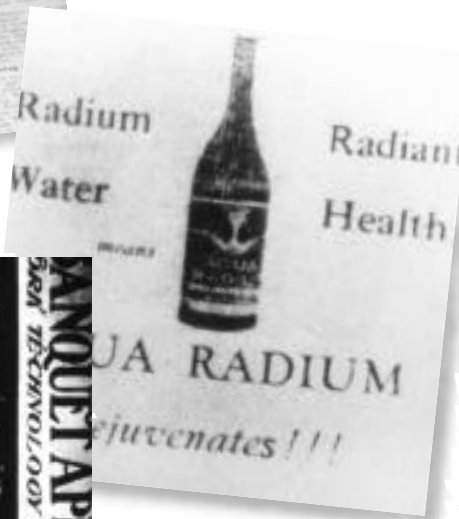


Radium—the Benchmark



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

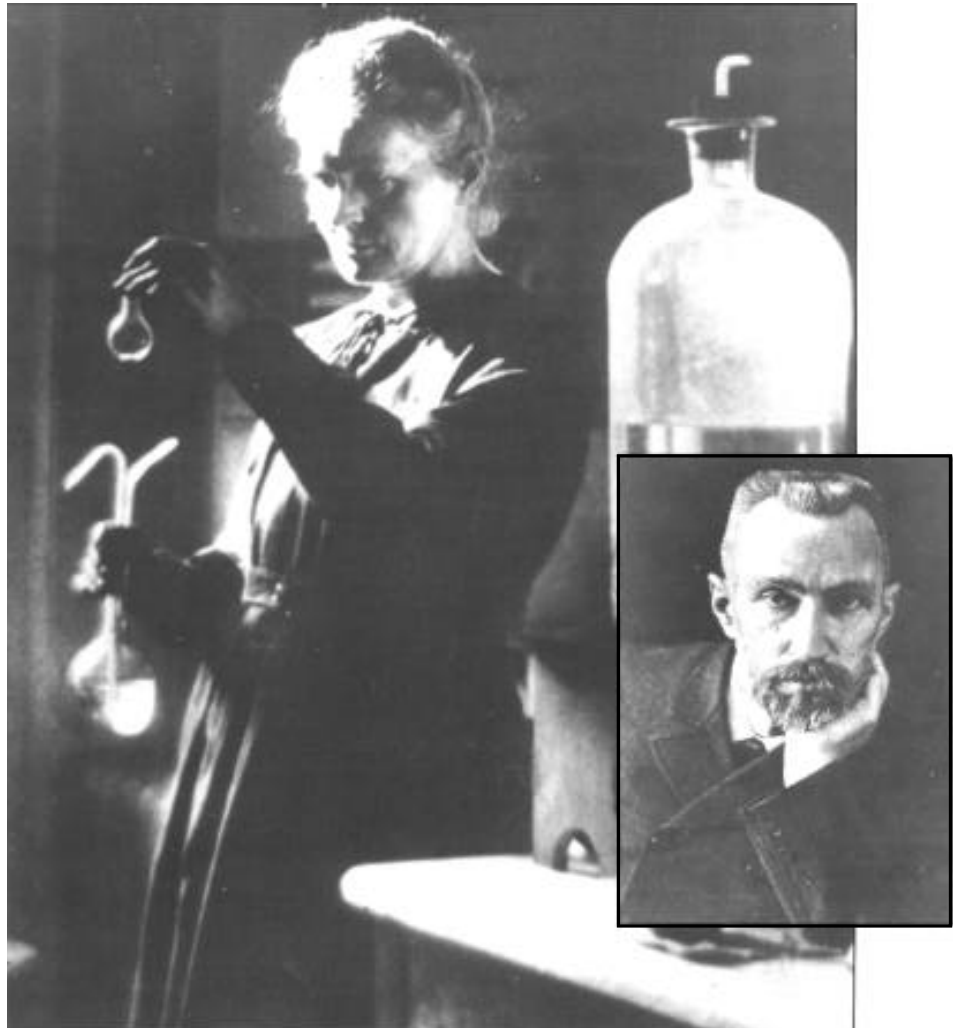
for Alpha Emitters

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.

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



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

Inset: Pierre Curie (1859-1906).

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 with permission from the Institut-Curie, Paris.)

