faulty helium valve, the furnace had not been properly depressurized. Upon removing the thermocouple, some contamination was released. My nose count was found to be very low. I think that what I have in my lungs is a result of the first incident. It is americium that is detected when a lung measurement is taken. [*Weapons grade plutonium has about a forty-year biological (residence in the body) half-life. Americium-241, which is a decay product of plutonium-241, is more easily detected in the lungs than plutonium-239, because it emits higher energy gamma rays.*]

Los Alamos Science: *Have you worried about that over the years?*

Harold Archuleta: I didn't worry until about three or four years ago. I started to get this discomfort in my left side around my pectoral muscles. I didn't think it was the plutonium. We had to lift a furnace that was inside the line, and I grabbed it with my left arm. It was pretty heavy. After that, I started to have a lot of weakness in my left arm. I went to all kinds of doctors. I thought it might be my heart. But the doctors determined that it wasn't my heart, it was the design of the glove boxes. All those years of working there had affected my neck, elbows, and lower back, and something in the fifth vertebrae in my neck was sort of pinching a nerve that would bring this weakness to my pectoral muscles. There's nothing I can do about it.

Los Alamos Science: *Did that explanation satisfy you, or do you still have questions?*

Harold Archuleta: No, I asked the doctors at Lovelace whether the problem could be from the plutonium in my

lungs, and they said no, they don't think it could be that. But when I talk to other people, they all say, "I bet it's the amount of exposure in your lungs." But I don't know—I don't think so.

Los Alamos Science: *Michael Martinez, will you be next?*

Michael Martinez: My first incident was about 1984. There were six of us in the vault getting ready to send a shipment to Rocky Flats. We sent materials in containers that resemble pressure cookers, and we use those units over and over again. This time we removed the bolts and took the lid off, and the stuff inside went airborne. This unit was empty, but it was hot, and we didn't know it. Nothing was marked on the outside to say it was contaminated, but it was. Another person and I, who were right by the container, had the highest nose swipes. That was my first intake.

The second incident was in 1993. We were doing reductions in the induction furnace, and we had just started working with the laser. If I remember correctly, it was right after a three-day weekend. We were doing a laser reduction. When the reduction took off, it sounded kind of funny compared to what we were used to hearing. We checked to see if our vent line inside the glove box was open. We had an argon line hooked up to the laser window, which separates the laser from the reduction chamber. We used the argon to clean the window after the reduction was done. This time we turned on the argon, and it broke or cracked the window. The plutonium that was airborne in the chamber went through the window, and we picked up quite a bit. After that incident, they shut the line down for a while, and I transferred out of TA-55 to the Chemical and Metallurgy Research building.

Los Alamos Science: *What happened after you knew you had an intake? Were you concerned?*

Michael Martinez: I wondered how bad it was. At first, they gave me urine kits and fecal kits once a day, and then once a month. I'm still giving urine samples. Awhile after the incident, they called me to the Health Division, and the doctor gave me the numbers relating to my exposure. And now you've given me another set of numbers.

Harold Archuleta

One particular Monday morning, I was given a casting ticket to retrieve plutonium buttons for casting. Upon opening the container, I noticed the buttons were oxidized. I then realized the freezer was not in operation. After reporting the problem, a nose count was taken immediately.

Los Alamos Science: *How was it having to fill all the bioassay kits? How did you feel bringing all that stuff home? Did your family ask questions?*

Michael Martinez: I never told them. I've never told anybody. I didn't want them to worry.

Jose Gonzales: I've got a long story, because as a monitor, you're always looking for the unknown. At least that was what it was like during my early years at DP Site. My first episode was at the waste-disposal site where they were treating americium in 55-gallon drums. I opened the door, and to my surprise, I could see the americium coming out the door. All I could do was call "Mayday!" and rope the area. Everything in the building was contaminated. The area eventually got cleaned up, but I probably picked up a dose there.

The second place where I might have picked up some dose was in the filter house. It wouldn't have been from inside the filter house, because I was wearing a respirator. But while undressing afterwards, I could have gotten some dose from contaminants that had fallen on my clothing. Another incident was in the electrorefining unit. We used to transfer 350-gram metal buttons in plastic bags. The technician was putting a button in the bag, and we were putting on our respirators to prepare for making the transfer. Suddenly the seams on the plastic bag gave out, and the button rolled on the floor. I held my breath, got a glove, put the button in the glove, and threw it back inside the hood. That was the only thing I could do. If the door had been open, the button probably would have rolled to the airport. Thank God it didn't. There are so many incidents I could relate. They weren't intentional errors. We were just doing things in the best way we could.

I'll tell just one more. It was 1977 on the metal prep line. I was holding a radiation-monitoring instrument close to where a metal reduction was being done. When the pressure surge came during the reduction reaction, a gasket blew on the reduction vessel. At that point in the reduction, the vessel was

Michael Martinez

There were six of us in the vault getting ready to send a shipment to Rocky Flats. We sent materials in containers that resemble pressure cookers, and we use those units over and over again. This time we removed the bolts and took the lid off, and the stuff inside went airborne.

under 2,000 pounds of pressure, so when it blew, it blew the gloves right out of the glove ports and caused the whole room to become contaminated. The only thing I could do was to yell as loud as possible for everyone to evacuate the room. We assembled on the outside, and thank God, everyone was safe. But we picked up a dose. I became a permanent fixture in the In Vivo Lab where gamma-ray lung counts are done. That incident bothered me a bit more than the others. I called my wife to tell her we had an incident and that I wouldn't be home as early as I had said. And sure enough, at ten o'clock it came on the news that there had been an accident at DP Site, and that five people were involved. My wife was concerned about it. But we got it straightened out. We put a safety valve on the pressure cylinder of the vessel so the same thing wouldn't ever happen again.

I had an incident at TA-55 when I was doing a reduction myself. The pressure in the reduction vessel—actually we call it a bomb—was 2,200 pounds per square inch. About 18 minutes into the reduction, four bolts that hold the reduction bomb in place came loose; I yelled for everyone in the room to evacuate. I saw some sparks so I held some wet cheesecloth close to the glove ports to keep the gloves from catching fire and waited to see if the reduction would stay inside the vessel. We didn't have time to go for respirators. Thank God we were able to keep everything contained inside the glove box. We had a 4-inch opening at the bottom of the box, but the negative pressure pulled everything back into the box and saved us.

All these incidents happened, and still, I didn't want to quit my job. I have pride in my work. When I felt kind of bad, I talked to my family. I have two healthy children and two grandchildren, and they understand. There were a few times when I had to leave my underwear at work, and my son would say, "Mom, daddy's hot again!" I'm so grateful that I can joke about those things today. At the time it happened, it was something serious. Today, I feel better physically, mentally, and spiritually than I ever have in my life. I'm still working at the Lab, helping to write a Lab report on the decommissioning of the metal prep line. I'm really proud to be doing that.

Art Beaumont: In about 1964, some 13 or 14 years after I came to DP West and began to work with plutonium-239, I started to work with plutonium-238. It was for the artificial-heart program. We had just produced the first plutonium-238 metal in a regular glove box, and I was up on the ladder to open the top of the furnace. I reached in with tweezers, pulled out a 25-gram button of plutonium-238, and then sparks started to fly all over the place. The plutonium-238 was oxidizing so rapidly because the atmosphere in the glove box was just the normal atmosphere. I handed the button to Larry Mullen who was working right next to me, and he dropped it, and then somebody else dropped it, and then finally we got it back into the furnace. That taught us that we had to work in an inert hood, one without any oxygen or nitrogen. But I don't believe I got any dose at that time.

Jose Gonzalez

All these incidents happened, and still, I didn't want to quit my job. I have pride in my work. When I felt kind of bad, I talked to my family. I have two healthy children and two grandchildren, and they understand. There were a few times when I had to leave my underwear at work, and my son would say, "Mom, daddy's hot again!"I'm so grateful that I can joke about those things today.

There was an incident, though, on another line in a room called 401. It was about 1972, and I was working in a set of gloves right next to another fellow. All of a sudden his glove ripped off from the glove port. He had this whole glove on his arm, and we were both looking into the glove box through the open port where the glove had been. We didn't hardly breathe. We yelled for our respirators, and the monitor came quickly and put them on our faces. That's the one incident in which I believe I could have gotten a dose, because I wasn't wearing a respirator. The whole room got contaminated. It took several weeks to clean it up.

I was told I couldn't work with plutonium in August 1973, about 23 or 24 years after I started, but I was never informed about any doses. I would send in urine samples, but they never gave me any of the results. I worked full-time at the Lab until 1985 when I retired, and I came back to work part-time as a Lab Associate until last year.

Ed Hammel: I have a suspicion that what Art is saying is not that unusual. Probably, there were a lot of people who were not informed of their internal exposures because they were considered too insignificant. And I suspect that the reason we are having this discussion today is because now it has suddenly become significant. The culture has changed, and the whole country is worrying about these things. Everybody is trying to play catch up.

Art Beaumont: If I was a person with a body burden, it would seem to me the Lab would be interested in it. At one point after I moved to DP East, I questioned Bill Maraman about why they weren't asking for urine samples. After a big discussion, it turned out that a secretary had taken me off the list.

Jim Ledbetter: The only incident I recall in which I picked up an exposure was in 1971 during the disassembly of the plutonium-238 Jupiter heat source. We were working in a hot cell with three-foot shielding. The atmosphere inside the containment was argon-purged and was maintained at a very low oxygen content, less than fifty parts per million.

Art Beaumont

I was working in a set of gloves right next to another fellow. All of a sudden . . . he had this whole glove on his arm, and we were both looking into the glove box through the open port where the glove had been. We didn't hardly breathe. We yelled for our respirators, and the monitor came quickly and put them on our faces.

The first disassembly was 100 per cent successful. We disassembled the source and welded the plutonium-238 metal into tantalum cans. Then we began preparing for the second source. By then, we'd gathered a lot of attention, and some of the renowned people involved in the heat-source program were present at the site for the second disassembly. Harold Agnew was there, Dick Baker was there, and so were the principal investigators, Stan Bronitz and Bob Mulford.

Once you start a disassembly, you can't stop until you have all the parts disassembled and packaged no matter how long it takes. Sometime late in the evening, odd things began to happen. For example, during the machining, we would get rings of fire around the plutonium capsule. We checked the oxygen level. It was low enough that oxidation shouldn't have been happening. We kept working, and we kept getting spontaneous bursts of flame. Somebody said, "We've got to switch to helium." So we hooked a helium trailer to the manifold and began purging the primary containment with helium. And then more strange things began to happen. The gas boots collapsed around the manipulators and wouldn't stay expanded.

Bob Mulford and I decided to go into the hot cell to do the welding. We were right next to the primary containment, and I was doing the welding. After a few minutes, a *cam* (continuous air monitor) alarm went off outside, within six feet of us. We called in the monitor, and he checked the cam. "I think we got a blip in power. There's nothing back here." So we went back to work. Shortly after that, the cam went off again. We decided to stop and check things out. Several people came into the hot cell, including our Division Leader, Dick Baker. We found a minor leak around a vacuum connection, repaired the leak, and went back to work. Finally, the alarm went off again, and Bob Mulford and I decided we shouldn't take a chance, so we put on our face masks. We were hurrying to weld the capsules and put them away. And while we worked, I could hear the floor monitor outside the three-foot wall starting to pick up a signal. I could hear it clicking away, and I recall saying, "Boy, something has

got to be wrong here!" The clicking got worse and worse, and we kept working faster and faster. Inside the hot cell where we were working, we weren't picking up anything on the radiation monitors. But when we looked down the corridor of the hot cell to the operating area outside, the personnel that had been in the operating area had taken off their clothes and were walking around in undershorts. They were trying to figure out what was wrong, and we were frantically trying to weld the plutonium containers.

As it turned out, the helium had caused a positive pressure in the boot around the manipulator so that the airborne plutonium was being sucked out through a puncture in the boot into the operating area outside. The people out there, including the TRW person who was asleep on the bench, received exposures. Ironically, we were the lucky ones who picked up the least exposure, because we were working inside the hot cell. It took about ten weeks of intensive decontamination to clean up the whole facility. We worked as a team, including Dick Baker. Even the group leaders and scientists were in coveralls. All of us were examined pretty carefully for internal contamination. We gave urine samples, and they put us through the whole-body counter a number of times. That's the only time I have ever received an uptake of plutonium, though I have worked with it in the form of breeder-reactor fuels prior to that experience and for many years after.

Jerry Taylor: I remember my accident to the day. It was April 1981, on Good Friday. I had been working on a process in which I had ended up with two one-liter bottles of fluid. When I came in on Good Friday, the bottles were collapsed. I decided to empty them before they collapsed all the way and made a mess over everything. I found a sharp pointed knife in the glove box, which, I learned later, should never have been there. I picked up the knife to vent the lids of the bottles, and as I made the puncture, the knife went through the lid like a piece of hot butter and right through my left glove into my left hand. I pulled my hands out of the glove box and told the supervisor, "I just got a puncture wound." We went to the decontamination sink and sat

James Ledbetter

By then we'd gathered a lot of attention, and some of the renowned people involved in the heat-source program were present at the site for the second disassembly. Harold Agnew was there, Dick Baker was there, and so were the principal investigators, Stan Bronitz and Bob Mulford.

there for about 45 minutes trying to scrub off the surface contamination. The wound was still hot, so we went over to H-2, Occupational Medicine, and they did the first excision. There were a lot of celebrities there, Dr. Grier and Dr. Voelz. I started using the chelating agents that day. They're supposed to help remove the plutonium. About a month later, I had to get another excision.

Los Alamos Science: *Were you aware at the time it happened that you had had a serious accident?*

Jerry Taylor: Yes. I knew what I was working with. But I didn't know how much I had received internally. Most everybody here received their doses by inhalation. I received mine internally right then and there. It was just like playing with a pocket knife. Usually you poke a hole in your hand, and you don't think much about it. There was plutonium on this knife. It's funny to think about. At first, I didn't think the dose was going to be that high. I hadn't been worrying about working with the material. But right after the accident, I started wondering how much of a dose I'd gotten. That first day the count on my wound was very high, and that's when I started worrying. It was very scary to me.

Los Alamos Science: *How did they explain the chelation process to you?*

Jerry Taylor: They just said that plutonium and americium are bone seekers, so they would give me DTPA [the chelating agent] either with zinc or calcium. These metals would more or less trade places with the plutonium, and the plutonium would come out in my urine. They gave me a shot of this chelating agent three times a week for almost a month. Then we went to an inhalation method because I was starting to look like a junkie with so many holes in my arms. Dr. Voelz gave me his card and said to show it to the police and have them call him at home if they ever stopped me and looked at my arms and thought I was a junkie. He said he'd get me out of trouble.

As far as my family went, they were pretty frightened. Even my best friend wouldn't come close to me for a couple of months, wouldn't even shake my hand. Actually, we were the type of

friends that would give each other a tug or a hug, but he was frightened of what I had gotten in me and what I still had in my hand. So he would talk to me at a distance. That really bothered me psychologically. But it's not like that anymore. For about a month, I went around wearing a surgeon's glove to try to sweat out the surface contamination.

I was only off work for a couple of days, and when I went back, I worked in the front office. They had to tell me to stay out of the hallway and away from the doors to the vault because I kept setting off the alarm just by walking near them. That first year was very long. I had a lot of chelating agents. A lot of urine kits. I saw a lot of numbers. Irene did a lot of whole-body counts.

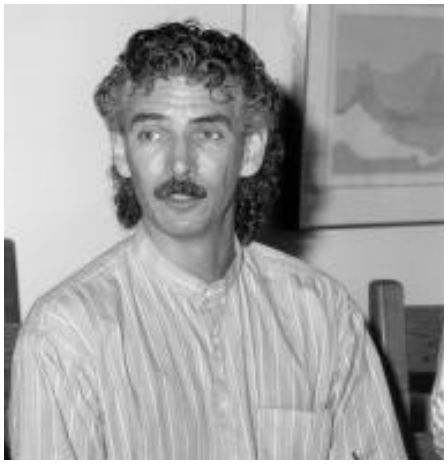
Los Alamos Science: *Did the chelating agents do any good?*

Jerry Taylor: Yes. From the numbers I remember seeing, my body burden went down by 90 per cent. That's including the amount they took out in the two excisions. The chelation did get to me. It made me kind of shaky and upset my stomach. I don't know if it was just the stress or the calcium in the chelating agent. Even to this day, if I take a multivitamin with calcium, I get a little shaky for an hour or so. I seem to be overloaded with calcium, but the numbers show that it worked real good.

I still have a fairly substantial contamination, but I don't think about it much—unless something like this meeting brings it up. It happened fourteen years ago. I've put it to the back of my mind. But when I first moved to Albuquerque eight years ago, it did concern me. My wife had gotten pregnant, and I worried that the radiation in me might have affected the baby. That was a pretty stressful time. My son was born, and he was fine. It was a concern then. But I don't think about it much anymore. I go on with my life, and I've been feeling healthy.

Los Alamos Science: *Do you think the Lab took good care of you since the time of the accident?*

Jerry Taylor: I think they could improve. During the first year they watched me very carefully, and it felt like almost too much with all the wound counting and the urine analysis. But after that, I always wanted to hear more. I wanted to know what had happened to other people who were contaminated. I wanted to know if any new studies had come out. I was hoping that if a similar thing did happen to someone else, they could use my experience to help that person. They did keep track of me for the five years I was at the Lab. The accident happened only six months after I started at the Lab. After I left, I didn't hear anything unless I called Dr. Voelz and asked for another body count. And then they would do it. I appreciate that, but I think they should be contacting me annually at least. The fact that I haven't been monitored regularly is one of the reasons I decided not to volunteer for the Transuranium Registry.



Jerry Taylor

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Los Alamos Science: *Would you explain what the registry is all about?*

Jerry Taylor: It's a way to donate your body for study following your death so they can see what actually happened to the intakes of plutonium or uranium or other nuclear materials that you had. [*For a discussion of the work done on autopsy tissues see "A True Measure of Plutonium Exposure—The Human Tissue Analysis Program at Los Alamos."*] I like the idea that they are doing those studies, but I feel I've already given enough of my body.

Los Alamos Science: *Do you have full use of your hand?*

Jerry Taylor: Pretty much. I can't spread it as far as the other guy. If I catch a baseball, it hurts near the area of the wound, because they took out all the fatty tissue around it. But there's nothing really wrong with it. I have full use of my hand.

Bill Gibson: My experiences with contamination had less to do with particular accidents and more to do with the very crude conditions under which we worked. We worked essentially in the open, and as a result, we were constantly exposed. Those old Wilson respirators just didn't do us much good. We kept working with larger and larger quantities of plutonium. As I said earlier, when I first came, we were working with the first 1-gram quantity ever made, but then we

worked with 8 grams, then 16, then 64, and on up to kilogram amounts.

Wright Langham and Louis Hempelmann kept us pretty well posted on our exposures. They were taking urine counts by 1945, and we saw the counts continue to be positive. When we started working with peroxide precipitations, things got worse. You know, that stuff bubbles, and we were working in the open. There was a fine mist of plutonium nitrate in the air all the time. We thought we were protected by our respirators, but we weren't, and boy, our urine counts just zoomed. It was about that time that I had an incident. I was shoving a piece of rubber tubing onto a side arm of a filter flask when the arm broke and a piece of glass got jammed into my thumb. As I pulled the glass out I could see a little trace of green under the skin. Green was the color of the plutonium hydroxide that was in the flask, so I knew I was contaminated. I told my supervisor immediately, and they rushed me over to the hospital and excised the wound. That was the only dramatic incident that ever happened to me, but I don't know that it added very greatly to my overall count. It was the crude conditions under which we worked—horrible by today's standards although they looked very reasonable to us at the time—that were responsible for my high count. I went over the allowed limit, and I wasn't the only one; there were three or four of us at the time who had to stop doing plutonium work because of excessive urine counts.

Most of us were in the army, and a soldier, you know, is expendable. But Wright Langham didn't think so. He expressed considerable concern over our rapidly rising urine counts. There were about three or four of us who went over the so-called limit, and we were kicked out of the laboratory. Wright and Louis were very concerned. Counts were rising so rapidly that a couple of us were measured as having about three times the limit, but those measurements may have been false.

Los Alamos Science: *Do you remember what the limit was at that time?*

Bill Gibson: As I recall, it was 7 counts per minute in a 24-hour urine sample. Supposedly, that rate meant we were carrying 1 microgram of plutonium. How accurate that is I have no idea. All I know is that today I'm healthy. The past is history. What happened, happened, that's all.

Bill Gibson

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Los Alamos Science: *At that time, in 1945, no one knew exactly what the count meant. The calibration that was needed to relate the counts in your urine sample to the amount of plutonium in your body had not been done yet. In fact, Langham's and Hempelmann's rationale for the human injection experiments was to obtain the data for that calibration. They were very anxious to have a valid basis for interpreting those counts and taking people off the job at the appropriate time.*

What do you think of the assertion that having plutonium in your body prevents colds?

Bill Gibson: I don't know about that. It's true that I've only had about one cold in the last twenty or thirty years, but it may not have anything to do with the plutonium. The interesting thing—which Dr. Voelz knows all about—is that the members of the UPPU club have better health and greater longevity than the national average, significantly greater. In other words, plutonium exposure doesn't seem to have hurt us, and if anything, it might have helped us a little.

Los Alamos Science: *How about you, Ed? What was your experience?*

Ed Hammel: I mentioned earlier that my section was responsible for remelting, alloying, and then casting plutonium. Essentially all the plutonium at Los Alamos, both recycled and original, passed through our section from the time we had gram quantities to the end of the war. We used open hoods when we had to; we used wooden dry boxes when we had to. But as far as I can remember, during that period, we didn't have any incidents of punctures or anything like that in our group. I don't think any of my people managed to be in the UPPU club.

Los Alamos Science: *But you could have been. Do you remember the circumstances when you received an intake?*

Ed Hammel: Not really. There was no specific instance. I knew I was

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A Recent Incident

Several weeks after the roundtable, Johnny Montoya was involved in an accident at TA-55. At our request he has been gracious enough to share his personal feelings and emotions connected with that accident. His words show the human side—separate from the technical risk, the media-hype, the political agendas, and the operational tasks. That is the side we, the health protection professionals, must always be aware of and must address in an accident—care of the mind, the emotions, and the body of the affected individual. Bill Inkret

I have worked at TA-55 for 14 years doing various aspects of plutonium processing. My accident occurred late in April 1995. I've always thought of plutonium as kind of a friend, but I'd placed boundaries on that friendship—as long as we stayed on our respective sides, we'd get along just fine. When the accident occurred, my first reaction was extreme anger. Our borders had been crossed, and I felt outraged and betrayed. I was also very scared when the busy activity of medical personnel started unfolding around me.

Johnny Montoya

Nose swipes indicated that I'd inhaled plutonium. A chest count, taken at the In Vivo lab, indicated that it was substantial. It was frightening to hear I might have received a large dose. Dr. Lowrey suggested a treatment called chelation that would help if my intake was extensive. One of the staff explained the process and how it would enhance removal of plutonium from my body. I recalled my father telling me about chelation agents at his feed store. I was also told that prompt action was vital, and based on the information, I decided to go ahead. I remember asking Gina Rey about her thoughts. She lifted my spirits immeasurably by saying, "You're doing the smart thing—if you have what the numbers are showing, you're better off chelating." The procedure was explained in great detail, and shortly thereafter, I was prepped.

I'm sure I was in shock because several attempts to get an IV into one of my veins failed—the veins in my arm had collapsed. It was a nightmare, but Gina remained at my side, telling me to be strong and to ask the Lord for help, and her faith gave me faith. Without Gina, I'm not sure I could have held together as well as I did. Everyone did a good job, and the chelation went smoothly.

Still, I was *totally* freaked out, and the most difficult part was about to begin: I had to tell my family. How do you explain this to people who have never worked with plutonium? People who love you and are concerned for your welfare. That was when Dr. Inkret gave me courage and support. I asked him, "How do I tell my wife and children?" He made suggestions, but he also gave me his home phone number in case I needed to talk. Well, believe me, I took *full* advantage of his generous offer. He explained that the emotional stress would do me *more* harm if I wasn't careful how I dealt with it. And he said, "In the long hours and days to come, I'll do my best to explain it all to you. Don't worry, I'll be with you every step of the way." Believe me, he was. But that first night was the hardest of my life; I was living a nightmare.

It was obvious the next morning that the anger hadn't left me. Driving up for another chest count at 7:00 A.M., I approached one of the trucks that bring plutonium shipments to TA-55. Again, I felt the intense anger of being betrayed by someone I'd worked with for the last 14 years. When I got to the lab, Dr. Inkret was waiting, and I described my emotional state as I'd approached that truck.

I showered and entered the counting chamber. It was the longest 30 minutes of my life. When I came out, I saw Dr. Inkret, Bruce Matthews, Tim George, Dave Post, and others. They were jubilant. I knew instantly they had good news. I was on top of the world. Dr. Inkret called his colleague, Dr. Smith, to explain the results. I got on to express my feelings of jubilation. Dr. Smith said, "Before you get too happy, let me say, we have a good result along with the initial bad one. Let's do the count again to see which it really is." Boy, it was as if someone had hit me over the head with a bat. I was at square one again.

To make a long story short, I had several more chest counts in the days to come, which were all favorable. I was then told that the true test would be the fecal and urine assays. I'd need to wait several days for those. As you can imagine, I went though hell. Finally, they determined that the dose was nowhere close to what had first been thought. The rest of the testing period has been a long wait. I've spent numerous hours educating myself and gaining valuable information on the implications of my intake. I now understand better what it means to my body. But most important, the anger is gone. More than likely, the positive way things turned out has had a lot to with this. My tests have all been low compared to what was first believed.

I hope my experience can, in some way, do some good. Perhaps I can help someone through similar circumstances, though I hope I will never have to. ■

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carrying some plutonium, but it wasn't enough to worry about.

Los Alamos Science: *OK, we're back to the beginning, Ted and Nick, and we want to hear about your intakes.*

We called Wright Langham, and Hempelmann said, "Hey, do you want to excise this thing and get it out of here?" We went to the hospital, and they thought they had cut it all out, but they hadn't—I still have some plutonium in one finger.

