Immune System Theories on Trial

Court experts say that chemicals in the environment are damaging the human immune system, but their theory has little support in the research community

I have had medical testimony before me that was shockingly suspect. Had a lawyer given equivalent misleading information I would have brought the matter to the attention of the disciplinary authority. What realistic threat exists against doctors? As to unlicensed economists and statisticians, the matter is now hopeless.—Jack Weinstein, Chief Judge of the U.S. Court for the Eastern District of New York

ONE man's expert is another man's quack, and Judge Jack Weinstein, who ran the complex and emotional trial of Agent Orange claims last year, thinks he has heard more than his share of the quacks.

Weinstein said in a recent speech (*1*) that he is not sure how it can be done, but he wishes it were possible to eject from court all doctors, statisticians, and other experts who promote shoddy scientific theories. In the Agent Orange trial, he tried this himself on a limited scale. He rejected technical affidavits—speculative statements on how chemicals cause cancer—given by two doctors for the Vietnam veterans' group.

Federal rules of civil procedure say that an opinion given by an expert "will be disregarded where it amounts to no more than mere speculation or a guess from subordinate facts that do not give adequate support to the conclusion reached." The principle is fine, but not easy to apply in cases where the basis of expertise is changing almost daily and the "subordinate facts" are not much clearer than the opinions.

Consider an example. The courts have been visited in recent months by a new breed of expert on environmental chemicals, specialists on the human immune system. They testify about the ways in which various chemicals cause cancer and other dread diseases by damaging immune functions (*Science*, 24 October, p. 418). These experts may have an unusual impact right now because any discussion of immune deficiencies conjures up AIDS, a disease that evokes fear and pity.

There is no question but that lawyers are interested in chemicals and immunity, says Michael Luster, chief of immunotoxicity at the National Institute for Environmental Health Sciences (NIEHS), part of the National Institutes of Health. In 1983, NIEHS held a workshop on immunotoxicity and published a small report. A trickle of requests for copies came in from scientists. Then, about a year ago, law firms from all over the country began asking for the obscure document. The trickle became a river, and the river became a flood. The legal readers now outnumber the scientists, Luster says, and the press office copes with the mail.

The legal research is beginning to pay off for plaintiffs. In a handful of major lawsuits this year, the immunotoxic thesis was used as a basis for seeking compensation. For example, in November a group in Missouri got $19 million in an out-of-court settlement from several companies they had accused of dumping dioxin and damaging their health. Earlier, plaintiffs won $8 million in settlement of a pollution case in Massachusetts, and others in Tennessee won an award of $12.7 million.

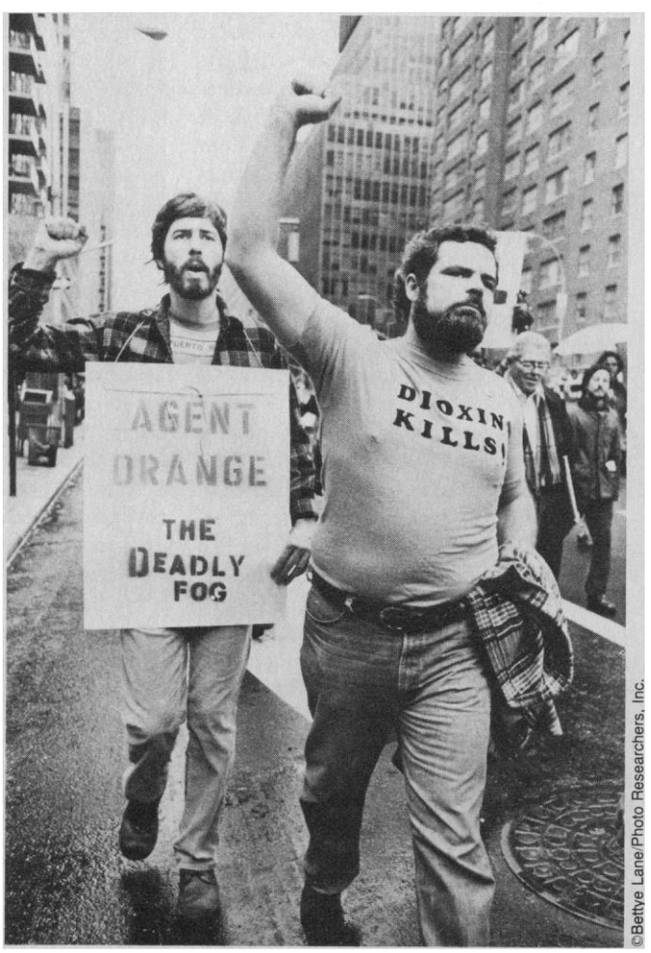
According to Michael Marcus, a corporate attorney versed in this area, these suits have been aided by a few "preachers"—expert witnesses who link chemical pollution, immunotoxicity, and cancer in a visionary polemic. Marcus is a partner of the Washington, D.C., office of a Texas firm, Akin, Gump, Strauss, Hauer & Feld, and for 16 years a defender of companies in environmental lawsuits.

