Radiation: Balancing the Record

Sensational news stories imply that dozens of unethical experiments placed unknowing people at risk. In reality, some studies were good, some were bad, and some were just ugly

The nation's press is in the midst of one of its classic feeding frenzies—but this time scientists, rather than politicians or celebrities, are the main course. On November 15, the *Albuquerque Journal* published the first of three horrifyingly detailed articles about Manhattan Project scientists injecting plutonium into human beings. Three weeks later, Department of Energy Secretary Hazel O'Leary told a press conference that she was "appalled, shocked, and saddened" by the report. The head of the agency—notorious in the past for secrecy—vowed to "open the archives," triggering a media firestorm. The ensuing tide of news reports, including cover stories in both *U.S. News & World Report* and *Newsweek*, flooded the nation with tales of evil scientists stuffing radioactive substances into prisoners, cancer patients, retarded children, even newborns.

Is it conceivable that just after the Second World War—when Nazi doctors tortured concentration camp inmates in the name of science—U.S. researchers treated unknowing patients with similar disregard? Or, as some researchers have claimed in defense, did the experiments have a historic context and scientific value that provides justification for these seemingly inhumane actions?

Press reports have overwhelmingly favored the former, cynical, explanation. The *Albuquerque Journal* described a single incident in which 18 terminal patients were injected with plutonium. Then newspapers such as *The Boston Globe* and *The Portland Oregonian* dug up research that involved feeding radioactive milk to retarded children and zapping the testicles of prisoners with high-energy radiation. Other journalists added to the impression of widespread abuse with their belated discovery of a 1986 congressional report detailing cases in which "nuclear guinea pigs" tested radioactive compounds such as tritium and technetium.

But an inquiry by *Science* shows that reality is, as usual, more complex than this sensational picture. For instance, at least five of the 31 experiments in the congressional report were apparently performed by researchers on themselves—hardly unknowing human guinea pigs. At least nine others cited in that document (known as the Markey Report, after Edward Markey (D–MA), head of the subcommittee that produced it) involved the use of minute, harmless quantities of radioactive isotopes to follow biochemical reactions within the body. "The trouble with the reporting today is that it doesn't make any distinctions," complains Sanford Miller, dean of the Graduate School of Biomedical Sciences at the University of Texas Health Science Center in San Antonio. "It's all radiation with a capital R. But there's various radiations—it's not a single golem rising out of the grave. And how people have thought about it over time is a lot more complicated than the newspapers make out."

That doesn't mean all of this research was valid—or even defensible. All evaluations are provisional, because some of the researchers are dead and complete explanations for their behavior are hard to come by, and records and accusations are still coming in. But at this point, it appears that the radiation experiments in the United States can be broadly classified in three groups. In one, researchers knowingly inflicted potential harm on patients, using methods that are difficult to justify even by the standards of the past. By contrast, a second, larger group of investigations involved perfectly good work by any standards, with appropriate safeguards taken. And a third group of studies falls between these extremes: The experiments provided useful information but had ethical flaws.

Defining a Dose

There are a variety of terms used to describe amounts of radioactivity. Herewith, a brief glossary:

Curie is the quantity of a radioactive material that undergoes 3.7×10^{10} nuclear transformations in a second.
Microcurie is a millionth of that amount.
Roentgens are units that describe x-rays and gamma rays in terms of their ability to ionize air.
Relative biological effectiveness (RBE) indicates the strength of a type of radiation in terms of its effect on living tissue. X-rays of the sort used in medicine have an RBE of 1; alpha particles (collections of two protons and two neutrons that are sometime emitted by radioactive nuclei) have a stronger RBE of 20.
Rems measure radioactive dose—the source's energy multiplied by its RBE.
Millirems are thousandths of rems.

Doing possible damage. Most of the media attention has been paid to the injections of plutonium that took place between April 1945 and July 1947—a period that began a few months before Hiroshima and ended at the time of the Nuremberg trials. The nation then faced a serious public health problem, recalls J. Newell Stannard, a health physicist at the University of California, San Diego, and author of the 2000-page study *Radioactivity and Health: A History*. "Thousands of workers at the Manhattan Project had been potentially exposed to plutonium," he says. "Physicians were able to monitor how much [plutonium] the workers excreted, but they didn't know how much they had taken in, because the exposures were accidental."

