Although two U.S. agencies disagree on whether an apparent rise in childhood cancer is real or due to better diagnosis, their dispute may end up aiding the fight against this terrible killer

No Meeting of Minds on Childhood Cancer

When Richard Klausner, director of the National Cancer Institute (NCI), picked up *The New York Times* one morning 2 years ago, he was thunderstruck. Fueled perhaps by a "growing exposure to new chemicals in the environment," claimed a front-page article in the 29 September 1997 issue, "the rate of cancer among American children has been rising for decades." Klausner had assumed that the rate of new childhood cancer cases was *stable*.

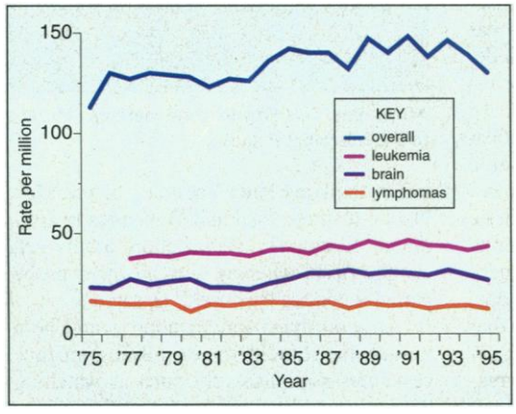
Klausner huddled with his institute's own experts, who persuaded him that his assumptions were sound—and the article's message, therefore, was off base. The alarming news had originated from a conference earlier that month, sponsored by the Environmental Protection Agency (EPA), on "preventable causes of cancer in children," an event that Klausner says his office was never consulted on. He picked up the phone and tried to reach EPA Administrator Carol Browner, whom the *Times* had quoted calling for new research on air and water pollutants and pesticides "and their effects on children," as well as "new testing guidelines" to confront what she described at the conference as a "dramatic rise in the overall number of kids who get cancer." "I was concerned about an injudicious description of the trends," says Klausner, who believed that EPA's "one-sided view" could mislead people into thinking the United States was in the midst of an epidemic of childhood cancers spurred by some environmental scourge. It would be weeks, however, before Browner got back to him.

In the months since the conference, EPA scientists and outside advisers have coauthored a research plan for childhood cancer that appeared in the journal *Environmental Health Perspectives*, while the agency itself has begun to tighten its regulations of chemicals to take into account the vulnerability of children to toxic effects (see sidebar on p. 1834). Spurring the agency on have been environmental groups and some scientists concerned that pesticides and other synthetic substances could be driving up childhood cancer rates.

Although EPA's critics do not necessarily disagree with the agency's focus on reducing risks to children, a debate continues to rage behind the scenes on the numbers underlying those thrusts. NCI sped up the pace of an already-planned review of childhood cancer rates, whose just-published conclusion is that there has been no dramatic rise in cancer among children. The authors attribute an uptick in the 1980s—seized upon by EPA as evidence of a problem—to better methods of detecting and classifying tumors rather than to a phantom environmental menace. "It's an easy and attractive hypothesis, but there is very little evidence that environmental risks are causing the majority of cancers," says Freda Alexander, a statistician at the University of Edinburgh in the United Kingdom. EPA scientists reject that conclusion. "I've spoken to many experts in environmental cancer and epidemiology about the NCI concept that there really is no increase in childhood cancer. They just don't buy it," says physician Steve Galson, former science director of EPA's children's health initiative and now in the agency's pesticides office.

U.S. Reshaping Cancer Strategy As Incidence in Children Rises

Alarm bell. *New York Times* story prompted NCI chief Richard Klausner to order review of childhood cancer data.



Grim numbers. Experts disagree over whether a rise in childhood cancer rates since 1974 reflects more cases or more accurate reporting.

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Stalking the young

If there's one indisputable fact in the debate, it's that too many children still succumb to cancer. Despite huge strides in the last few decades in raising the odds that any particular cancer-stricken child will survive into adulthood, this devastating disease remains the second leading cause of death for children after accidents. Concerns about an accomplice lurking in the environment rose in the late 1980s, when studies pointed to a possible link between childhood leukemia and exposure to electromagnetic fields generated by power lines and home wiring. Overall, childhood cancer rates appeared to be creeping upward, driven by a 35% rise in pediatric brain cancers from 1973 to 1994. "It was really brain cancer that everybody was freaking out about," says Jim Gurney, an epidemiologist at the University of Minnesota, Minneapolis. But the fresh leads on potential killers in the environment grew stale as study after study came up empty (see sidebar).

