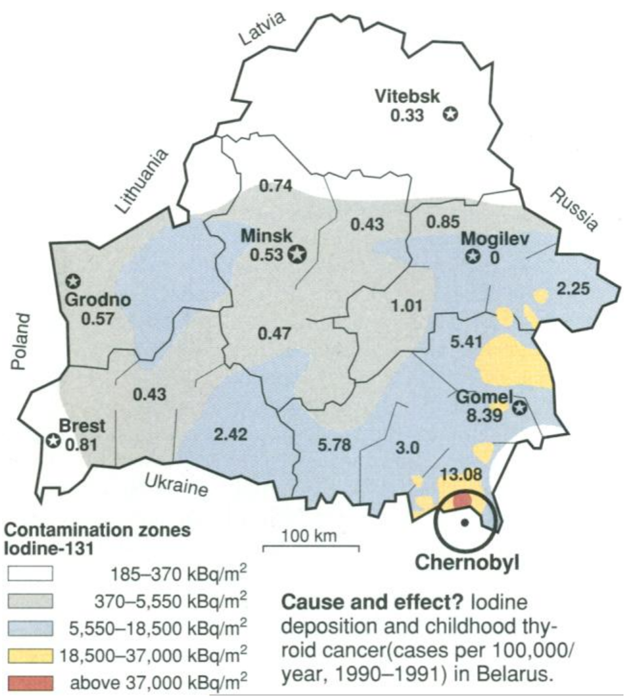
THYROID CANCER

Children Become the First Victims of Fallout



Cause and effect? Iodine deposition and childhood thyroid cancer (cases per 100,000/year, 1990–1991) in Belarus.

SOURCE: T. ABELIN, J. I. AVERKIN, M. EGGER *ET AL.*, SOZ PRAVENTIVMED. 1994 ILLUSTRATION: K. SUTLIFF

PARIS—When pediatric endocrinologist Larisa Astakhova presented her findings at a scientific meeting in Munich in October 1991, Western scientists were, at best, skeptical. Astakhova, then at the Radiation Medicine Institute in Minsk, Belarus, described a dramatic increase in thyroid cancer among the children of her newly independent nation. She said half the new cases, which had begun to appear the previous year, were concentrated in the region of Gomel, north of Chernobyl. The implication was ominous: During the first few hours following the accident, Gomel received heavy doses of radiation, including large amounts of iodine-131 and other radioactive iodine isotopes, which the body selectively takes up into the thyroid gland.

"The initial feeling was that the cases couldn't be related to Chernobyl," recalls Dillwyn Williams, a thyroid cancer expert at Cambridge University in the United Kingdom. "They occurred far too early and in far too great a number based on previous experience." Although earlier studies had indicated that young children are particularly vulnerable to radiation-induced thyroid cancer, any effects of the Chernobyl fallout were not expected to show up for at least 6 to 8 years. The Belarus cases had begun to appear only 4 years after the accident. Moreover, a team of scientists from the International Chernobyl Project, a program coordinated by the International Atomic Energy Agency in Vienna, had concluded after a 1990 visit to the contaminated areas that the total exposed population faced only a doubling in the average lifetime risk of thyroid cancer. Yet scientists from Belarus were already claiming that the incidence of childhood thyroid cancer in Belarus had reached at least 30 times preaccident rates. In 1991, for example, 59 cases were diagnosed nationwide, compared to only two in 1986.

But Williams says he "became an instant convert" when he and a handful of other Western experts visited Belarus in July 1992 to see for themselves. Williams told *Science* he saw more tumors during that one visit "than I had seen in a lifetime of studying childhood thyroid cancer." And that was just the beginning: So far, more than 700 cases have been diagnosed in regions of Belarus, Ukraine, and Russia that bore the brunt of the contamination.

This tragic epidemic—the most pronounced health effect of the accident so far—has sparked intense collaborations between Western and Eastern radiation scientists, eager to find out why the number of cases is so much higher than anticipated. This research may ultimately lead to new knowledge about how radiation damages a cell's molecular machinery, as well as a better understanding of the interaction between radiation exposure and other possible risk factors for thyroid cancer—including iodine deficiency, genetic predisposition to developing tumors, and the special risks that radiation poses to young children.

Fight for recognition. Many of Williams's colleagues did not immediately share his epiphany, however. When his team returned and published its findings in *Nature*—along with a report by Astakhova and her co-workers in Minsk—the reaction was not enthusiastic. In a celebrated exchange of letters, several scientists suggested that other factors—especially intensive screening after the accident—might explain much or all of the apparent increase in thyroid cancers.