Ted Magel: Within weeks of making the first 1-gram button, I had an incident in which I was working in a dry box scraping the slag from another of those 1-gram buttons, and the needle I was using slipped, went through the rubber glove, and embedded in my finger. Nick would remember that incident. I could see some black stuff in my finger. OK, I thought, that's plutonium oxide. We called Wright Langham, and Hempelmann said, "Hey, do you want to excise this thing and get it out of here?" We went to the hospital, and they thought they had cut it all out, but they hadn't—I still have some plutonium in one finger. They began taking urine samples in 1945, which was when the procedure for measuring excreted plutonium was first available.

Sometime between March and July of 1944, they developed a method of monitoring how much plutonium we were getting from breathing. The nose counts were the primary method for that. This girl would come around and swab our nostrils.

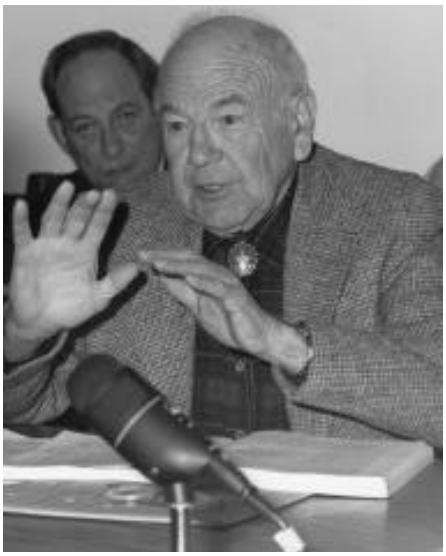
One time I was getting ready to do a reduction, and I decided to take a last quick look inside this little tiny crucible to make sure I had put all the ingredients into it. I bent down close to it and lifted the lid without bothering to put on my respirator. Apparently I got a very high nose count from doing that. But the big dose was from the needle stick. Dr. Voelz told me recently that I have the fifth highest dose of the 26 members in the UPPU club.

Los Alamos Science: *Were you worried about having plutonium in you?*

Ted Magel: I didn't get too excited or worried about it. I'm not super patriotic or anything like that, but it was war, and we had a job to do. Nick took the same stand, and we continued to work together to get the buttons made.

Nick Dallas: The day Ted got his high nose count, I got one too, but it wasn't as high as Ted's because I was wearing my respirator. Mackenzie would do nose counts twice a day, and she would give us calcium phosphate pills to enrich the calcium in our bones.

Ted Magel: By then, they knew from animal studies that plutonium goes to the bone. They thought that if we built up our calcium content, there would be less reason for plutonium to want to reside there. They had to develop health procedures from scratch, because there was no plutonium before that time and, of course, no experience working with it. Nick and I were there, so we were the guinea pigs for trying out new health procedures. We are also two of the original 26 members of the UPPU club. We've been monitored by Los Alamos since that time for any damage that plutonium might cause. Every year, I would send them a gallon of urine from a 24-hour period so they could measure the plutonium content.



Ed Hammel

Essentially all the plutonium at Los Alamos, both recycled and original, passed through our section from the time we had gram quantities to the end of the war. . . . As far as I can remember, during that period we didn't have any incidents of punctures or anything like that in our group. I don't think any of my people managed to be in the UPPU club.

Follow-up Studies, Expert Opinions, and Future Prospects

Los Alamos Science: *This is a good time to switch the focus from the accidents to the questions and concerns you may have about possible health effects and about the way the Laboratory has treated you over the years. We have several experts here to answer your questions. They're probably all familiar to you. First is Dr. George Voelz, who was the head of the Health Division at the Laboratory for many years and is a recognized leader in the field of plutonium epidemiology. Next is Don Petersen, who was trained as a pharmacologist and served as George's deputy for many years. Next to Don is Mario Schillaci, a physicist who recently joined the radiation dosimetry group. And of course, there are Bill Inkret and Guthrie Miller, who organized this meeting and prepared the dose estimates you received before coming here today.*

Ted Magel: I can't speak for all UPPU members, but in 1971, they decided to bring all 26 of us back to Los Alamos to do complete physical examinations and to get whole-body counts, urine counts, x rays, and blood work. They were using the urine data to measure the long-time excretion rate of plutonium compared to the amount retained. They're still collecting basic chemical and medical information on the rate at which the body rids itself of plutonium once there is an uptake.

They've also worked very hard to measure the amount in our lungs and to monitor our lung performance. They were looking for any effect that might confirm or dispute the news media claim that one speck of plutonium will kill the population of the Earth. The media keeps writing that story over and over to the point that I get very very mad. I've been after George Voelz to write an article and stop this nonsense. Sure, it's a hazardous material, but there are at least twenty-six of us who've been carrying it around for decades, and eighteen of us who, after fifty years, are still healthy and just getting older.

Nick Dallas: I think the main medical worry after carrying this stuff in you for many years is that you may get bone cancer.

Ted Magel: Nick, tell them about your lung problem and what they saw under the microscope.

Nick Dallas: In about 1970, a lump was discovered in the lower third of my right lung, and I went to the City Hospital at Johns Hopkins University to have it removed. Dr. Hempelmann, who was then at the medical center at Rochester, came down especially for the operation. The biopsy showed that the tumor was nonmalignant. It was what they call a hamartoma, [*hamartoma is a congenital nonmalignant collection of various cell types*]. The medical people claim that those types of tumors can grow on any of your internal organs and are not caused by radiation. Dr. Hempelmann arranged to have the lung tissue packed in dry ice and mailed to Los Alamos for analysis. He also sent along a bone sample, a piece of my rib that they had removed during the operation, and also a lymph node. I believe they wanted to see how much plutonium I really had in me and to check that against the amount they'd predicted on the basis of my urine counts.

Wright Langham was the one at Los Alamos directing the analysis. He took a thin section of the lymph node and wrapped it in photographic film to make an autoradiograph. Sure enough, you could see a few stars on the film. Those stars were evidence of radiation—they're the alpha tracks emanating from each small particle of plutonium, and they form what looks like a star at the spot where each particle is located [*see autoradiograph, page 152*].

The Los Alamos medical people have collected certain organs from other people, like myself, who were operated on and analyzed them to determine the fraction of plutonium that goes to the liver, the lungs, the bone, and so forth. That information allows them to predict strictly from the urine samples how much radioactive material you have in other parts of your body.

George Voelz: Los Alamos has sponsored a tissue-analysis program since 1959 to study the deposition of plutonium and other actinide elements in the body. So your samples became part of that study.

Nick Dallas: You know, I wasn't told until after the operation that they'd taken extra tissue samples, and I was quite upset at first. But Ted calmed me down, and now I'm kind of proud that I've contributed to a greater understanding of how plutonium distributes itself once it gets into the body. But it was upsetting that they didn't ask for my consent ahead of time.

Ted Magel: That reminds me of something. A long time ago, Hempelmann and Voelz gave me a consent form to fill out and sign that gives them permission to do this kind of analysis on my organs after I die. I'm in favor of it, but I haven't signed the form yet because my wife is still not sure she wants it to happen. Nick, did you sign yet?

Nick Dallas: To tell you the truth, my wife doesn't particularly care for that either, and since I've already given some of my lung tissue, some of my bone, and my lymph node, I think they've got enough data from me.

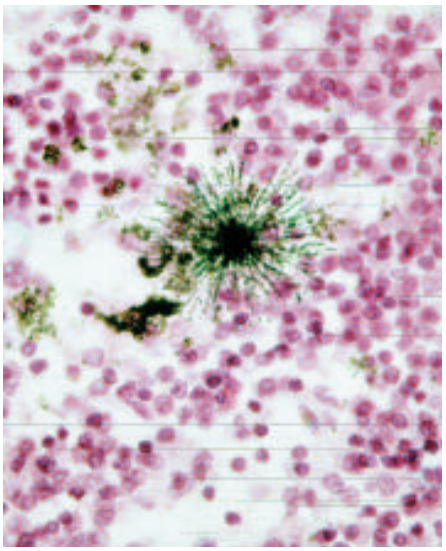
Los Alamos Science: *Ted, have you had any symptoms associated with your body burden?*

Ted Magel: Not that I'm aware of. I'm in very good health, and I've fathered six healthy children, three boys and three girls.

Nick Dallas: And I've had four healthy girls.

Los Alamos Science: *How about you, Bill?*

Bill Gibson: I've lived fifty years in good health, and I have two healthy children. I'm 74 now, and I don't see any reason that I shouldn't get to 84 or 94. I don't really have any concerns about the plutonium in me.



The image is an autoradiograph of a tracheobroncial lymph node from a former worker at the Laboratory. It shows an alpha track radiating in a typical star pattern from tiny alpha-active clumps of material.

Los Alamos Science: *Well, Bill, Ted, and Nick, all members of the UPPU club, seem sanguine about their health prospects. But maybe George Voelz, our resident expert on the epidemiology of plutonium workers, would like to tell us what the data says. George?*

George Voelz: Let me begin with a few very simple facts. Each one of us in this room, without considering the possible effects of occupational exposures, has a one-in-three chance of getting cancer in our lifetime. And we each have a one-in-five, or 20-per-cent, chance that we'll die from cancer. That means of the 21 people in this room, 7 of us will probably get cancer, and 4 of us will probably die of cancer.

Now if your occupational exposure is within the limits set by the Department of Energy, or even if your exposure is well above those limits, your increased risk of getting cancer is not so very great compared to this basic rate. The problem is that if you do get cancer you begin to wonder, "Did I get it from the radiation exposure?" And there's no way to answer that question because there's no way to tell whether radiation was the cause. As a physician responsible for the health of radiation workers, that bothers me a great deal.

Another thing that bothers me is our past failures in communication. Art Beaumont spoke about that earlier. The medical people were doing a lot of worrying and studying and thinking behind the scenes, but we probably didn't share enough of our thinking with the workers who were getting exposed. We had a particularly hard time monitoring inhalation exposures, because once plutonium gets in the lung, it may be anywhere from 6 months to several years before any of that material migrates to other parts of the body and shows up in the urine. In some autopsies, we've seen that 30 or 40 years after the exposure, 75 per cent of the inhaled plutonium is still in the lung.

It's similar for Jim Ledbetter's accident. His urine count didn't show anything until several months after the inhalation, and then the counts rose for a period of 3 to 5 years as the material gradually got deposited in other parts of the body and was excreted in proportion to the amount deposited. We didn't communicate very well with either Art or Jim, and I'd like to apologize for that.

I think we did much better with the members of the UPPU club. Those were the people who had unusually high exposures in the old D Building. Wright Langham started keeping track of those folks in about 1948 and 1949. The first official examinations were done by physicians in the areas where they were living in about 1952. It's been about fifty years since most of them had their major exposures in 1945, so this is a sort of golden anniversary for them.

As Ted alluded to earlier, they've fared pretty well as a group. Of the original 26, only 7 have died, and the last death was in 1990. One was a lung-cancer death, and two died of other causes but had lung cancer at the time of death. All three were heavy smokers. In fact, 17 of the original 26 were smokers at the time they worked in D Building. Smoking was a very social activity during World War II. The military offered free cigarettes, and if you turned someone down when they offered you a cigarette, it was almost taken as an insult.

In any case, there were the three deaths involving cancer, which is consistent with the national cancer mortality rate for a group of this size and age. Then there were three deaths due to heart disease and one due to a car accident. According to the national mortality rate, one would have expected 16 deaths in this group by this time, so the mortality rate for the group is about 50 per cent lower than the national average. That's due to good lifestyle more than anything else. People who are well-behaved, predictable, and responsible generally live longer than the average, and those are the characteristics selected for in plutonium workers.

We compared the mortality rate of the twenty-six UPPU Club members with the rate of unexposed Los Alamos workers from the same period. This comparison eliminates the so-called healthy-worker effect, the fact that the employed population has a lower frequency of disability and disease than does the general population. The risk ratio for all causes of death was 0.60 and for deaths from all cancers was 0.82. A risk ratio of less than 1.0 indicates the risk of death in the exposed group is less than in the unexposed. Because of the small number of people in the exposed group, even these low risk ratios were not statistically significant. Nevertheless, it is of some considerable comfort that they are low.

We recently published a study of all the males who have been employed at the Los Alamos Laboratory during the period from 1943 through 1977. That is some 15,000 people. The important finding from the standpoint of radiation exposure is that we did not find any increase in the rate of leukemia or other blood-cell cancers that tend to increase with increasing exposure to radiation.

George Voelz

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We did a trend analysis that showed the rate of three cancers (esophagus, brain, and Hodgkin's disease) correlated statistically with increasing exposures to doses of external radiation. These particular cancers, however, have not been known to be caused by low-dose radiation in other studies. This inconsistency, plus the absence of excess leukemias, made us conclude that the significance of the observed findings was indeterminate. We also compared cancer rates in workers exposed to plutonium with those in unexposed workers. There were no statistically significant elevations of cancers in the plutonium-exposed workers.

So far, we have not seen any significant health effects from plutonium, but that doesn't mean that plutonium isn't very hazardous. It is. But we've taken great care from the beginning to operate with conservative limits on the permissible body burden for plutonium workers, and those limits are not special for plutonium but rather are equivalent to the occupational limits placed on all types of radiation exposure.

Los Alamos Science: *George, can you explain what that limit is in a way that everyone will understand?*

George Voelz: I used to be able to explain the limit quite easily, because it was based on the amount of plutonium you had retained internally. That amount had a definite activity, or gave rise to a definite number of alpha particles per second. For many years, the maximum permissible body burden for plutonium was an activity of 40 nanocuries, which corresponds to 1,480 disintegrations per second. That body burden by weight is 0.65 micrograms.

The health-physics community has now gone to another system for computing doses. In the new system, all doses are given in rem, which is related to the energy deposited by the radiation and the effectiveness of the type of radiation at causing biological damage. Now you

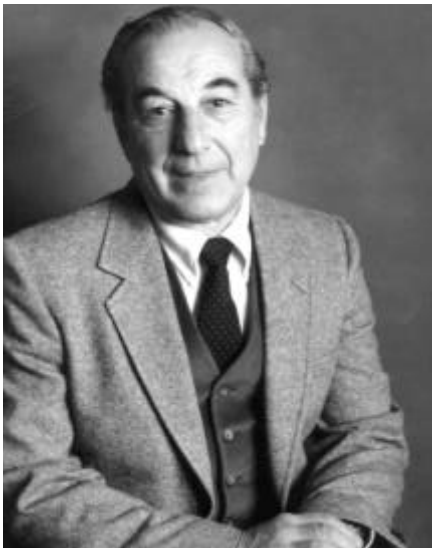
can add external doses and internal doses to come up with the total dose without doing any conversions along the way.

The complication with the new system is that we are computing committed doses. That computation is simple for external doses—whatever exposure you received is the committed dose because that's all the dose you will get from that source. But for internal exposures, the committed dose is much more complicated. For every additional amount of material that you retain in your body in a particular year, the health physicists compute the dose you will receive from that material over the next 50 years. That 50-year total is called the committed dose, and it is added to your recorded dose in the year that the material is deposited in the body. That means that if you retain, say, one additional nanocurie [*one billionth of a curie or about 16 billionths of a gram of plutonium-239*] in a period of less than a year (which gives you a yearly dose of about a tenth of a rem), you will be taken off the job because your committed dose increased by about 5 rem, the maximum allowable dose increase per year. In terms of risk, this procedure equates the health risk from a 50-year internal exposure to a nanocurie of plutonium with the health risk from a 5-rem, external, whole-body exposure to x rays or gamma rays accumulated over one year.

Jerry Taylor: I used to understand the numbers when they were expressed in terms of body burdens. Now that they've changed the system, I'm really confused, and it makes me wonder whether they are telling me everything.

Los Alamos Science: *Jerry may be particularly concerned because he has the highest dose in this group. George, perhaps you could tell us whether you have ever seen a direct effect of plutonium exposure?*

George Voelz: The only thing we've seen is one case of a bone tumor in the UPPU group. Statistically we can't say that the tumor was due to the plutonium exposure, but it's certainly suspicious. That's the kind of tumor we see resulting from animal exposure to higher amounts of plutonium. But occupational exposures are kept so low in the United States that I don't expect we will be able to see any extra risk associated with plutonium exposure. We are beginning to see some things coming out of the Russian experience. They've had rather poor working conditions for a long time, the equivalent of fifty years of D Building, whereas D Building lasted only a little over a year in this country. There are Russian plutonium workers with lung disease, breathing problems, fibrosis, and so on, the kinds of things we've never seen here. So the Russian experience is likely to give us some definitive data on which to base our risk estimates.



Nick Dallas

You know, I wasn't told until after the operation that they'd taken extra tissue samples, and I was quite upset at first. But Ted calmed me down, and now I'm kind of proud that I've contributed to a greater understanding of how plutonium distributes itself once it gets into the body.

Los Alamos Science: *What have you learned from monitoring the UPPU club members over the years?*

George Voelz: It's been pretty interesting to watch. We've seen their plutonium levels go down to about half of the original levels over those fifty years. Up until about 20 years ago, it was thought that very little of the plutonium would come out of the body. We thought the bone half-time (the time for the amount of plutonium in the bone to be reduced in half) was 100 years, but now we believe the half-time is 50 years. We thought the liver half-time was 50 years, and now we believe that it's only 20 years. By monitoring the UPPU members, we've learned that plutonium moves out faster than we had expected.

Jerry Taylor: I've been wondering why people like myself who had a lot more exposure than the UPPU guys are not being monitored.

George Voelz: There is no simple answer to that question, Jerry. The UPPU Club study was set up in the late 1940s and early 1950s when knowledge about the plutonium dosimetry and health risks was very limited. Dr. Louis Hempelmann and Wright Langham thought it was essential to follow these men, most of whom had left Los Alamos after the war. They decided it was a good thing to do, and it was done. There were no proposals for approval by agencies, no human-study review boards, and no funding problems in those days. By 1974, other studies were started that included the more highly exposed persons to plutonium.

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Laboratory Initiates New Voluntary Plutonium Monitoring

Roundtable participants Jerry Taylor and Art Beaumont voiced concern that several groups of plutonium workers with significant depositions were being followed by epidemiology studies. However, Jerry and Art were not being followed even though they both have depositions as large or larger than many of the persons in the study groups. The reason they were not included is simple, although not necessarily acceptable. Two groups are being followed at Los Alamos to compare their morbidity and mortality to unexposed populations, and those groups were identified before Jerry Taylor's accident occurred and Art's deposition was identified. Following single individuals would not yield significant information for an epidemiology study.

Jerry Taylor is being measured at the Los Alamos In Vivo Measurements Laboratory for the presence of various radioisotopes. The device, part of which is being placed over his chest, has four separate detectors that work together to measure the energies of the photons being emitted by radioactive materials. In this way, the staff are able to identify the type and amount of the plutonium, uranium, americium-241, and a wide range of fission products that may be present in the person's chest, liver, or other organs. A whole-body assessment can be made as well. Such information will help workers, past and present, understand the type and level of the exposures they have experienced while working with radioactive materials at the Laboratory.

However, the question raised by Jerry and Art brings into focus the most important aspect of monitoring for plutonium (or any other toxin)—letting the individual understand their own risks so they can make personal decisions about the acceptability of those risks. The single most important theme of the Human Studies Project is that the individual has a right to know what is happening to his or her body, has a right to judge the acceptability of any workplace-related risks for themselves, and then can accept or reject employment based on that judgement. The other information we garner from our measurements, such as increased understanding of risks, are secondary to the information requirements of the individual.

As a result of Jerry's and Art's questions, the Laboratory will now provide bioassay monitoring to individuals who have been identified as having significant body depositions of plutonium or americium but are no longer employed at the Laboratory. The individuals will be encouraged to participate, and they will be provided with all data, analysis results, and the opportunity to discuss these results with the dosimetry and medical staff at the Laboratory on an annual basis. ■

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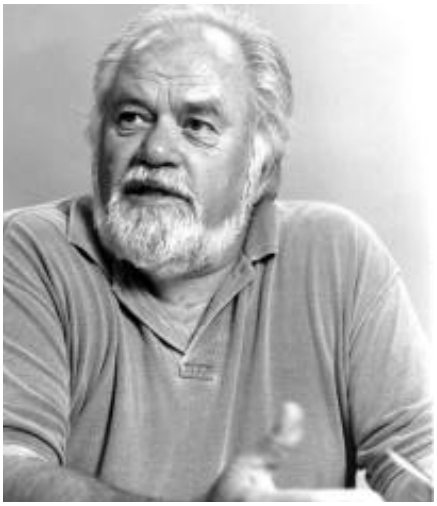
Again, it was just done without outside approvals, budgets, or funding. The overall findings (not identified by individual results) have all been reported in the scientific literature.

By the 1980s, we had gathered a significant body of information on plutonium. Medical examinations were not giving us as much information as epidemiologic studies involving hundreds and thousands of people. By then, we were doing studies of the entire worker populations at several DOE locations. The larger population studies are necessary to give us data that can be analyzed statistically. They have the potential to give us information on health risks that we cannot get from doing medical monitoring of an individual or a small group of individuals. In fact, the trend now is going toward pooling data from multiple studies to get still larger statistical sampling. Earlier this year, Los Alamos scientists participated in preparing a paper that analyzed the combined data on over 95,000 workers from nuclear facilities in the United States, the United Kingdom, and Canada. We have also continued the long term follow-up of the small UPPU Club, which has now reached 50 years since exposure, but we have not initiated new medical follow-up studies on individuals.

I realize that this history is not a very satisfactory answer for an individual who wants to know how things are going for them personally. A few months ago, we proposed a follow-up project to help former employees of the Laboratory. The program included a telephone information line, newsletters, epidemiological surveys, and the potential for doing some additional individual studies of special merit. It is under review by an outside agency for a possible funding grant. We think the proposal is great, but the odds for funding are poor.

In the meantime, we have had an interest in getting periodic urine samples and lung counts on some individuals with high internal depositions of plutonium. In fact, we have been extremely pleased that you, Jerry, have volunteered for those studies on several occasions since you left the Laboratory.



Don Petersen

The take-home message from this experiment is that radiation injury is much more likely to cause a lethal event than to cause a change in the genes that will be perpetuated through the generations. . . . Only in experiments with fruit flies, bacteria, and molds, where you can get billions of them in a jar, do genetic effects of irradiation show up. With people, it apparently doesn't show either because there are simply too few of them or bad genetic material gets weeded out by natural processes.

We hope to keep working with you in the future.

Los Alamos Science: *What about the chance of hereditary effects from internal exposures? Do plutonium workers need to worry that they may affect their potential offspring through exposure to plutonium?*

Don Peterson: The notion that radiation exposure will lead to genetic effects goes back to experiments with fruit flies. There, the populations are huge, the number of progeny are huge, and one can follow many successive generations in just a few months, so the genetic effects of irradiation can be seen. However, the absolute rate of genetic change is very low.

I'd like to tell you about one particular experiment with mice, because I think it may provide you with some reassurance with regard to the dangers of genetic effects in irradiated people. Jake Spaulding over in the Los Alamos Health Research Lab did a multi-generation experiment with mice in which the matings were restricted to brother-sister matings.

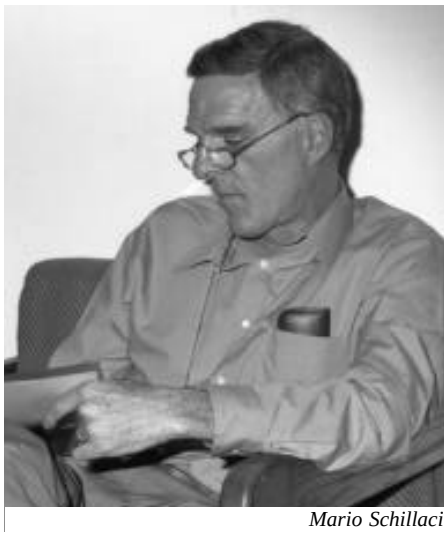
To understand the experiment you need to have a little birds-and-bees information. Sperm cells have a lifetime of only about 75 days. In other words, if you're a male you have a full turnover of sperm in about 75 days. If you're a female, you're born with all the reproductive cells you are ever going to have, and so you can accumulate radiation damage in those egg cells.

In the mouse experiment, the idea was to expose members of each generation of males to half of a lethal dose of radiation. An exposure of 400 rem kills a mouse, so those males were exposed to 200 rem. After radiation, a waiting period was given to allow new adult sperm cells to grow in from the basic stem cells. This eliminates any effects from direct damage to adult sperm, but not the mutations induced in stem cells.

The irradiated male mice were then allowed to breed with nonirradiated females. As a control, nonirradiated males were also bred with nonirradiated females. Now the catch in this experiment was that it started out with only a few mice from a single litter, and all the matings in each generation had to be brother-sister matings. Jake and his coworkers bred these mice through 87 generations, which in human terms takes you back to the time of the Ptolemies in Egypt, to Cleopatra and the like. The total dose to the germ cell line was 87 times 200 rad, or 17,400 rad. Now the Ptolemies believed that brother-sister mating was the way to go; all the pharaohs were married to their sisters. Genetically, this practice may get the family line into trouble in a hurry. We have laws against the practice. However, the addition of irradiation to the mouse reproduction failed to show radiation damage detrimental to the well-being or continuance of the species. There were no gross abnormalities and the litter sizes and survival rates were equal in the two populations.

The take-home message from this experiment is that radiation injury is much more likely to cause a lethal event than to cause a change in the genes that will be perpetuated through the generations. Usually, if mutations occur, they are rapidly eliminated by spontaneous abortion, and you don't see them survive in the population. Only in experiments with fruit flies, bacteria, and molds, where you can get billions of them in a jar, do genetic effects of irradiation show up. With people, it apparently doesn't show either because there are simply too few of them or bad genetic material gets weeded out by natural processes.

Mario Schillaci: Even in the case of the Japanese atomic-bomb survivors, a population of over 80,000 individuals, some of whom were exposed to very large doses, there have been no hereditary effects seen. That null result is consistent with the extremely low rate of radiation-induced hereditary changes seen in animal studies.