What had been a low-profile debate burst into the public arena in 1997. That September, EPA's new Office of Children's Health Protection sponsored what it billed as the first-ever conference on children's cancer and the environment, where participants would hammer out "a blueprint for childhood cancer research for the next decade." According to a conference brochure, "the occurrence of new cancer cases continues to rise, and we don't know why. One potential cause is environmental toxins." Galson says EPA based this statement on data from NCI, as well as work by epidemiologist Les Robison of the University of Minnesota, Minneapolis, who co-authored a report in the journal *Cancer* in 1996 that found that childhood cancer rates had risen by 1% a year since 1974.

Some attendees, however, say that although the conference stirred a lot of productive scientific discussion, it was clear where the blueprint was headed from the outset. Activists, parents of cancer victims, and journalists made up a large portion of the 240 participants. The scarcity of scientists in an effort meant to guide a research course made for "a very odd conference," says attendee Seymour

The Elusive Causes of Childhood Cancer

Researchers who probe whether environmental hazards cause cancer in children have an advantage over colleagues who study adults: It should be simpler to track what children have been exposed to in their brief lifetimes than to sift through decades of exposures. But making an unequivocal connection between tumor and toxicant has proved to be anything but easy.

Experts caution that each of the dozens of subtypes of childhood cancers must be grappled with on its own, as each takes root in different cell types at different ages—and thus may spring from a variety of causes. For the most common childhood cancer, acute lymphoblastic leukemia (ALL), the only confirmed risk factor is ionizing radiation—from x-rays of pregnant mothers, for instance, but apparently not from radon. Most experts believe that recent results from the largest ever ALL study in the United States, involving about 2000 cases, have eliminated two suspects: a mother's smoking during pregnancy or electromagnetic fields from power lines. Pesticide studies have been inconsistent: "We've found quite a few suggested associations," for example with no-pest strips in homes, "but we're underwhelmed by the evidence," says Jonathan Buckley, an epidemiologist at the University of Southern California (USC) in Los Angeles.

Researchers haven't given up the hunt, however. Studies have shown that newborns later diagnosed with ALL often have a rearrangement in a carcinogen-detoxifying gene, called *MLL-AF4*. The genetic shuffle is common in infants whose mothers were treated during pregnancy with chemotherapy drugs that inhibit a DNA replication enzyme called topoisomerase II. That has fueled speculation that other chemicals that inhibit topoisomerase—such as benzene breakdown products, certain antibiotics, and flavonoids in foods—might also trigger the mutation.

Some older children with ALL are born with a mutation in another gene, *TEL-AML-1*. A fraction of children who do not contract ALL also have this mutation, so study chief Melvyn Greaves of the Institute for Cancer Research in London thinks something in the environment may trigger a mutation in an unidentified gene that, combined with the *TEL-AML-1* mutation, leads to cancer. Greaves thinks weakened immune responses in infants may be partly to blame. Childhood ALL, it turns out, is more common in families with higher income levels in developed countries, where children experience fewer infections—challenges that help gird the immune system (*Science*, 19 June 1992, p. 1633). Greaves speculates that, upon entering school and the attendant milieu of germs, a child with a relatively untested immune system might be no match for a pathogen that damages the DNA of the immune system's white blood cells, causing them to proliferate. The culprit might be a specific virus or a bacterium, or it could be a general response to any number of agents acting on a frail immune system.

The evidence for either scenario is "equivocal," says statistician Freda Alexander of the University of Edinburgh in the United Kingdom. Studies in several countries that surveyed parents about their children's infections and immunizations as well as proxies for infections—such as when a child began day care—have not always found that early infections protected against leukemia. On the other hand, U.S. researchers reported in the *Journal of the National Cancer Institute* in October that breast feeding appears to reduce the risk of childhood leukemia, which supports the immune system idea: Breast feeding is well known to protect against infections, apparently by passing antibodies to infants via the milk. Results from the largest study yet to probe the infections hypothesis, which looked at 1000 ALL cases in the United Kingdom, are due out next year.

MAJOR U.S. CHILDHOOD CANCERS*

Type	Cases per year
All leukemias	3250
Acute lymphoblastic leukemia	2400
Brain tumors	2200
Hodgkin's disease	850–900
Non-Hodgkin's lymphoma	750–800

* Under age 20.