Among the early doubters was Elaine Ron, an epidemiologist at the U.S. National Cancer Institute (NCI) in Bethesda, Maryland, who had earlier led a series of groundbreaking studies demonstrating that children exposed to even relatively low doses of radiation during medical treatment were at a measurably higher risk of thyroid cancer. Ron and her colleagues cited a screening program set up at a Chicago hospital to monitor a group at risk of thyroid cancer: The increased screening alone led to a sevenfold increase in detection of thyroid malignancies. Similar doubts were expressed by Oxford University epidemiologist Valerie Beral and others.

Episode	I-131 released (curies)
Three Mile Island	15–20
Windscale (U.K.)	20,000
Hanford (1944–47)	690,000
Chernobyl	40–50,000,000

Although some of the early skeptics still have reservations about how to interpret the thyroid cancer statistics, most have now come to agree that the Chernobyl accident is responsible for at least a part of the increase. "There's no doubt there are more cases being diagnosed as a result of the Chernobyl accident," says Beral, but "some of that increase is due to increased ascertainment, although I don't know how much."

Once the scale of the epidemic had been recognized, researchers set about trying to pin down which radioactive isotopes were involved. Although large amounts of radioactive cesium were released from the reactor after the accident, suspicion quickly fell on iodine. Not only does the body concentrate iodine in the thyroid gland, incorporating it into the thyroid hormones tri- and tetraiodothyronine, but the distribution of cancer cases also closely fits the deposition pattern of iodine isotopes, which took a somewhat different path from that of cesium.

A study by Nikolai Tronko, head of the Institute of Endocrinology and Metabolism in Kiev, Ukraine, provided some of the first clear evidence of the link. Of more than 200 childhood thyroid cancer cases diagnosed in Ukraine by the end of 1994, says Tronko, "two-thirds were in the five most [iodine] contaminated regions, and the rest were in the remaining 20 regions of the country." And in a more recent study of 110,000 children under the age of 18, a team led by Tronko and Ilya Likhtarev of the Scientific Center for Radiation Medicine in Kiev found a significant correlation between thyroid-cancer incidence and radioactive iodine levels, based on iodine-131 measurements made shortly after the accident.

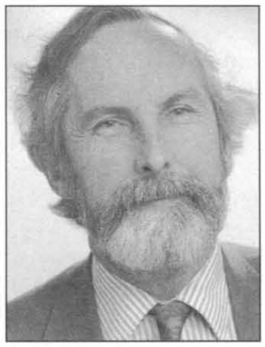
Dose uncertainties. Although these studies point to radioactive iodine as the prime suspect, one big uncertainty is just how much radiation the local population was exposed to. One problem is that direct thyroid monitoring in the three republics contaminated by Chernobyl did not begin until about 6 May 1986, 10 days after the accident. That was soon enough to allow rough extrapolations of exposure to iodine-131, which has a half-life of 8.05 days, but much too late to give useful information on exposure to the shorter lived isotopes iodine-132 (half-life 0.1 days) and iodine-133 (half-life 0.85 days). "Calculating the actual doses presents a horrendous task," says Fred Mettler, a radiation health expert at the University of New Mexico. "But to make predictions [about future cases] we've got to know what they were."

"There is possibly some problem in DNA repair" in some exposed groups.
—Elisabeth Cardis

Nevertheless, several research institutes in the three republics are collaborating with American colleagues from the NCI and the U.S. Department of Energy to try to reconstruct the total doses. Lynn Anspaugh, a dose reconstruction expert at the Lawrence Livermore National Laboratory in California who is participating in this work, says that, if good thyroid measurements were made after the accident and researchers know how much milk—an important source of iodine absorption—the child was accustomed to drinking, individual dose estimates can be made with an error of roughly ±50%. "That's not too bad," Anspaugh told *Science*.

Accurate dose information is key to studies such as a recent one by Astakhova, now at the Medical Center of Thyroid Pathology in Minsk, along with Anspaugh, Gilbert Beebe of NCI, and others, which compared 107 cases of children who were under age 15 at the time of the accident, and who have since fallen victim to thyroid cancer, with two carefully matched control groups. The results, which are not yet published, indicate that children who had received more than 1 gray (a measure of radiation exposure) to their thyroids had a risk of thyroid cancer nearly six times as high as that of children who received 0.3 gray or less.