Since it already seemed clear that many more workers would be exposed to radioactivity over time, plant safety officials were frantic for information about the effects of plutonium. But nobody even knew whether it was quickly excreted, limiting its potential for danger, or retained in the body, where it could keep irradiating tissue for years. A few studies had been done with rats, mice, rabbits, and dogs. But the data were contradictory, partly because different species metabolize plutonium differently. So radiologist Stafford Warren and the other members of the Manhattan Project Health Group came up with the plan of introducing known quantities of plutonium into the bodies of terminally ill volunteers. Their already-short life expectancies would both duck the question of long-term harm and allow any remaining plutonium in their bodies to be measured at an autopsy. Warren's team chose 18 men and women, all terminal patients, from San Francisco, Chicago, and Rochester.

Today, any research like this must obtain human subjects' "informed consent." Such consent means that the subjects of the experiment appreciate the known—and suspected—risks of participation and voluntarily agree to participate even after knowing those risks. At the time of Warren's plan, the term "informed consent" was not yet widely used, but the principle had been established in court cases during the 1930s, and other researchers did follow it. The idea was ex-

plicitly codified during the prosecution of the Nazi doctors, which began in December 1946.

For plutonium, though, informed consent was out of the question—because the military wouldn't hear of it. General Leslie Groves, director of the Manhattan Project, was "paranoid about security," says Stannard. "Plutonium couldn't even be named—it had to be called 'product.' All [Warren and the other doctors] could tell them was that they were going to get a product in a small dose."

Even taking the rigid constraints imposed by the military into account, there is little to suggest that the subjects were thoughtfully chosen—a necessity if one has a small number, says Richard Griesemer, deputy director of the National Institute of Environmental Health Sciences (NIEHS). According to the *Albuquerque Tribune*, at least six had been wrongly diagnosed and were not about to die; two more were suffering from conditions disrupting the metabolic pathways the investigators were examining. Many injectees were apparently lost to follow-up. Only five are known to have been autopsied, one of the express purposes of the research.

According to toxicologists such as James Huff, a senior scientist in the environmental carcinogenesis program at NIEHS, researchers usually minimize possible toxic effects by administering slowly increasing doses to subjects. This did not occur. The first three doses were .29, .04, and 3.54 microcuries respectively (see box on dose definitions). The second dose was the lowest given; the third, administered less than a month later, was the third highest.

"The experiment did not have a rigid protocol established by some central authority," says biophysicist Patricia Durbin from Lawrence Berkeley Laboratory, who worked with the plutonium data for decades. Nonetheless, she says, the study was invaluable. "It is the *only* human data where the actual quantity inside the body is known and the time it was acquired is known." And Kenneth L. Mossman, president of the Health Physics Society, told Congress on 18 January that data from this "extremely important" study "serves as the principal database for current plutonium standards."

But even if the results stand up, many scientists say, the ethics do not. "People didn't know a lot of the things we know now," says Huff. "Toxicology didn't really exist as a field. Still, they knew that you shouldn't give people things that might harm them in the long term and try to get around it by saying they would die soon, anyway."

Two other sets of experiments raise similar concerns. Between 1963 and 1971, Carl G. Heller of the University of Oregon and the Pacific Northwest Research Foundation exposed the testicles of 67 prisoners at Oregon State Prison to ionizing radiation. One of Heller's protégés, C. Alvin Paulsen of the University of Washington, irradiated the testicles of 64 inmates at Washington State Prison between 1963 and 1970.

The reason for the testicular work was a 1962 accident at the Hanford Nuclear Reservation, in Richland, Washington, which exposed three workers to high doses of gamma radiation. Hanford officials asked Paulsen, a reproductive physiologist, to inform the men about their prospects for fatherhood. Little was known, it turned out. This was alarming to contemplate in an era that envisioned the rapid spread of nuclear power.

"We didn't have the knowledge for effective safety standards," Paulsen says. "I decided it was important to have certain information, such as the ED-50—the effective dose that would impair sperm production in 50% of men." Some animal research had been done, but, as in other areas of radiation research, the behavior of animal and human reproductive systems often differs. The best way to learn more, Paulsen reasoned, was to expose men to single blasts of radiation and measure the reaction, gradually increasing the amount with each group of subjects to construct a dose-response curve. "And that," he says, "brought up the issue of what type of population should be exposed."

Experimentation with prisoners was not unusual at the time—Heller, Paulsen's mentor, had been using them for years. "You had a wonderfully controlled population that was highly cooperative," dryly observes Wil Nelp, chairman of the department of nuclear medicine at the University of Washington. "They couldn't go anywhere, so follow-up was easy." Inmates often were housed in special state-hospital wards and fed fancy diets. Researchers sometimes filed notices of cooperation in their records. These were hard things for prisoners to turn down. "It was a good deal for them," Nelp says. "Probably too good of a deal."