The idea that a toxicant may be to blame for childhood brain cancers also has little solid support. At a workshop at the University of Minnesota, Minneapolis, in July, researchers mainly discussed three possible culprits: n-nitrosopyrrolidine compounds in cured meats; polyomaviruses; and folate (a B vitamin) deficiency or defective folate metabolism. Some studies have indicated a twofold higher risk in children whose mothers ate a lot of cured meat during pregnancy, and the notion that hot dogs can cause brain cancer is "one of the most compelling still," says USC epidemiologist Susan Preston-Martin. Polyomaviruses that are passed from mother to fetus such as the JC virus have come under suspicion because they can cause DNA mutations, while infants whose mothers take prenatal vitamins with folic acid—needed to repair and synthesize DNA—may have a lower chance of brain tumors.

Still, childhood cancer experts say they have been seeking answers in studies ill equipped to provide them. Studies "haven't been able to disentangle exposure that well," says molecular epidemiologist Federica Perera of Columbia University. Any major new efforts should depart from earlier ones in two key ways, Perera and others say: Instead of relying primarily on parents' memories of foods or chemicals they or their children were exposed to, researchers should collect direct evidence of exposure—for instance, molecular changes that occur when carcinogens latch onto DNA. And they should look for inherited variations in genes that may predispose children to cancer, say, by poorly metabolizing folic acid or carcinogenic phenols found in foods. **–J.K.**

Grufferman, an epidemiologist at the University of Pittsburgh School of Medicine. But if arousing public concern over childhood cancer was a goal, the conference triumphed: It made newspapers coast to coast.

In the wake of that publicity, Klausner asked NCI epidemiologist Martha Linet, who has tracked childhood cancer rates for 10 years, to explain the data to the National Cancer Advisory Board at its December 1997 meeting. Linet told the group that although health officials had indeed reported an overall rise in childhood cancer incidence since the early 1970s, recent data show that rates for most childhood cancers have been stable since the mid-1980s and that new diagnostic techniques could explain some earlier increases. The presentation left advisory board chair J. Michael Bishop, a Nobel Prize–winning oncogene researcher at the University of California, San Francisco, scratching his head. "How can federal agencies within the same city reach such diametrically opposed conclusions?" he asked. Klausner offered to sum up NCI's findings and disseminate them widely.

With that in mind, Klausner set in motion an extensive analysis of the data, including the brain cancer results, which NCI pediatric oncologist Malcolm Smith had already begun to examine. The EPA conference "made these data an issue," says Smith, whose team analyzed the surge in reported brain cancer cases around 1985, when hospitals were switching from computed tomography (CT) scanners to magnetic resonance imaging (MRI) machines as the main tool for finding brain tumors. In the September 1998 issue of the *Journal of the NCI* (*JNCI*), Smith argued that the switch to MRI—along with reporting changes in which some slow-growing tumors, previously classified as benign, were now counted as

SOURCE: SEER

malignant—could explain much of the 35% rise between 1973 and 1994.

In the meantime, Lynn Ries and colleagues at NCI finished a pediatric cancer monograph they had begun before the EPA conference. The work is an analysis of data from NCI's Surveillance, Epidemiology, and End Results (SEER) program, which tracks cancers in 14% of the U.S. population. Published last month, the monograph reports slight increases since 1975 in some very rare childhood cancers, such as testicular cancer and retinoblastoma. But overall, conclude Ries, Linet, and others in a report published in the June issue of *JNCI*, there has been "no substantial change in incidence for the major pediatric cancers, and rates have remained relatively stable since the mid-1980s." The NCI team argues that the increases in the mid-1980s likely "reflected diagnostic improvements or reporting changes ... rather than the effects of environmental influences."

Several outside experts consulted by *Science* say the two NCI teams together make a compelling case. "They're both superb" papers, says Susan Preston-Martin, an epidemiologist at the University of Southern California in Los Angeles. Although the findings don't rule out a long-standing mysterious cause of childhood cancer, she says, they show "there's nothing new in the environment that we need to scramble to discover."

To Klausner, the case is closed. NCI has issued a series of fact sheets and has brought EPA scientists to Bethesda, Maryland, to allow NCI epidemiologists to explain their methods. "I think they [EPA] fully agree with us," Klausner says.

Worlds apart?

