EcoCancers

Do environmental factors underlie a breast cancer epidemic?

By JANET RALOFF

Throughout countries rich and poor, industrial and rural, breast cancer incidence is on the rise. No one knows what's fueling that increase, especially since recent studies have all but thrown out what had been the primary suspect: dietary fat.

In following up a variety of promising new leads, oncologists and epidemiologists have discovered a common thread that appears to tie together many tantalizing alternative suspects: They all appear able to boost the amount of estrogen in the body.

Most carcinogens disrupt the body's normal operations by throwing a monkey wrench into its genetic machinery. Thus, scientists typically scout for potential carcinogens by investigating a suspect agent's ability to break, disable, mutate, or otherwise alter DNA.

But in a number of laboratories around the world, researchers are now investigating other, more circuitous mechanisms to explain breast cancer's rise. Though far from conclusive, their findings suggest that an unintended side effect of industrialization is an environment that bathes its inhabitants in a sea of estrogenic agents. Some of these agents, such as pesticides and ingredients in plastics, mimic the hormone estrogen in their effects on the body. Others, such as magnetic fields and certain combustion by-products, can boost the concentration of estrogens circulating in the bloodstream.

And that's beginning to worry toxicologists and epidemiologists, because factors that increase a woman's lifetime exposure to estrogen, such as early puberty and late menopause, are among the leading known risk factors for breast cancer.

Although scientists don't understand exactly how estrogen fosters breast cancer, they do know that this steroid hormone stimulates cell proliferation in the breasts during each menstrual cycle. To some, this suggests that an excess of estrogen might drive the high rate of cell proliferation characteristic of cancer.

But even after accounting for estrogen and other known risk factors, "we still cannot explain 60 to 70 percent of breast cancers," observes Devra Lee Davis, a toxicologist with the Department of Health and Human Services.

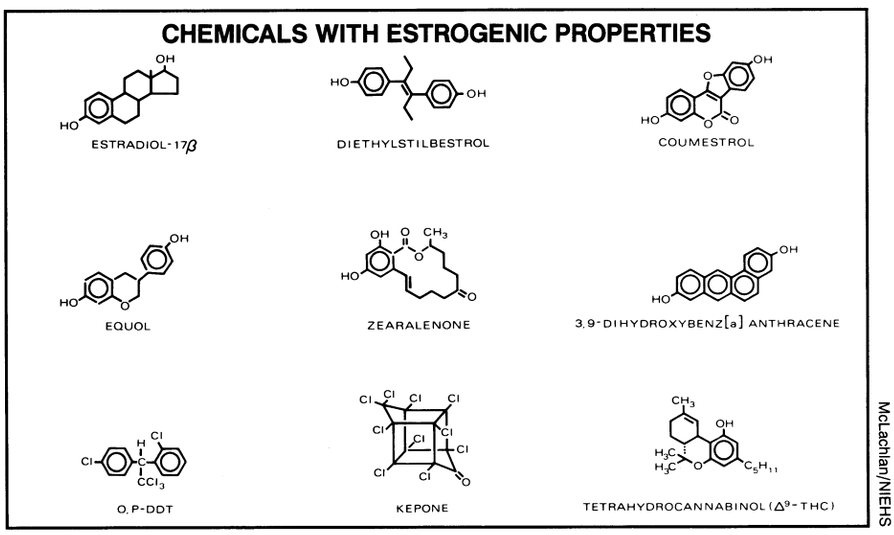
However, she points out, this accounting ignores a population's exposure to what she terms "xenoestrogens." Such agents are not produced in the body, she explains, but when they interact with the body, they "have the effect of functioning directly or indirectly as estrogens and thereby increasing your lifetime exposure to estrogens."

In the forthcoming August ENVIRONMENTAL HEALTH PERSPECTIVES, Davis and researchers at five medical centers will review studies that together provide what they believe to be compelling evidence of widespread human exposure to xenoestrogens. They note, for example, that many nearly ubiquitous pollutants possess estrogenic properties. These include pesticides such as DDT, heptachlor, and atrazine, as well as several polycyclic aromatic hydrocarbons (PAHs), petroleum by-products, and polychlorinated biphenyls (PCBs). Indeed, they note, many of these pollutants are known to induce or promote mammary cancers in lab animals.