The new immunotoxicity experts use familiar terminology to advance their arguments, Marcus says. But they go beyond the facts, leaping off into a "twilight zone" of interpretation that many other scientists will not enter.

Prominent among these new experts is Alan Levin, a San Francisco physician. He appears frequently in court, but has not committed his expertise to paper in peer-reviewed

The legacy of dioxin:

Agent Orange, the defoliant sprayed in Vietnam, contained dioxin as a contaminant. Although there is little evidence that exposure to dioxin at low levels causes the problems in litigation, the belief that "dioxin kills" remains strong. More recent lawsuits over toxic spills claim that low-level exposure to dioxin can damage the human immune system, increasing the risk of cancer. The evidence for this is hotly disputed.



scientific journals. Levin belongs to a group based on the West Coast and in Texas calling itself "clinical ecologists." They treat allergies and more severe ailments as symptoms of poisoning of the immune system by environmental irritants.

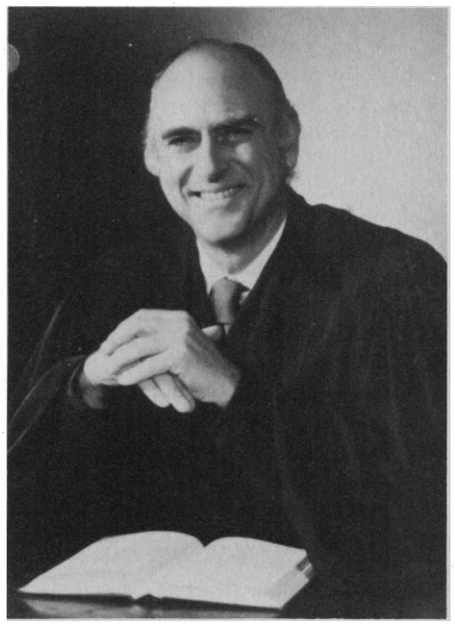
In a Tennessee case last summer (*Woodrow Sterling* et al. *v. Velsicol Chemical Corp.*), Levin testified that the malady he treats is called "chemically induced immune system disregulation." It can be manifest by any of a long list of symptoms, ranging from coughs, sneezes, and headaches to cancer, paranoid schizophrenia, and almost everything in between. The causes may be just as numerous. Among the irritants that may spell trouble, even in small exposures, are petrochemicals, formaldehyde, sulfur compounds, shampoos, metal polish, vinyl plastics, polyester, oven cleaner, pesticides, and natural gas combustion products.

In an affidavit, Levin said that substances such as these enter the body, combine with natural proteins, and overstimulate or debilitate critical cells in the immune system. Their impact is reflected in high or low cell counts and abnormal cell function tests. Levin has cited no clear guidelines for identifying immune aberrations that may presage later illness. He says it is a matter of clinical judgment.

A patient who wishes to be cured of "dysregulation" must adhere to a spartan regime, as described by Levin in the Tennessee case:

> It's wise to use foods that are minimally chemically contaminated, like stop using processed foods where there [are] all sorts of preservatives and food coloring and food additives in it. Also many canned foods have phenol in them and things in it that leach from the canning process into the foods. Liquids that are stored in plastic bottles taste of the polymers from the plastic. And those are the kinds of things that they should avoid. And new carpets and new drapes and wall paneling that outgasses formaldehyde. . . .

Two strong professional reviews repudiated the clinical ecologists this year, one by the American Academy of Allergy and Immunology (AAAI) and another by the California Medical Association (CMA). The AAAI report, published in August, said there is no factual basis for the malady the clinical ecologists claim to treat and "no immunologic data to support [their] dogma." The method of treatment often consists of imposing rigid diets, confining patients to safe rooms, restricting their social lives. At present, the AAAI ruled, such procedures must be regarded as "unproven and experimental." The CMA paper issued in February found that "clinical ecology does not constitute a valid medical discipline." After a long investigation, the CMA could see "no convincing evidence that patients treated by clinical ecologists have unique, recognizable syndromes, that the diagnostic tests employed are efficacious and reliable, or that the treatments used are effective."



