pressed the view that totally eliminating the use of animals in testing appears unlikely for the foreseeable future. Stokes explained that despite some limitations of current animal models used for testing, they remain useful and necessary for the protection of human health. "The degree of relevance of information [to humans] depends on the specific animal model used, our understanding of the model, and toxicity endpoint studied," he pointed out. Balls, however, believes that animal testing can be entirely replaced in the future. "When I'm optimistic, I think it can be done in 25 years. When I feel pessimistic, I think in terms of 50 years."

Although a specific deadline for replacing animal models was not an outcome of the meeting, George Lucier, director of the Environmental Toxicology Program at the NIEHS, believes the meeting was a significant step in the right direction for several reasons. "This meeting produced a significant broadening of the definition of alternative models to include such things as mechanistic data and mathematical models," he said. "And most importantly, all of the stakeholders bought into the ideas put forth for improving, especially streamlining, the approaches by which we determine human toxicity."

Great Lakes on the Mend

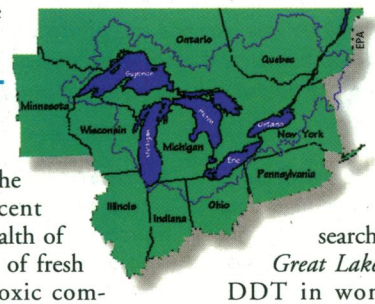
The Great Lakes are on the mend, according to recent reports on the overall health of the world's largest body of fresh water. Yet persistent toxic compounds continue to be dumped into the lakes, and PCBs, DDT, and other chemicals can still be detected in lake sediments and fish, causing potential health problems for people who eat the fish. New health studies indicate that pollution of the Great Lakes could be contributing to subtle health concerns in the region including a reduction in human sperm counts, higher rates of breast cancer, low birth-weight babies, and learning disabilities in children.

The U.S. EPA and Environment Canada concluded that water quality and human health are improving in the Great Lakes region, but the results are mixed. The agencies presented these findings in the *State of the Great Lakes 1995*, a biennial report released in September.

"I think it's safe to say this: there's no doubt that contaminants are declining," says Harold Humphrey, veteran research scientist for the Michigan Department of Public Health. "Things are a bit better. But the question remains, what is going to happen with all of these subtle health effects? No one can answer that question yet."

The Great Lakes have been a receptacle for a wide variety of pollutants for decades, including DDT, PCBs, pesticides, dioxin, and more. It is a heavily industrialized region: about one-fifth of American industry and one-half of Canadian industry are located along the Great Lakes or tributary streams. Forty-two shoreline areas in the Great Lakes, such as Indiana Harbor, Milwaukee Harbor, and Green Bay Harbor, have been designated as "areas of concern"—the most degraded sites in the basin—by the EPA and Environment Canada. Thirty-five of the areas of concern have public advisories against fish consumption.

In view of the number of people consuming fish and the potential human health impacts, the International Joint Commission (IJC) Great Lakes Water Quality Board called for a zero discharge of persistent toxicants into the Great Lakes in its seventh biennial report titled *1993–1995 Priorities and Progress Under the Great Lakes Water Quality Agreement.* "Society must adopt a clear and comprehensive action plan to virtually eliminate persistent toxic substances that are threatening human health and the future of the Great Lakes ecosystem," the report said. That goal has yet to be achieved.



On the bright side, research detailed in the *State of the Great Lakes 1995* shows that levels of DDT in women's breast milk (from women living in a number of Canadian cities in the Great Lakes area) have declined 87% from more than 150 parts per million in 1967 to 20 ppm in 1986. The levels of PCBs in women's breast milk also has declined. Results of a Lake Michigan study conducted by the Wisconsin Department of Natural Resources show the amount of PCBs in lake trout and salmon has decreased by 80%.

In its report, the IJC advocates pollution prevention as an immediate step that industry can take to help reduce persistent toxicants in the Great Lakes. The water quality board recommended that binational initiatives be adopted to build on those gains, including new benchmarks, management guidelines, and increased monitoring.

John Westendorf, manager of water quality and corporate environmental affairs for Occidental Chemical Corporation in Niagara Falls, New York, said his company's Niagara Falls plant has reduced its air, water, and hazardous waste discharges by 73% in the past five years.

"Industry is committed to doing a better job as long as we're given some flexibility," Westendorf says.

But Occidental opposes a zero-discharge standard, Westendorf says. At minimum, chemicals are needed to control exotic species such as the sea lamprey and zebra mussel, he says. Sea lampreys prey on lake trout and other game fish, and zebra mussels clog water-intake pipes for utilities and industries. Both exotic species have proliferated in the Great Lakes by the millions.

Burkhard Mausberg, executive director of Great Lakes United in Buffalo, New York, says his organization supports zero discharge and ecosystem management to improve the Great Lakes. But he sees few advances toward those goals in the politically charged policy arena.

Mausberg notes that the U.S. Congress has pondered deep cuts in renewing the Clean Water Act and EPA enforcement. "What we're finding is the environmental programs that are most progressive are being cut. We don't need that right now," he says.

The Great Lakes Initiative, launched by former President Bush and carried on by President Clinton, envisions uniform pollution-discharge standards for all the Great Lakes states. It has been opposed by most states thus far for economic reasons, officials say.

While politics muddies the waters for now, the IJC's Great Lakes Science Advisory Board has called for more research into the impacts of chemicals on the reproductive, developmental, and immune systems in animals and humans. New research indicates that the discharge of PCBs, pesticide residues, and dioxin into the Great Lakes could be causing hormonal changes in some fish, birds, and mammals.