Human data, though scant, also suggest that several of these chemicals — especially certain chlorinated organic compounds and PAHs — may increase a woman's risk of breast cancer. For instance, Davis and her coauthors cite studies showing elevated breast cancer rates in women who work in the chemical industry, who were exposed to PCBs in Japan, who were exposed to PAH contamination in drinking water, or who carried high concentrations of DDT in breast tissue (SN: 4/24/93, p.262).

The researchers conclude that xenoestrogens may play a significant role in breast cancer worldwide. And if that's true, says Davis, identifying the most pervasive, persistent, and potent of these could go a long way toward helping shape strategies to thwart the upward trend in breast cancer incidence.

John A. McLachlan has been studying chemicals with estrogenic activity at the National Institute of Environmental Health Sciences (NIEHS) in Research Triangle Park, N.C., since 1972. But the "revelation" that there were so many such chemicals out there didn't really sink in, he says, until NIEHS sponsored a conference on the subject in 1979. He believes this was the first such meeting to pull together scientists from the range of disciplines — from agriculture to medicine to environmental tox-



Chemicals that functionally mimic estradiol, the body's natural estrogen, may bear little structural resemblance to the hormone. Though drug companies deliberately designed diethylstilbestrol to substitute for estradiol, no one knows why plants produce estrogens such as coumestrol, equol, zearalenone, and tetrahydrocannabinol. Other surprising estrogen mimics include the pesticides DDT and kepone and a combustion by-product (center right).

icology — working with these chemicals, often unbeknownst to one another. The breadth of agents able to elicit estrogenic effects immediately suggested that they might constitute a public health problem, recalls McLachlan, now director of intramural research at NIEHS.

Those concerns continue to drive much of his interest in endocrine biochemistry. At a meeting of the President's Special Commission on Breast Cancer, held in New York City in April, McLachlan described a superfamily of cell receptors that normally trigger genetic activity when a hormone or vitamin binds to them. But the discovery over the past two years that a variety of pollutants also can bind to these receptors represents a "really enormous breakthrough" in understanding the estrogenic effects of chemicals in the environment, he says.

Receptors function like locks. For years, scientists assumed that each particular lock would yield only to keys bearing one particular chemical structure. The keys would fit into a receptor and turn its "tumblers" to unlock gene action — such as the estrogen-modulated biology of breast growth.

It now turns out, however, that many chemicals with vastly different structures can unlock the estrogen receptor.

Some enter the keyhole but don't fully unlock the receptor's normal activity, McLachlan says. Others, behaving like rusty keys, sometimes turn in the lock and sometimes don't. Still others fit neatly into the receptor and fully unlock its gene action. The drug diethylstilbestrol (DES) is probably the best example of this last category. To date, DES represents the only xenoestrogen that unlocks estrogen-receptor activity even more effectively than the body's own estrogen, estradiol.

McLachlan showed the Breast Cancer Commission line drawings of a number of chemical keys for the estrogen receptor (see diagram, p.10). The important message, he emphasized, is how little these chemicals must resemble the body's natural estrogen to functionally mimic it.

But timing can also influence the overall significance of a cell's access to these keys, he notes. Between puberty and menopause, a woman's body circulates high concentrations of estradiol on a monthly basis. If, during these times, breast cells encounter lots of rusty keys — such as the relatively weak xenoestrogens produced by some plants — the net effect may be to *diminish* the breast's overall estrogen exposure, McLachlan says. That's because weak xenoestrogens may tie up receptors otherwise available to the stronger, natural estrogen.

Seen in this light, "plant estrogens in the diet may actually be good for you," McLachlan told SCIENCE NEWS.

However, he adds, if these imperfect keys circulate abundantly in persons who otherwise carry a low estrogen load — such as men, young children, or postmenopausal women — they may boost the breasts' otherwise low exposure to estrogenic effects. In this context, he says, chronic exposure to even weak xenoestrogens might be seen as increasing a person's breast cancer risk.

Other researchers have turned up evidence of a more indirect modus operandi for environmental modulation of estrogen. Over the past decade, endocrinologist H. Leon Bradlow of Cornell University's Strang Cancer Prevention Center in New York City and his colleagues have identified a number of agents that change how the body metabolizes estradiol.

Two enzyme systems compete for a chance to modify the 18-carbon hormone by inserting a hydroxyl (OH^-) at either the 2-carbon or 16-carbon position. Though some of the body's natural estrogen is diverted down each metabolic pathway, the share handled by either pathway can vary widely. For instance, says Bradlow, "if you're a vigorous exerciser, like a marathon runner, then the 2 pathway goes up very high and the 16 pathway goes down."

