# Filtering a River of Cancer Data

Little is known about the health effects of long-term, low radiation doses. Now, in Western Russia, a series of terrible accidents is giving researchers a chance to learn from calamity

CHELYABINSK, RUSSIAN FEDERATION—For the past three decades, Mira Kossenko and her fellow researchers at the Urals Research Center for Radiation Medicine (URCRM) have been keeping a grim vigil. Their subjects: 64,000 people here in the southern Ural mountains, villagers who had the misfortune to live near the former Soviet Union's first nuclear weapons facility during the early days of the Cold War. Between 1949 and 1956, the Mayak plutonium production plant, about 65 miles northwest of here, dumped some 76 million cubic meters of liquid radioactive waste into the nearby Techa river. And villagers along the river drank it, washed clothes in it, and bathed in it. During this period, those who lived nearest the plant received total radiation doses up to 1700 times the annual exposures permitted by today's international radiation protection standards.

Unlucky inhabitants of this region were also exposed to radioactivity from a series of nuclear disasters at Mayak during the 1950s and 1960s. The most famous was a massive explosion in a liquid-waste storage tank in 1957 that spread 2 million curies of radiation throughout three Russian provinces.

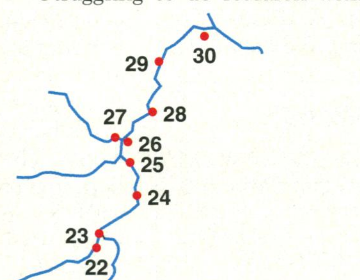
In the 1960s, Kossenko and her colleagues began to watch the local population for cancer and other radiation-related diseases. The task, grisly though it may be, could turn out to have exceptional scientific importance. "They have a large number of people who have been exposed to fairly high doses over a very long period of time, and we don't have that for many other sources," says Elaine Ron, an epidemiologist with the National Cancer Institute's (NCI's) Radiation Epidemiology Branch. Long-term exposure, however, is precisely what threatens most people at risk from radiation today.

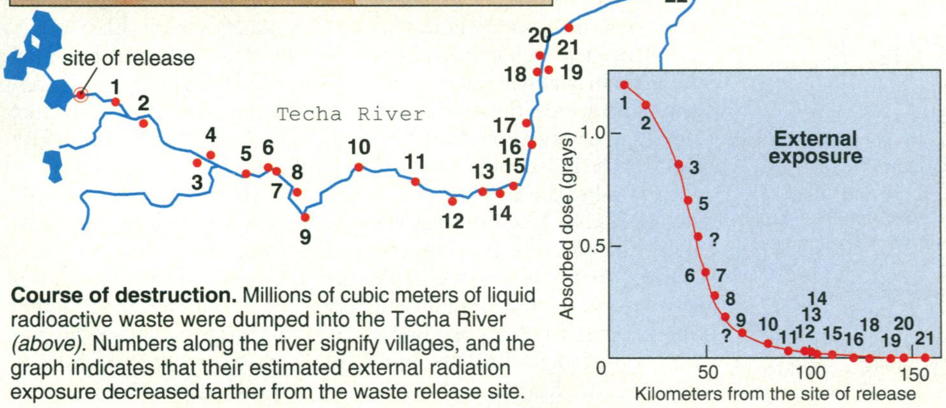
Yet Kossenko and her team worked under a shroud of secrecy. They were forbidden from reporting their work to the outside world, and only after the collapse of the Soviet Union did bits and pieces of the story emerge (*Science*, 22 January 1993, p. 451).

Last month that shroud was lifted . More than two dozen leading radiation biologists from the United States, Europe, and Japan arrived in Chelyabinsk for a 3-day meeting* with their Russian counterparts to get their closest look yet at the data. The visiting scientists were not disappointed. "I'm really very impressed with what they have been able to accomplish up to now," says Ron.

Struggling to do research with very little funding, the Russian scientists have carried out some unique studies, including the only reliable research on the long-term effects of plutonium exposure. At the Mayak plant and along the Techa River, they have found elevated levels of leukemia and other cancers in populations exposed to a variety of types of radiation, and have tried to link them to specific radiation doses. Marvin Goldman, a biophysicist at the University of California, Davis, says, "The Techa River is almost a designed dose-effect relationship, because as you go down the river away from the [Mayak] plant the dose was smaller."

But detailing that relationship may prove difficult. Indeed, the excitement at the meeting was tinged by uncertainties about how accurately events of the past three decades can be reconstructed. Scientists pointed out that it is hard, many years after the fact, to calculate radiation doses received over an extended period and to verify diagnosis and mortality figures. Amy Hopkins of Yale University's School of Medicine cautions that such ambiguities "could be one of the greatest impediments to developing a chronic radiation model in this region."