I saw more childhood thyroid cancer cases "than I had seen in a lifetime."
—Dillwyn Williams



These studies are an important test of whether the dose-response relationship holds true on a case-by-case basis, but they do not explain why there have been so many more cases than originally predicted. Williams believes the answer may be straightforward: "People have underestimated the sensitivity of very young children," he says. "The young child is both biologically more sensitive to radiation and has a higher uptake of iodine" into his or her thyroid. Williams also points to shifting estimates of how much iodine was actually released from the reactor during the accident. For example, although earlier studies indicated that about 20% of the entire iodine content of the reactor core escaped, more recent estimates put the figure at close to 60%.

But other researchers believe the answer may be more complex. They argue that additional factors—including iodine deficiency and possible genetic predisposition to thyroid cancer—may have played an important role as well. For example, despite the marked dose-response correlation in the Astakhova study, many of the children with thyroid cancer received relatively low doses of radiation.

Additional support for the idea that factors other than radiation dose are involved may come from early projections from a study conducted by an international group of researchers from Ukraine, Belarus, Russia, France, Japan, and the United States. The team used mathematical models, based on dose-response data from survivors of the atomic bombing of Japan and medical exposure to radiotherapy, to predict the theoretical risk of thyroid cancer to Belarus children who were younger than 15 at the time of the accident. When the team plugged in average estimates of the iodine doses the Belarus children received, the model significantly underpredicted the number of cases actually observed in many regions. In the Gomel region, says team member Elisabeth Cardis of the International Agency for Research on Cancer in Lyons, France, the prediction was "about 10 times" too low.

Fertile ground for iodine. One factor that might explain the excessive number of cases is iodine deficiency, which was chronic in many of the contaminated areas during the years leading up to the accident. A thyroid gland low in iodine would have quickly taken up isotopes of the element inhaled from a radioactive cloud or ingested from contaminated milk supplies. Children in Belarus had received iodine supplements in the 1970s and early 1980s, but by 1985 the policy had been discontinued. Keith Baverstock, co-coordinator of the World Health Organization's (WHO's) International Thyroid Project, says that even today "40% of the population is still suffering from iodine deficiency."

To help determine the role iodine deficiency may have played, the International Thyroid Project has begun a survey of adolescents to see how many have enlarged thyroids, a "rough-and-ready" sign of whether they were iodine deficient when children, says Baverstock. Moreover, Baverstock says the study may have more than just academic interest: Thyroid-stimulating hormone, which is produced at a higher level in iodine-deficient glands, stimulates thyroid growth and may increase the rate of cancer progression as well. So giving radiation-exposed children and adolescents additional doses of iodine today "could delay progress of the cancers," says Baverstock.

Another hypothesis, favored particularly by Cardis, is that some subgroups of the exposed population might have been genetically predisposed to develop thyroid cancer after radiation exposure. Some support for this notion comes from a preliminary survey of 50 children with thyroid cancer in Belarus, which indicated that two of the children had brothers or sisters with the disease. Because thyroid cancer is quite rare, despite the dramatic increase seen after the accident, Cardis says that this is a much higher percentage than would be predicted by chance alone.

"What I am thinking is that there is possibly some problem in DNA repair" among members of some ethnic groups in the population around Chernobyl, says Cardis, referring to the mechanism normal cells use to patch up genetic damage. People suffering from some rare conditions characterized by defects in DNA repair, such as ataxia telangiectasia and xeroderma pigmentosum, are highly suseptible to radiation-induced cancer.

And in a series of preliminary—as yet unpublished—studies, a team of French researchers led by Martin Schlumberger of the Gustave-Roussy Institute near Paris claims to have found a link between radiation exposure and anomalies in DNA repair function among children who developed thyroid tumors after receiving radiotherapy for other types of cancers. Geneticist Arthur Bloom, president of the Paris-based International Scientific Committee on Environmental Health, cautions, however, that "in the general population it is not

Poor Dose Data Hamper Study of Cleanup Workers

When news of the accident at Chernobyl gripped the world 10 years ago, public opinion quickly blamed the villainy of the Soviet system—a view reinforced by later revelations of cover-ups, faulty reactor design, and sloppy safety procedures. But if Chernobyl had its villains, it also produced some heroes: some 100 firefighters from Chernobyl and the nearby town of Pripyat—who immediately went into action, battling desperately to douse the blazing reactor and prevent it from igniting the three others at the plant—and 300 or so plant staff members and medical personnel who joined them at the scene.

