



The Philadelphia Inquirer / AKIRA SUWA

The names of children who died of cancer are inscribed on a memorial in Toms River, N.J.

A cluster conundrum



For The Inquirer / ANIMY MCGINLEY

On a map in the office of a nonprofit family support group, markers pinpoint Toms River-area children diagnosed with cancer.

Local concentrations of cancer cases occur all the time. But environmental causes are hard to pinpoint scientifically, and the clustering itself could be a coincidence.

This spring, medical researchers will launch a door-to-door search in Toms River, N.J., for the cause of an apparent spate of childhood cancer cases in that Ocean County community. It will be one of the most comprehensive community epidemiology studies of its kind. It will involve getting detailed medical histories from families, as well as soil and water tests throughout the town. But if the past is any indication of the outcome, the researchers will be unable to find a cause. The image of a cancer

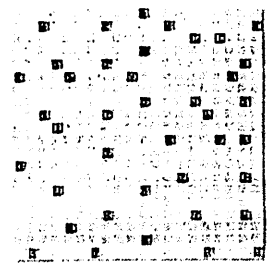
"cluster" — an abnormally high incidence of the disease in a single locale — could even dissolve into statistical insignificance. And families will be left uncertain and frustrated. In 22 years the federal Centers for Disease Control and Prevention has investigated 108 possible cancer clusters in 29 states and five foreign countries. The CDC used eight different data collection methods, four different types of laboratories, on four different specimen types. The result: No clear cause was found for any cluster. "It has been very difficult, next to im-

When Cancer Comes in Clusters

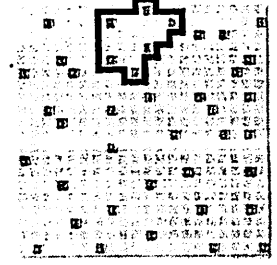
This spring researchers in Toms River, N.J., will investigate a cancer "cluster" — an abnormally high incidence of the disease in a single area. Their goal: Determine if something caused the cluster, or if it's merely a random, yet statistically expected, occurrence.

How a cluster occurs randomly

Forty red squares are randomly distributed on a grid of 400 squares.



By drawing a boundary around groupings of squares, you can find clusters. Of the 20 squares circled below, 6 are red, three times more than the expected 2 squares.



But when you look at the larger picture — the entire grid — you find the expected number of red squares. The cluster didn't exist until the boundary was drawn around it. What looks like a cluster of red squares isn't anything more than what would be statistically expected in the larger area.

The Philadelphia Inquirer / MATTHEW ERICSON

possible, to find or explain a genuine environmental cancer cluster," said Robert Miller, the retired chief of epidemiology for the National Cancer Institute. The environmental disease cluster has emerged as a modern-day chimera, testing and trying epidemiology and environmental health science and the sense of well-being in dozens of communities across the nation. The techniques for examining disease clusters, scientists say, are improving, although they do not yet guarantee answers. But they do provide a checklist of things that ought to be done to maximize See **CLUSTERS** on F12.

Local concentrations of cancer cases: Clusters, or just coincidence?

CLUSTERS from F1
 the chances of determining whether a cluster is real and providing clues to its cause.

Still, the odds of finding an environmental villain remain thin. "It can be a very controversial, very emotional issue, a very frustrating issue," said Louise Ryan, a researcher at the Dana Farber Cancer Institute in Boston.

That has been the experience of communities around the country, such as:

- McFarland, Calif., which had 21 cases of childhood leukemia in the last 20 years — three times as many as would be expected in that farming community of 8,000. But last year a detailed state health department study could find no clear cause. The federal Environmental Protection Agency is now conducting follow-up soil and water testing. "You get angry but you don't know where to direct your anger. You want someone or something to blame but there's no one or nothing to point a finger at," one resident said when the state study was released.
- Cape Cod, Mass., had a rate of breast cancer 20 percent above the state average, between 1982 and 1994. But epidemiological studies have now ruled out tainted drinking water, powerful military radar, a nuclear power plant, and estro-

gen-mimicking synthetic chemicals.

- A flurry of childhood leukemia cases in suburban Denver and seven cases of brain cancer in Connecticut initially appeared linked to high-tension electric transmission lines. But a comprehensive national epidemiological study released last June could find no link at all.

"The real question is not whether clustering occurs," said Allen Neugegt, a professor at the Columbia University School of Public Health. "Clustering occurs all the time. The question is whether it is meaningful."

Communities and researchers dispute statistics bitterly.

To understand Neugegt's point one has to delve into statistics; it is in those numbers that communities and researchers have their most bitter disputes.

A cluster constitutes a number of incidences above the norm. "If you were flipping a coin, what would be the chances of getting 50 heads in a row? Well, it would be very small," said Sandy Zabel, a professor of statistics at Northwestern University.

"Now, if you have thousands of people flipping coins, somebody would get 50 heads. It wouldn't be caused by the coin or the person. It would be a chance event, a cluster of heads," Zabel said.

Communities across the country raising children and living every day lives are like the coin flippers: Some of them will have clusters of auto accidents, fires or disease.

"If it's really a chance occurrence, you could look forever and you'd never find a cause," said the National Cancer Institute's Miller.

Sometimes, epidemiologists say, how the boundaries are set may give the appearance of clustering. In a study of childhood leukemia deaths in Los Angeles, Miller found a "striking uniformity of the mortality rate over 32 census tracts." But he said by tightening — gerrymandering — the boundaries it was possible to create a cluster. "It's just one example of how you can draw the wrong conclusions."

How time boundaries are drawn may make a difference in one breast cancer cluster being evaluated.

