British Radiation Study Throws Experts into Tizzy

Debate is raging over a new study that links a father's radiation exposure to leukemia in his children

JUST WHEN RADIATION EXPERTS thought they had a pat hand, a new study on England's Sellafield nuclear plant has thrown a wild card onto the table.

The study, by Martin J. Gardner, a respected epidemiologist and medical statistician at the MRC Epidemiology Unit in Southampton, England, comes to the startling conclusion that a father's exposure to low-level radiation on the job may increase his children's risk of leukemia. But that flies in the face of the largest study ever conducted on radiation effects—the 40-year investigation into the atomic bomb survivors in Hiroshima and Nagasaki. Indeed, based on the Japanese data, a National Academy of Sciences panel concluded just last December that the risk of genetic effects from radiation is lower than previously believed.

If Gardner is right, then radiation protection standards around the world may have to be changed. But is he? Many experts would like to write off Gardner's study, which was published in the 17 February *British Medical Journal*, but they can't—it is too well done. Instead, they are stuck trying to make sense of seemingly contradictory data. And a month after the study came out, opinion is still divided on just what it means.

"You won't find anyone to stand up and say it is wrong. But people are skeptical. It is just so different from what you would have expected," says Alfred Knudson, a cancer biologist at the Fox Chase Cancer Center in Philadelphia.

Others, like Arthur Upton, head of environmental medicine at New York University and chairman of the recent NAS panel, call the findings intriguing and say they cannot be ignored. "Just because I haven't seen the effect before, I certainly wouldn't dismiss it," agrees epidemiologist David Hoel, director of biometry and risk assessment at the National Institute of Environmental Health Sciences. He and Upton also say that, first impressions aside, the study may not contradict the Japanese data after all.

In all the dispute over the Sellafield study, one thing, at least, seems clear: there is an unexpectedly high incidence of childhood leukemia in the village of Seascale in northwestern England, where the Sellafield nuclear reprocessing plant is located. Similar leukemia clusters have been found near the Dounreay reprocessing plant in Scotland and the Ministry of Defense weapons labs at Aldermaston and Burghfield.

Since a television documentary first brought the Sellafield cluster to light in 1983, attention has focused mainly on environmental contamination from the plant, which has been plagued with a number of "incidents and accidents," says Gardner. Still the radiation connection was far from firm as the expected dose to village children from those radioactive releases seemed too low to account for the cancers.

Leo Kinlen, an epidemiologist at the University of Edinburgh, has proposed the "new town hypothesis" instead. He speculates that the leukemia clusters might have a viral origin, as the nuclear plants bring an influx of new workers, who then are exposed to viruses for which they have no immunity.

Epidemiologist Richard Doll of the Imperial Cancer Research Fund in Oxford, England, has suggested that the culprit might be some inherent characteristic of the locations deemed suitable for a nuclear site. He has found leukemia clusters at "phantom" sites that were considered—but passed over—for nuclear installations.

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In 1984, following a suggestion of the government committee that investigated the Sellafield cluster, Gardner and his colleagues set out to determine whether the Sellafield plant was to blame. By culling birth and medical records—and when possible, reanalyzing pathological specimens—they identified 74 cases of childhood leukemia and non-Hodgkins lymphoma, diagnosed between 1950 and 1985, in the county of West Cumbria, and matched them with 1001 controls. They then investigated four possible causes: prenatal x-rays, which are known to increase the risk of childhood leukemia; viral illness in the mother, a suspected risk factor; anything that might enhance environmental radiation exposures, such as eating lots of shellfish or playing on the beach near the plant; and finally, parental occupation and exposure to radiation.

The only one that stood out strongly was the father's employment at the plant, and especially his radiation dose before his child's conception. The father's dose was ascertained from film badges worn at the plant. Children whose fathers were exposed to the highest levels of external radiation—either a total dose of 100 milliSieverts, typically accumulated over about 6 or 7 years, or 10 milliSieverts in the 6 months before conception—were six to eight times more likely to develop leukemia than were the controls.