**Course of destruction.** Millions of cubic meters of liquid radioactive waste were dumped into the Techa River *(above)*. Numbers along the river signify villages, and the graph indicates that their estimated external radiation exposure decreased farther from the waste release site.

## Looking at low doses

Researchers say they dearly need to develop such a model. Most of what's known today about the effects of radiation on humans comes from long-term follow-up of survivors of the atomic bombing of Hiroshima and Nagasaki—and thus so do the international and U.S. protection standards, in large part. Yet people in these studies received relatively high doses of radiation delivered over short periods of time. That's nearly the opposite of the situation for those populations that might be at risk today: nuclear energy workers as well as those who live near nuclear waste sites, who get low doses of radiation over protracted periods.

Most human epidemiological studies of such low-dose exposure have been of little help, because they are "fraught with all kinds of problems," says physicist Warren Sinclair, past president of the National Council on Radiation Protection (NCRP). The result has been years of debate among radia-

* First International Symposium, "Chronic Radiation Exposure: Risk of Late Effects," Chelyabinsk, Russia, 9–13 January 1995.

## A Joint Russian-U.S. Investigation

For many of the two dozen radiation experts who traveled to Chelyabinsk last month to get their first full look at radiation data amassed by their Russian colleagues (see main text), the trip was just the beginning of a long-term collaboration. The Chelyabinsk meeting was inspired by an agreement, signed last year by the United States and the Russian Federation, to fund scientific collaborations on the health effects of radiation contamination.

The agreement includes a pledge of $1 million from each country for the first year—all earmarked for studies in the Chelyabinsk region. Although the agreement is to run for 5 years, the two governments are still working out future funding levels.

This promise of funds and expertise from the West is good news for financially ailing research organizations on the Russian side, such as the Urals Research Center for Radiation Medicine (URCRM) in Chelyabinsk. "The financial situation of our institutions is very unfavorable, to put it mildly," says Alexander Akleyev, director of URCRM. "We now receive only 30% of the amount needed" to carry out current research.

Disbursement of funds and other aspects of the collaboration will be supervised on the Russian side by a state committee charged with investigating radiation exposure and on the U.S. side by the Department of Energy (DOE). Other participating agencies will probably include the U.S. Centers for Disease Control and the National Cancer Institute—and NCI has asked the Radiation Effects Research Foundation in Hiroshima, the organization responsible for studying the atomic bomb survivors, to join in.

But the involvement of DOE is not seen as good news by some outside observers. DOE has to clean up a number of its own nuclear messes in the United States, notes Jack Geiger, a founder of Physicians for Social Responsibility and a member of the Department of Health and Human Services' advisory committee on health issues associated with federal nuclear installations. Geiger fears the agency's involvement could compromise the objectivity of research—such as that conducted at Chelyabinsk—that might tighten radiation cleanup standards. A number of scientists contacted by *Science*, who wished to remain anonymous, said they share this concern. "It would be much more reassuring if an independent organization such as the Centers for Disease Control were the lead agency," Geiger says.

**–M.B.**

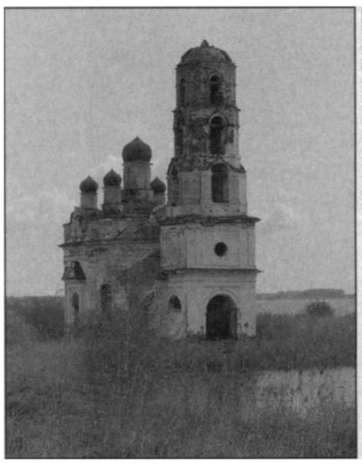
tion experts about the pitfalls of extrapolating from the atomic bomb studies to low-dose situations.

Those experts are, however, unanimous on one thing: The Urals radiation disasters may provide a rare opportunity to resolve these issues. The reason, explains Donna Cragle, director of epidemiologic research at the Oak Ridge Associated Universities in Oak Ridge, Tennessee, is that the statistical power of epidemiological studies on radiation effects "depends on the size of the population as well as the degree of exposure." And in the Chelyabinsk region, says Cragle, both are "quite adequate" to do the job. Over 400,000 people lived in the contaminated areas, in addition to several thousand plant workers at Mayak. By comparison, one human low-dose study that radiation experts do take seriously—a study of nuclear industry workers in the United States, Canada, and the United Kingdom published last October in *The Lancet*—used a cohort of 96,000 workers. It found a statistically significant increase in leukemia mortality.

