

PCBs linked to rise in lymph cancers

The incidence of non-Hodgkin's lymphomas—a family of cancers that attack the body's infection-fighting lymph system—has mushroomed since World War II. Because the dramatic rise has occurred globally, even in areas with traditionally very low rates of the disease, epidemiologists have been examining whether exposure to one or more environmental agents might be propelling the cancer's climb.

A new study has found provocative evidence that polychlorinated biphenyls (PCBs)—banned but still ubiquitous oils used to insulate electric transformers and other equipment beginning in the late 1930s—may be one such agent.

Several studies of agricultural workers had suggested a link between DDT and lymphomas, so Nathaniel Rothman of the National Cancer Institute in Bethesda, Md., and his coworkers decided to investigate this possibility. They tapped into the Campaign Against Cancer and Stroke study, sponsored by Johns Hopkins University in Baltimore, Md., which had enrolled nearly 26,000 healthy participants in 1974.

Over the years, 74 of the volunteers had developed non-Hodgkin's lymphoma. Rothman's team identified two healthy study participants matching the age and sex of each cancer patient and then measured DDT and other organochlorines in samples of blood serum that had been collected from these individuals some 20 years earlier.

To our surprise, Rothman says, "we saw no DDT link." Instead, they observed an unexpected correlation between PCBs and the disease. In the July 26 *LANCET*, his team reports that people with PCB concentrations of more than 1,050 parts per billion (ppb) in their blood's fat globules have a 4.5 times greater risk of this cancer than people with 250 to 650 ppb.

"The size of this effect is bigger than what we see in a lot of epidemiology studies," Rothman says, but it needs to be confirmed—with more patients.

Oncologist Lennart Hardell of the Örebro (Sweden) Medical Center Hospital offers support for the link, though in a far smaller population. Last year, his team reported data from 28 people with the lymphoma and 17 healthy individuals. Compared to the healthy people, the cancer patients tended to have higher PCB concentrations in body fat but equivalent amounts of DDT.

Does such a link make sense biologically? "I think most people would say yes," argues NCI epidemiologist Patricia Hartge. Several studies have indicated that PCBs can suppress the immune system, she notes. Moreover, a number of small studies by Hardell and others have turned up hints that other organochlo-

rines might pose a non-Hodgkin's risk.

Finally, she observes that although AIDS, organ transplantation, and certain rare genetic disorders appear to predispose individuals to developing non-Hodgkin's lymphomas, these risk factors "couldn't begin to explain the level of increased incidence that has occurred throughout the world." For instance, in white U.S. men, the annual rate rose from 6.9 cases per 100,000 before 1950 to 17 per 100,000 by 1988.

The new U.S. study also hints that active infection with the Epstein-Barr virus greatly exacerbates the cancer risk of PCBs. "It's a hypothesis I suggested

several years ago," Hardell notes, and one he plans to probe further in non-Hodgkin's lymphoma patients.

Some researchers worry that the PCB link indicates the cancer may also be associated with dioxins—ubiquitous chemicals structurally similar to PCBs. Some PCBs resemble dioxins in their effects on health, but Rothman's new study did not measure conventional dioxins, notes Linda S. Birnbaum of the Environmental Protection Agency in Research Triangle Park, N.C. So it's unclear whether the link between PCBs and non-Hodgkin's lymphoma traces to activation of the cell receptor where dioxins attach. To understand how PCBs work, she notes, "you'd like to be able to rule that out." —J. Raloff

Staying alive: Cell protein guards cancers

In a move that can protect the organism, individual cells that have somehow gone awry often commit suicide. Indeed, this self-sacrifice may eliminate most mutated cells before they become fully cancerous.

Yet tumors sometimes arise, and researchers are now finding evidence that the cells of those cancers have found ways to inhibit apoptosis, the process by which cells kill themselves (SN: 7/27/96, p. 55).

One such survival tactic may employ a gene used primarily during fetal development, report Grazia Ambrosini of Yale University School of Medicine and her colleagues in the August *NATURE MEDICINE*.

This newly discovered human gene encodes a protein, called survivin, that seems to delay or prevent cell suicide.

"The cancer cells turn this gene on so that apoptosis is inhibited and the cells keep growing," explains Ambrosini.

Because it appears that most tumor cells, but very few normal adult tissues, produce survivin, the protein offers an appealing target for cancer drugs. Compounds that block its function may thwart tumor growth while producing few side effects, says Ambrosini.

The discovery of survivin is "very exciting," agrees John C. Reed of the Burnham Institute in La Jolla, Calif., who studies the role of other apoptosis inhibitors in cancer. "Having read the paper, we'll start working on it immediately," he adds.

Ambrosini and her colleagues chanced upon survivin's gene while looking for another gene. When they searched databases for proteins similar to the amino acid sequence predicted by the gene, they discovered that survivin belongs to a small family of proteins known to stymie cell suicide.

Over the last few years, genes encoding these apoptosis-inhibiting proteins have been found in viruses, insects, and most recently, mammals, including people.

The Yale investigators created antibodies that bind to survivin and used them

to show that cancer cells grown in the laboratory invariably contain the protein. Many fetal tissues, including kidney, lung, and liver, also have lots of survivin.

Yet when the researchers examined many adult tissues, including lung, liver, brain, blood, and heart, they found no evidence of survivin. Only in the adult thymus and the placenta did they detect even small amounts of it.

Ambrosini and her colleagues also studied tissue from some of the most common human cancers: lung, colon, pancreas, prostate, and breast. They found survivin in every tumor sample but not in nearby normal tissue. In addition, they observed that the protein is rarely present in the less aggressive forms of non-Hodgkin's lymphoma but is abundant in the most dangerous ones.

Finally, the investigators added the gene for survivin to laboratory-grown cells whose lives normally depend upon a chemical called interleukin-3 (IL-3). After IL-3 was withdrawn, the cells making survivin died significantly more slowly than unaltered, IL-3-dependent cells.

The scientists have begun to examine whether survivin helps cancer cells to resist the drugs traditionally used in chemotherapy.

Reed notes that cancer cells may also employ other proteins in survivin's family, but that notion has been difficult to assess. Unlike survivin, those apoptosis-inhibiting proteins are normally made by most adult cells. Consequently, investigators face the subtle task of determining whether cancer cells make even greater amounts of the proteins.

With survivin, he says, "it's such a night-and-day comparison between normal tissues and tumors."

In the July 17 *NATURE*, Reed and his colleagues provide data to explain how such survivinlike proteins halt cell suicide. They bind and apparently inhibit apoptosis-induced proteases, enzymes that chop up other proteins. —J. Travis