Mario Schillaci

Even in the case of the Japanese atomic bomb survivors, a population of over 80,000 individuals, some of whom were exposed to very large doses of radiation, there have been no hereditary effects seen. That null result is consistent with the extremely low rate of radiation-induced hereditary changes seen in animal studies.

Bill Gibson: I particularly appreciate these comments because my son was born with cancer. He still survives now; he is 45 years old and has his own business. But at the time he was born, I was quite concerned that my radiation exposure may have affected him.

Ed Hammel: I have a question regarding the size of doses. Many people are familiar with the tragedy of the radium-dial painters, who ingested quantities of radium as they sucked on their paint brushes to make a nice sharp point. Many of those workers developed radium poisoning and died very horrible deaths. I was wondering if you could tell us the size of the radium doses compared to the doses of the people around this table.

George Voelz: The radium data are sort of mind boggling. Among 4,000 dial painters, essentially all women, there were several hundred cases of bone tumors. Of those, I believe there were only two who received cumulative doses to the bone of less than 20,000 rem.

Now for plutonium. Like radium, plutonium is a bone seeker. It is not surprising then that beagles given high amounts of internal plutonium developed an excess number of bone tumors compared with the number observed in unexposed dogs. The cancer induction is dose dependent; the higher the dose, the higher the excess cancer risk.

The average effective (whole-body) dose among the members of the UPPU club is about 125 rem, and the person with the highest plutonium deposition has received a little over 700 rem. Because plutonium is not uniformly deposited in all tissues, the doses vary for different organs. For example, the average bone dose for the group is estimated to be about 45 rem. Plutonium deposits initially on the surface of the bone, which is also the area where the active bone cells are located. Bone cancers arise from those cells; thus, the dose to that specific area is most important. In humans, the dose to the bone surface from plutonium is about 20 times higher than the dose averaged over the whole bone mass. Thus, the average bone-surface dose among the UPPU men is calculated to be about 900 rem, and the man with the highest deposition has an estimated bone surface dose of 5,000 rem. They sound high, but those doses are much less than even the lowest radium doses that induced bone tumors.

The current risk estimate for plutonium exposure indicates 15 excess bone cancers would be expected for each million person-rem. A million person-rem could consist of, say, 1,000 people each having a dose of 1,000 rem to the bone surface. If the risk estimate holds true, there would be 15 cases of bone cancer among the 1,000 persons; each individual would have a risk of 15/1,000 or 1.5 per cent. As a physician, I like to think of this problem in the reverse. There is a 98.5-per-cent chance for a person with a 1,000-rem dose to the bone surface to escape without an effect.

Los Alamos Science: *As a result of fallout from atmospheric testing, a large fraction of the general population is carrying around some plutonium in their bodies. How large is the dose from that source?*

George Voelz: I just looked this up recently. About 6 tons, or nearly 6 thousand kilograms of plutonium, fell to the earth throughout the world as a result of nuclear testing. That's kind of astounding when you think that today we've been talking about body burdens of millionths of a gram. Of course, a great fraction of the plutonium fallout was dispersed in the oceans and didn't get to any of us. But we know from autopsy studies of the general population that we all carry detectable levels of plutonium, mostly in the lung, the bone, and the liver. The main route for intake was inhalation of tiny particles that were in the air. Some may have been ingested through the food chain, but plutonium has a very low rate of absorption in the GI tract. Unlike radium, it goes right through your gut with very little absorption into the blood stream. So whatever was retained in the body probably entered through inhalation and was initially deposited in the lung.

The Los Alamos autopsy studies and other research show that the 50-year dose commitment to the lung from plutonium fallout is about 40 millirem. That's for a person who was alive from the beginning of nuclear testing in 1945 through 1970. This 50-year dose is a tiny fraction, actually less than 0.3 per cent of the average annual dose (300 millirem) that we receive from natural background and other man-made sources over a 50-year period. To put it another way, the lung now receives less than 1 millirem per year from internally deposited plutonium, and the bone receives about 5 per cent of that, or 0.05 millirem per year, an entirely negligible amount compared to our average annual radiation dose.

I should mention the complication of smoking. Data suggest that the risk of dying of lung cancer from smoking a pack of cigarettes a day is 20 times greater than that of a non-smoker, or the risk increases by 1,900 per cent. In contrast the increased risk of a lung cancer death from the maximum allowed committed dose from plutonium is only a small fraction of 1 per cent. Since most plutonium workers of the 1940s and 1950s were smokers, it's very difficult to separate out the plutonium risk from the much greater smoking risk.

Harold Archuleta: When you have plutonium in your lung, does it ever get out? Is it expelled out?

George Voelz: If you first breathe in plutonium particles that are fairly large, most of them will be deposited on the cilia, the tiny hairs on the lining of the air passages in the bronchi. During the first few weeks after inhalation, the natural action of the cilia will bring much of this material up to the throat, and you end up swallowing the particles. They then pass through the gastrointestinal tract and come out in the feces. That's one reason we take fecal samples after an accident involving inhalation.

However, if the particles are very small, say a micrometer or less in diameter, which are the size you get in a fume or a small fire, they will travel deeper into the lung. Their fate then depends on their solubility. Nitrates and other soluble forms will dissolve in the body fluids, go into the circulation, and be deposited primarily in the bone and the liver.

If the particles are an oxide form produced at high temperatures, then they are not very soluble, and they remain for very long periods of time in the lung tissue or the lymph nodes, the filter system around the lung.

We have examined autopsy tissues from five of the seven deceased members of the UPPU club, and to our amazement, we found that in three of them 35 to 60 per cent of the plutonium in the body at the time of death was in the lung or the tracheo-bronchial lymph nodes and had evidently remained there for the 30 to 40 years following inhalation.

Now plutonium, like radon, is an alpha-particle emitter, and therefore, the accumulation in the lung causes us to worry about the risk of lung cancer. In fact, the risks of plutonium exposure are presently based on radon, on the correlation between lung cancer and radon exposure in the mining industry. My feeling, however, is that the risk of lung cancer from plutonium may turn out to be lower because the mechanics of deposition and difference in half-lives

from those of radon and its products. When you breathe in radon or its radioactive daughters, those nuclei dump their alpha activity very, very quickly. Their half-lives are very short, on the order of 30 minutes. So within 30 to 60 minutes, they have dumped into the linings of the lung airways one-half to three-quarters of all the energy (radiation) that they're ever going to emit. And lung tumors start from the linings of those airways.

Plutonium, in contrast, has a very long half-life, 24,000 years. Its radioactive emission is slow and steady over many years. Moreover, it stays only a short time in the airways before it's redistributed in lung tissue and lymph nodes, areas that are not targets for lung cancer. Therefore, I expect that the present estimates, which are based on radon, may be substantially reduced if we ever get sufficient data.

I should mention the complication of smoking. The risk of dying of lung cancer from smoking a pack of cigarettes a day is 20 times greater than that of a nonsmoker, or the risk increases by 1,900 per cent. In contrast, the increased risk of a lung-cancer death from the maximum allowed committed dose from plutonium is only a small fraction of 1 per cent. Since most plutonium workers of the 1940s and 1950s were smokers, it's very difficult to separate out the plutonium risk from the much greater smoking risk.

Mario Schillaci: Although there may not be a direct correlation between radon and plutonium, I think everyone might be interested in a new study regarding radon in the home and the incidence of lung cancer. In more than half the counties in the United States., representing 90 per cent of the population, this study found that the incidence of lung cancer *decreased* with increasing concentrations of radon. That anticorrelation between cancer incidence and radon exposure held up to a radon concentration that produces a dose equivalent of 3 to 4 rem per year (ten times the average annual dose from all sources). So there's some evidence that small doses of radiation might not be that harmful and, more speculatively, might even be beneficial.

Art Beaumont: I have a question about the dose calculation you've done for me. It suggests that I got an intake at a time after I had stopped working with plutonium. Can you explain that?

George Voelz: I mentioned before that if you have inhaled some plutonium and if it's in an insoluble form, it will migrate very slowly to other organs in the body. Therefore, the amount that shows up in the urine may increase very slowly over time or may not even be measurable until a year or two after the inhalation. That could explain the discrepancy between the dose reconstruction and your experience.

Los Alamos Science: *As I think you all know, Guthrie Miller and Bill Inkret in our Dosimetry Group are the ones who prepared the dose information that you received in preparation for this meeting. Guthrie, do you want to comment on the dose calculations?*

Guthrie Miller: I would like to remind everyone that doses are estimated from the amount of plutonium in the urine samples that you give us. That data is used along with a mathematical model, describing the rate at which plutonium is excreted from the body. The combination allows us to predict the amount of plutonium that was originally taken into the body. This is a difficult inverse problem, and there are significant uncertainties in the results.

George Voelz: In the early days, say before the mid-fifties, the data had huge errors. First, there were errors in the chemical separation methods, in the analytical techniques used to precipitate the plutonium from the urine. Second, there was the problem of contamination: the urine sample was often accidentally contaminated by the sample bottle or by contaminated hands or clothing or what not, and there was no way to tell. Some of you may recall that around 1946 or 1947, Wright Langham created the health-pass ward at the local hospital to get around this problem. Anyone thought to have had an intake was given a 48-hour health pass and asked to report to the hospital where uncontaminated samples could be collected. I understand that the guys got to drink their share of beer on those health passes. They had some sort of beer delivery system from the PX that Wright was never able to figure out. He didn't work very hard on the problem.

Opinions about the Plutonium Injection Experiments

Guthrie Miller: *You all have personal experiences with plutonium intakes. I think many people would be interested in your opinion of the plutonium injection experiments that were done in 1945-1947. Recall that Langham and other people of that era wanted to be able to determine how much plutonium a worker had retained, and at the time, they had no definitive experiments to relate the amount of plutonium in the urine to the amount in the body. They only had data from animal experiments. So they decided to do an experiment in which small quantities of plutonium would be injected into the bloodstream of some eighteen hospitalized individuals. The earliest subjects were diagnosed as terminal and a few of them were given quantities well above the allowed dose for plutonium workers in order that the deposition pattern of plutonium in the body could be determined at autopsy. Most of those individuals were indeed terminal and died of expected causes. One individual was misdiagnosed and lived for many years. He apparently never had any symptoms from the plutonium that had been administered.*

A number of nonterminal patients were also involved. They were given a dose of 5 micrograms, which, based on the experience of the radium-dial painters, was considered to be small. Neither acute nor long-term effects were expected, nor were any seen, but the dose was large enough to allow reasonable measurements of the amount of plutonium excreted in urine and feces. The idea of the experiment was to measure the rate at which the injected plutonium was excreted in the urine. Those data could then be used to interpret the excretion data of people, such as yourselves, who were working with large quantities of plutonium and needed to be taken off the job if the contamination got too large.

There has been a huge outcry about these experiments. What's your opinion about the experiments, and specifically, do you think that they were morally wrong?

Bill Gibson: My personal opinion is that as long as the people were informed of the experiments there was no wrong done. Many of these people were fatally ill anyway and were expected to die within a short period of time. But if some of the people were not informed, I believe that was pretty reprehensible. There's no reason why a person should be included in such an experiment without being told what the experiment is about and given a chance to decide not to participate.

Ted Magel: Those experiments were essentially tracer experiments, and they did no harm. But Hazel O'Leary and others in our government went off the wall. They made a big deal out of nothing because they were ignorant of the facts. The news media is the same. They don't have the background; they don't research their stories. They hear a rumor, and they put it in the news. The problem is that we've been dumbing down the schools. Nobody gets any science education nowadays. From the teaching colleges to the school boards to the parents, we've got to revamp the whole system.

Ed Hammel: I believe there are no moral absolutes. What's moral at one time in history may be immoral at another. Looking back on what was done fifty years ago, it seems very immoral. Today's physicians would not perform an experiment on any individual without first getting his or her informed consent in a written document. But during wartime, many things were done that were just considered urgent under the circumstances. But you can't apply a set of moral criteria from one era to a completely different era. It doesn't make sense to do that. I believe that the people who did those experiments believed they were doing what was best for the country at the time.

Bill Gibson: The same is true of the bombings of Hiroshima and Nagasaki. At the time, it was considered a moral imperative; it was something that had to be done. Now people are saying how immoral it was. That's because we are living in a different era with different circumstances, moralities, requirements, and so on.

Harold Archuleta: I believe that if the people were told what was being done and if someone explained to them what might happen after being injected, then the experiment was OK. It would have been up to the individual to decide whether or not to go through with it. But if it had been me, I wouldn't have done it.

Michael Montoya: That's the same way I feel. If people were told about it, then things were fine. But if the doctors went ahead without those people knowing what was happening, then it was bad. It would be very hard to be used as a guinea pig.

Jose Gonzales: It's immoral to put people on the electric chair, but we see it happening. Now here's the word plutonium. We who have worked with it understand what it is, and we accept the consequences of our mistakes.

Also, I think the Laboratory has done everything it could to get the data it needs to keep us from having too much contamination. But I think it's immoral to be fooling around with people who don't know what the word "plutonium" means. And it's immoral to do something without letting a person know the effects that might happen.

Art Beaumont: I also feel the same way. I sincerely believe that all the people that participated should have been told what was happening and what the consequences might be. Otherwise, it was immoral.

Jim Ledbetter: Under the circumstances of those times, the doctors and scientists were probably justified in what they did. And I think the benefits gained were worthwhile. I don't know whether the people were informed or not. Perhaps, they just didn't understand. In fifty years, you can forget a lot of things. I've had a doctor tell me about the injection I was getting, and even though I didn't understand totally, I still accepted his judgment. And maybe fifty years later, I'll be saying, "This is really bad news." So I believe the experiments were all done under the highest morals and with a national need in mind. I don't believe the doctors deliberately set out to misrepresent what they were doing. I believe the people knew but just didn't understand it.

Jerry Taylor: Well the experiments needed to be done. The question of what happens when you get exposed—that question had to be asked as they started making plutonium. It was a new material. But nobody has the right to play God with anybody else. So I agree with everyone else. The experiments were all right as long as the people were informed and still wanted to do it. Otherwise, it wasn't right. We may find that out some day. It's being investigated. But you don't know if the truth is going to come out. It's like the OJ Simpson trial. I don't know that we'll ever know who did what. And again, I don't know if you can really say that the experiments were morally right or wrong. It's funny to ask that question. Look at the morals in our country today. Instead of looking at those, the press and the public are going back fifty years and finding wrong in something that we needed to do back then. But the bottom line is that if the people were not informed and were being used as human guinea pigs, then it wasn't right in my eyes. ■

William C. T. Inkret joined the Laboratory in 1986 as a postdoctoral fellow, and his research included development and application of computer algorithms for analysis of chest-count data to detect plutonium and americium and the development and application of methods for estimating internal dose from gamma-emitting radionuclides based on whole-body count. Bill also led the design, construction, and dosimetry of a plutonium-238 alpha-particle irradiation system used in radiation biology studies at the Laboratory, and later, he assisted Harvard University in building an identical system. In 1991, Bill became team leader of the Radiological Dose Assessment Team. In 1995, he took over leadership of the Laboratory's Human Studies Project and brought the project to closure. Bill received his B.A. in biology in 1979 from Carroll College in Montana. After a two-year tour as a ski-area avalanche-control specialist and a union laborer in high-rise construction, he earned his M.S. in health physics from Colorado State University. In 1986, he earned his Ph.D. from Colorado State University, College of Veterinary Medicine and Biomedical Sciences. Bill serves on several national radiation protection committees, including the National Council on Radiation Protection and Measurements Scientific Committee on plutonium-238 power sources for space applications. Bill enjoys yardwork, tending the family farm in Nebraska, skiing, finding antique collectibles, and teaching his children about these interests.

Guthrie Miller received his B.S. in physics from the California Institute of Technology and earned his Ph.D. in high energy physics from Stanford University. His thesis was part of the work awarded the Nobel prize for physics in 1990 (to Taylor, Friedman, and Kendall) for the first experimental verification, by electron scattering, of the quark model of the nucleon. He came to Los Alamos National Laboratory in 1974 to work in the Controlled Thermonuclear Research Division (magnetic fusion energy). In 1991, Guthrie joined the dose-assessment team and continued the research on plutonium internal dosimetry of James N. P. Lawrence after his retirement. With William Inkret and Harry Martz, Guthrie has pioneered the use of Bayesian statistics in health physics. He currently chairs the American National Standards committee on plutonium internal dosimetry. Guthrie has two sons, Geoffrey 16 and Owen 12. His outside interests, aside from parenting, include wilderness activities, co-counseling, dance, and music.

Plutonium Metal

Ted Magel

Nick Dallas

In 1943, the Manhattan Project was pursuing two routes to a nuclear bomb, both dominated by the problem of acquiring the necessary nuclear materials. One route involved isolating the rare isotope uranium-235 from the abundant uranium-238 in sufficient quantity to build a weapon. The two isotopes are chemically identical and differ in mass by only about 1 per cent. Somehow the slightly lighter uranium atoms would have to be teased away from the heavier ones. Several separation techniques were under study—gaseous diffusion, electromagnetic separation, thermal diffusion, and the use of a centrifuge—but it was very uncertain whether any of them could produce the required kilogram quantities in a reasonable amount of time.

The second route to the bomb involved plutonium-239, an isotope that physicists predicted would support a nuclear-fission chain reaction at least as well as uranium-235. But only insignificant traces of plutonium occur naturally on Earth. Large quantities would have to be made in a uranium-fueled nuclear reactor. When the reactor was operating, some of the neutrons from the chain reaction would be absorbed by uranium-238 to produce the unstable isotope, uranium-239. Almost immediately after being formed, uranium-239 would emit a beta particle (electron) to become a new element, neptunium-239, which would emit a second beta particle to become plutonium-239.

The total amount of man-made plutonium in existence in 1943 was the approximately 1.5 milligrams that had been made in accelerators. Not until February 1944 could gram quantities become available from the uranium reactor under construction at Clinton, Tennessee, and the needed kilogram quantities could not be expected to become available from the production reactors being built at Hanford, Washington until sometime in 1945.

In the meantime the metallurgists needed information as soon as possible on the bulk properties of the metallic form of plutonium including its melting point, its hardness, and especially its ductility and density. After all, they would be responsible for fabricating the metal into the shapes specified by the bomb designers. Solid pieces of pure plutonium metal large enough for metallurgical experiments—that is, not much less than a gram—were required to make the measurements.*

The need was so urgent that chemists at the University of Chicago's Met Lab and at Los Alamos began research in 1943 on chemical techniques to reduce plutonium compounds to pure metal. Compounds of other metals, particularly uranium, were used as stand-ins in the experiments.

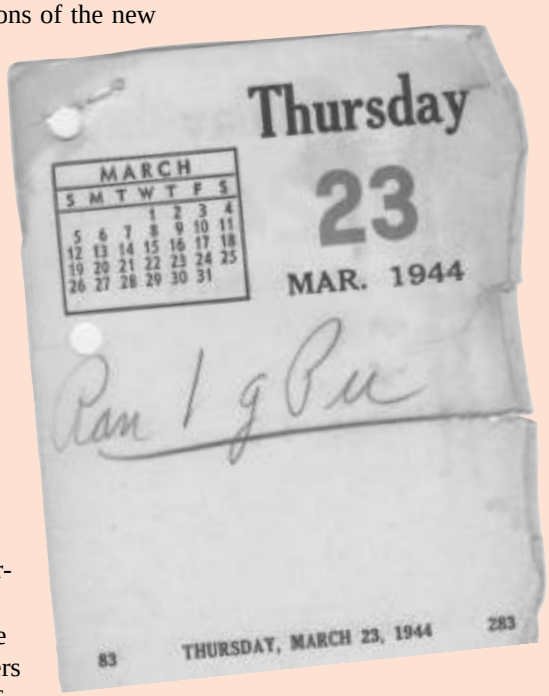
Two young men at the Met Lab, Ted Magel and Nick Dallas, (see the plutonium-worker roundtable, “On the Front Lines”) were the first to solve the plutonium metal reduction problem on a scale larger than a few micrograms. Since parallel work at Los Alamos was going poorly and gram quantities were soon expected

*The first unequivocal production of plutonium metal was carried out on November 6, 1943, at the Met Lab by H. L. Baumbach, S. Fried, P. L. Kirk and, R. S. Rosenfels (Manhattan Project Report CK-1143, December 1943). It was in the form of a few small globules of silvery metal weighing 1-3 micrograms each, scarcely large enough to permit any meaningful measurements of physical properties.

The First Gram

by Ed Hammel

from the Clinton reactor, Oppenheimer wrote a memo on January 18, 1944 requesting that Magel and Dallas come to Los Alamos. About a month after their arrival on February 3, 1944, they produced a shiny 20-milligram button of plutonium easily visible to the naked eye, and three weeks later they prepared a 520-milligram button of pure plutonium metal. These were the first amounts of plutonium metal produced at Los Alamos as well as the largest single buttons of the new element produced anywhere in the world. The technical story of their work is recounted here to illustrate the science and the intense atmosphere of the early plutonium metallurgy work and also to give them long overdue recognition for their contributions.



One basic reaction for reducing a plutonium or uranium salt to a metal is a metallothermic reaction. For uranium, a typical starting compound is uranium tetrafluoride and a typical reduction reaction is:

$$UF_4 + 2Ca \rightarrow U + 2CaF_2,$$

where calcium is the reducing agent. Heating the reagents to temperatures in the vicinity of 400 to 500 degrees centigrade initiates the reaction, which proceeds in the direction shown because fluorine has a much higher affinity for calcium than for uranium. At the same time, and for the same reason, the reaction gives off a great deal of heat—hence the name "metallothermic." Because of the high temperatures and pressures and the high reactivity of the reducing agent, the reaction was run inside a sealed metal container, which the Manhattan Project researchers called a “bomb.” The bombs were lined with crucibles made of refractory materials such as metal oxides that would remain intact at the thousand-degree-centigrade temperatures produced in the reaction.

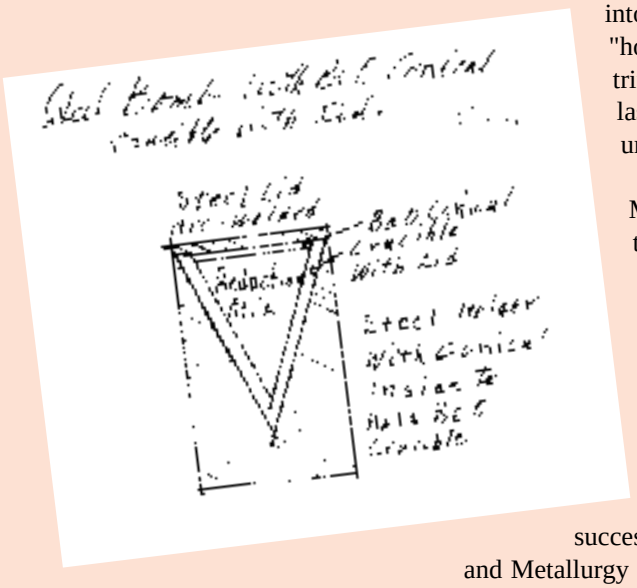
To maximize the yield and purity of the metal product, chemists had to optimize many parameters: the form of the initial uranium or plutonium salt, the reducing agent, the layering of the reagents in the bomb, their mesh sizes (the reagents were powdered), deviations from the stoichiometric proportions, the refractory material for the liner, the rate of heating, the optimum temperature required for initiating the reaction, the time spent at the maximum temperature reached, and finally, whether or not to add other materials that would simultaneously react, thereby producing additional heat (so-called boosters).

Yet another choice was how to separate the pure molten metal from the slag formed by the reaction products (CaF_2 in the above example). One way was to leave the bomb alone during the heating and let gravity do the work. Uranium and plutonium are far denser than the slag and should therefore naturally coalesce into a single molten globule of metal at the bottom of the crucible. Dick Baker’s group at Los Alamos used this “stationary bomb” approach.

But the first batches of plutonium compounds would be very small indeed. The smaller the scale of the reaction, the worse the stationary-bomb approach could be

expected to work. A smaller bomb has more interior surface area in proportion to its volume than a larger bomb and is therefore more likely to lose a larger proportion of the reaction heat through the liner and bomb walls to the external environment. The reaction products might solidify before the new metal could flow through them and coalesce at the bottom of the liner.

Magel and Dallas, while working at the Met Lab in Chicago under Dr. John Chipman, recognized this problem and decided to assist the separation by performing the reduction inside a graphite centrifuge. The bomb was placed on its side in the centrifuge and rotated rapidly as it was being heated. The rotation rate could be adjusted to make the centrifugal force on the molten metal about 50 times larger than the force of gravity, enough to propel the molten metal outward to the tip of the cone-shaped interior of the refractory liner where it would cool into a consolidated mass. The components and operation of their "hot centrifuge" are shown in the box "The Magel-Dallas 'Hot Centrifuge' Technique," page 165. By the end of 1943 Magel and Dallas were using their new technique to make 1-gram buttons of pure uranium metal from uranium fluoride.



Meanwhile, the Los Alamos efforts in metal reduction, using stationary bombs and other methods, were floundering. Baker's group tried to prevent the slag from solidifying too quickly by using an iodine booster which not only adds heat to the reaction but also adds reaction products with low-melting points to the slag. Both effects keep the slag in the liquid state for a longer time. The iodine booster improved the results, but the reductions on the 1-gram scale still produced finely divided metal mixed with slag rather than a coherent metal slug. In January 1944, Baker also tried the centrifuge approach, but his efforts were not successful. Consequently, J. W. Kennedy, the Leader of the Chemistry and Metallurgy Division, his Associate Director Cyril Smith, and eventually, as noted above, Oppenheimer himself requested Dr. Chipman to transfer Magel and Dallas to Los Alamos as quickly as possible.