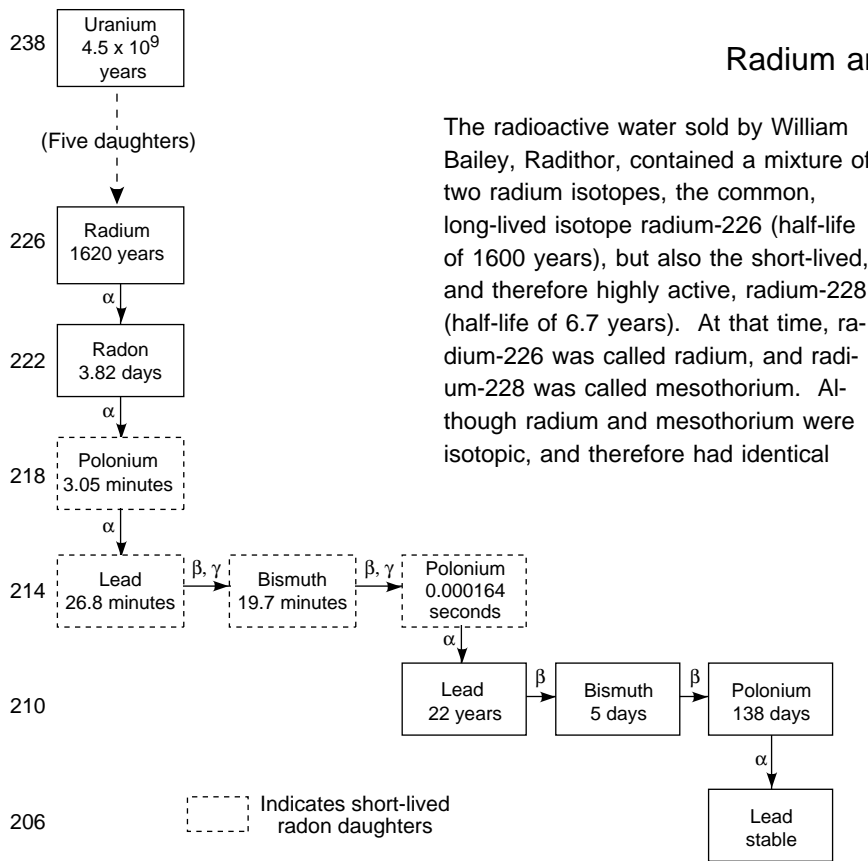
to treat the chronic pain in his arm. Byers reported feeling rejuvenated and invigorated by the nostrum. However, in 1932, four years and about 1000 to 1500 bottles of Radithor later, Eben Byers died, having suffered severe anemia and weight loss, massive destruction of the bone in his jaw, skull, and entire skeleton, and finally kidney and bone-marrow failure.

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

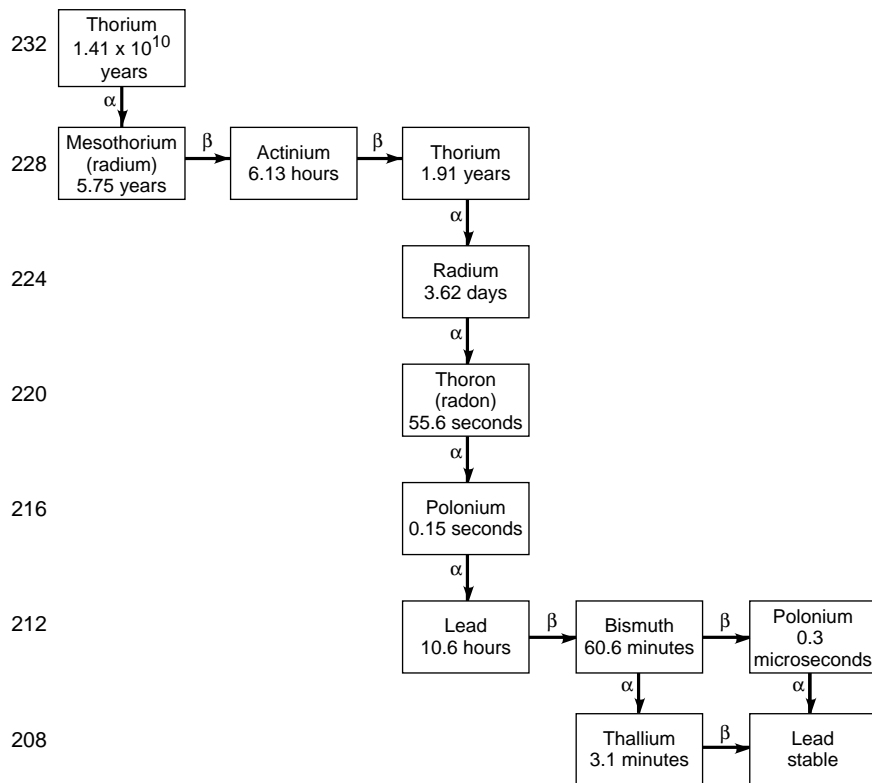
Mass number



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.

Mass number



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.