Paulsen obtained permission for his study from the university, the state, and the prison. He then asked for volunteers among the inmates, asking them to promise to have vasectomies afterward. Before starting, Paulsen says, he privately interviewed each volunteer "and gave him every opportunity to say yea or nay." Then he gave all the participants (except a control group) between 7.5 to 400 roentgens, a high dose. Heller began a similar program a month later, with still higher doses: 8 to 600 roentgens.

Despite the chance to "say yea or nay," questions soon arose about the nature of the prisoners' consent. In 1966, the late anesthesiologist Henry Beecher published two landmark articles in the *New England Journal of*

ETHICS IN RADIOACTIVITY EXPERIMENTS

In some of the radiation studies cited in newspapers and in a congressional report, known as the Markey Report, subjects did not freely consent to the experiments. In other studies it is doubtful whether informed consent was obtained. But in some of the studies informed consent was truly given. Here are examples from each category.

Date	Experiment
Possible Infliction of Harm or No Informed Consent	
1945-47	Injecting 18 supposedly terminal patients with high doses of plutonium to learn whether the body absorbed it.
1946-47	6 hospital patients injected with uranium salts to determine the dose that produced renal injury.
1963-71	67 prison inmates had testicles exposed to x-rays to measure radiation damage to production of sperm.
1963-70	Another 64 prison inmates had testicles exposed to x-rays to relate radiation damage to sperm production.
Questionable Consent (6 other studies cited in Markey report)	
1946	17 retarded teenagers at the Fernald School in Waltham, Massachusetts, ate meals with trace amounts of radioactive iron to learn about iron absorption in body.
1954-56	32 retarded teenagers at the Fernald School drank milk with trace amounts of radioactive calcium to learn whether oatmeal impeded its absorption by the body.
1953-57	Injecting 11 comatose brain cancer patients with uranium to learn whether it is absorbed by brain tumors.
Informed Consent (17 other studies cited in Markey Report)	
1951	14 researchers at Hanford Nuclear Reservation voluntarily exposed patches of their skin to gaseous tritium.
1945	10 researchers and workers at Clinton Laboratory, in Oak Ridge, Tennessee, voluntarily exposed patches of their skin to radioactive phosphorus.
1965	Trace doses of radioactive technetium given to 8 healthy volunteers to determine its utlility as medical diagnostic tool.
1963	54 hospital patients volunteered to take trace amounts of radioactive lanthanum in effort to measure effects on large intestine.

Medicine arguing, among other things, that patients' consent to a procedure that will harm them indicates some coercion, since people who are free to choose won't usually allow themselves to be hurt. Further extension of this reasoning implies that prisoners cannot give informed consent at all, since their circumstances make them particularly prone to such coercion. The articles provoked enormous controversy, and, concerned about the combination of radiation and prisoners, the University of Washington halted Paulsen's work in 1969, rejecting his pleas to continue with additional measurements. Heller had a stroke in 1972, ending his efforts before anyone else could.

Consent or coercion? C. Alvin Paulsen conducted troubling experiments on prisoners.

Yet the ethical flaws did not obviate its scientific interest. A 1974 paper based on Heller's prisoner work has been cited 135 times, according to the Institute for Scientific Information, a rate that places it in the top 1% of all the papers they track. And Paulsen says, "My colleagues were interested in what I was doing. I was not off by myself."

Valid research. In sharp contrast to these experiments, much of the other work attacked in the Markey Report seems entirely blameless. Five 1950s-era experiments, for example, involved volunteers bathing patches of their skin in tritium, a radioactive form of hydrogen gas. One subject was exposed over his entire body. These people, the report charges, "thus became nuclear calibration devices." True. But the saving grace, which the report doesn't mention, is that in at least five of these studies the calibration devices apparently were the experimenters themselves.

At the time, atmospheric nuclear tests were creating lots of tritium, and scientists like Harry A. Kornberg of Hanford wanted to find out whether people could absorb tritium from water and air. After exposing rats, the team learned that living systems could, in fact, absorb tritium. But, again, the key question was whether the rat data could be applied to people.

The only way to find out was to perform tests on human beings. According to Chester W. DeLong, a team member who is now retired in Virginia, the volunteers were other researchers at the Hanford health lab. Kornberg insisted on doing the whole-body immersion himself. "He said, 'Well, I'm past child-bearing stage and I can tolerate it,'" recalls DeLong. "And I don't want anybody else exposed this way.'" And the work paid off, showing that people absorbed tritium four times faster than rats.