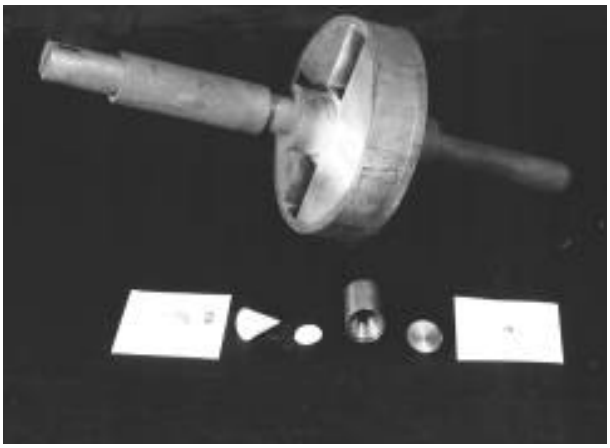
After Magel and Dallas arrived with their equipment, they immediately began performing centrifuge reductions of uranium. Reductions in a centrifuge worked best when the reducing agent was lithium and the liner was made of beryllium oxide. Magel and Dallas also concluded that an iodine booster had essentially no effect on reductions using lithium. Evidently the heat generated by the booster was of little value since the slag in lithium reactions had a sufficiently low melting point to permit plutonium and uranium metal to sink through it easily. Therefore, any further lowering of the melting point by adding iodine was unnecessary.

By March 2, an amount of fluoride (PuF_3) containing 50-milligrams of elemental plutonium was available for reduction. It had been prepared by Laboratory chemists from shipments of plutonium nitrate sent from the Clinton reactor. Magel and Dallas were given the material to reduce to plutonium metal. Probably with some reservations, they first followed the Los Alamos protocol of using calcium as the reducing agent and an iodine booster. The result was a grayish cokey mass containing no agglomerated plutonium. But on March 8, they tried again with another sample, this time using lithium (and iodine again). That experiment produced a shiny 20-milligram button of plutonium. Although the yield of 40 percent was disappointingly low, the result was the first plutonium metal made at Los Alamos and the first made anywhere in sufficient quantity to see without mag-

continued on page 166

The Magel-Dallas "Hot Centrifuge" Technique

The photograph below shows the components of Magel's and Dallas's apparatus for small-scale metal reduction of plutonium and uranium compounds. On the paper in front of the centrifuge rotor is a charge of metal halide (such as PuF_4) and a reducing agent. To the right of the paper is a cone-shaped crucible or liner made by powdering BeO, forming it in a mold, and firing it as clay is fired. Magel and Dallas put the reducing agent into the crucible first and put the halide on top. They covered the crucible with a double lid (shown to the right of the crucible): the first layer made of either sintered NaCl, $BaCl_2$, or LiF, was topped with one made of MgO. They put the crucible inside the cone-shaped interior of the cylindrical steel bomb, displaced the air inside the bomb with argon, covered the bomb with a steel lid, and sealed it shut by welding.



They mounted the bomb into one of the slots of the rotor and packed it tightly in place with more MgO. The rotor was about 15 centimeters in diameter and was made entirely of graphite to give it both strength and heat resistance. It had four slots so that four reductions could be performed at once. (If the experimenters didn't have four charges, they put dummy bombs into the slots for balance.)

The photograph at right shows the centrifuge. The loaded rotor was placed inside a coil that was attached to a high-frequency electrical generator, and the shaft of the rotor was attached to a drill press through a slot-and-pin connector. When the generator was turned on, the coil would produce a rapidly alternating magnetic field, which would heat the rotor and bombs by induction. During the heating, the rotor would be spun by the drill press at 900 revolutions per minute, which made the force on the bomb's contents about 50 times that of gravity. Magel and Dallas found that the best procedure for plutonium reduction was to heat the spinning rotor and bombs to about 1,100 centigrade, which took somewhat less than five minutes, maintain that temperature for three minutes, and then turn off the generator and let the whole thing cool but continue the rotation until the temperature reached 400-500 centigrade. When the bomb cooled to room temperature, they sawed it open at the top and removed its contents for examination.

The photograph at left show a longitudinal cross section of a bomb that was fired in the graphite centrifuge. In this particular specimen, the layer of slag is clearly seen on top of a button of uranium metal. The button is located in the tip of the crucible. The black spongy deposit clinging to the upper part of the cone is metal mixed with slag, which meant that the yield of pure metal was low in this particular reduction.

continued from page 164

nification. Many other 50-milligram runs were made with PuF_4, PuF_3, and $PuCl_3$, as well as with other reducing agents. At this scale the results varied (about one third of them were successful).

Ted Magel

During the three weeks following the initial success, Laboratory chemists prepared in succession two samples of PuF_4, each containing a gram of plutonium. Much to the dismay of Magel and Dallas, Eric Jette, the leader of the Plutonium Metallurgy Group, and Cyril Smith decided to give the first 1-gram sample to Dick Baker for an attempt at reduction in the stationary bomb. The attempt produced only questionable microscopic droplets of plutonium dipersed in slag.

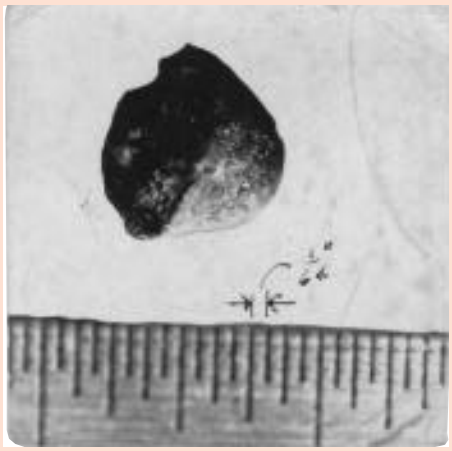


Figure 1. The first gram-scale piece of plutonium metal in history. It was made by Ted Magel and Nick Dallas at Los Alamos on the night of March 23, 1944 and weighed 520 milligrams.

When the second sample became available, Jette and Smith requested Magel and Dallas to attempt a centrifuge reduction on March 24th in the presence of a number of dignitaries. Magel decided on the 23rd to do the experiment without a crowd present. That night he and Dallas performed the reaction with lithium and no booster. When they cut open the bomb, they found a 520-milligram button of plutonium, shown in Figure 1. Again the yield was inexplicably low, but the metal was shiny and soft enough to cut with pliers; both qualities indicate purity. The button was immediately used for crucial metallurgical and chemical studies. From April to early June, Magel and Dallas made eight more buttons on the one-gram scale, all of which were successful, and four of which are shown in Figure 2. In total, they performed about 300 centrifuge reductions between February and June; twenty-five of them were plutonium reductions.

During the course of their work, both Magel and Dallas experienced various accidental exposures to plutonium, which later qualified them for membership in the so-called UPPU club, Wright Langham's follow-up study of wartime plutonium workers who received intakes of plutonium (see "On the Front Lines").

In the summer of 1944, Magel and Dallas started small-scale work on purifying plutonium, especially from light-element contaminants. They set up high-vacuum, high-temperature remelting systems to evaporate residual light element impurities from the reduced buttons of plutonium. Light-element impurities are a problem because they absorb alpha particles from the decay of plutonium and emit neutrons. The neutrons can then initiate a chain reaction in the plutonium before two subcritical assemblies have been able to come together to form the planned supercritical mass. The removal of light-element impurities was therefore considered crucial for minimizing the neutron background and preventing a preinitiation of the gun-type plutonium weapon.

During that summer, Baker made a systematic study of small-scale, stationary-bomb reactions. He found that $PuCl_3$ was a better starting material than PuF_4 and then went on to develop reliable techniques using this halide for producing gram-scale buttons of plutonium. Because stationary bombs were much more convenient than centrifuges and did not require lithium as a reductant nor the use of

beryllium oxide crucibles (both of which contributed high levels of light-element impurities to the resulting plutonium), Baker's method turned out to be preferable for production of plutonium in quantities greater than one gram.

Figure 2. Four more plutonium metal buttons made by Magel and Dallas during the spring of 1944.

The availability of gram-scale quantities of plutonium permitted the Los Alamos metallurgists to attack in a multi-faceted and coherent way the so-called variable density and crystal-structure problems. Puzzling variations in density and crystal structure had been seen in different metal specimens since the time of plutonium's first production on the microgram scale at the Met Lab, and the possibility of allotropism had been raised as early as February 1944 by R. Mooney and W. H. Zachariasen at the Met Lab. Nevertheless, at Los Alamos, the results of specific attempts to settle this issue were ambiguous until June 1944. Research did finally show that plutonium has more complex allotropic behavior than any other known metal, and this property made the task of producing the necessary shapes for weapons even more difficult.

Toward the end of the summer of 1944, the light-element impurity problem suddenly became irrelevant: It was discovered that reactor-produced plutonium from Hanford would contain significant amounts of plutonium-240. That isotope undergoes spontaneous fission and therefore would add much more to the neutron background than the light elements ever could. Since there was no practical way to remove it, the project had to abandon the gun-type weapon and replace it with an implosion device in which the speed of the assembly would eliminate the possibility of neutron-induced preinitiation. It also meant that Magel and Dallas were no longer needed to solve light-element purification problems, and they decided to leave Los Alamos and join Dr. Chipman, who had moved to MIT. There they helped make large crucibles of various refractory materials for use by Baker's reduction section and Ed Hammel's remelting, alloying, and casting section. Thus their work for the Manhattan Project continued even after they left Los Alamos. ■

Edward F. Hammel joined the Laboratory in 1944 as a section leader in the Chemistry and Metallurgy Research Divsion, where his principal responsiblity was remelting, alloying, and casting plutonium metal. In 1945 he was appointed group leader of the Metal Physics Group, which was responsible for determining the pyhsical properties of plutonium. In 1948 Ed became group leader of the Low Temperature Physics and Cryoengineering Group and was responsible for organizing a program to study helium-3. During that year Ed and his collaborators were the first to liquefy helium-3 and to test its properties at low temperatures. They searched for superfluid behavior down to 0.7 kelvin, a remarkable feat for the times. Their search was unsuccessful because helium-3 becomes a superfluid at an unexpectedly low temperature of less than 3 millikelvins. From 1970 to his retirement in 1979, Ed held management positions in various energy related projects including the study of superconducting transmission lines and energy storage. In 1955 Ed was awarded the American Chemical Society gold medal for his work on helium-3. He received his A.B. in chemistry from Dartmouth College and his Ph.D. in physical chemistry from Princeton University.

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The Future Role of

From the time the first gram of reactor-produced plutonium was shipped to Los Alamos in 1944 to process into pure metal, the Laboratory was called upon to develop the knowledge base and the technology to handle, process, and utilize this man made material for both wartime and peacetime uses. Now, over 50 years later, the Cold War is over and difficult problems regarding the safe dismantlement of nuclear warheads and deposition of plutonium are requiring development of new technologies. Again the Laboratory is being challenged to fulfill this responsibility.

Leading edge research on special nuclear materials such as plutonium, enriched uranium, tritium, and others naturally requires specially designed and managed facilities. It is not an accident that those facilities exist at Los Alamos, nor that they are configured to meet constantly changing national needs as well as the highest safety, health, and environmental standards. In fact TA-55, the modern plutonium facility at Los Alamos, is touted as one of the "Crown Jewels" in the Department of Energy's inventory of facilities.

But things didn't start out that way. D Building, the first facility at Los Alamos for handling plutonium, turned out to be less than adequate. It had been specially designed in the spring of 1943 to minimize contamination of plutonium by light-element impurities. When that need disappeared (see "Plutonium Metal—The First Gram"), it became very clear that the more serious problem was preventing plutonium contamination of the workers. Unfortunately, D Building was not ideally suited to meet that need, and so very soon after the building was occupied and plutonium began arriving in larger quantities, plans were made for erecting a new facility at DP Site. The structures were standard prefab metal buildings outfitted with high-integrity metal gloveboxes and carefully designed ventilation and plumbing systems to insure material containment and worker safety, at least during normal operation.

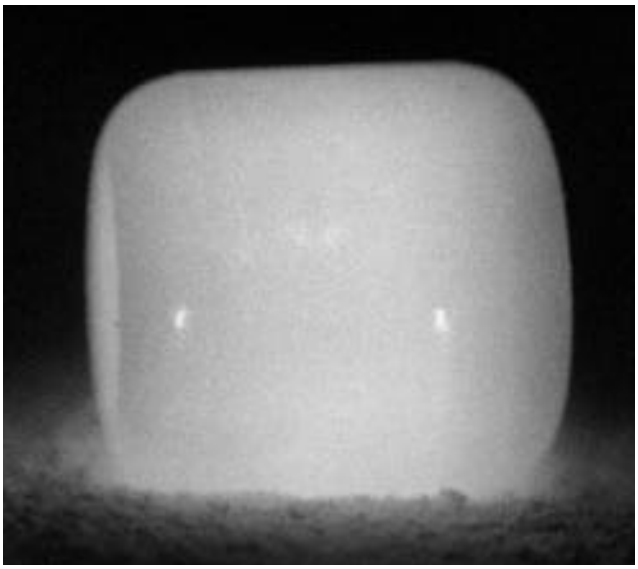
DP Site served as the nation's center for plutonium research and development through the 1950s and 1960s. The responsibility for fabricating plutonium weapon components, which Los Alamos had carried out during WWII, was transferred instead to the Rocky Flats Plant in north central Colorado starting in the early 1950s. In May 1969 a fire at the Rocky Flats facility, which was devastating to the physical plant, caused a temporary shutdown of the plutonium operations and prompted the Atomic Energy Commission (then in charge of nuclear technologies) to perform a "critical systems analysis" of the nation's plutonium infrastructure. The analysis pointed out that the infrastucture was fragile and shallow in nature. Improved handling practices as well as new facilities would be necessary to insure continuity of operation as well as the health and safety of workers, the public, and the environment not only under ordinary operations but also in the event of extraordinary circumstances (accidents, natural disasters, terrorist activities, and so on). The end result of the Commission's study was the decision by the U.S. Congress in January 1971 to build two new modern plutonium facilities, one to be located at Rocky Flats for the purpose of making of plutonium weapon components and the other to be located at Los Alamos for performing plutonium research and development.

The new plutonium facility at Los Alamos, referred to as TA-55 (TA stands for

Plutonium Technology

by Dana Christensen

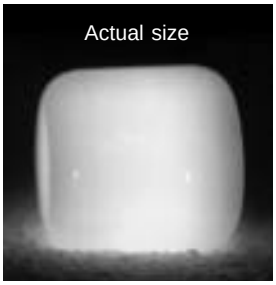
technical area), was designed to withstand earthquakes, tornadoes and all manner of natural disasters. It was also designed to protect workers under extraordinary circumstances such as power failures, fires, and other accidental occurrences. When it became fully operational in December 1978, the major activities in the facility revolved around support of nuclear weapons research, development, and testing. The materials work included purifying plutonium metal, developing and testing new plutonium alloys, performing mechanical and structural strength tests, and making measurements of physical properties such as the equation of state of the various complicated phases of the metallic form of plutonium. On the fabrication side, research was done on manufacturing technologies, and the results were directly applied to the fabrication of components for the new designs being tested underground at the Nevada Test Site. Small-scale recycling (about 200 kilograms per year) of materials and residues from research and development activities was another essential component of the effort, and the Laboratory became involved in developing more efficient and safer chemical separation techniques to carry out those recycling activities. Surface analysis and material-aging studies in support of stockpile-lifetime analysis were also carried out on a modest scale.



In addition to weapons-related work, the facility housed a modest capability in the design, fabrication, and safety testing for plutonium-238 heat sources. These are very compact, long-lasting power sources developed especially for space missions (see Figure 1). Although the heat sources were fabricated and assembled elsewhere, the safety, design, and fabrication parameters were developed and demonstrated at Los Alamos. Finally there was a modest capability to design, fabricate, and test advanced nuclear reactor fuels, such as mixed uranium and plutonium carbides, nitrides, and oxides. The entire population at TA-55, at the time of start-up in 1978, totaled less than 150 employees, including all of the health and safety, and operational support personnel.

Figure 1. Power Source for Deep-Space Applications

This long-lasting radioactive power source of plutonium-238 oxide is very compact indeed. Its 150-gram mass fits into a cylinder having a height and a diameter of only 2.75 centimeters. The initial power output of 62.5 watts decays with a half-life of 87.4 years. The heat from this type of source is converted to electricity through thermal-electric converters, and the electricity is then used to power instruments onboard a spacecraft .



Over the years, this facility, designed in a modular fashion for flexibility and change, has undergone significant modifications and upgrades in response to new demands. Some of those demands began to appear in 1980 when the DOE realized that its new production facility at Rocky Flats would not be on-line in time to meet weapon-component production requirements. Los Alamos was therefore asked to produce pure plutonium metal on an interim basis. By 1983 when it became clear that the new facility at Rocky Flats would not operate as designed, the DOE asked Los Alamos to assist Rocky Flats with the selection and installation of technologies so as to expedite the start-up of their facility. Los Alamos was also asked to continue providing production assistance so as to maintain component production.

A formal program funded by the Department's Office of Production and Surveillance was soon established to support these production-assistance activities. The new program represented a significant change in direction and an increase in

the level of activity at the Los Alamos plutonium facility. Research, development, and demonstration of chemical-separation technologies for plutonium recovery became the cornerstone activity, and pure plutonium metal continued to be prepared at Los Alamos and shipped to the Rocky Flats Plant.

Figure 2. High-Purity Plutonium Ring

This ring of plutonium metal has a purity of more than 99.96 per cent. It is typical of the rings that were prepared by electrorefining at Los Alamos and shipped to Rocky Flats for weapon fabrication. The ring weighs 5.3 kilograms and is approximately 11 centimeters in diameter.

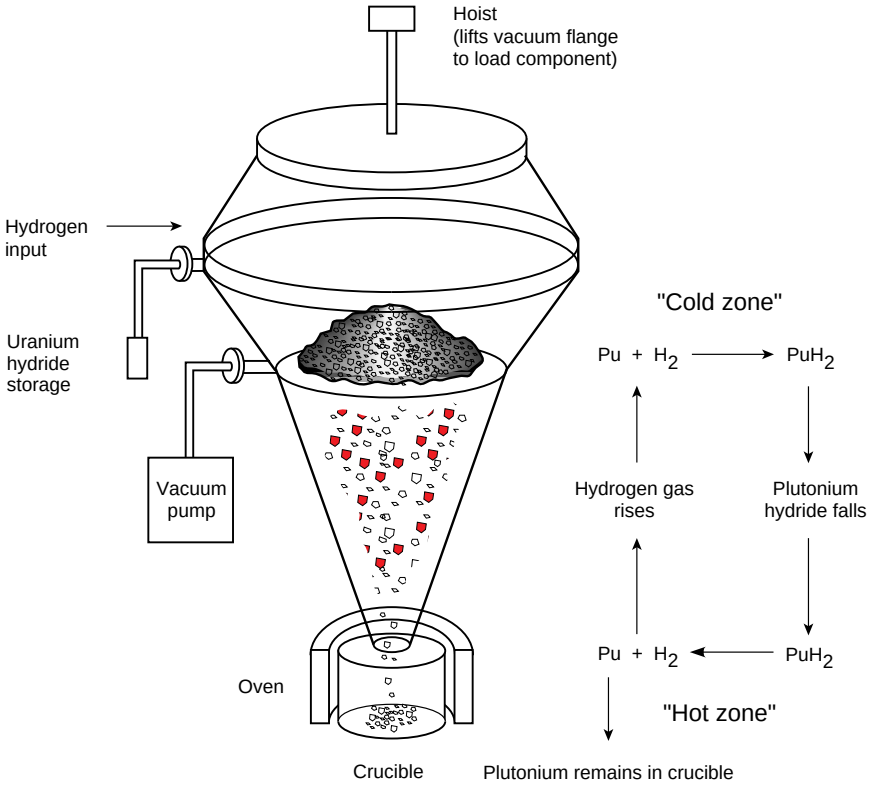
The new plutonium processing mission provided the seeds for innovation and discovery of new and novel separation/purification techniques. Dozens of patents were issued and an untold number of publications were prepared. The population of the facility grew rapidly to exceed 600 employees. Because of the facilities modular design, old technologies were easily removed and replaced by the latest technology available. Also, new health and safety features were easily incorporated as soon as the need was identified. As a result, the plutonium facility has been able to respond to constantly changing operational, and health and safety standards.

Today the combination of a very flexible facility and a very experienced staff is proving to be a tremendous asset in meeting the new demands on plutonium technology. It may come as a surprise that the demands have become more complex, not less, since the ending of the Cold War, and the Laboratory has been challenged more than ever to find innovative solutions. For example, the dramatic down-sizing of the nation's nuclear arsenal in accord with recent treaties requires new technologies to support safe, waste-free dismantlement of nuclear warheads under stringent regulatory conditions. The plutonium facilities ARIES project has become the approach of choice for cost-efficient, waste-free separation of plutonium from weapon components. This project is designed to bring in plutonium assemblies, remove the plutonium as either a metal ingot or oxide powder, and package the plutonium for long term storage according to the DOE Packaging Standard. Figure 3 shows the hydride-dehydride process, which is the centerpiece of the ARIES project. This technology base is being actively exchanged with our Russian counterparts.

The ultimate disposition of the excess plutonium, whether it be transmutation, energy conversion, vitrification as waste, or some other option must also be faced and will require a deep understanding of the fundamental science and technology involved in each as well as a definitive evaluation of the various trade-offs among them. The DOE has named Los Alamos the lead laboratory for plutonium stabilization, packaging, and storage research. The Laboratory is also involved in studying conversion of excess weapon materials into reactor fuels, transmutation of materials by either accelerators or nuclear reactors, stability of nuclear materials in waste forms such as glass or ceramics, and other long-term disposition options.

Surveillance of the remaining U.S. nuclear stockpile has also become more challenging. Since no new production of nuclear weapon components is taking place, the old approach of discovering manufacturing and material flaws at the time a weapon is retired and then correcting the flaws in the next-generation weapon is no longer acceptable. Now the goal is to understand phenomena that might cause changes in materials performance and to predict the rates of those changes so that deterioration in materials performance can be anticipated long before it affects the behavior of a weapon component . The plutonium facility has recently taken on the responsibility for the surveillance of all stockpile plutonium components. The idea is to implement a centralized cost-effective approach for determining safe and

Figure 3. Hydride-Dehydride Recycle System—An Elegant Technique for Nuclear-Warhead Dismantlement



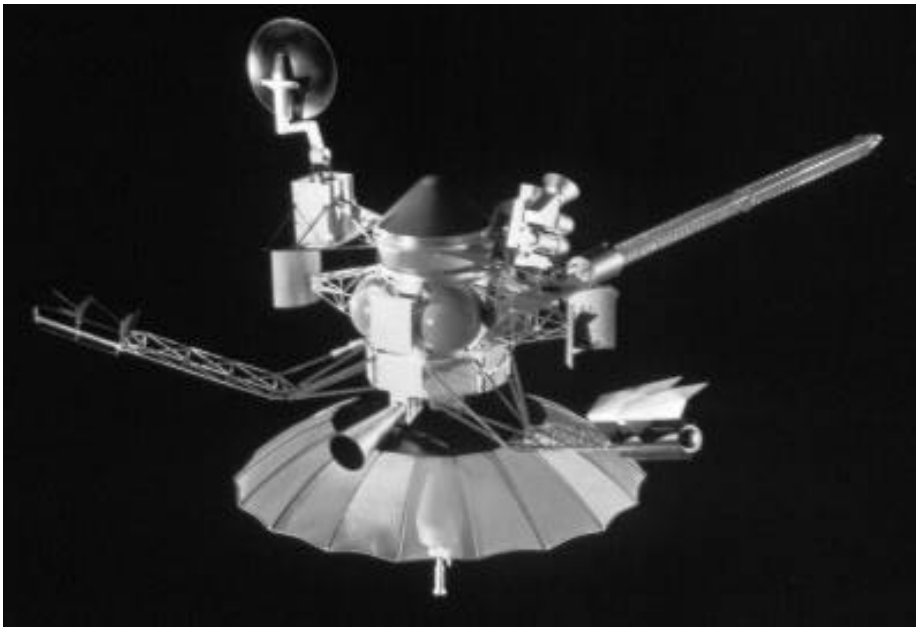
The hydride-dehydride recycle process for extracting plutonium from a warhead exploits the fact that, when plutonium comes in contact with hydrogen gas, it reacts with the hydrogen to form a hydride at a rate that is thousands of times faster than that of any other metal. The diagram shows the vacuum chamber in which the process takes place. (The chamber is installed inside of a glovebox to insure that no plutonium escapes into the work environment.) The heated crucible at the bottom of the chamber is the "hot zone" and the upper part of the chamber, where the weapon component is placed, is the "cold zone." Hydrogen from a heated uranium-hydride storage bed flows into the cold zone where it reacts with the plutonium to form plutonium hydride. The hydride falls as a powder into the hot zone, and there it decomposes into hydrogen gas and pure plutonium. The released hydrogen rises to the cold zone where again it can combine with the plutonium and "carry" that plutonium down to the crucible below. The cycle continues until all the plutonium has been separated from the weapon component. The signal that the process is complete is a sudden rise in the pressure inside the chamber, indicating that all the hydrogen has been released. The hydrogen gas is then pumped out of the chamber and re-absorbed by the uranium-hydride bed. When the process is complete, 99.9 per cent of the plutonium in the weapon component is in the bottom of the crucible where it will be melted and incorporated into a storage-ready ingot. Thus plutonium recovery is contained from beginning to end within a compact unit that occupies a 36-square-foot glovebox.

Standard acid-leach plutonium recovery methods generate hazardous mixed chemical and radioactive waste that are very difficult kind to dispose of. In contrast, the new hydride-dehydride recycling method is essentially a zero-waste process—generating no mixed or liquid waste of any kind.

reliable stockpile lifetimes. A comprehensive program involving both destructive and non-destructive testing of stockpile weapon components and systems is being put in place. Also, new approaches and technologies are being developed that are predictive in nature so that the goal of predicting accurate lifetimes can indeed be realized. (For example, ultrasonic techniques can be used to pinpoint changes in physical dimension that occur over time as a result of radiation effects on various materials.) In addition to surveillance, the facility will also maintain the technology base for component fabrication so that, if weapon components need replacement, they can be refabricated quickly and efficiently.