"There's no reason why the eastern end of Long Island would have any more risk," said Columbia's Neugegt. "They used data for a five-year time frame that showed elevated rates. But the five years before that had a lower rate of breast cancer."

Sometimes a variety of cancers are lumped together in a cluster, and that also scrambles the issue. Cancer is believed to be a genetic disease that emerges when the basic instructions regulating cells go awry. It is believed this is largely inherited.

But there are some environmental exposures that can clearly promote cancer, such as high levels of radiation. Most environmental promoters are linked to specific kinds of cancers — for instance, inhaling asbestos fibers can trigger a lung cancer called mesothelioma.

The more cancers that are lumped together, researchers say, the more difficult it is to pinpoint the environmental culprit, if any. If a population is exposed to some particular environmental contaminant, researchers say, there should be some consistent effect.

In McFarland, there were cases of childhood liver cancer, bone cancer, adrenal gland cancer and lymphoma. In Toms River, the 24 childhood cases logged in 16 years included leukemia, neuroblastoma and brain cancer.

Limiting the ability to find environmental causes even more, said the National Cancer Institute's Miller, said, is the fact that there are only about 50 known chemical carcinogens.

Even trying to limit the cluster to a single cancer is sometimes tricky. "Say, there are a lot of brain tumors," Miller said. "The question is, was that the initial source of the cancer or did it metastasize to the brain from someplace else?"

As these types of problems are sorted out, the significance of a cluster can sometimes slowly fade. Jonathan Samet, a respected epidemiologist at the Johns Hopkins University School of Public Health, studied brain cancer in Los Alamos, N.M., the site of a major federal laboratory and nuclear test site.

"We did a fairly extensive evaluation," he said, "and as we looked more closely, the excess in cancer cases) went away."

Nevertheless, there have been documented clusters — chemical workers in Kentucky with liver cancer, mustard-gas factory workers in Japan with lung cancer, and cervical cancer in the daughters of women who used the drug DES to prevent miscarriages.

"When it's a true cluster you don't need a lot of cases to prove it. The DES cluster was found with just four cases," Miller said.

The best known environmental cancer cluster in the United States occurred in Woburn, Mass., where 20 cases of childhood leukemia were diagnosed in the town of 37,000 during a 20-year period.

The suspected cause was a public water system well contaminated with the solvent trichloroethylene (TCE) by the W.R. Grace Co.

In 1986, Grace reached an out-of-court settlement in a civil lawsuit with town residents for \$8 million. But while it was a fact that the well had been contaminated and that Woburn clearly had an above-average number of childhood leukemia cases, it was not possible to definitively prove — even with good estimates of exposure to the pollution — that the contaminated water caused the leukemia.

Still, despite the limitations of epidemiological techniques, many researchers feel something in the environment is at work.

The rate of cancer among children nationwide has been rising since the early 1970s. Childhood brain cancer rates have increased about 40 percent, and rates for lymphoblastic leukemia are up 27 percent between 1973 and 1990.

Nationally, about 8,000 new cases of cancer, the most common form of fatal childhood disease, are diagnosed every year.

Breast cancer rates also rose about 4 percent nationally during the 1980s. On average, Long Island's rate has been above the national average.

A 1994 New York State Department of Health study found a higher risk of breast cancer for postmenopausal women who lived within half a mile of a chemical, petroleum, rubber or plastics plant.

But the study was unable to show any relationship between the plants and the cancers. Critics argue that it is just as likely that social or economic factors — poor people who live closer to chemical plants — can't afford preventive treatment may explain the effect. The state called for further studies.

Some public health experts say clusters should be looked at in a broader context.

"We can't think of these situations as a cluster of a single isolated disease — a cancer cluster. We have to start thinking in terms of community health," said John Groopman, a professor of environmental health sciences at Johns Hopkins University.

"Unless there is a singular exposure that is so overwhelming that produces a disease at a particular site, you aren't going to be able to pick it up," he said, even though something in the environment might play a role.

Groopman said that in Woburn researchers looked beyond the 20 leukemia cases and found immune system and other health problems in family members.

"The community pushed on TCE contamination and they were right," Groopman said.

"If this [a cluster] is environmentally driven, there should be a higher level of other health-related problems — absenteeism in school, childhood illnesses, things like that."

But Ryan of Dana Farber Cancer Institute, who is serving as an ad-

viser to citizens groups in the Cape Cod cluster, cautioned that "Woburn was lucky in two regards. It was able to define and measure the exposure."

The working theory was that the TCE was the cause of the problem. The state Department of Health calculated how much of the contaminated water each family received. Researchers could then look at families with the highest exposure to see whether they had the most severe health problems.

"That enabled the statistics to work," Ryan said.

But in most cases, such as the one she is working on in Cape Cod, it is difficult to define a single exposure or measure it. "We are looking at a whole range of different sources," she said.

In trying to define and understand a potential cluster, the experts contend that a study should:

- Start with a hypothesis of what the potential threat may be. In Woburn it was a contaminated well.
- Draw a logical and realistic boundary for the area under study. Based on Woburn's hypothesis, the target area was the one served by the municipal water supply.
- Verify the cases and make sure they are consistent — as in Woburn, which dealt with only leukemia cases. The rate should also be checked against the baseline rates to make sure the incidence of the disease is really above what would be expected.

- Try to assess exposure to the suspected source. Do the cases conform to some expected way the source would affect health? These numbers also have to be adjusted for demographic and social effects.
- See what else is going on in the cluster area in terms of health and environmental issues. Do these have some link or relation to the cluster disease?