"On a statistical basis, at least, that can explain the excess leukemia in the area," says Gardner, who concedes nonetheless that numbers involved are very small—the fathers of just four cases and nine controls received such high doses—and thus the uncertainty is large. And that means that the link could be due to chance, as some of his critics contend. But Gardner considers the evidence convincing, since all but one of the five Seascale children with leukemia had a father who had received a high dose. What's so disconcerting is that their exposures were well within the current occupational limit of 50 milliSieverts a year.

If Gardner is right, then some unexpected mechanism must be at work. Gardner suspects that the external dose of radiation is causing a mutation in sperm cells that, when passed on to children, predisposes them to leukemia. Other interpretations are possible, he admits, such as internal exposure from inhaling or ingesting radionuclides or perhaps exposure to chemicals in the nuclear plant, but he considers them "unlikely."

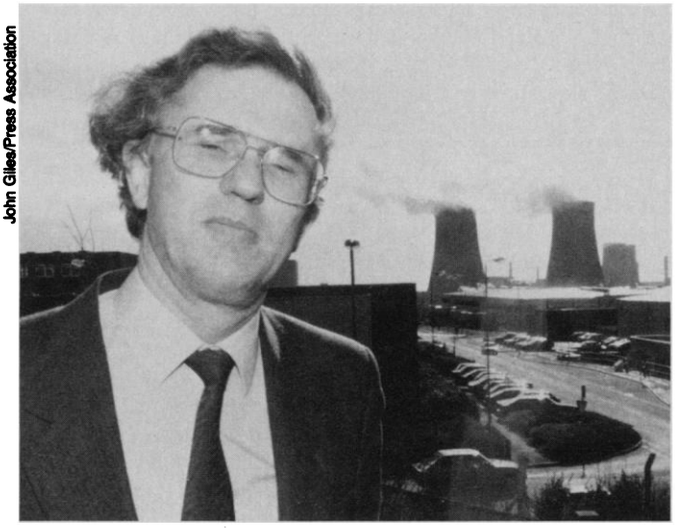
And that is where Gardner and many radiation experts part company. The skeptics, like A-bomb researchers William J. Schull of the University of Texas Health Science Center in Houston and James Neel of the University of Michigan, are not necessarily quarreling with the association between the father's employment at the plant and childhood leukemia. Rather, what they question is that the external dose of radiation is causing a heritable mutation, as Gardner posits.

And they have good reason, they say, as the 40-year investigation of the atomic bomb survivors in Hiroshima and Nagasaki has turned up no hint of such an effect. For 30 of those 40 years, Schull, Neel, and Hiroo Kato and Yasuhiko Yoshimoto, their colleagues at the Radiation Effects Research Foundation in Hiroshima, have followed 75,000 children whose parents were irradi-

ated by the two blasts. And in a study to be published this June, they have just reanalyzed the data with the new, more accurate dose estimates for the Japanese survivors (*Science* 18 December 1987, p. 1649). Their findings are unequivocal: there is an increase in leukemia in those who were directly exposed—but not in their children.

Indeed, the researchers have found no evidence of any genetic effects at all in the children who were conceived after the blast—no genetic diseases, cancer, or congenital abnormalities. And they have scoured the data with a fine-toothed comb, even scanning protein sequences for any telltale variation that would indicate a genetic mutation.

So why, they ask, should genetic effects show up in the children of the Sellafield workers, whose highest doses were about 10 or 20 milliSieverts, when they don't show up in the children of Japanese survivors, whose average exposure was 450 milliSieverts. Moreover, there is good reason to expect a smaller, not a larger, effect if the dose is spread out over time, says Schull, citing mouse studies by William Russell at Oak Ridge National Laboratory. Explains Russell's colleague, mouse geneticist Paul Selby: "10 rads in a single dose produces a bigger effect than 10 rads over a lifetime." (1 rad equals 10 milliSieverts).



John Gilles/Press Association

Nuclear sleuth. *Martin Gardner thinks he has solved the long-standing mystery of the leukemia cluster around the Sellafield nuclear plant.*

But Gardner is not cowed by the preponderance of data militating against his Sellafield conclusions. "A lot of people spent a lot of time looking at the Japanese data, and by and large it is a good set of data. But when something comes along that doesn't fit, it is not necessarily the new thing that is wrong.