Plutonium-238 heat-sources are still the best power sources for unmanned deep-space exploration. Recently the plutonium facility has been declared the nation's center of expertise in that technology, and its historic involvement in research and development has now been expanded to include the actual production of heat sources. Figure 4 shows elements of the latest project—the heat sources to power the deep-space probe to Saturn and the Saturn moon, Titan (Cassini mission). Future heat-source requirements for similar missions will be supplied out of TA-55.

Finally, the end of the Cold War has opened up new opportunities for technical exchange and collaboration regarding plutonium technology. Whereas in the past, the plutonium technology base in each of various countries was kept secret and closed, today that knowledge is being more openly discussed. In particular, the states of the Former Soviet Union (principally Russia) are beginning to participate through interactions with the U.S. national laboratories in the control of nuclear materials and the stabilization of excess materials and facilities. This initiative enhances the non-proliferation of weapon technology and materials to non-declared states and terrorist organizations.



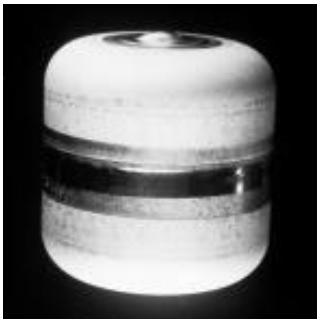


Figure 4. Plutonium-238 - Powered Deep-Space Probe
This deep-space probe (right) is typical of those that are powered by radioisotope thermoelectric generators. Those electric generators run on power from plutonium-238 heat sources like the one shown below. The Cassini mission to Saturn will require three thermoelectric generators, each loaded with 72 of those heat sources.

New cooperative agreements are being formulated to bring consistency to the way that nuclear materials such as plutonium are identified, controlled, stabilized, packaged, and stored. Indeed, most of the weapon production facilities of the past are no longer needed, and safe decommissioning and dismantlement can now begin. Those activities, however, require a significantly new technology base. Scientists at the plutonium facility have been working on those problems and have already developed several exciting new technologies including plasma and electrolytic methods for removing plutonium contamination from solid surfaces (see Figure 5). Those methods render the equipment free of contamination and therefore disposable through standard industrial routes rather than through transuranic-waste routes. Another demonstrated approach is liquid waste-stream polishing whereby liquid wastes can be stripped of plutonium and other noxious contaminant's prior to discharge. That technology is now being demonstrated in treating liquid effluents from TA-55.

The end of the Cold War has opened up opportunities to reduce nuclear arsenals and to minimize the availability of weapons-grade plutonium. It also means that the country and the world must wrestle with decisions on the clean-up of plutonium residues, facilities, and contamination, and on the eventual disposition of excess plutonium. Clearly a strong, reliable technology base is essential to implement the technical and political decisions as they are made. Realistically, the country will down-size its investment in nuclear facilities and infrastructure, which will make the remaining infrastructure even more important for future missions. A stronger investment in science and technology will be essential to overcome the inherent vulnerability associated with reduced production capacity. It will also be essential for solving the problems of the plutonium disposition and for making future generations free of this difficult Cold War legacy.

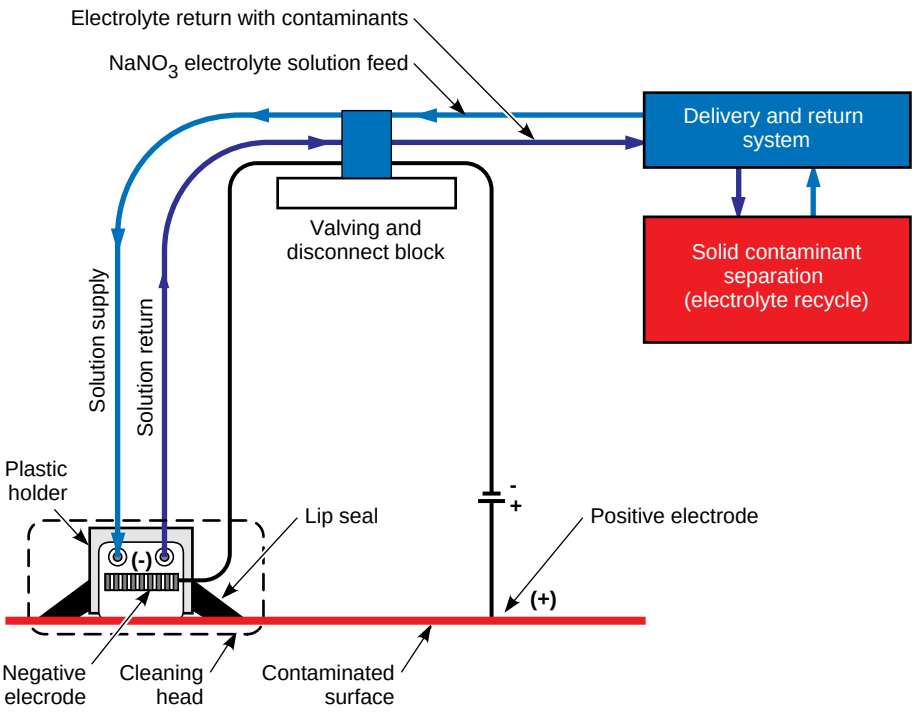


Figure 5. New Solution to Glovebox Decontamination

This new clean-up technology uses sodium nitrate as an electrolyte to remove plutonium and other contaminant's from metal gloveboxes. The surface to be cleaned functions as the anode and the cleaning head functions as the cathode. Plutonium ions and other contaminant's are pulled into solution by the voltage difference as the electrolyte passes through the layer between the cleaning head and the contaminated surface. The electrolyte then passes through a unit where the contaminant's precipitate out of solution. Thus there is no primary waste stream from this process. The system is designed to handle gram quantities of plutonium. Different cleaning heads are used to accommodate different glovebox-surface configurations. Numerous successful demonstrations of this methodology on a variety of surfaces have been done.

Dana C. Christensen is Deputy Division Director of the Nuclear Materials Technology Division at the Laboratory and is internationally known for his work in nuclear materials management, principally plutonium. Dana joined the Laboratory in 1979 after completing a research associate position at Battelle Pacific Northwest Laboratory. Since that time he has held a number of program and group management positions within the Laboratory, and has served on numerous national and international committees focused on chemical separations, waste minimization and pollution prevention, as well as facility design and operation, and weapon materials management. Dana has established and manages technology exchange activities in the field of actinide materials management with other DOE contractors and in foreign countries. Dana's research interest in the pyrochemical separation processes for extracting and purifying actinide elements led him to co-found the Actinide Pyrochemical Workshop, now in its fourteenth year. Dana received his B. S. and his M. S. in chemical engineering from New Mexico State University and earned a master's degree in business management from the University of New Mexico - Anderson School of Management.

Introduction to the

Alan McMillan, Gary Sanders, Ken Groves, and Michael Yesley

In January 1994, Laboratory Director Sig Hecker announced the formation of the Human Studies Project Team under the sponsorship of the newly organized Environment, Safety, and Health Division. The team was formed in support of the Department of Energy's openness initiative and in response to the public outcry concerning media stories that linked human radiation studies to Los Alamos. Sig felt it was essential to find and release all relevant documents as quickly as possible so that the public could evaluate the various accusations and assess the science and the ethics of those human radiation experiments in which Los Alamos had been involved.

Dennis Erickson

George Voelz

Clara Salazar, Cecilia Barrone, and Eulalia Newton

John Taschner

The Human Studies Project Team was staffed by a number of Laboratory scientific and administrative personnel, some of whom were retirees who had been involved in the experiments in question. Ethicists Joan Gibson from University of New Mexico and John Carey from St. John's College were brought in to enhance the team's social and ethical awareness. Representatives from state government were also invited to attend meetings. The primary objective was to search for, review and catalogue, and release to the public any documents from the Laboratory's records holdings that related to radiation and human experimentation.

Team members poured over hundreds of thousands of pages of documents from the Laboratory's archives, records center, and report library. Retirees reviewed personal notes and document collections. Many people expected that we would find horror stories. We didn't! What we did find was a lot of evidence that Wright Langham, Louis Hempelmann, and their contemporaries were solid scientists and caring individuals. They worked at a feverish pace to provide a high level of safety to people working with plutonium and other radioactive materials. It is hard to believe that Langham or Hempelmann would purposely neglect the people involved in any of their studies. The highest radiotracer doses, aside from the plutonium injections, were the tritium doses Langham gave to himself during a study to construct a bioassay model for monitoring people working with tritium. Wright wanted answers before people got hurt. Earlier, during the intense pressures of the Manhattan Project, Dr. Hempelmann constantly defended the rights of the workers to a safe and healthy work environment.

Somewhere in the feverish pace, the plutonium injectees were forgotten by physicians, scientists, the military, and the politicians. In the scientific literature, each subject became a nameless, faceless statistic identified by an acronym such as HP-3 or CHI-1. Aside from some media sensationalism, journalist Eileen Welsome should be thanked for bringing forward the names and faces of the plutonium injectees. We will never really know what, if any, consent was involved, and we cannot hide behind the fact that the experiments were well thought out, and the injected plutonium caused no harm. It is evident that people were used and then forgotten.

Human Studies Project

William C. Inkret

This introduction is not complete without some comments on my predecessors who also served as leaders of the Human Studies Project Team. During the initial public outcry, Alan McMillan, our first leader, used his considerable communication skills, gained as a federal regulator, to show the world we were very serious about our task and were performing it honestly. Gary Sanders, who took over in the summer of 1994, used a physicist's approach to hone a fine edge on the then battle-hardened team. Openness and sensitivity to the rights of the individual and the local communities were Gary's prime concerns. In the fall of 1994, Ken Groves, a broadly experienced health physicist, took over as the team began to interact with the President Clinton's Advisory Committee on Human Radiation Experiments. Ken successfully guided us during the period when a mistake would have had major political fallout. Attorney Michael Yesley took on the leadership role in December 1994, and his tireless efforts were crucial to the publication of a high quality report by the President's Advisory Committee.

The articles that follow were written by several of the team's scientist/retirees who worked on different aspects of radiation studies involving human subjects. Their stories give some insight into the practices and needs of the period from 1943 to the early 1980s. In light of the many unfounded accusations cast their way, these individuals have shown much courage and stamina both as team members and as authors. They are good people and outstanding scientists. They have followed the rules, used integrity in their judgements, and provided invaluable scientific information for the good of humankind. They have weathered a lot of pain and hurt; here they have a chance to provide some history and insight.

The individuals in the photos on these two pages were members of the Human Studies Project Team with the exception of Duncan Thomas and Marissa Caputo of the President's Advisory Committee and Staff and journalist Eileen Welsome. Although not shown here, team members Lynn Cline, Carmen Gallegos, and Chris C'de Baca deserve special thanks for maintaining administrative continuity through the many stages and leadership changes of this unique project.

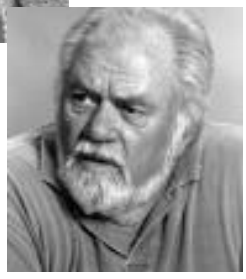
Finally, grateful acknowledgment is extended to Dennis Erickson, who, as Director for Environment, Safety, and Health, served as institutional champion for this project throughout its existence. Denny provided unflinching support, demanded rigor and quality, and always found ways to recognize excellence.■

Bill Inkret

Michael Yesley and Marissa Caputo

Clarence Courtright

Margo Clark



Don Petersen

Eileen Welsome and Joan Gibson

Bill Moss and Duncan Thomas

The Human Plutonium Injection Experiments

William Moss and Roger Eckhardt

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

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

Louis Hempelmann

similar radiation experiments with humans.

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

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

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

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

The Manhattan Project and Its Need for Plutonium

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

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

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

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

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

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

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

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

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

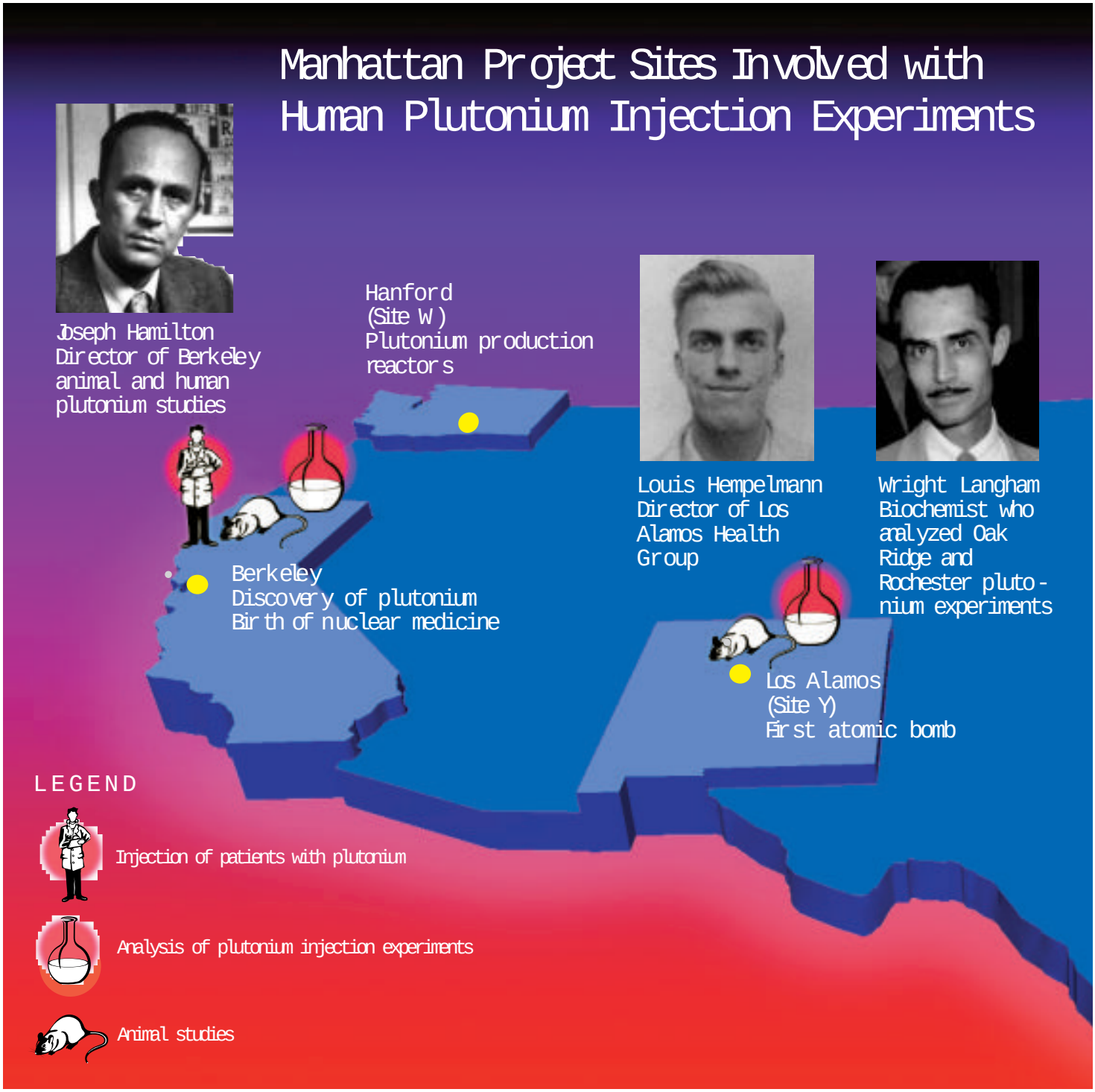
In March 1943, the Los Alamos Project became operational under the direction of J. Robert Oppenheimer. The responsibility of this laboratory was the design of the uranium-235 and plutonium-239 weapons. Two months later, Los Alamos was also assigned responsibility for the final purification of plutonium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

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

The Making of Plutonium-239

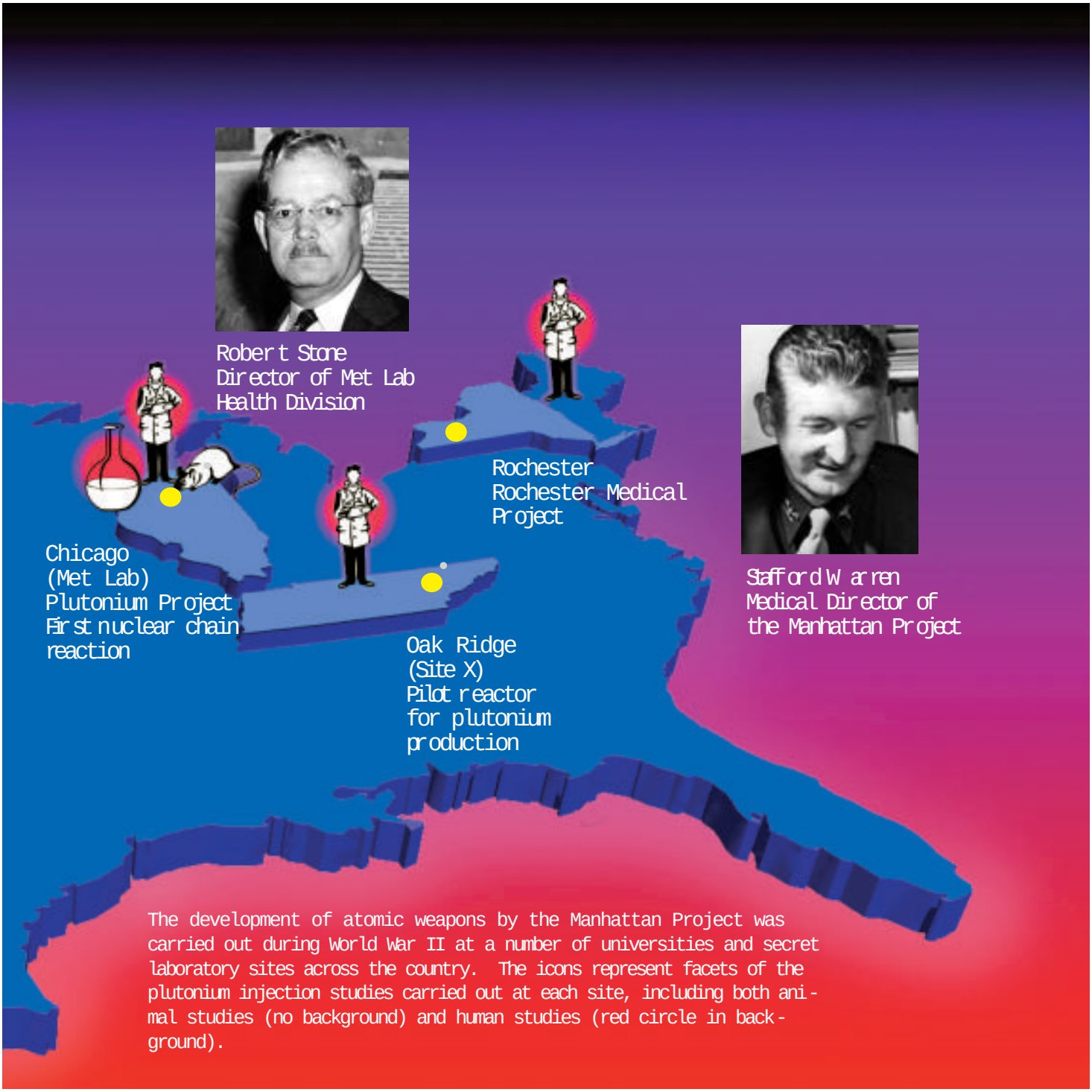
In 1940, Edwin McMillan and Philip Abelson demonstrated with the cyclotron at the University of California Radiation Laboratory in Berkeley that when uranium-238 was bombarded with neutrons, a new element was produced (neptunium-239) that was chemically distinct from the uranium. In 1941, Glenn Seaborg,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

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



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

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



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

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

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

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

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

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

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

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

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

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

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

Worries About the Health Hazards of Plutonium

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

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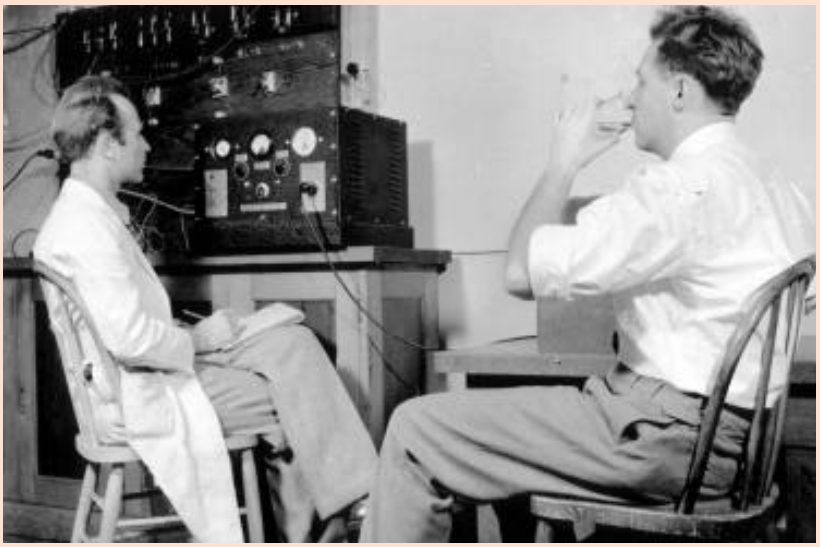
The Medical Researchers

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

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

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



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

continued from page 182

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

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

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

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

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

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

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

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

Tolerance limits. According to the

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

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

Compton added:

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

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

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

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

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

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

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

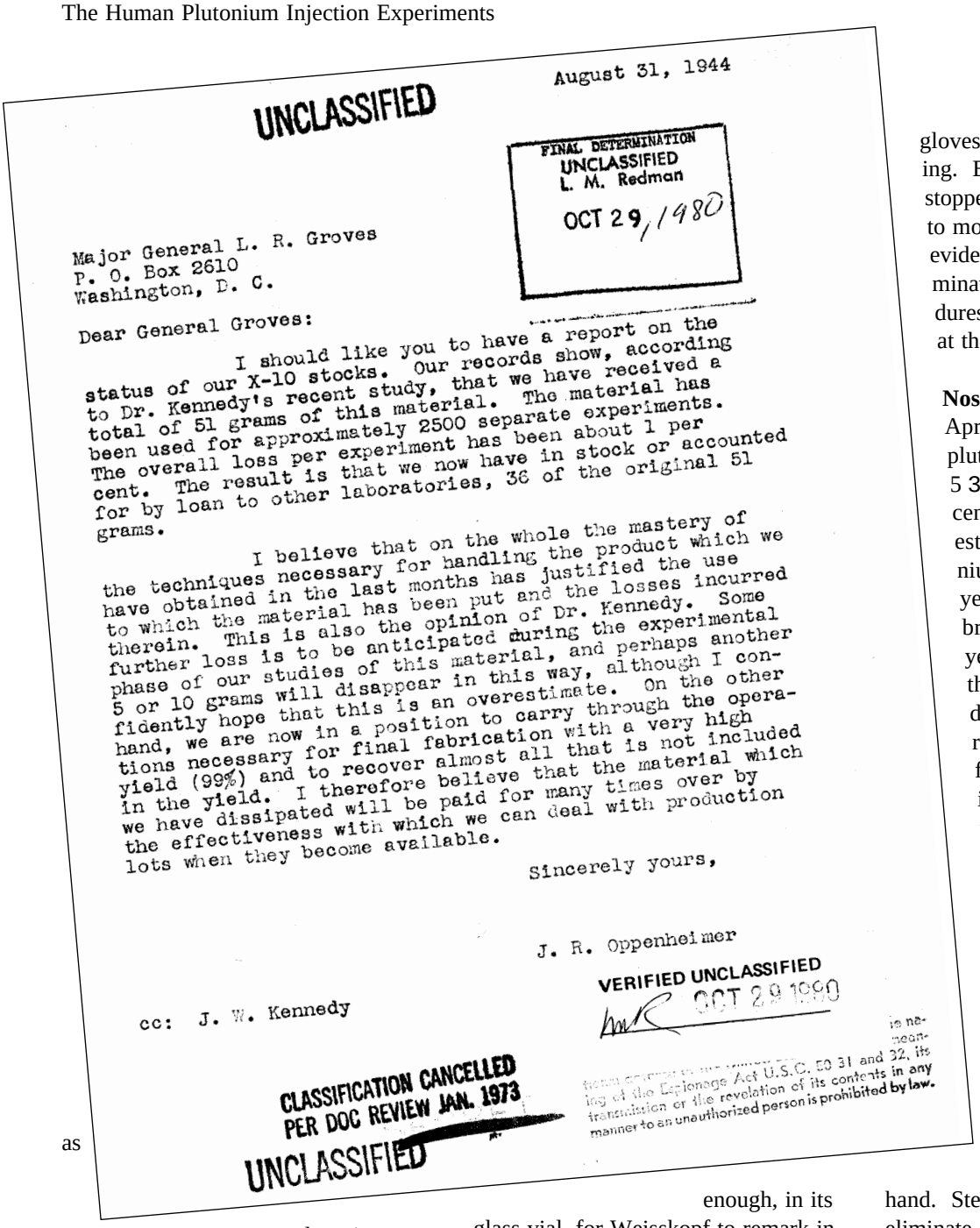
Thus, people throughout the Manhattan Project were aware of the potential dangers of plutonium. But their thinking involved the various assumptions about plutonium's biological behavior and toxicity. Because the number of people working with plutonium was increasing rapidly, the people responsible for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

Working With Plutonium

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

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

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



UNCLASSIFIED

August 31, 1944

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

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

Dear General Groves:

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

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

Sincerely yours,

J. R. Oppenheimer

cc: J. W. Kennedy

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OCT 29 1980

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PER DOC REVIEW JAN. 1973

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

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

Nose swipes. By the end of April, the Met Lab proposed a plutonium air tolerance limit of 5 3 $10^{2\,10}$ micrograms per cubic centimeter of air (arrived at by estimating the build-up of plutonium in the lungs over a two-year period for a worker breathing the air 300 days a year). A procedure to detect the inhalation of plutonium dust using nose swipes had already been initiated. A moist filter-paper swab was inserted into the nostril and rotated, then the swab was spread out, dried, and read in an alpha detector. A reading of 100 counts per minute or higher was considered evidence of an exposure.