Judge Jack Weinstein: *Rejected expert testimony in the Agent Orange trial.*

The clinical ecologists have few friends, even where one might expect to find them. Ellen Silbergeld, staff scientist for the Environmental Defense Fund and an advocate of strong chemical regulation, finds this group "unspeakable." Silbergeld fears they will scare away good scientists. "I hate to see a novel area of science being worked out in the courts. If it discourages good people from getting involved, it would be unfortunate," because work needs to be done.

"It took 15 to 20 years for people to realize that ionizing radiation was linked to a higher incidence of cancer," says Levin, arguing that clinical ecology is now in the early stages of development, as radiation health research was in the 1940's. In time, Levin says, his field will be respected.

"The big question," according to Silbergeld, is "what is normal?" Industry and government researchers agree. "There's not a lot of data" on the normal distribution of human measurements, says Jack Dean, head of cell biology at the Chemical Industry Institute of Toxicology in Research Triangle Park, North Carolina. Although mean values can be determined, it is not clear at what point an off-mean value becomes an abnormal one. It is important to learn more about the resiliency of the immune system, according to a recent workshop at Georgetown University chaired by Joseph Bellanti, an immunologist at the university's hospital. The clinicians at this meeting raised the possibility that the immune system may tolerate a great deal of stress before it crosses a threshold to impaired health.

In the same way that normal values remain blurred, so do abnormal ones. "Until we know what the variance around the norm looks like, it's hard to say what a subtle alteration means in terms of health risk," says Dean. Once an unusual pattern is discovered, it should be analyzed repeatedly. "If there is an abnormality, you need to reproduce it" to establish its validity. Very few abnormal patterns in humans caused by environmental chemicals have been reproduced. While the experts might agree that a particular T8 cell count is high, they might find widely different meanings in that high measure. Thus, the field is wide open to speculation.

Luster of NIEHS says there is "a lot of evidence" that some chemicals, when given to rodents, cause immune suppression. And "in certain instances" there is evidence that these chemicals affect humans. But there is "no clear evidence that low-level exposure to chemicals in the environment is causing damage" to peoples' immune systems.

Animal studies have resulted in a list of at least 15 chemicals and metals that alter the immune system and increase the risk of disease, according to a recent review by Dean and others (*2*). The list includes natural substances such as arsenic, lead, ozone, and the cannabinoids (marijuana), along with man-made compounds such as 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (dioxin), polycyclic aromatic hydrocarbons (a product of the combustion engine), and polyhalogenated biphenyls (PCB's and PBB's—plasticizers and a flame retardant).

In addition, Dean identifies five major categories of prescription drugs that are known to suppress the immune system. Other materials overstimulate the immune system, producing allergic or autoimmune reactions. These include many things found in the workplace, including cotton, silica, and asbestos dust; isocyanates; formaldehyde; and many pharmaceuticals.

So much for animal studies. The information on human biology is weaker. A review (*3*) of this subject, written for NIEHS by a panel chaired by Dean, lists five groups of chemicals that impair the immune systems of animals and people. For example, near the top of the list are the polyhalogenated aromatic hydrocarbons, including PCB's. The best human data on PCB's come from Japan and China, where people who consumed rice oil tainted with PCB have been studied for nearly a decade. Researchers found that

some of the more seriously exposed individuals were more susceptible to respiratory infections, had fewer antibodies circulating in their blood, and showed a weaker response to immunological skin tests. In addition, their T-cell counts and tests of T-cell function proved abnormal. Rodents exhibit a similar pattern after exposure to PCB. Other chemicals that have been shown to suppress the immune systems of animals and humans are polybrominated biphenyls (PBB's), dumped accidentally in dairy cattle feed in 1973, and therapeutic drugs, including cortisone.

Perhaps the most controversial chemical in this area is dioxin. It is ubiquitous, and in this country it is often found in peoples' fatty tissue, where it may persist for 5 to 8 years. Dioxin was a contaminant in some commerical products and in the defoliant, Agent Orange, sprayed over Vietnam.

According to Dean, the consensus is that dioxin suppresses the immune system in rodents. The big question is whether the same data can be applied to humans. In rodents, dioxin appears to attack the thymus, doing its damage by interfering with the development of T cells, key regulators of the cell-mediated immune system. In young rodents, in which the thymus is still a key immune organ, dioxin exposure can do permanent damage. The thymus is less important for the immune system in older animals (it begins to be less important for humans between ages 6 and 10). Therefore, dioxin's impact on older rodents, and perhaps on older humans, may be less enduring.