That's hardly the message coming from EPA scientists and colleagues outside the agency who have helped shape its childhood health program. Philip Landrigan of Mount Sinai Medical Center in New York City takes issue with Smith's brain cancer paper in particular. "I'm a pediatrician. I see children with brain cancer. It's inconceivable to me to imagine that 25 years ago we were missing one-third of children with this disease," Landrigan says. A colleague at Mount Sinai, Clyde Schechter, argues that if MRIs pick up tumors once too small to detect, then the rates should have ebbed after the new technology had flagged all the cancers that would have been caught eventually by the previous technique. Smith counters that some of the nervous system tumors the MRI scans catch neither grow nor cause symptoms readily traced to the tumors—thus they would never have been detected by CT scans, so the rate should not necessarily recede.

Opposite corners. EPA's Galson and NCI's Linet have different takes on childhood cancer trends.

"One could conclude that [NCI] is trying hard to explain away the increased childhood cancer incidence demonstrated by their own data," says Galson. "The increase has been going on over such a long period of time that it is just stretching the bounds of believability a little bit to say [the rise] is absolutely all the result of these 10 things [new diagnostics, etc.] that have happened and you really don't have to worry about it." And as for NCI's conclusion that childhood brain cancers are not on the rise: "That's their opinion," says an official in EPA's Office of Children's Health Protection. (Administrator Browner declined to be interviewed for this article.) Epidemiologist Devra Davis of the World Resources Institute in Washington, D.C., also questions Smith's results, noting that a 1992 Canadian study in which a neurologist did a blind review of hospital records found that in only about 20% of cases did doctors rely on MRI or CT scans to detect tumors.

Despite their differences in "world view," says Galson, he and others at both agencies say the conflict has spurred some constructive engagement. This is happening mainly through a children's environmental health task force chaired by Browner and Health and Human Services Secretary Donna Shalala. The panel has compiled a database of ongoing children's health research (www.epa.gov:6710/chehsir/owa/chehsir.page) and is laying plans for a cancer registry that would pool data collected by clinics. By expanding the number of cases far beyond the 14% of U.S. cases now studied by SEER, the registry could greatly increase the statistical power of population studies. The registry is part of EPA's research agenda, which also recommends toxicology tests using young animals, molecular biomarkers to identify susceptible subpopulations, and better exposure measurements.

To some researchers, these fruits make the scuffle over cancer rates worthwhile. "Children have been ignored and neglected," asserts University of California, Berkeley, epidemiologist Martyn Smith. It's "great" that EPA and NCI are ratcheting up efforts to understand the causes behind childhood cancers, adds Minnesota's Gurney. There may be no love lost between the two agencies, he says, but "I couldn't be happier."

–JOCELYN KAISER

CREDITS: (LEFT TO RIGHT) EPA; URI

A Broader Push on Childhood Health

The Environmental Protection Agency's (EPA's) interest in childhood cancer is part of a new focus on children begun 4 years ago by Administrator Carol Browner and President Clinton, who in 1997 ordered that all new federal safety standards take into account children's health. Although some observers charge that the drive is more politics than science, many researchers say it's an idea whose time has come.

A large share of the credit for heightening interest in children's health belongs to a report, "Pesticides in the Diets of Infants and Children," issued by the National Academy of Sciences in 1993. Prepared by a panel chaired by pediatrician Philip Landrigan of Mount Sinai Medical Center in New York City, the report argues that regulatory standards for pesticides and other chemicals may not sufficiently protect children. Babies and young children are more vulnerable because their bodies are developing, it says, and they are exposed to more toxicants by body weight, partly because of behaviors such as crawling and eating more fruits.

Congress picked up on this theme, passing two laws in 1996 calling on EPA to take into account the risk to children when revising water and food safety regulations. EPA's initiatives include an Office of Children's Health Protection opened in 1997 and funding, with support from the National Institutes of Health, for eight university-based children's health centers that study asthma, exposure to pesticides on farms, and other environmental health issues pertaining to children. Among major regulatory steps in the works, EPA is expected to reduce exposure 10-fold for some pesticides and to work with manufacturers on a testing program for chemicals posing particular risks to children.

Some observers have harshly criticized these initiatives. The academy report cites no studies showing that children are being harmed, points out Kenneth Chilton of the Center for the Study of American Business at Washington University in St. Louis. He argues that EPA is focusing on "very tiny" environmental risks: "Putting bicycle helmets on children is going to have way more impact." But EPA has backing from many top scientists. "It's not all politics," says Bernie Goldstein, director of the Environmental and Occupational Health Sciences Institute in Piscataway, New Jersey. He notes that ferreting out an individual's susceptibility to disease is the wave of the future as scientists exploit genomic findings. Focusing on children, he says, "is in a sense a part of it."–J.K.