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

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

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

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

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

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

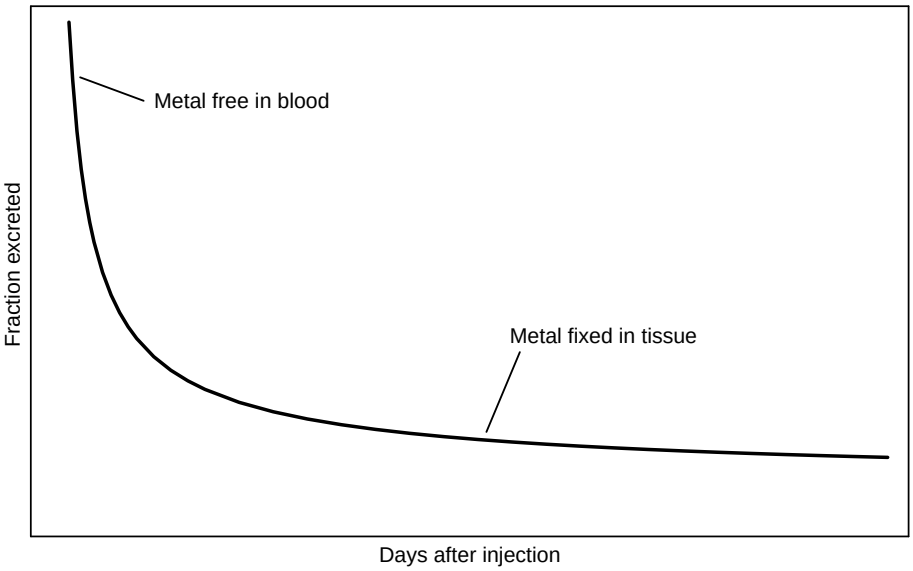


Figure 1. Daily Urinary Excretion for an Internal Exposure

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

Plutonium Animal Studies

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

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

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

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

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

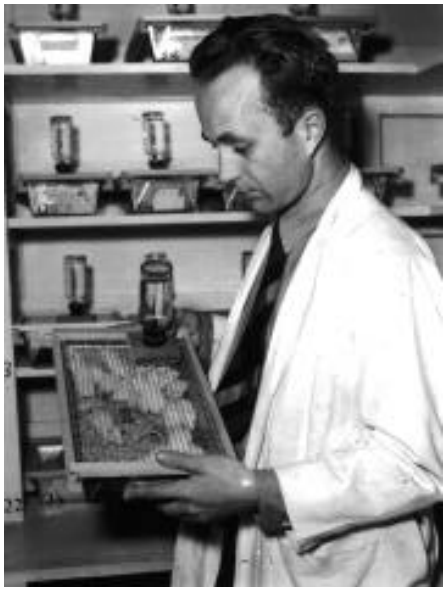
A Met Lab progress report for February containing Hamilton's input stated:

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

And the report for March noted:

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

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



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

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

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

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

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

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

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

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

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

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

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

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

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

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

Planning for the Human Injection Studies

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

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

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

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

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

A Swallow of Plutonium

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

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

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

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

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

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

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

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

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Detection of Internal Plutonium

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Estimates of the Detection Regime

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

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

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

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

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

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

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

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

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

The Los Alamos Urine Analysis Method

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

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

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

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

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

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

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

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

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

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

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

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

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

The First Human Experiments with Plutonium

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

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

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

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

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

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

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

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

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

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

Polonium Human-Injection Experiments

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

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

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

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

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

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

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

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

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

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

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

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

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

A Cross-Check of Analytical Procedures

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

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

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

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

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

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

*Recalculated in 1976 by Patricia Durbin

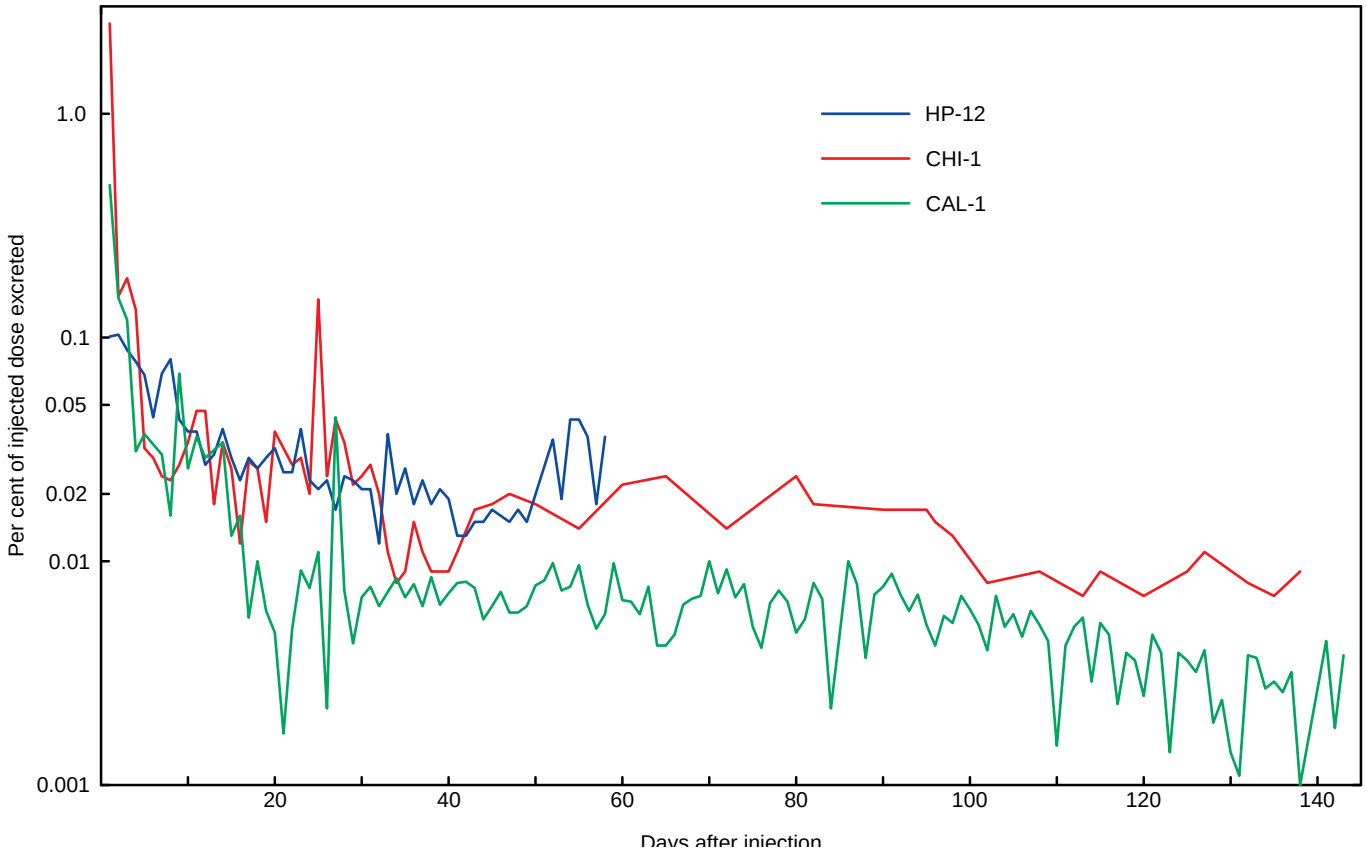

Figure 2. The First Plutonium Urinary Excretion Curves

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

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

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

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

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

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

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

In regard to fecal excretion, the report stated:

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

The May 31 report of Hamilton's group concluded:

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

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

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

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

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

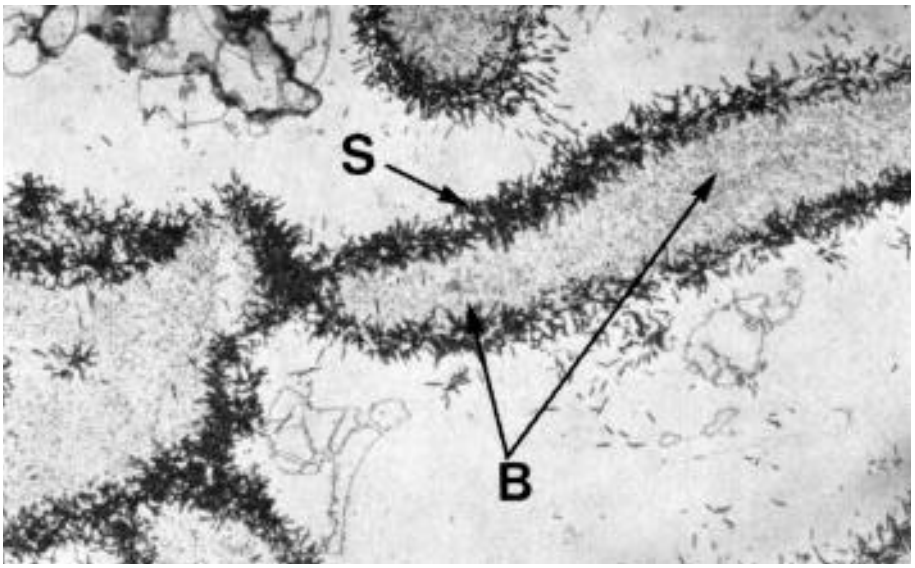

Figure 3. Deposition of Plutonium in the Bone

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

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

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

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

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

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

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

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

The level established for plutonium was

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

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

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

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

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

Further Human Plutonium Injection Experiments

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

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

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

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

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

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

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

Louis H. Hempelmann—1914-1993

Louis Hempelmann (right) with George Voelz looking on.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

It was also stated in the plan that:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

District.

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

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

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

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

Estimating Effects of the Injection Dose

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

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

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

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

Wright Haskell Langham—1911-1972

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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Table 2. The Eighteen Patients Injected With Plutonium

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Results of the Injection Experiments

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

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

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

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

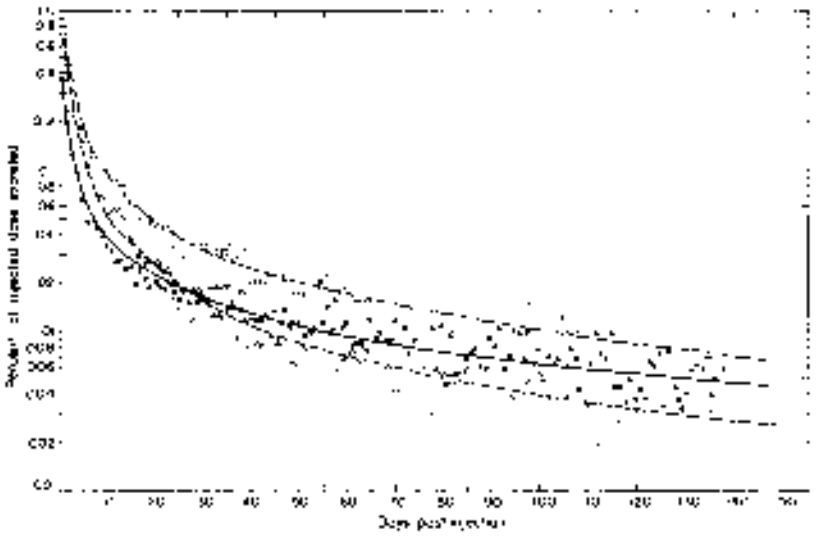

Figure 4. Plutonium Excretion for 138 Days

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

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

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

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

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

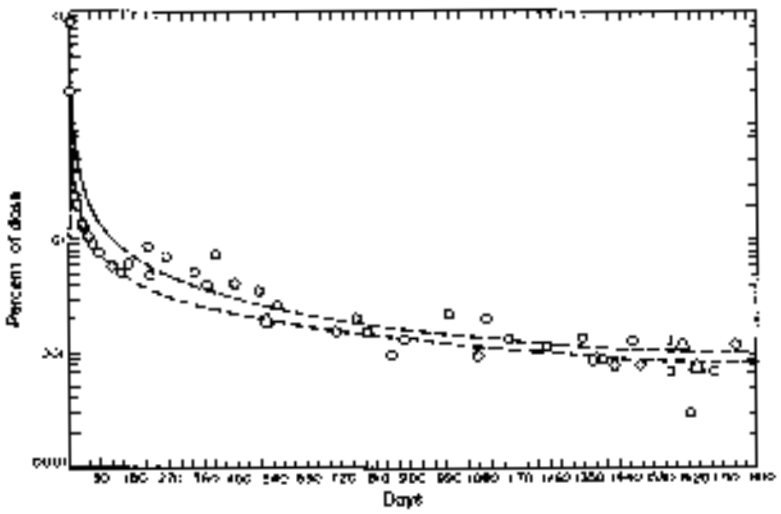

Figure 5. Plutonium Excretion for 1750 Days

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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Consent in the Human Plutonium Injection Experiments

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Changes in the Maximum Permissible Body Burden

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

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

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

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

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

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

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

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

Additional Data from the Plutonium Patients

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

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

A Computer Analysis of Plutonium Excretion

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

A Recent Analysis of the Excretion Data

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

Bill Moss and Eileen Welsome

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

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

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

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

Moss and Tietjen next used the sparse

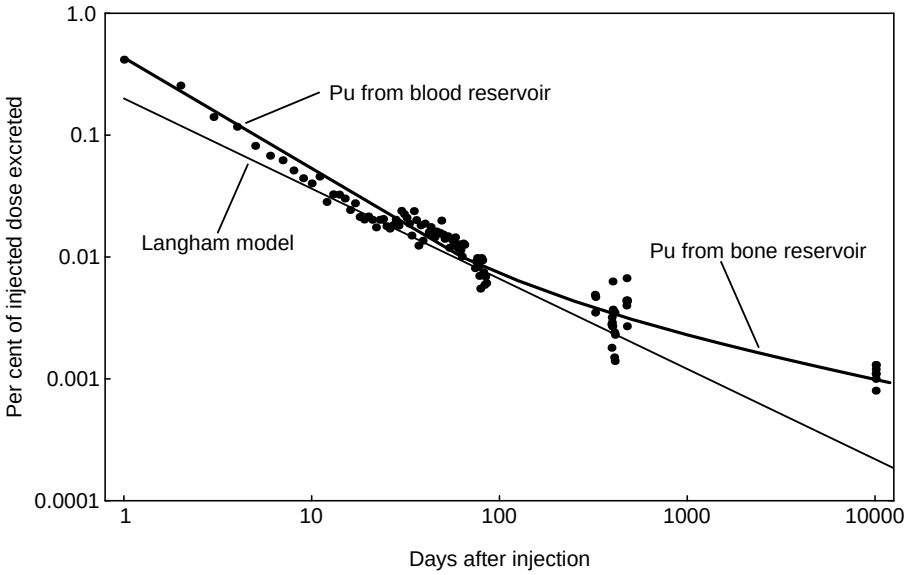

Figure 6. A Re-analysis of the Plutonium Urinary Excretion Data

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

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

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

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

Table 3. 10,000-day Excretion of Plutonium

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

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

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

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

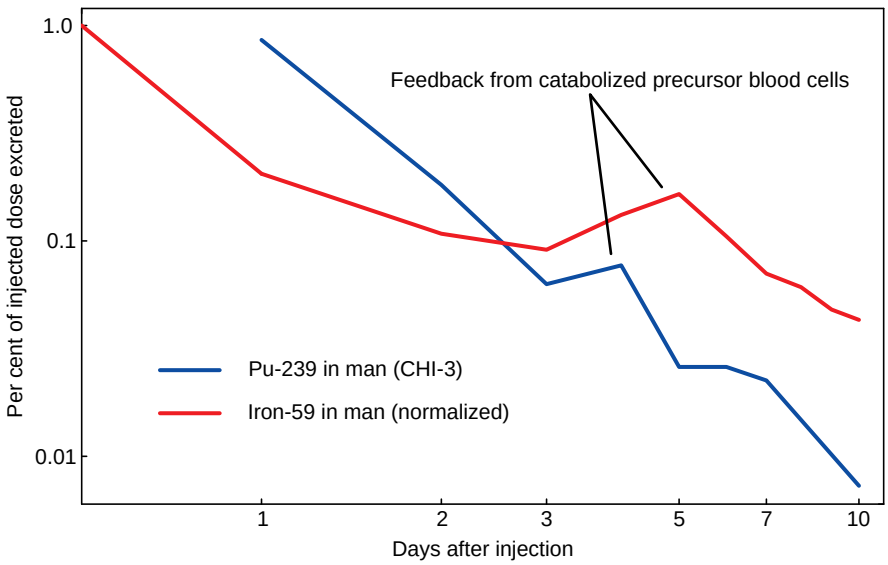

Figure 7. The Four-day Peak for Red Blood Cells

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

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

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

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

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

Implications of the Plutonium Injection Studies

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

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

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

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

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

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

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

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

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

Acknowledgements

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

Further Reading

A collection of copies of the documents gathered

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

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

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

Radium–the Benchmark

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

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

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

for Alpha Emitters

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

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

Inset: Pierre Curie (1859-1906).

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

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

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

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

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

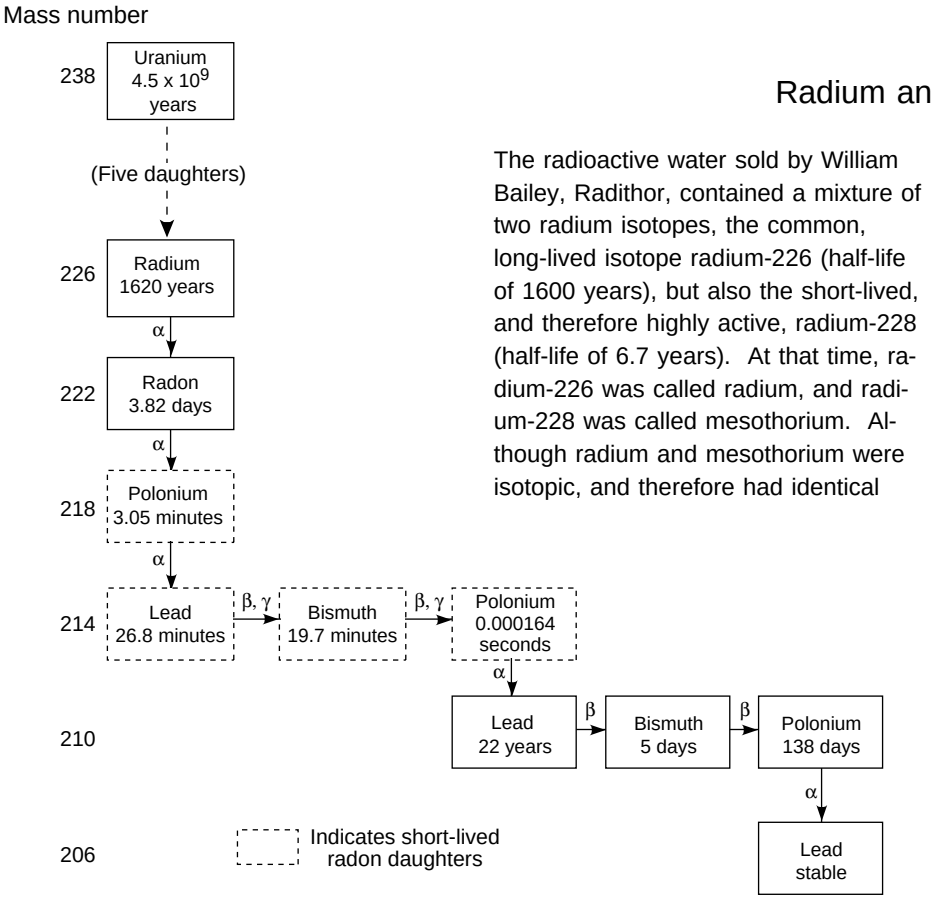
Figure 1. A Miracle Cure Brought about through Radium Treatments

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

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

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

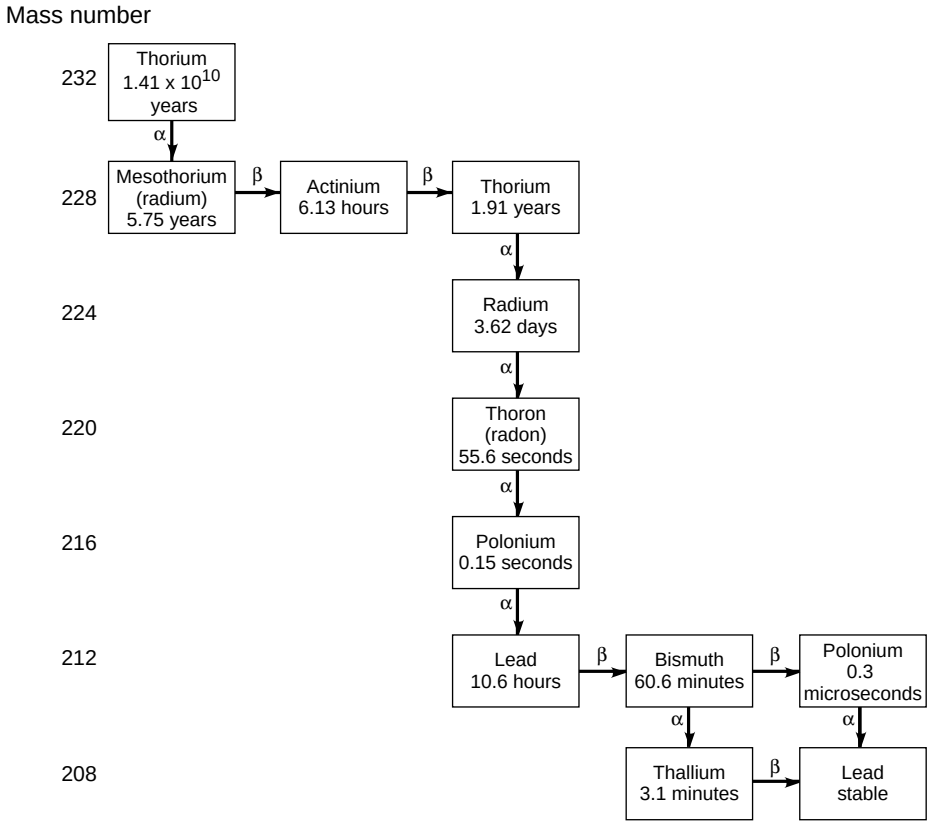
When the United States entered the war in 1917, a factory in Orange, New Jersey, became a major supplier of radium-dial instruments to the military. The factory employed hundred of workers, most of whom were very young women. Those women were in the practice of "tipping" their brushes, that is, using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



Radium and Mesothorium

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

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



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

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

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

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

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

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

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

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

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

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

Robley Evans in his laboratory at MIT.