These results became mostly irrelevant, however, after the atmospheric test ban treaty was signed in 1963. But such self-experimentation was and is considered acceptable, and even heroic, according to *Who Goes First?*, Lawrence Altman's 1987 book on the subject. As for the "guinea pig" characterization in the Markey Report, DeLong says, "They never bothered to call and ask me about the work."

Four other experiments involving radioactive tracers that are mentioned in the Markey Report seem to be equally acceptable ethically. In those experiments, researchers introduced tiny amounts of short-lived radioactive isotopes into human subjects. The radioactivity allows the tracers to be followed through the body. Afterward, they decay into harmless substances. In some media reports, this has been described as feeding people radioactivity. True enough—but the technique has been used for 60 years with no apparent ill effect.

In one example from 1965, the University of Washington's Nelp and two colleagues from the Pacific Northwest Laboratory, then a nonprofit organization based in Richland, Washington, injected technetium-95 or -96 into eight students and housewives in Seattle. Because technetium has a half-life of just a few hours, doctors hoped they would be able to inject it into patients, use its radiation to take a kind of internal x-ray, and then have it decay quickly into a harmless substance.

"I said that the first thing we ought to do was find out the ABCs of how technetium behaved in the body," Nelp says. He found eight volunteers—students and housewives—by word of mouth. After he explained the procedure to them, the volunteers signed consent forms. They stayed in or visited hospitals for up to 2 months while researchers collected samples of their blood, tears, perspiration, urine, and feces.

Partly as a result of this work, which revealed that the body quickly excretes technetium, it is now widely used in nuclear medicine. Doctors attach it to phosphate compounds and inject the ensemble into patients and wait for the body to incorporate the phosphates into bone, along with the technetium. "Afterward, you take a total body survey," Nelp explains. "You can see every bone in the body with much less radiation than if you took a series of x-rays."

So why was Nelp's research singled out in the Markey Report? Apparently because the dose given to the volunteers—20 to 60 microcuries—was up to six times higher than what the report described as the "occupational maximum permissible body burden" for these isotopes. But a "body burden" refers to the long-term buildup of a substance within the body, not a one-time shot, as in Nelp's experiment. And "you can't translate a one-time exposure for a volunteer into a standard designed for workers who might be breathing in something 8 hours a day, five days a week," says Lauriston S. Taylor, former head of the National Council on Radiation Protection and Measurements, the independent advisory panel that has recommended U.S. radiation safety standards since 1930. The difference, in other words, is the difference between a heart patient's one-time binge on six hamburgers and a diet of one greasy hamburger a day, which is more harmful.

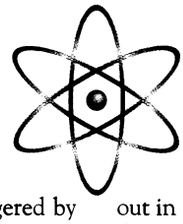
Much of the research now being denounced in the media was tracer research, Taylor says. "It's not generally appreciated, apparently, that the magnitude of the dose from these tracer tests is just awfully small."

The gray area. In between the reprehensible and the praiseworthy are studies that appear to have been designed to ensure no harm came to people, but fell short on informed consent. Particularly worrisome is research on disabled or unconscious people—a red flag to medical ethicists today. Perhaps the best-known cases occurred in 1954 and 1956, when scientists affiliated with the Massachusetts Institute of Technology (MIT) Radioactivity Center fed radio-tagged milk to 36 mentally-retarded children at the Fernald School in Waltham, Massachusetts. The purpose was to answer a then-current puzzle: whether children who eat oat cereals, which are rich in compounds that bind to calcium, are thereby flushing calcium through their systems before their bones can use it to grow.

Like Nelp, the MIT researchers used a radioactive tracer—in this case, calcium-32. The idea was to "label" children's milk with this isotope and find out whether eating oat cereal would affect the amount that stayed in the body. This involved feeding children a uniform diet and collecting all their urine

Hot spot. Some studies were prompted by concern about radiation and A-bomb workers.

Political Fallout: A National Bioethics Board?



Biomedicine has been shaken in recent months by a series of "seismic ethical events," says Gary Ellis, director of the human subjects protection office at the National Institutes of Health (NIH). One was the announcement last October that biologists at George Washington University were ready to clone a human embryo. But that was a mere foreshock of the jolt felt in December, triggered by news reports of unknowing people exposed to radiation during a series of experiments (see main story). And now there may be an aftershock: Government science officials are talking about creating a new, national bioethics review board.

The move began last week, after the president issued an executive order establishing an outside panel to guide a federal investigation of the radiation research. The panel will include 15 people and will be chaired by Ruth Faden, director of the Law, Ethics, and Health Program at Johns Hopkins University. This panel, the executive order says, will "determine the ethical and scientific standards" to be used in judging the radiation research, which began in the 1940s. The investigative group itself will be an interagency team that will comb through government files reaching back to the early days of the atomic era, checking on experiments between 1946 and 1974. It will also randomly sample studies conducted after 1974, when the government first issued regulations on human subject research.