"My view is that the Japanese exposure was very different from a work situation. We must bear that in mind and work it through carefully." Gardner speculates that perhaps DNA can repair itself after an instantaneous exposure, like that in Japan, but not in the face of continuous, low-level exposure.

Gardner's "cavalier" dismissal of the Japanese study, as Schull describes it, has clearly irked some of the A-bomb researchers, who are among his toughest critics. "I can't imagine a more relevant study than the Japanese, but Gardner passes it off," Selby comments.

But scientists less immediately involved in the recent Japanese work say Gardner may have a point. "It is not obvious to me that this is inconsistent with the A-bomb studies," says Hoel of NIEHS. Upton and Seymour Jablon, a statistician who has followed radiation effects for years, first at the Academy and now at the National Cancer Institute, agree.

What it comes down to is which dose at Sellafield is important—the total accumulated dose or the dose received in the 6 months just before conception. Gardner was unable to determine that in his study. "If the culprit is the total dose, you would expect something to show up in the Japanese data," says Jablon. But if it is really the 6 months prior to conception, "then the Japanese data would be almost irrelevant."

There simply weren't a lot of children conceived in the first few months after the bomb, Jablon explains. Moreover, systematic studies did not get up and running for 5 years or so, adds Upton, who says it is quite possible that the blast caused some early leukemias that thus went undetected. And in the several years that elapsed before the children now under study were conceived, whatever damage was done to their parent's DNA might have repaired itself.

But the Gardner study has other strikes against it, according to the critics like Knudson of the Fox Chase Cancer Center. Until now there has been no evidence to suggest that leukemia has a strong hereditary component, as do other childhood cancers, like Wilm's tumor and retinoblastoma.

That doesn't mean it can't happen, says Upton. "It does not require a stretch of the imagination to suppose a mutation inherited by a child would predispose him to leukemia. We know that x-rays and ionizing radiation are mutagens that can damage DNA. And certain kinds of mutations are carcinogenic."

And then there is the question of why radiation might cause only leukemia and not other cancers or congenital abnormalities? "I agree there is a conundrum," says Gardner, who is continuing to look for other genetic effects in the Sellafield children. "This is the first study to look at leukemia with good radiation exposure data. We do not understand all the findings yet."

What's urgently needed, everyone agrees, is to replicate Gardner's study with U.S. radiation workers. "If I were in charge I would immediately start studies at DOE," says Hoel. "It would be a top priority, to see if we need to rethink exposure limits for workers and to get at the biology of it."

But the Sellafield study comes at an awkward time for DOE, which has just been roundly criticized by a DOE advisory committee for its "uncoordinated and inconsistent" epidemiologic studies. Last week DOE Secretary James Watkins announced that the agency will turn over its long-range epidemiology to the Department of Health and Human Services (*Science*, 5 January, p. 22). For the moment, at least, DOE is unlikely to launch a major new study.

The nuclear industry might, however, says Leonard Sagan, program manager for radiation studies at the Electric Power Research Institute. EPRI is not only considering an epidemiologic study of radiation workers and their children, says Sagan, but also a rodent study.

Follow-up studies of the other leukemia clusters are already under way in the United Kingdom. They should be complete within a year. And Gardner is continuing his study at Sellafield, where he is examining, among other things, worker exposure to chemicals.

In the interim, two NCI studies now under way may shed some light on the Sellafield question: a study of cancer mortality around 62 nuclear facilities in the United States, due out in June, and a massive study of x-ray technicians and their children.

Until more data are in, the National Council on Radiation Protection and Measurements, which recommends worker exposure limits, is sitting tight, says director Warren Sinclair. "We have to worry about the study," says Sinclair, who agrees it is well done, "but there is not much we can do about it until we get more information. One swallow does not a summer make."

Meanwhile, at the Sellafield plant, British Nuclear Fuels has announced that any worker who is alarmed about his exposure can, after counseling, be transferred to another job. Several have come in to talk to the managers about the risk; none has decided to be transferred. ■ LESLIE ROBERTS