### A matter of accuracy

Kossenko and her co-workers at URCRM have already done one epidemiological study of 28,000 people who lived on the banks of the Techa River and found a statistically significant increase in leukemia incidence, as well as an overall increase in cancer mortality, compared to control populations that did not live in the contaminated zone. Still, the leukemia risk per unit of radiation dose was at least two times smaller than that of the atomic bomb survivors. If validated by further studies, this might support the hypothesis that lower dose rates are less harmful to humans.

That validation will depend on just how accurately researchers can reconstruct dose rates for individual villagers. So far, that task has proven "very complicated," URCRM's Vyacheslav Kozheurov told the meeting. The problem is that the population was exposed to both external radiation—gamma rays from radioactive material deposited on the river banks or in the villages—as well as internal radiation, primarily from absorption of strontium-90 and cesium-137 from drinking river water and eating contaminated vegetables. For external exposure rates, the Russian researchers had to rely on estimates made by a technical team back in the 1950s that are difficult to validate today. And internal exposure rates are hard to reconstruct, because it is impossible to know how much river water people drank and how many vegetables they ate 40 years ago.



VENDELA ENGLUND-BURNETT

**Radiation effects.** This abandoned church lies in a contaminated area along the Techa River.

In contrast, it's easier to reconstruct the dose rate for the Hiroshima and Nagasaki survivors. "In the case of the atomic bomb we have one single shot," says Kiyohiko Mabuchi, chief of epidemiology at the Radiation Effects Research Foundation in Hiroshima, which carries out the atomic bomb studies. "It's very easy to ask people where they were at the time of the bombing. But in Chelyabinsk we are talking about continuous exposures extending over several years."

In the Urals, the solution so far has been to derive average doses for each village. Kozheurov, along with Marina Degteva and other co-workers at URCRM, was able to partially surmount the internal exposure obstacle by taking advantage of one of the features of radiation that also makes it dangerous: its persistence. Strontium-90 has a 28-year half-life, and since 1974, roughly half of the residents of the contaminated areas have been measured in a whole-body radiation counter at URCRM and with a counter for measuring strontium-90 deposition in teeth. Combined with the estimates of external exposure, this allowed Kossenko and her co-workers to calculate village averages and thus estimate individual doses.

Yet refining these estimates will be critical. Bruce Napier, chief scientist for the Hanford Environmental Dose Reconstruction Project at the Hanford plutonium plant in Washington state, says that the Russian work "is very good, but it is incomplete. I would like to be sure they are not omitting something just because they didn't know it was released."

Plutonium studies, in contrast, were not subject to as many dose reconstruction problems because they involved Mayak plant workers, whose exposure to the decaying element's high-energy alpha particles could be measured in several different ways, including radiation badges and excretion of plutonium in urine. Nina Koshurnikova and her colleagues at Branch No. 1 of Russia's Institute of Biophysics—located in Chelyabinsk-65, a once-secret city of 85,000 people adjacent to the Mayak plant—found that workers at the facility's radiochemical plant had a leukemia rate about three times the Russian national average.

A parallel study, in which Mayak employees who worked with plutonium were compared with a control group who did not, found the risk of lung cancer among male workers increased by about 30% for each Sievert of plutonium radiation absorbed by the lungs. (Sieverts are units of the effect of an absorbed radiation dose on living tissue and vary with different types of radiation.) The workers received lung exposures ranging from 0.38 to 453 Sieverts.

The plutonium story is particularly exciting to radiation scientists, because it provides a set of data found nowhere else in the world. "We have very few people in the U.S. who were ever exposed to plutonium," says Sinclair. "And for those who were, the doses were too low and the populations not large enough" to accurately measure effects. According to Goldman, the Chelyabinsk data could help set radiation standards not only for plutonium but also for radon, which, like plutonium, emits high-energy alpha particles.

This potential treasure-trove of data will provide enough challenges and opportunities to keep the world's radiation experts working for many years to come. Russia and the United States have already set up a funding mechanism for more detailed studies (see box on p. 1085), and scientists are beginning to draw up plans to carry them out. To help calculate external exposure, for example, scientists such as Goldman have suggested using a new technique known as thermoluminescence dosimetry (TLD), which can detect very low levels of radiation absorbed by some inanimate materials, such as the tile roofs of village houses. NCI's Ron, who is planning a collaboration with some of her Russian counterparts to do more epidemiology, says that major tasks will be to "extend and improve the follow-up" of the various populations being studied, and "verifying the diagnoses on the death certificates."