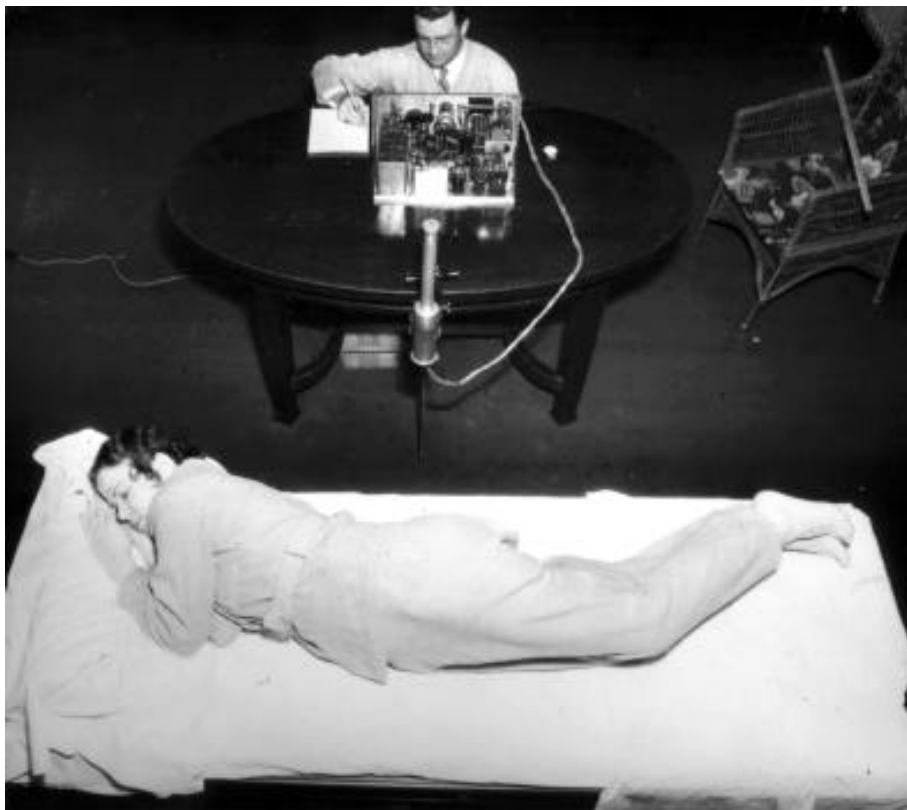
Evans became interested in the uptake, metabolism, and excretion of radium in living persons and realized that the key to studying those problems would be the ability to accurately measure the amount of radium present in the living body. However, the alpha particles emitted by radium are only weakly 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, radioisotopes 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.

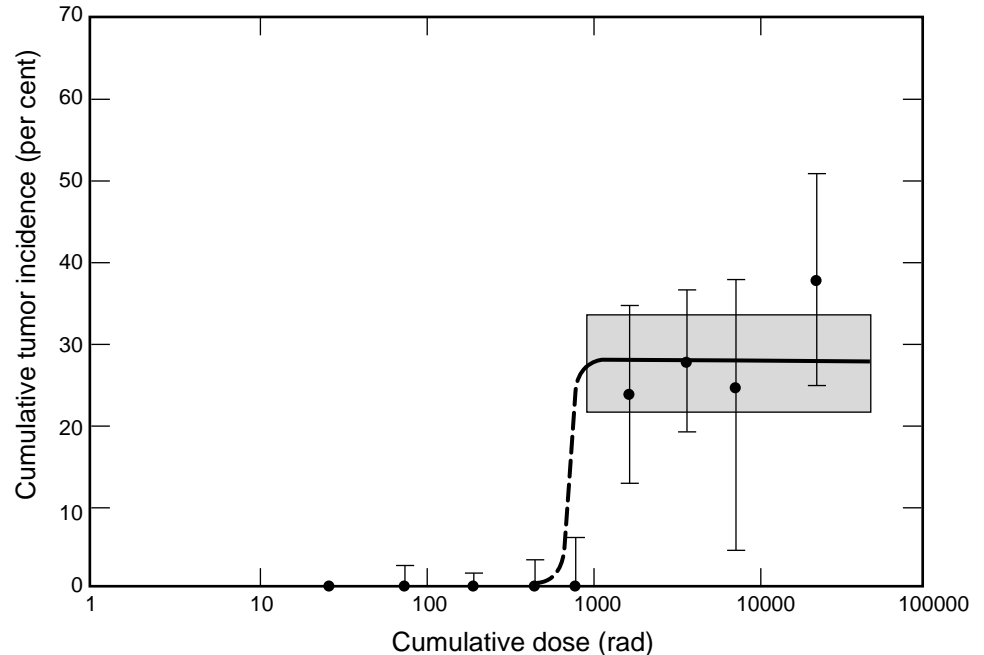
In 1944, when plutonium began to be produced in kilogram quantities, the experiences with radium forewarned scientists about plutonium's probable toxic effects and provided an essential quantitative basis for the creation of a plutonium standard. Robert Stone, the head of the Plutonium Project Health 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 dearth 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.



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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).