This can have health implications, he points out, because while the 2-metabolite (2-OHE) appears innocuous, his team's data show that the 16-metabolite (16-aOHE) "is, at a minimum, breast-cancer-risk promoting, and actually genotoxic [toxic to DNA]." For instance, the 16-metabolite stimulates cell proliferation and allows a community of cells to grow without anchoring to a surface — two major factors required for cancer development.

Bradlow's group has also demonstrated that the 16-metabolite is unique among bodily produced chemicals in its ability to form a tight chemical attachment (covalent bond) to the estrogen receptor. In animal studies led by Bradlow, this bond prolonged the biochemical and physiological effects normally seen with the parent estradiol, in some cases exaggerating the expression of certain genes, including cancer-causing genes.

Bradlow's team and others have observed that cigarette smoking, dioxins, and indole-3-carbinol (a compound in brassica vegetables, such as cabbage and broccoli) stimulate the preferential production of the benign 2-OHE over 16-aOHE. Bradlow and his co-workers have also demonstrated that indole-3-carbinol, when fed to mice, can suppress the natural, spontaneous incidence of mammary tumors.

By contrast, alcohol, human papillomavirus, the combustion pollutant benz[a]pyrene, and certain drugs preferentially depress the 2-pathway, allowing the more toxic 16-pathway to take over. In fact, Bradlow notes, cimetidine — widely prescribed to treat stomach ulcers — has "caused [breast enlargement] in men who take it." Human studies conducted by his group show that cimetidine also inhibits formation of the 2-metabolite, increasing production of the highly estrogenic 16-metabolite.

An unintended side effect of industrialization may be an environment that bathes its inhabitants in a sea of pollutants with estrogenic effects.

These provocative findings don't prove that chemicals that selectively foster 16-aOHE metabolism instead of the 2-OHE route will cause breast cancer, says Davis. However, she adds, "anything that causes breasts to grow in men should be considered highly suspect because it's already stimulating breast cell proliferation."

Chemicals aren't the only agents that can exhibit a hormonal alter ego. Animal studies have shown, for instance, that both light at night and magnetic fields can influence a brain secretion that regulates estrogen concentrations.

Though speculative, these findings might explain why breast cancer rates tend to be higher in more industrialized nations, says Richard G. Stevens of the

Pacific Northwest Laboratory in Richland, Wash. "Electric power is almost a hallmark of industrial development," he says. "And its use results in two things that we did not have in our environment 100 years ago: bright light at night and a range of electromagnetic fields, including 60-hertz magnetic fields [the frequency associated with U.S. household electric current], microwaves, and most radio waves."

These new studies also offer a possible explanation for the reported association between electromagnetic fields and breast cancer in men (SN: 9/28/91, p.202).

Since the late 1970s, researchers have puzzled over epidemiologic data linking electromagnetic fields and several cancers. Their bewilderment stems from observations that the extremely low-frequency fields encountered by most people "are not acutely toxic to any biological system that's been investigated," says Scott Davis, an epidemiologist with the Fred Hutchinson Cancer Research Center in Seattle. Moreover, he notes, those fields "are too weak to break chemical bonds or to induce the types of genetic change that we [typically] think of as necessary in cancer causation."

In the April 1987 AMERICAN JOURNAL OF EPIDEMIOLOGY, Stevens proposed a novel theory. The pineal gland, located in the center of the brain, secretes its primary hormone, melatonin, during nighttime darkness. While melatonin's major function in humans remains elusive, several animal studies suggest that nighttime levels of the secretion inhibit the body's production of estrogen and prolactin, a hormone that stimulates milk production. Citing other animal studies showing that exposure to either light at night or electromagnetic fields can suppress melatonin secretions, Stevens theorized that such chronic exposures in humans might increase an individual's cumulative lifetime dose of estrogen—and hence breast cancer risk.

A year and a half later, two researchers at the University of Arizona in Tucson published data supporting that hypothesis. David E. Blask and Steven M. Hill found that melatonin could directly inhibit the proliferation of human breast cancer cells in culture. "Even more significant, we were able to demonstrate that the concentration of melatonin needed to inhibit the growth of those cells was comparable to what's present in human blood at night," recalls Blask, now at the Mary Imogene Bassett Hospital Research Institute in Cooperstown, N.Y.