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

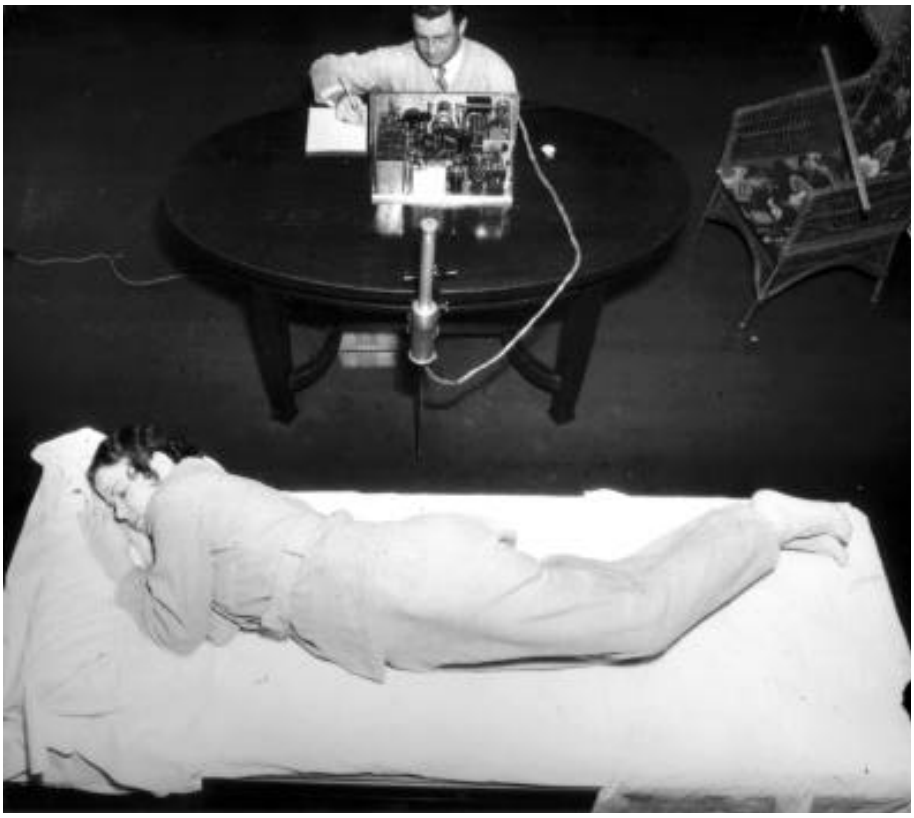
Evans became interested in the uptake, metabolism, and excretion of radium in living persons and realized that the key to studying those problems would be the ability to accurately measure the amount of radium present in the living body. However, the alpha particles emitted by radium are only weakly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

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

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

In Vivo Measurements of Radium

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



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

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

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

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

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

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

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

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

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

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

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

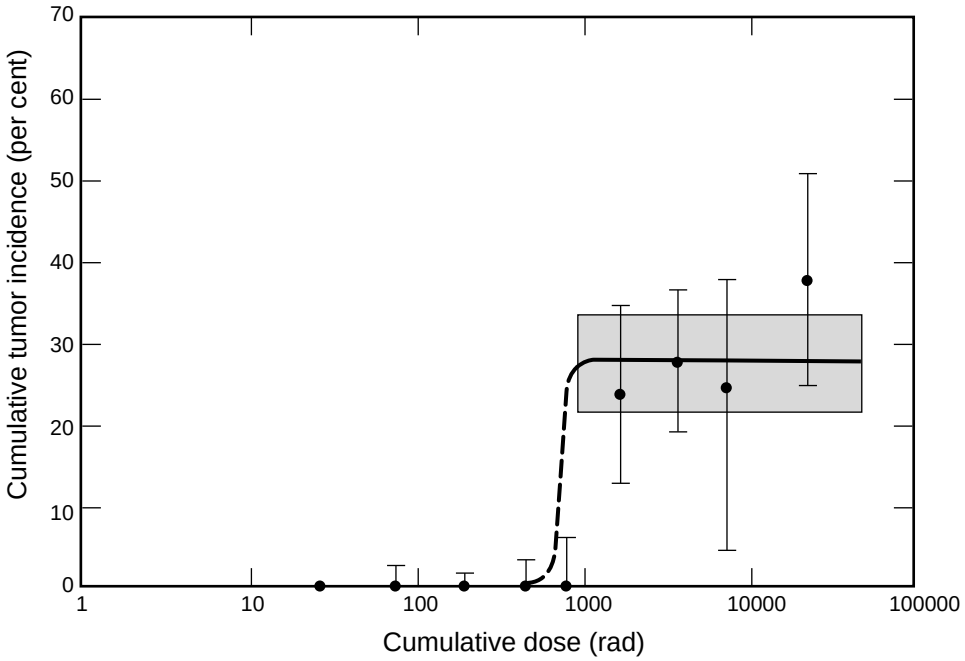


Figure 2. Radium-induced Cancers

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

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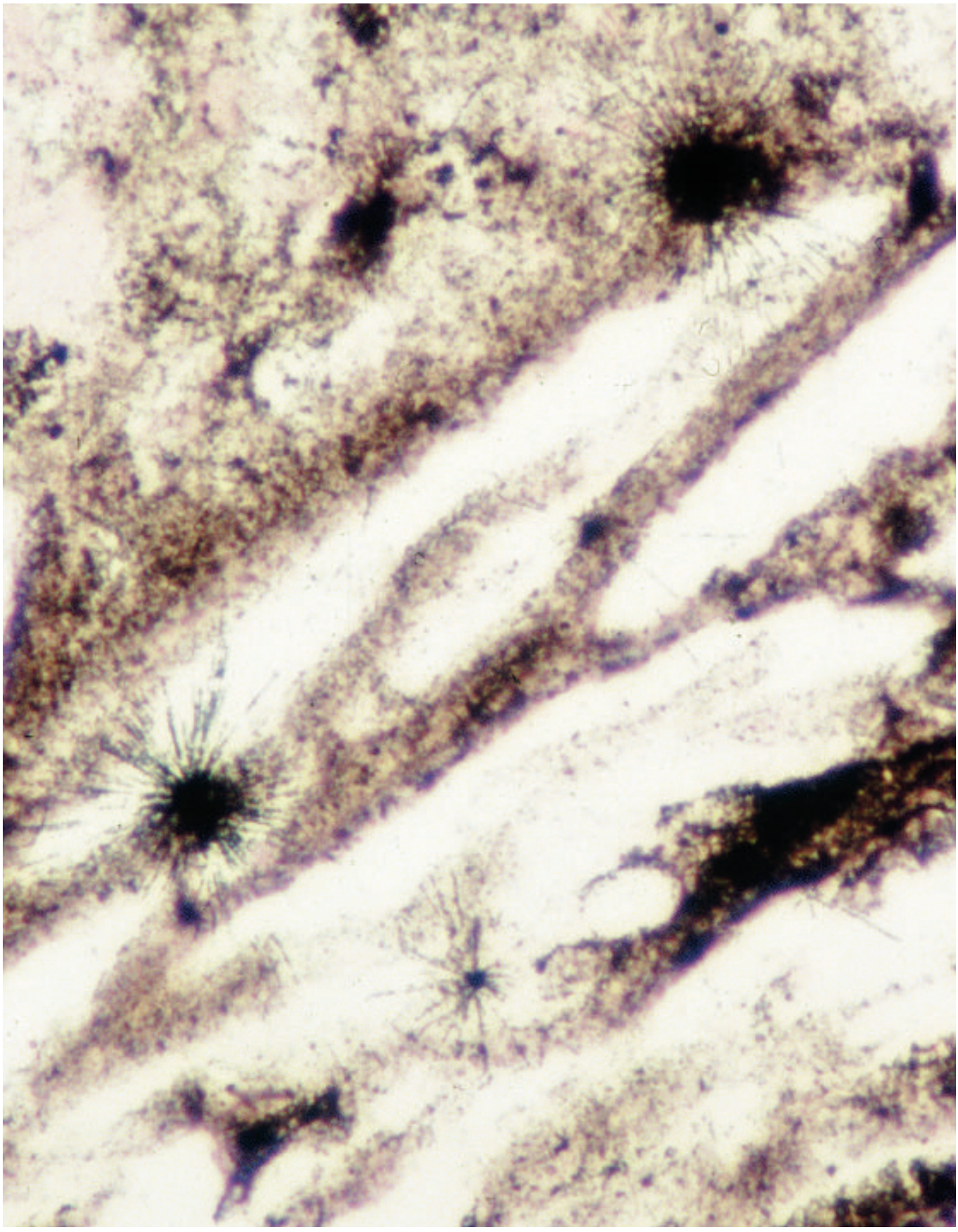

A TRUE MEASURE OF EXPOSURE

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 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 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 matierial. 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.

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. Lushbaugh, 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 conserted 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, tracheobronchial 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 perfomed 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.

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.

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.

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.

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.

While the body cavity lies empty, a piece of the vertebrae is sliced off the interior side of the vetebral 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 shortening 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.

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.

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

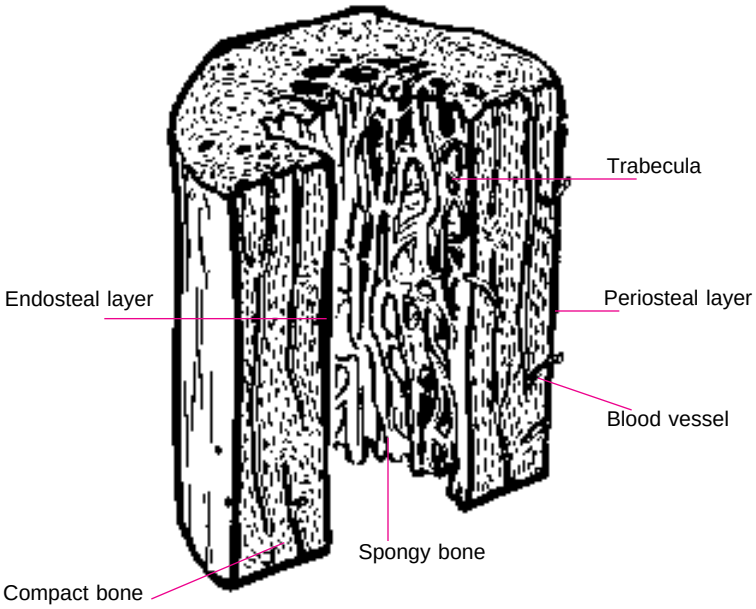

Figure 2. Spongy versus Compact Bone

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,

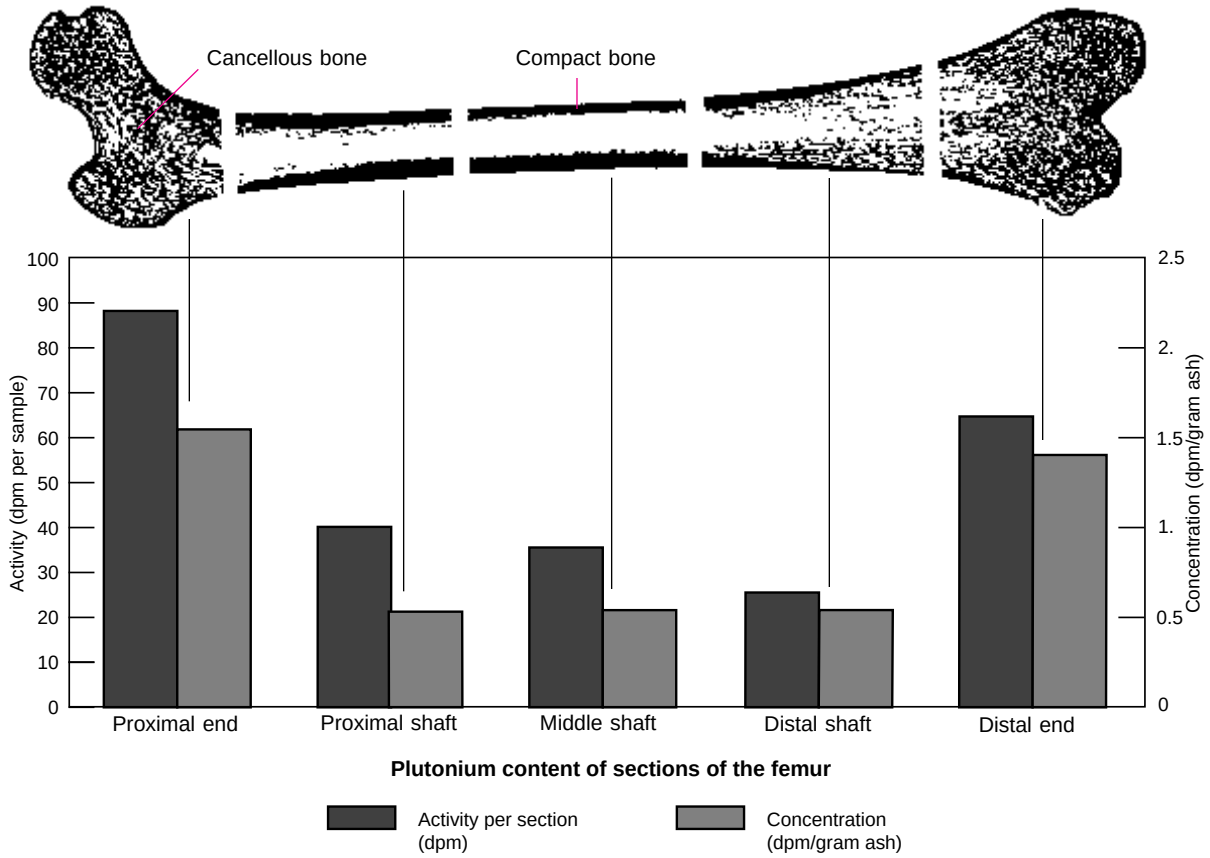

Figure 3. Deposition of Plutonium in a Thigh Bone

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 stucture 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-

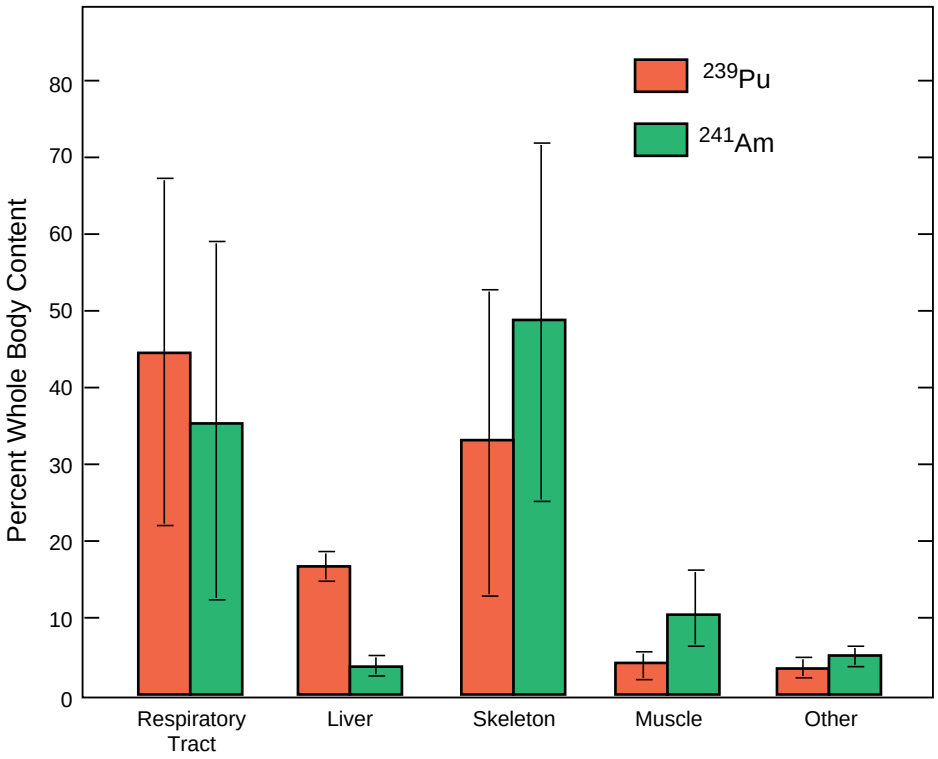

Figure 4. Whole-body Distibution of Plutonium and Americium

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 hepatitus-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

		Systemic Burden of Plutonium-239* (nanocuries)			
Biokinetic Model	**Date**	**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 Leggert 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 andendosteal 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 nearby 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 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.

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.

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

1967-68

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

The table summarizes the results of statistical testing for geograhic differences in the plutonium content of different tissues. The two-letter abbrevations 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 shipping 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 know 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 uncontroled 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 inadvertantly 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 determine 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

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The Karen Silkwood Story

Karen Silkwood died on November 13, 1974 in a fatal one-car crash. Since then, her story has acheived 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

what we know at Los Alamos

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 Cresent. 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.

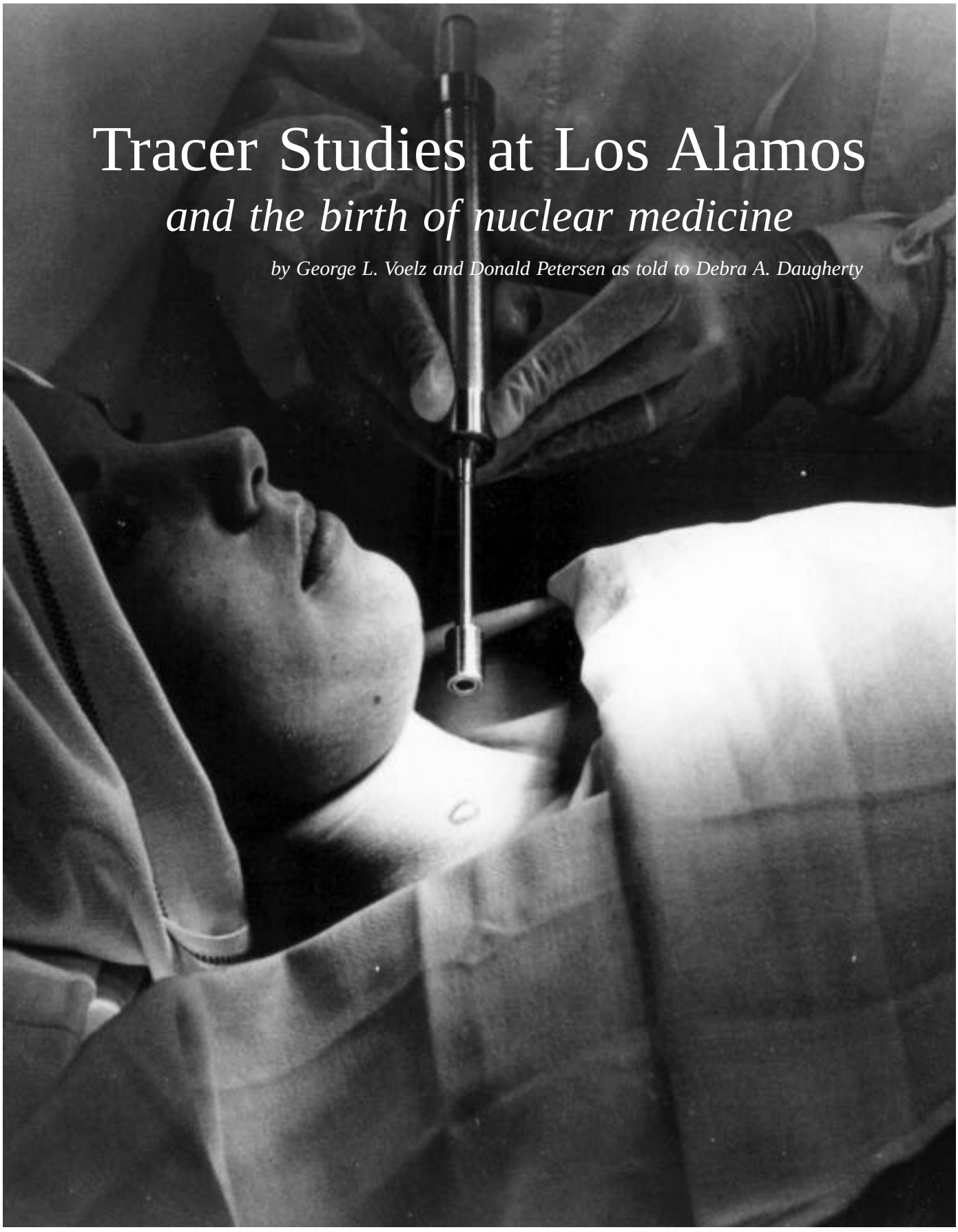
With the exception of the left lung, the remaining unanalyzed tissues were repackaged and kept frozen until it was determined whether or not additional analyses were required. The left lung was thawed, inflated with dry nitrogen until it was approximately the size that it would have been in the chest, 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.

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

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. ■



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

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

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.

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

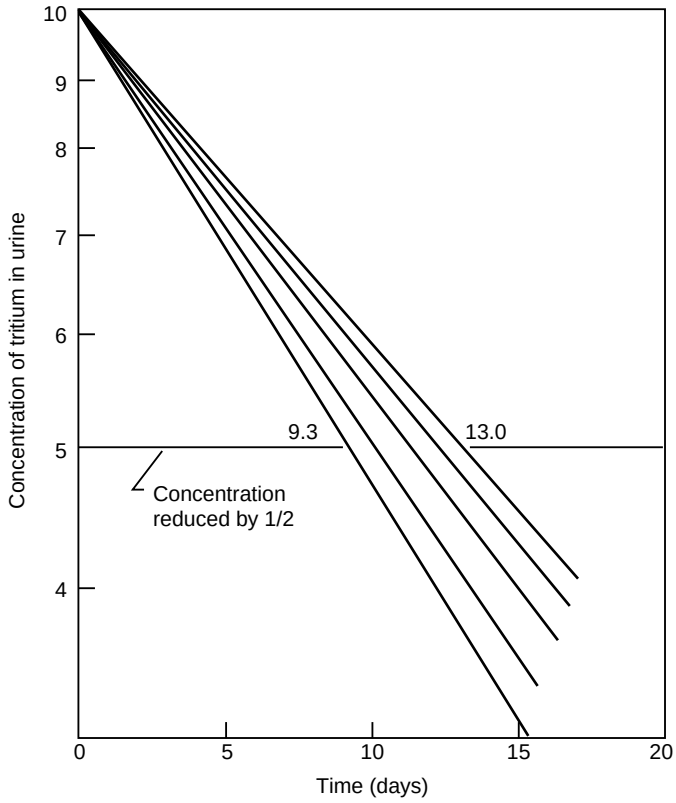


Figure 2. The Tritium Accident
The concentration of tritium in the urine of six accidentally exposed scientists was measured daily for over two weeks. This logarithmic plot of the concentration (arbitrarily normalized to the same initial value) versus time, shows that the biological halftime for tritium 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

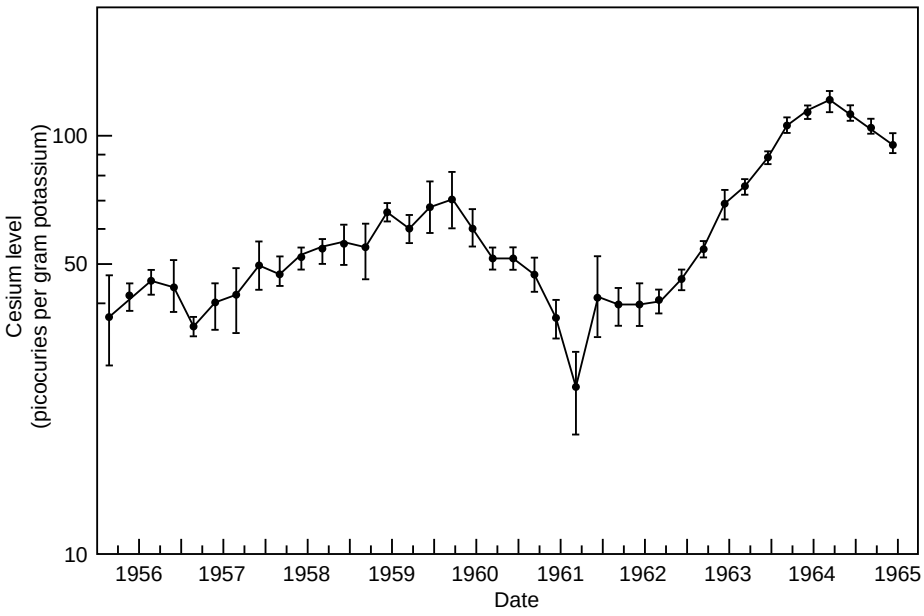


Figure 4. The Rise and Fall of Fallout

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

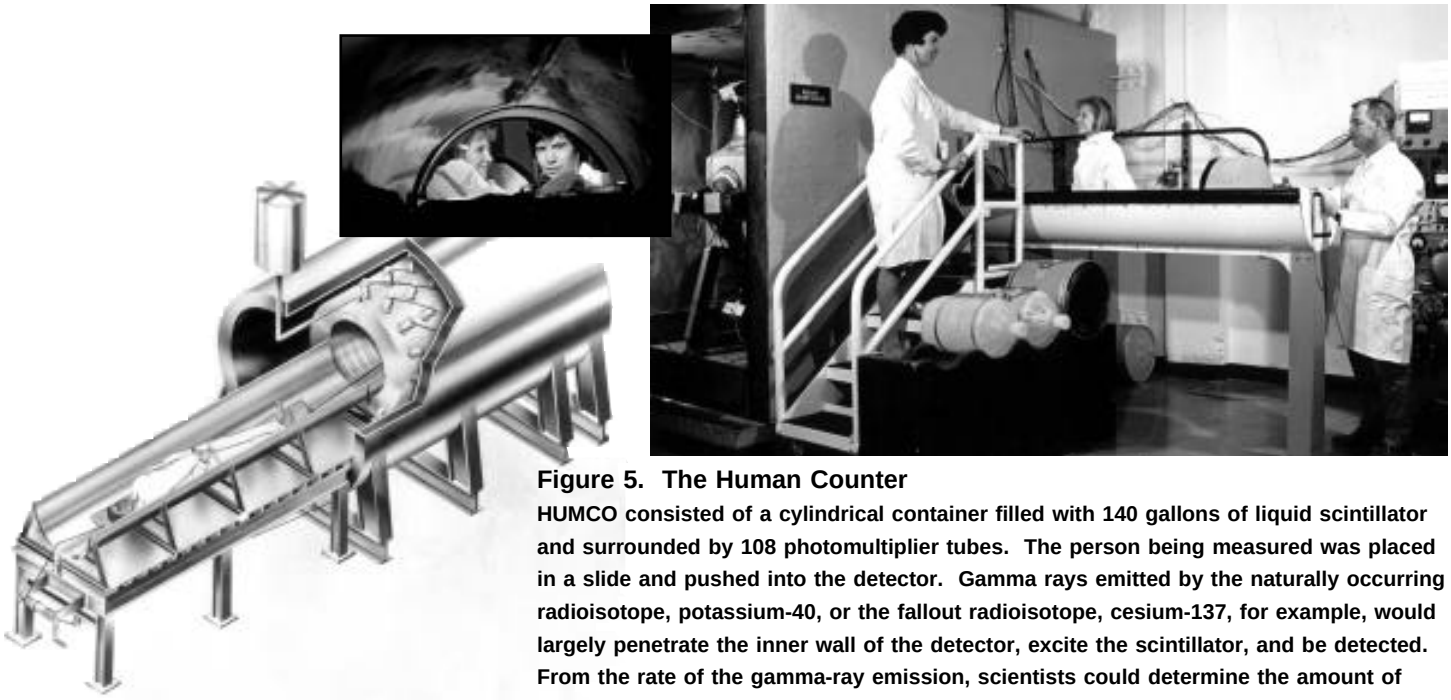


Figure 5. The Human Counter

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-

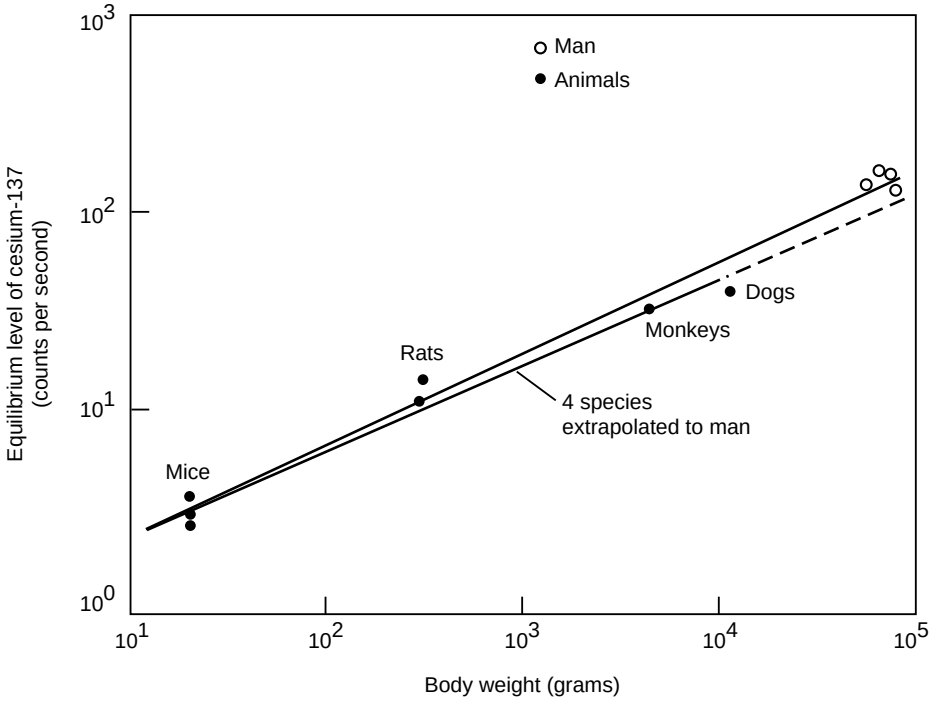


Figure 6. From Mammals to Man

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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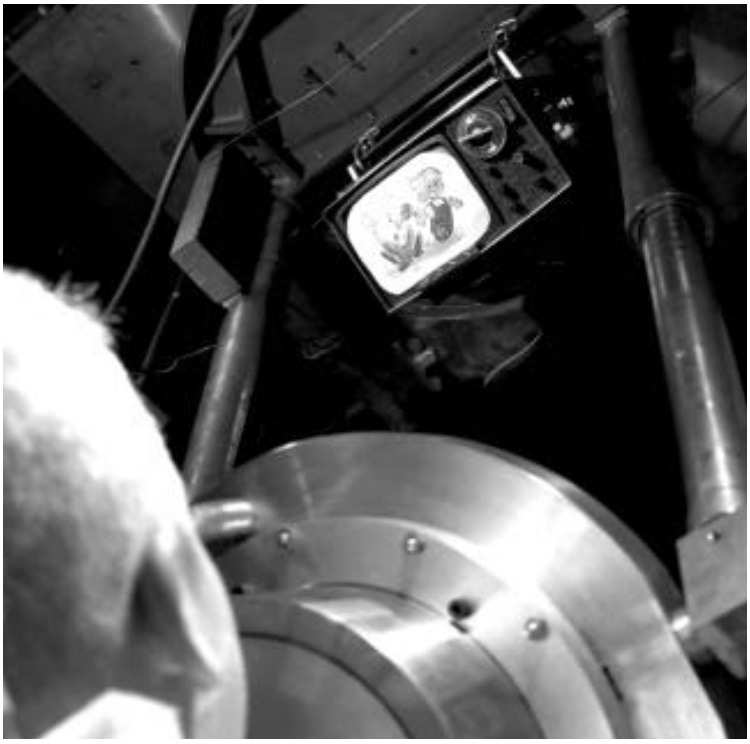
Child Volunteers: One Dad Tells the Story

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.