The Russian scientists, for their part, have eagerly welcomed the intense interest of their international colleagues in the Southern Urals accidents. "I worked for all those years just to put my papers in a safe," says Kossenko. "Now I can show my data to all the experts of the world."

–Michael Balter

BREAST CANCER

# NIH Gets a Share of *BRCA1* Patent

A 6-month battle over the future spoils from the discovery of the breast cancer gene known as *BRCA1* ended quietly last week when the combatants signed a peace treaty. In a settlement announced by the National Institutes of Health (NIH), three gene-hunting groups formally agreed to divvy up the patent rights. Their agreement gives recognition to federal researchers who were ignored in patent applications on *BRCA1* filed last summer by the University of Utah on behalf of itself and Myriad Genetics Inc. of Salt Lake City.

Echoing a widely held sentiment, one breast cancer researcher said this should end a "weird period" for *BRCA1* research, terminating a competitive frenzy that often appears in big gene hunts. Indeed, many top scientists in this area have recently joined a group called the International *BRCA* Consortium (IBC) and are freely sharing data and laboratory materials on mutations that are showing up in breast cancer genes.*

This is a big change from the ill will generated last summer, when the Utah team sent its claims to the Patent and Trademark Office shortly before submitting a paper to *Science* announcing the discovery (*Science*, 7 October 1994, p. 66). The Utah patent application named only Utah and Myriad scientists as inventors in the work, which tracked down a gene responsible for about 3% of all breast cancers. Not mentioned were two government biologists—Roger Wiseman and Andrew Futreal of the National Institute of Environmental Health Sciences (NIEHS)—who had sequenced small fragments of *BRCA1* that proved critical in Myriad's effort to assemble the entire gene. Speaking on background, a Myriad scientist acknowledged NIEHS's contribution, but described it as fairly limited.

The paper in *Science*, which cited NIEHS's work, went to press before NIH had time to file a patent application of its own.

**"We're just happy that it's settled and we can focus on doing science once again."**

**—Roger Wiseman**

Nevertheless, NIH filed a competing application last fall on NIEHS's behalf (*Science*, 14 October, p. 209). The move was designed to block Patent Office action on the Utah submission, says a government source. And NIH's tactic paid off. The Utah team understood that the entire patent might be invalid if the Patent Office agreed that there was an error in the list of inventors, and so, after a long negotiation, agreed to revise their filing.

The terms of the settlement—signed by NIH, the university, and Myriad—are being kept confidential. But sources say that NIH has agreed to abandon its patent application, and the Utah filers will amend theirs to name the NIEHS scientists as co-inventors and ensure that the government will get a 25% share of potential royalties. The agreements do not give NIH a role in setting the price of any products that may be developed.

In a mild declaration of victory, NIH Director Harold Varmus last week said, "I am very pleased that our collegial discussions ... have resolved the inventorship issues." Richard Koehn, Utah's vice president for research, embraced NIH as "a partner," and in a telephone interview, Wiseman said, "We're just happy that it's settled and we can focus on doing science once again."

Meanwhile, the scientific effort to characterize the mutations in *BRCA1* and track down a second breast cancer gene called *BRCA2* appears to be picking up speed. Wiseman and many would-be competitors have joined the IBC to share data on mutations among women who carry the *BRCA* genes. This consortium, founded by Stephen Friend of the Massachusetts General Hospital, includes most important gene hunters in this field. One notable exception, Mary-Claire King of the University of California, Berkeley, is planning a separate collaboration. King could not be reached for comment.

According to Friend, the IBC has already created a database with the help of Thomas Marr at the Cold Spring Harbor Laboratory and hopes to plug the system into the Internet by summer. That goal is possible, although "optimistic," says Marr. He adds that "It's really exciting to have so many good people collaborating on a hot gene." It means that the race to find clinical applications "is just going to accelerate."

–Eliot Marshall

* The IBC steering committee includes Stephen Friend of the Massachusetts General Hospital (chair); Anne-Lise Borresen of the Radium Hospital in Oslo, Norway; Graham Casey of the Cleveland Clinic; Francis Collins of the National Center for Human Genome Research; Peter Devilee of the University of Leiden in Amsterdam; Patricia Murphey of OncorMed in Gaithersburg, Maryland; Bruce Ponder of Cambridge University; Mark Skolnick of the University of Utah and Myriad Genetics Inc.; Barbara Weber of the University of Pennsylvania; and Roger Wiseman of the National Institute of Environmental Health Sciences.