"We have also come up with what we think may be an even more fundamental mechanism for melatonin's inhibition of cancer — its ability to increase the levels of naturally occurring antioxidants in breast cancer cells," he says. Scientists have linked oxidative reactions to a number of diseases characteristic of aging, including glaucoma, heart disease, and cancer. Blask presented his team's antioxidant data in May at the first Locarno (Switzerland) International Symposium on Neuroendocrinoimmunology.

Experiments by Hill, now at Tulane University in New Orleans, and Blask also indicate that melatonin may be capable of reducing the number of estrogen receptors on breast cancer cells. Since estrogen effectively feeds the growth of hormone-responsive breast tumors, reducing the receptors might slow tumor growth.

Nor are theirs the only labs studying such effects. Dzhemal Sh. Beniashvili and his co-workers at the Republic of Georgia's Ministry of Health and Social Security in Tbilisi published related data two years ago in

Plastics may shed chemical estrogens

Many of the flasks used in labs are made of polycarbonate, a tough plastic produced by linking building blocks of an estrogenic material, bisphenol-A (BPA), into long chains. High-temperature cleaning can break down the chain's carbonate linkages, releasing some of the xenoestrogen building blocks.

Stanford Univ.

Krishnan using a polycarbonate flask.

Aruna V. Krishnan of Stanford University School of Medicine and her colleagues discovered this the hard way when BPA contamination derailed experiments they were conducting on the potential of certain yeasts to produce estrogens. Every time they sterilized a flask of the growth medium used to feed the yeast, BPA leached into it.

Polycarbonate manufacturers were aware of their plastic's potential to shed BPA, but they considered safe any release below their general limit of detection — roughly 10 parts per billion, the researchers note in the June ENDOCRINOLOGY. However, Krishnan's team found that BPA exhibited hormonal activity at concentrations of just 2 to 5 ppb in cultures of human breast cancer cells.

This suggests that "estrogenic effects could occur in the absence of confirmation [of the contaminant's presence] by chemical analytical methods," concludes Kenneth S. Korach of the National Institute of Environmental Health Sciences, who wrote an editorial accompanying the research report.

BPA-based plastics are used in many molded products, from tubing and prosthetic devices to consumer appliances. Indeed, U.S. manufacturers have the capacity to manufacture more than 1 billion pounds of BPA annually, Krishnan and her coauthors note.

Nor are these the only plastics that leach xenoestrogens.

Ana M. Soto and her co-workers at Tufts University in Boston have found that certain polystyrene tubing could at room temperature taint blood serum with a xenoestrogen. They isolated the contaminant and identified it as a common industrial additive known as nonylphenol, used to strengthen plastics and to prevent oxidative degradation during the production of certain plastics. In the May 1991 ENVIRONMENTAL HEALTH PERSPECTIVES, Soto and her colleagues reported that the nonylphenol they isolated is strongly estrogenic both in cultured human breast cancer cells and in rodents.

These two studies illustrate how unsuspected sources of environmental estrogens can disrupt experiments. "Equally disturbing," says Korach, "remains the likelihood that these agents may also affect human health."

— J.A. Raloff

ago in CANCER LETTERS. In their study, caged rats exposed to static or variable magnetic fields developed more mammary tumors upon exposure to a chemical carcinogen than did rats not exposed to magnetic fields. Tumors also developed sooner in the rats exposed to either type of field, although the variable fields promoted cancer more effectively.

Last month, Wolfgang Löscher of the School of Veterinary Medicine in Hanover, Germany, and his co-workers described results of a similar experiment at the Bioelectromagnetics Society meeting in Salt Lake City. Like Beniashvili's team, they found that low-power, alternating magnetic fields increased mammary tumors in rats fed a carcinogen — "strongly indicating that magnetic field exposure exerts tumor-promoting and/or co-promoting effects."

And at the University of California, Berkeley, scientists led by Robert P. Liburdy have just demonstrated that magnetic fields can limit or block melatonin's ability to inhibit the proliferation of human breast cancer cells in culture. But there appears to be a threshold to this effect. Liburdy and his co-workers find that a 12-milligauss field will shut down melatonin's suppression of cancer growth, while a 2-milligauss field will not.

The Berkeley researchers acknowledge that it remains unclear whether the observed effect can be explained by the magnetic field interfering with melatonin's binding to hormone receptors on breast cells — itself an unproven scenario — or by some process more directly involving estrogen. But "future studies should consider the possibility of estrogen-receptor involvement," they conclude in the March JOURNAL OF PINEAL RESEARCH.