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.

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 .

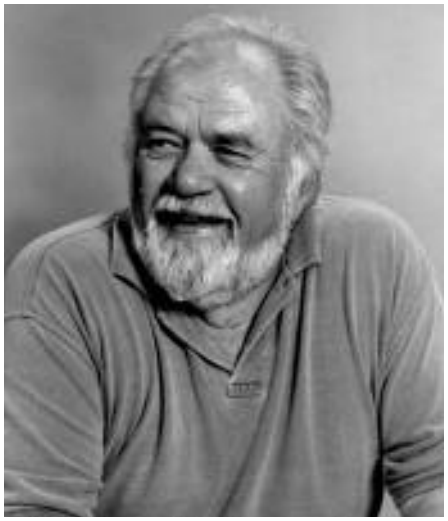
The iodine-131 in fallout was a problem for children in particular. You see, the radioactive iodine produced by nuclear weapons falls on pastures, cows eat the iodine, the iodine is concentrated in the cow's milk, and then people drink the milk. Because the thyroid picks up iodine preferentially, the 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.

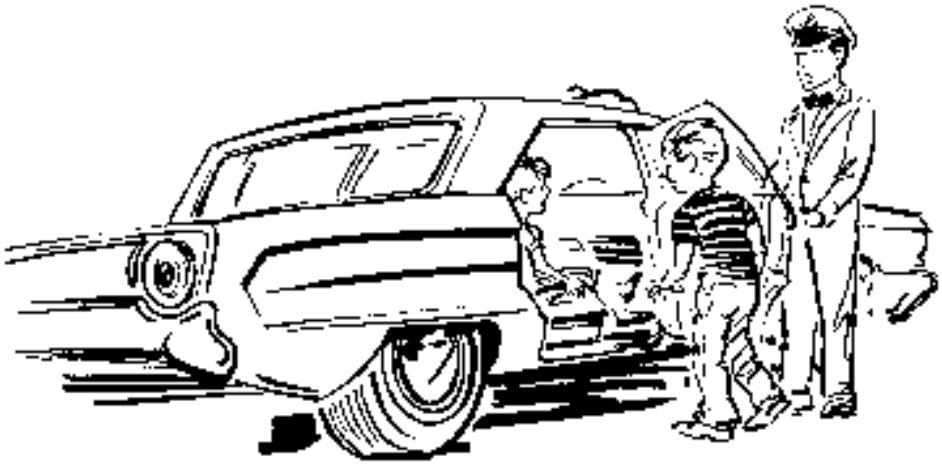
Van Dilla and Fulwyler made sure that the kids who were interested would be available for the length of the study because you wouldn't want the children to leave in the middle of the experiment to go on vacation. In the end, four of one of the investigator's kids, two of my kids, and two of someone else's 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.

Christy

. . . with Sarah

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.

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.

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.

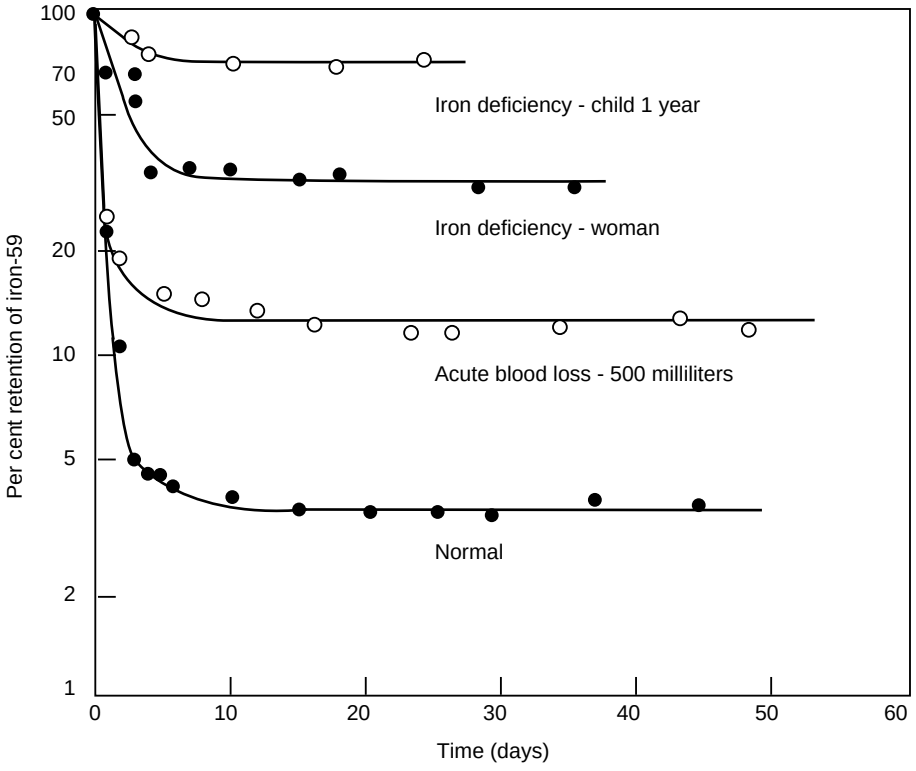

Figure 7. Anemia and Iron Retention

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

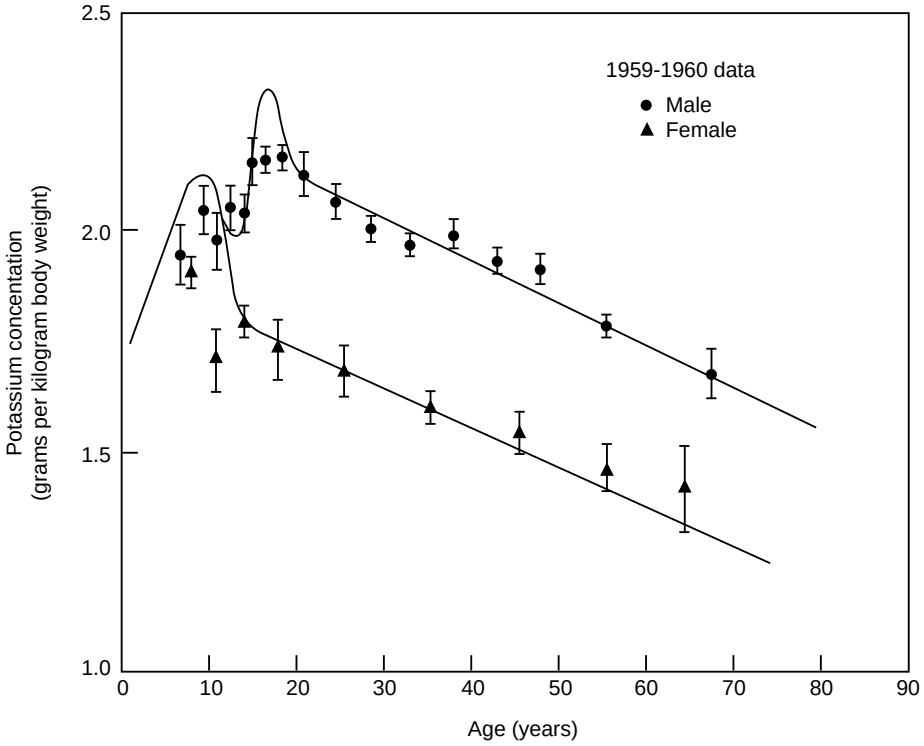

Figure 8. Muscle Mass by Age and Sex

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 ex-

periments. 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.

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.

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."

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. ■

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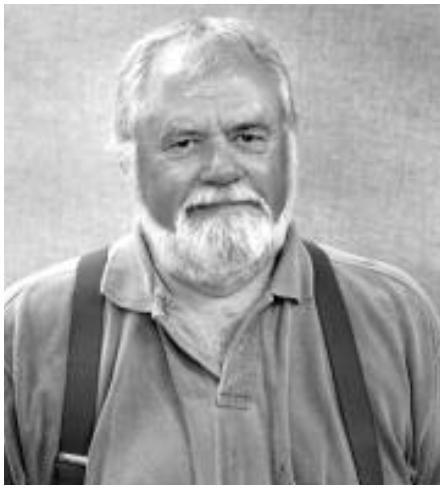

George Voelz, a native of Wisconsin, received his M.D. degree in 1950 from the University of Wisconsin Medical School followed by an internship at the University of Oregon Medical School Hospital and Clinics. In 1951 George completed an Atomic Energy Commission Fellowship in Occupational Medicine at 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.

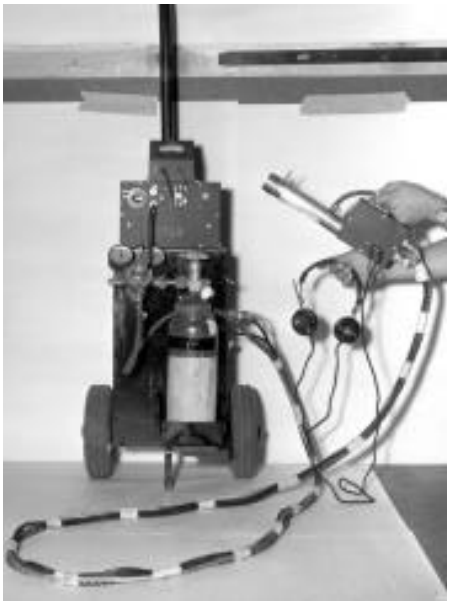

Figure 1. Supersnoop

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

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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).

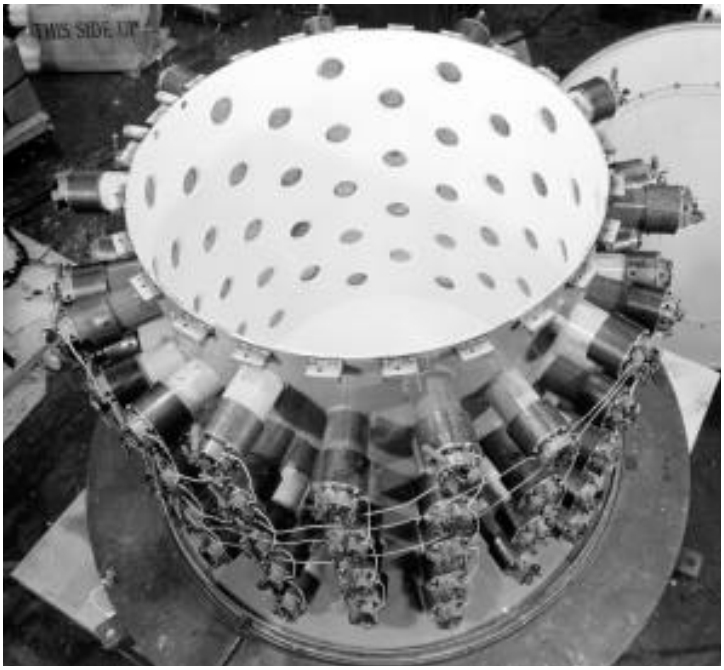

Figure 4. The Neutrino Detector
This top view of the giant Hanford neutrino detector shows the interior of the ten-cubic-foot vat for the liquid scintillator and the 90 photomultiplier tubes peering inside. This detector was the first step toward the discovery of the neutrino, work for which Fred Reines (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 5×10^{-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.

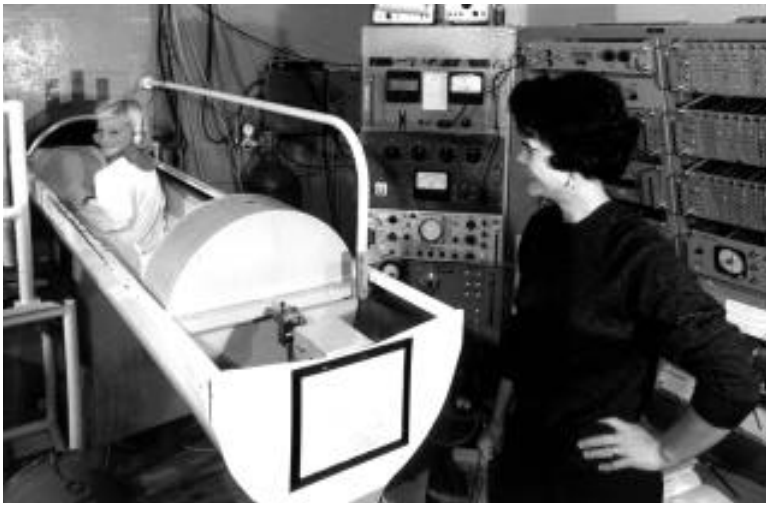

Figure 7. A Young Volunteer
Many New Mexican residents were monitored for the level of fallout radionuclides in their body. Here, a young resident enters the cylindrical opening of HUMCO I under the supervision of the attendant, Annie Hargett. Several young volunteers were counted weekly to determine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

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"Ethical Harm" and the

During the 1940s researchers in the United States injected plutonium into eighteen hospital patients without their informed consent. Reports of this research in the scientific literature and investigations during the following decades did not raise public concern, but in 1993 a series of news articles identified five of the patients and drew more attention to the plutonium injections. DOE Secretary O'Leary publicly questioned the ethics of the research. Subsequent news articles described additional studies that had exposed human subjects to radiation without their informed consent. Public concern mounted, Congress held hearings, and President Clinton appointed an Advisory Committee on Human Radiation Experiments.

The Advisory Committee's assignment was to determine the ethical and scientific standards for the human radiation experiments and to evaluate whether the experiments met those standards. After reviewing a mass of information, conducting hearings, and deliberating at monthly meetings for a year and a half, the Advisory Committee issued its Final Report in October 1995. We review this report and the issues it attempts to resolve below; the human research with plutonium is described in "The Human Plutonium Injection Experiments" in this volume.

As first recounted in the news, the plutonium injections seemed disturbingly similar to the experiments for which several Nazi doctors were imprisoned or executed after trials at Nuremberg. The scientists in the United States had opportunistically used hospital patients as unwitting subjects in non therapeutic studies of exposure to radiation. Although the researchers expected the patients to die soon of their existing illnesses, some survived for decades after the plutonium injections. Their survival intensified questions about the effects of the experiments.

Clarification of the news was soon forthcoming. Radiation scientists familiar with the plutonium research pointed our that the patients received very small amounts of radiation considered unlikely to cause injury or illness. Furthermore, the purpose of the research was not to determine the effects of exposure to plutonium, but its pathway through the body. Comparison of the amount of injected plutonium with the amount of plutonium excreted by the patients enabled the researchers to develop a model for estimating occupational and accidental exposures of atomic weapons workers from their excretion. In its investigation, the Advisory Committee found no evidence that the plutonium injections injured anyone. Also, the Committee agreed with the scientists that the plutonium injections "produced results that continue to benefit workers in the nuclear industry today."

The Committee confirmed, however, that the patients "were not told that they were to be used in experiments for which there was no expectation they would benefit medically, and, as a consequence, it is unlikely they consented to this use of their person." The failure to inform the patients might be attributed to the difficulty of discussing a substance whose very existence was classified, and to the customs of medical research at the time. The Committee determined that "it was not uncommon in the 1940s for physicians to use patients as subjects in experiments without their knowledge or consent" even when the research held no prospect of benefiting the patients. Thus, some have argued, the plutonium injectees suffered only "ethical harm"—an unexceptional invasion of their rights without practical consequences. By contrast, the moral transgressions of the Nazi doctors involved unspeakable acts of maiming and murder.

The Advisory Committee confronted several difficult issues in evaluating experiments that did not cause physical harm or deviate from common practice. The problem of "retrospective moral judgment" was especially challenging: could the Committee apply current ethical standards to research conducted a half-century ago, or should the ethical evaluation be limited to the standards and values of that time? The Committee also considered whether the families of the patients (now all dead) should be compensated for "ethical harm" and if so, by what measure. Perhaps most important, the Committee drew lessons for the future from its review of the plutonium research.

Judging the past

Federal regulations now require informed consent for most experiments with human subjects. At the time of the plutonium injections, however, there were no regulation or professional standards that required the consent of hospital patients to participate in research. On what basis, then, could the plutonium injections be criticized?

From the outset of its deliberations, the Committee attempted to avoid judging the past by today's standards. The Committee concluded that in addition to government rules and professional standards, which are applied only prospectively, there are also "basic ethical principles" that are not limited by

Plutonium Injection Experiments

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time. These fundamental principles, which include obligations to respect self-determination and not treat people as means to others' ends or deceive them, provide an ethical framework for judging past actions.

Informed consent

The principal of respect for a competent individual's right of self-determination serves both practical and idealistic goals. The idealistic goal appears to predominate: respect for the individual is a fundamental, virtually unquestioned value in western society. But informed consent serves practical goals as well, including the encouragement of rational decision-making, enhancement of the physician-patient relationship, and reduction of unfavorable public reaction. Clearly, obtaining informed consent to the plutonium injections would have served the last goal well and avoided the subsequent outcry.

Although informed consent was not obtained in either the Nazi medical experiments or the plutonium injection experiments, significant distinctions can be drawn. Hospital patients are a vulnerable population, but they do not endure the inhumane, sharply reduced circumstances of the concentration camp victims. Competent hospital patients retain the ability to give informed consent, but voluntariness was impossible in the concentration camps. Also, there was a substantial difference between the drastic experimental procedures of the Nazis and the injections of tracer amounts of plutonium. Exposure to radiation above certain levels will have severe consequences, but the Advisory Committee found no evidence that the low doses of the hospital patients caused harm.

Still, the low risk of the plutonium injections and the important national security interests served by the research did not justify the failure to obtain informed consent. If the eighteen hospital patients had been asked, most of them—or others in their place—would probably have consented to the plutonium injections. They would have been told the research posed little risk to them and was important to assure the safety of workers involved in protecting national security. During the post-war period when the plutonium research was conducted, the patients' response to this patriotic appeal would likely have been positive. Although they would have based their decisions to participate in the research on limited knowledge, their consent would have been recognized in later years. Their story in the 1990s would not have been about exploitation, but about their contribution to this country's efforts to become a nuclear power.

The Committee concluded that in addition to government rules and professional standards, which are applied only prospectively, there are also "basic ethical principles" that are not limited by time. These fundamental principles, which include obligations to respect self-determination and not treat people as means to others' ends or deceive them, provide an ethical framework for judging past actions.

Ethical evaluation

In the absence of informed consent, however, the Advisory Committee concluded that the plutonium experiment was unethical. Using patients as means to the ends of the researchers and deceiving the patients about the nature of the procedures violated basic moral principles without justification. The needless failure to obtain informed consent, not the research methodology, drew the Committee's condemnation. "Only extraordinary circumstances can justify deception and the use of people as mere means by government officials and physicians in the conduct of research in the conduct of research involving human subjects. . . . [W]e see no reason that the laudable goals of the research could not have been pursued in a morally acceptable fashion."

Furthermore, the Committee was dismayed that the government kept the identity of the plutonium subjects secret for many years, not for national security purposes, but apparently out of concern for public relations and legal liability. The Committee concluded that the secrecy deprived the subjects and their families of any opportunity to pursue grievances based on the plutonium research.

Distinguishing actions and actors

Although the Committee condemned the failure to obtain informed consent, it did not severely censure the well-in-

tentioned researchers who had followed the customary practices of the time. The Committee distinguished between the wrongfulness of actions and the blameworthiness of the actors: "Even when wrong was done, it does not follow that anyone should be blamed for the wrong." Although a wrongful act should be condemned, the individual who committed the act might be excused for "culturally induced moral ignorance" that the actor could not reasonably be expected to remedy, or because the details of applying a principle evolved subsequently.

The Committee concluded, somewhat opaquely, that "government officials and investigators are blameworthy for not having had policies and practices in place to protect the rights and interests of human subjects" in nontherapeutic research. But "to the extent the research was thought to pose little or no risk, government officials and biomedical professionals are less blameworthy".

Compensation and other remedies

The Advisory Committee was not specifically asked to make recommendations about compensation, but this topic was unavoidable. It received much attention at the Committee's meetings, particularly in testimony by individuals who were exposed to radiation in occupational, environmental, and research settings. Those exposed persons face many legal obstacles to securing compensation, including government immunity, the difficulty of proving that illness or death was caused by radiation exposure, and, for those who were not physically harmed, the absence of a legal remedy solely for an infringement of rights.

The Committee adopted a position that distinguishes ethics from law, holding that "people who were used as research subjects without their consent were wronged even if they were not harmed". However, the Committee also concluded that financial compensation is not an appropriate remedy in the absence of material harm—a result that reintroduces the legal standard. In such cases, the government should apologize to those who were wronged.

Thus, the plutonium research subjects—or their families, since the subjects are all dead—are due an apology from the government. In addition, the Committee found that the government's self-protective policy of secrecy for many years following the plutonium research had denied subjects and their families the opportunity to pursue potential grievances, thereby compounding the original wrong in a manner that could have had material effect. Accordingly, the Committee recommended that financial compensation be provided to the families of the plutonium research subjects—a remedy that may require legislation.

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Lessons for the future

What lessons can be gained from the human radiation experiments? Members of the Advisory Committee believe their assignment offered a valuable opportunity not only to redress past wrongs, but also improve existing mechanisms for the protection of human research subjects.

In particular, the current informed consent requirements were found ineffective. Jay Katz, a member of the Advisory Committee who has long been concerned with this issue, saw problems in three-quarters of the current protocols for greater-than-minimal-risk studies reviewed by the Committee. Although local committees (Institutional Review Boards, or IRBs) had approved the informed consent forms in these studies, the forms failed to distinguish the research goals of the studies and their consequences for the subjects. Instead, a mass of unnecessary detail obscured the significance of participating in the research.

There were even indications of a problem uncovered more than two decades ago: the Committee's interviews with many subjects revealed they did not know they were participating in research, although they had signed informed consent statements. The legal niceties of the consent process had been observed and the signed forms pro-

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duced. But the research subjects were still treated as a means to the scientists' ends, not as informed participants in the research.

To improve subject protection in the future, the Committee recommended that IRBs (1) focus on more-than-minimal-risk experiments; (2) assure that consent forms clearly distinguish research from treatment, identify the sponsors and purposes of the research, and specify the financial implications of participating or not participating in the research; and (3) assure that participation in research does not diminish the subjects' opportunity for medical benefits that would be available to nonparticipants.

"Ethical harm"

The effects of the plutonium injections were not as damaging to the subjects as the early news stories painted, nor were they so inconsequential as many scientists, then and now, believe. Our society demands that human subjects of experimentation not be treated merely as means to the researchers' end. In retrospect, the greatest harm of the plutonium injections may be the erosion of public trust in the institutions of science and government for having appropriated decisions that belong to individuals. ■

Further Reading

Advisory Committee on Human Radiation Experiments. 1995. *Final Report*. U.S. Government Printing Office (October 1995).

Michael S. Yesley came to Los Alamos as a staff attorney in 1989 and has provided legal advice to Laboratory management on protection of human research subjects, information practices, taxation, and environmental litigation. Most recently Michael has been working on preventive law and legal information projects, intended to make legal considerations and materials more accessible to Laboratory employees. Michael was the staff director of the National Commission for the Protection of Human Subjects from 1974 to 1978, whose reports were implemented in the federal regulations that now govern human experimentation. Following the National Commission post, Michael has practiced law and has held several positions on bioethics committees, among them Chairman of the Institutional Review Board at RAND, and coordinator of the DOE program on the Ethical, Legal and Social Implications of the Human Genome Project (ELSI). As co-ordinator of the ELSI, he compiled a basic ELSI source, a bibliography, and has spoken on ELSI issues at numerous meetings in the United States and abroad. Michael is a member of the Human Genome Organization (HUGO), the American Society of Law, Medicine and Ethics, and the Bioethics Committee of St. Vincent Hospital in Santa Fe. From October 1994 to February 1995 Michael directed the Laboratory's Human Studies Project Team. He earned a B.A. in philosophy in 1960 and a law degree in 1963 from Harvard University.

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