Some officials would like the investigations to go even further. They hope the White House will charter a national bioethics committee to look at issues other than radiation exposure. There have been several such panels in the past. The most recent, called the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, expired when its charter ran out in 1983. Now public health leaders such as D.A. Henderson, deputy assistant secretary for health science at the Department of Health and Human Services (HHS), and M.R.C. Greenwood of the President's Office of Science and Technology Policy (OSTP), think it's time to try again. Greenwood says it would make sense to set the panel up as an adjunct to the new Science and Technology Council in the White House.

The powers and jurisdiction of such a panel have not yet been defined. If it were modeled on the previous commission, it would examine issues at the cutting edge of research and clinical practice—such as the patenting of genes—and make policy recommendations; agencies would be free to take or leave the advice. Nor is it clear how close the plan is to reality. It appears to have the backing of top research officials at HHS, the Department of Energy, and the White House, and some support in Congress. But it remains to be seen whether the president, after asking federal agencies to cut their staffs and outside consultants, wants to create yet another advisory panel.

–Eliot Marshall

and feces for some time—a complicated prospect. Team leader Robert Harris had decided that such experiments would best succeed if the subjects were in a confined location and under medical supervision. The Fernald children met those criteria. The experiment suggested that oatmeal did indeed flush calcium from the system, but at a slow rate that would only affect children with very low-calcium diets.

Only "a tiny, tiny amount" of radioactive calcium was used, says Constantine Maletskos, a member of the team. According to MIT Radiation Protection Office director Francis Masse, the dose was 4 to 11 millirems above background. (Typical background levels are about 300 millirems.) By comparison, a typical treatment for hyperthyroidism involves hitting the thyroid with a drink that delivers about 10 million millirems. "They would have had more if they had flown to Denver for a while," Maletskos says, where they would have been exposed to that high-altitude city's greater number of cosmic rays.

Although the doses of radiation were small, the consent for the experiment would not have met today's standards. "In those days doctors were the kings of their facilities," says Maletskos. "They were in charge of their patients. [The Fernald supervisors] told us they had consent, and it would never have occurred to us to question them." Maletskos says he was horrified to learn on 26 December in a story from *The Boston Globe* that the consent forms sent to the parents by the school had neglected to mention "radioactivity." The school merely asked parents about participating in nutritional experiments. But even if the forms had mentioned radioactivity, there are doubts consent could ever be properly obtained from retarded subjects or their parents. Indeed, today the whole issue of informed consent by the mentally impaired is regarded as so blurred that experimenters believe they should not be used as a study population.

Similar questions of consent dog some of the cases mentioned in the Markey Report. An example is the injection of radioactive uranium-235 into at least 11 comatose, terminal cancer patients between 1953 and 1957 by William Sweet of Massachusetts General Hospital, in Boston, and his associates. The procedures were done as part of the development of what is called "neutron-capture therapy." Neutron-capture therapy takes advantage of the fact that tumors absorb more of certain isotopes than healthy tissues do. After placing those isotopes in the body, doctors bombard the patients with neutrons, which split the isotopes, releasing radiation that kills surrounding cancer cells.

In the 1950s, this idea was little more than plausible-sounding speculation. No one knew which isotope would best be absorbed by tumors. Sweet decided to find out. After obtaining permission for the injections from the patients' families, he carried out the study. The results were disappointing. Uranium, it seemed, was not absorbed in sufficient quantities by the tumor to make the therapy practical; in current attempts at neutron-capture therapy, boron is used.

Even at the time this work could have aroused qualms. In 1953, the year Sweet began his experiments, the British Medical Council campaigned against the use of comatose subjects in research. And as far back as 1948, the Federation of American Societies of Experimental Biology expressed concern that experimenting on the "hopelessly incurable" would "corrupt" the doctor-patient relationship, because it could make their rapid deaths desirable if an autopsy was needed. Nowadays, research with no potential for direct benefit to the terminally ill subject is generally avoided.

Yet these matters of consent and safety frequently fall into gray areas, as researchers acknowledge. People with AIDS, for instance, clamor to be experimented on with medications whose effects are so poorly understood that neither physician nor patient can give consent truly informed by knowledge of risks and benefits. "Who knows what people will think of that in the future?" Stannard says. "We should be humble and wonder what we now are doing that will horrify our descendants." Unlike radioactive decay rates, the rate of change in morality standards has never been accurately measured.

–Charles C. Mann

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