The research is preliminary, according to Theo Colborn of the World Wildlife Fund, who is authoring a book on environmental estrogens. But the effects on fish could also materialize in humans, she says. According to Humphrey, it's too early to tell how substantial the risk is for humans. "The concern among public health professionals is that we don't cry wolf too much so people believe us when the real wolf comes along," he says.

East Meets West for Improved Antimalarials

Malaria is one of the world's greatest public health problems, striking 200–300 mil-

lion people yearly, and killing at least a million. The intracellular protozoan parasites that cause the disease are endemic in tropical areas and are spread by mosquitoes. In many areas, especially southeast Asia, the parasite has become resistant to existing antimalarials such as chloroquine.

Now with some help from western science, an ancient Chinese herbal remedy may serve as the prototype for a new family of antimalarial drugs. At least three million malaria patients have been treated with the folk medicine, but it is far from a perfect remedy. Western scientists hope to improve the drug by changing its chemical makeup. In 1972, Chinese scientists rediscovered *qinghaosu*. This plant extract is derived from the leaves of *Artemisia annua*, a prolific shrub related to wormwood, and has been used against fever for 2000 years. The western name for the active component is artemisinin. When the Chinese found that it fought malaria, they put it into clinical use. So far, the malaria parasites have shown no resistance to the substance, nor is artemisinin toxic at clinical doses. And it works quickly.

"It's very good for treating severe, life-threatening malaria," says Steven R. Meshnick, a parasitologist, biochemist, and associate professor of epidemiology at the University of Michigan School of Public Health. Artemisinin revives comatose patients much faster than quinine. But it's not a cure. It's less useful in milder cases and the disease frequently returns. The drug is also poorly water soluble and difficult to administer orally. And the body eliminates it quickly, so it must be taken frequently.

However, "Once you know exactly where the drug works, and how, you can then design it to work better," says Meshnick. The essential part of the artemisinin molecule is a peroxide bridge, a chemical structure that's unusual and often unstable. The molecule's selective toxicity is due to the malaria parasite's diet of hemoglobin. The parasite digests the globin portion but can't metabolize the iron-containing heme structure, which it stores in hemozoin granules. The peroxide bridge interacts with the iron and heme exposed in these granules to produce short-lived, highly reactive free radicals. These free radicals or related reactive intermediates damage critical proteins in the parasite, killing it. Though heme exists throughout the human body, it's tucked inside proteins and thus protected from this reaction.

Artemisinin is a complex, multiringed molecule, but all the rings aren't necessary for the antimalarial effect. "We've tried to simplify the structure and arrive at compounds that are equally potent and yet are much easier to prepare in the lab," says Gary Posner, a medical chemist at Johns Hopkins University. Posner and others have used this mechanism-based design strategy to synthesize hundreds of artemisinin analogs, some of which are as effective as artemisinin in animal studies.

Michael Bentley, chairperson of the Department of Chemistry at the University of Maine, has employed a different tactic. Bentley attached artemisinin to polymers of polyethylene glycol, a nontoxic, nonallergenic compound used in foods and drugs. Resulting compounds tend to be soluble both in water and in nonpolar solvents. Such structural modifications may lengthen artemisinin's stay in the body. Plus, each polymer carries two peroxide bridges. In studies with mice, some of Bentley's compounds show improved activity over artemisinin alone, or chloroquine alone.

Artemisinin-based drugs are promising, experts agree, but the coevolutionary arms race with the malaria parasite will continue. Given the opportunity, the parasite will develop resistance. "Nothing is a cure-all, magic bullet for all time," says Bentley. Meshnick concurs, but notes that although penicillin wasn't perfect either, it served as a prototype for a whole new family of antibiotics. "I really think the same thing can happen for artemisinin," he says.

Steven Meshnick

Natural remedy. Workers at the Institute of Malaria, Parasitology, and Entomology in Hanoi, Vietnam, gather leaves of *Artemisia annua*, which contain a potential malaria treatment drug.

What's Causing Parkinson's?

The cause of Parkinson's disease has baffled doctors ever since this chronic neurological syndrome was first described by James Parkinson in 1817. Now scientists may finally be closing in on the culprits. The disease is likely to be caused by "some admixture of genetic predisposition, aging, and exposure to environmental toxicants," says Doyle Graham, chair of the pathology department at Vanderbilt University Medical Center in Nashville.

Sorting out multiple potential causal agents and the interactions among them will never be easy. However, thanks to increasingly sophisticated research techniques, it may now be possible. A prime example of the kind of meticulously designed research needed for this purpose is a case–control study currently being completed at Henry Ford Health System in Detroit. "This is one of only two population-based studies to date in Parkinson's epidemiology, and it's the only one of which I'm aware in which an industrial hygienist's assessment of exposures, based on detailed occupational histories, has been used," says Jay M. Gorell, lead investigator and director of the hospital's Parkinson's disease center.

The study, now in the final data analysis stage, included 144 Parkinson's patients and 469 control subjects who were matched for age, race, and sex. Preliminary analyses, based on all but 10 of the patients and all but six of the controls, suggest an increased risk of Parkinson's disease associated with exposure to manganese, copper, and lead, as well as exposure to herbicides and insecticides used at work. However, it may take some combination of factors to produce Parkinson's disease. "It's possible that an agent might act in a cumulative way over time to partially disable a cell, but it might take several agents together to cause the cell either to fail to function or to die prematurely," says Gorell.

While some researchers are devoting their energies to determining which envi-