"During that first night, the people working on the site received enormous radiation doses," says Michael Balonov of the Institute of Radiation Hygiene in St. Petersburg. And over the following days, as an intense graphite fire spread radionuclides and fission fragments high into the atmosphere, 29 members of this team lost their lives to radiation sickness or burns. During the months and years that followed, an estimated 800,000 workers from all over the former Soviet Union took part in cleanup operations and construction of the concrete "sarcophagus" that now covers the destroyed reactor. Virtually all of these "liquidators" were exposed to doses well above those received by the population at large. As a result, they represent a unique resource that epidemiologists are now studying in the hope of garnering new information on the effects of radiation.

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Cleanup crew. Some 800,000 "liquidators" who worked at the site received high radiation doses.

The liquidators were exposed to a wide range of doses, over different time scales, and by a variety of pathways. "Some of them got their doses in a couple of minutes on the roof of the reactor, and others over 6 months or 1 or 2 years," says Elisabeth Cardis, head of the program on radiation and cancer at the International Agency for Research on Cancer in Lyons, France. "They are a perfect population for looking at the effect of exposure rates and radiation type on cancer risk, some of the big questions in radiation carcinogenesis today."

Under the auspices of the European Commission's (EC's) collaborative program on Chernobyl, Cardis—along with Alexei Okeanov of the Center for Medical Technologies in Minsk, Belarus, Viktor Ivanov of the Medical Radiological Research Center in Obninsk, Russia, and other colleagues—recently conducted a pilot program in Belarus and Russia to see if meaningful epidemiological studies of the liquidators are possible. Similar studies of liquidators from Ukraine, Latvia, Lithuania, and Estonia—involving the U.S. National Cancer Institute and colleagues in the United States, Ukraine, Finland, and the Baltic states—are either under way or in the planning stages. These studies are focusing initially on the two types of cancer most likely to result from radiation exposure: leukemia and thyroid cancer.

The work done so far indicates that the research will be tough going. The most serious obstacle is uncertainty about the estimates of radiation doses the liquidators received—a crucial parameter for discerning dose-response relationships. Much of the exposure data comes from special registries set up after the accident, documenting where an individual liquidator worked and for how long. But these "official doses," as they are sometimes called, are notoriously unreliable. Cardis points out, for example, that if all the liquidators who said they worked on the roof of the reactor actually did so, "the roof would have been incredibly cluttered with people."

And attempts to validate the official doses with sophisticated biological dosimetry methods have so far proved discouraging. For example, during the EC-sponsored pilot project, investigators took blood specimens from a random sample of 62 liquidators living in or near the Russian city of Obninsk and checked them for chromosome aberrations using a technique called fluorescent in-situ hybridization. The result: No correlation was found between the number of aberrations and the individually recorded official dose. Researchers have not given up, however. They are also using more sensitive techniques, such as electron spin resonance (ESR) measurements of tooth enamel, to validate dose estimates. "ESR is perhaps the most promising," says Hans Georg Menzel, a dosimetry expert with the EC's radiation research group in Brussels. "But all of these techniques are still elaborate and time-consuming, and only work above a certain threshold of radiation dose."

To get around these problems, Cardis and her co-workers are designing a questionnaire for certain groups of liquidators—particularly those from the Soviet atomic-energy agency and the military—whose radiation doses were more carefully monitored after the accident. "We will use them to validate a possible gradient of exposure on the basis of time and place and activity," Cardis says. "That will at least allow us to discriminate between high and low doses, and hopefully have four or five data points along the way."

As these studies get under way in earnest, radiation experts caution that, with the long latency period for many cancers, it may be years or decades before significant results are available. But if the procedural difficulties can be overcome, the heroism of the liquidators may have long-lasting value, not only by preventing an even worse catastrophe but also by helping guide future radiation safety standards.

–M.B.

clear at this time that differences in DNA repair competency determine cancer risk."

A better understanding of the epidemic, and particularly why children have been so cruelly targeted by the disease, may help radiation protection experts to be better prepared in the future than Soviet authorities appear to have been when the Chernobyl disaster struck. Much of the radiation exposure, for example, could have been countered by rapid administration of nonradioactive iodine to "flush out" the radioactive isotopes from binding sites in the thyroid. Although reports vary, it appears that any such efforts by the Soviet authorities were too little and too late. Indeed, although many scientific questions remain to be answered, WHO has already begun recommending that all schoolchildren in Europe have immediate access to iodine supplements in the aftermath of a nuclear accident on the continent (*Science*, 15 December 1995, p. 1758). Says Baverstock: "The scientist can afford to be skeptical much longer than the person concerned with protecting public health."

–Michael Balter