Dioxin given to rodents at low levels produces an exaggerated T- and B-cell proliferation response, a pattern found also among schoolchildren in one early study in Seveso, Italy, according to Dean. (A pesticide factory in Seveso blew a cloud of dioxin into the air in 1976, contaminating a large area.) However, the suggestive data from Seveso are contradicted by a recent study of Vietnam veterans who handled Agent Orange, financed by the U.S. Air Force. It found no immune system abnormalities.

The dioxin debate entered a new round last April when researchers from the Centers for Disease Control and the Missouri state health department published a study on people who had lived in the Quail Run trailer park near St. Louis. Dioxin-tainted oil was sprayed along the park's main road in 1971 to keep dust down. As a result, many former residents retain high concentrations of dioxin in their tissue, five times that seen in other Missourians tested this year. The CDC researchers reported that people from Quail Run showed a weaker response to an immunologic skin test than nonresidents (a statistically significant result). Some of them also had abnormal T-cell counts, but not a significantly large number. None showed any clinical signs of illness. The researchers speculated that they had detected early, latent signs of immune problems that could lead to illness later on.

Medical experts employed by one of the companies responsible for the dioxin in Missouri have challenged this report for its reliance on volunteer readers of skin tests, who are notoriously inconsistent. Furthermore, as the company experts pointed out, while some T-cell counts may have been off, T-cell function in both groups was normal.

"I hate to see a novel area of science being worked out in the courts. If it discourages good people from getting involved, it would be unfortunate," says Ellen Silbergeld.

This debate will resume next January, when members of the CDC-Missouri group plan to release another report on Quail Run.

Studies of another chemical this year sparked a major row behind the scenes over its potential effect on animal and human immune systems. The compound is aldicarb (also known as Temik), a pesticide manufactured by the Union Carbide Company and heir to a checkered history (*Science*, 27 September 1985, p. 1369). The aldicarb furor began about a year ago when a group at the University of Wisconsin at Madison under Ronald Hindsdill claimed that the immune systems of mice fed aldicarb at low levels (0.1 part per billion) are depressed. At higher doses, the mice are normal.

The paper reporting these results has not been published, but was leaked to the press last year. It has received wide attention. As one researcher said, "It is the most widely publicized nonpublished study I know." It caused an uproar in Wisconsin, where ground water is contaminated with aldicarb. Hindsdill says the British tabloids also had a field day reporting on the "AIDS chemical."

Meanwhile, Union Carbide hired Peter Thomas, Hindsdill's former student and coauthor on several research papers, to repeat Hindsdill's study. Thomas now works for the Illinois Institute of Technology Research Institute. He found no effects.

A second study performed at Madison by CDC researcher Michael Fiore has found that women who drank aldicarb-laden water had unusually high numbers of T8 cells in circulation. However, the T-cell function tests were normal and the women had no signs of illness. Fiore's paper is due to be published this month, and has already received wide attention.

This tangled controversy has been dumped in the lap of Environmental Protection Agency, which soon must make a decision on future uses of aldicarb. Theodore Farber, speaking for the agency, says EPA "hasn't tied down an absolute bottom line," but found the Wisconsin data less credible than Union Carbide's. It may be necessary, he added, to refer the whole matter to the agency's scientific advisory panel.

These are among the most recent studies of low-level chemical exposure and related effects on the human immune system, says Luster of NIEHS. He finds it significant that in most of the recent studies, even when cell counts are abnormal, there is no reduction in cell function. Thus, people who argue that the immune system has been damaged by low-level chronic exposure to chemicals in the environment are relying on sketchy data. They would have a stronger case, Luster says, if they could show multiple and overlapping changes in the immune system (as seen in AIDS patients, for example). Most convincing would be evidence linking chemical exposure with a consistent pattern of immune system irregularities, manifesting itself finally in a disease. But no one has that kind of evidence.

In evaluating toxicity, Dean and Luster said, it is important to study the immune system in its totality and not pay too much attention to any single abnormal measure. In general, the researchers were not impressed by findings of damage that did not report at least two kinds of immune abnormality: one in quantity and another in function. Of these two measures, the functional test is the more persuasive. To be credible, the abnormal effect must be reproducible.

All agreed that testing for immune system problems needs to be standardized and that normal values must be established before epidemiology can go much further. ■

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