These data suggest that melatonin is a naturally occurring cancer-inhibiting hormone, operating through one or more independent mechanisms, Blask says. If scientists confirm this role for melatonin in humans, he adds, it would strongly suggest that "suppression of melatonin might be a mechanism by which electromagnetic fields and light promote cancer, especially breast cancer."

However, other environmental or lifestyle forces may also influence estrogen through melatonin, he points out. For instance, virtually all beta-blocker drugs used to treat high blood pressure suppress melatonin production in humans, he notes. That could pose some problems, he notes, since patients requiring such drugs tend to be older — and age, too, diminishes melatonin production. Severe diet restriction, on the other hand, boosts nighttime melatonin secretion, offering yet another possible explanation for why chronically starved animals develop fewer cancers, he says (SN: 11/21/92, p.346).

Stevens suspects that melatonin also plays an unacknowledged role in a newly reported association between alcohol and estrogen. A study described in the May 5 JOURNAL OF THE NATIONAL CANCER INSTITUTE indicates that even moderate alcohol consumption raises estrogen levels in premenopausal women. Marsha E. Reichman of the National Cancer Institute (NCI) and her colleagues conclude that this may explain why women who drink face a 40 to 100 percent greater breast cancer risk than teetotalers.

But it's also possible, Stevens says, that "while [alcohol's] proximal influence on breast cancer may be estrogen, the actual risk factor that matters is its effect on melatonin." A 1986 study showed that alcohol consumption reduces melatonin production in rats, he notes, and a study published in the late 1970s indicated that humans suffering from alcoholism also secrete less of this pineal hormone than do healthy individuals.


Mary Washington College Publications Office

How much nocturnal illumination would it take to raise estrogen concentrations in humans? No one knows. However, oncologist David Blask estimates that "a night light is probably not sufficient, though a fairly intense reading light may be."

In their paper in the August ENVIRONMENTAL HEALTH PERSPECTIVES, Devra Davis and her coauthors map a strategy for coordinated studies — one that calls for intensifying research efforts to identify environmental factors that can increase estrogen exposure.

Many such investigations are planned or under way.

In May, for instance, Scott Davis launched a three-year assessment of the light and electromagnetic field exposures of 1,600 Seattle-area women, half of whom have breast cancer. In an attempt to estimate past exposures, questionnaires will survey participants on diet, medical history, occupation, and appliance use. Monitors will meter lighting and magnetic fields within each woman's bedroom at various times of the year. And to gauge indoor exposures from outdoor sources, the scientists will prepare detailed diagrams of the electrical transmission lines and outdoor hardware, such as power transformers, within 140 feet of each woman's home. Some women will even wear a 24-hour personal metering device to record their exposures outside the home.

Devra Davis and H. Leon Bradlow are launching a small study to assess the capacity of certain suspect xenoestrogens — including several chlorinated organic chemicals — to alter the body's metabolism of estradiol.

McLachlan and his colleagues are setting up what they hope will be a good *in vitro* screen for the estrogenic activity of different chemicals. "This is still sort of an undeveloped area," McLachlan says.

At the Breast Cancer Commission meeting in April, Susan Sieber, deputy director of NCI's Division of Cancer Etiology, reviewed about 20 NCI-supported epidemiologic studies on environmental factors that may foster breast cancer — from polybrominated biphenyls and DDT to ionizing radiation.

NCI is also evaluating grant applications for up to five "innovative" studies to tease out why breast cancer rates are higher than expected among women in certain regions, such as the eastern seaboard from New England to Washington, D.C. In particular, the agency has asked applicants to consider investigating the risks posed by pesticides, automobile exhausts, water contaminants, landfills, electromagnetic fields, and other environmental exposures. NCI has also explicitly expressed interest in studies that evaluate possible effects on hormonal or metabolic pathways.

Indeed, Sieber notes, NCI's plan to establish a laboratory of hormonal carcinogenesis and cellular proliferation during the next year or two "is being given very high priority."

Most researchers working on xenoestrogens offer two general cautions: that the mechanisms being offered to explain the effects of these agents are not mutually exclusive and that the relative significance of these environmental factors to human disease, while plausible, remains unproved. However, Devra Davis maintains, "we cannot afford to wait until the causes and mechanisms of breast cancer are fully understood before embarking on prevention-oriented research." □