

# Psychiatric Side-Effects of Interleukin-2

Interleukin-2, the sometimes-promising, sometimes-disheartening experimental anticancer drug, last week took another stumble in the medical literature. In the September *ANNALS OF INTERNAL MEDICINE*, the genetically engineered immune-system booster is blamed for a variety of "clinically significant neuropsychiatric" effects, including severe paranoid delusions and hallucinations. No new data were reported on the drug's anticancer properties.

Perhaps no other drug undergoing clinical trials has so encouraged, then disheartened and again inspired its would-be beneficiaries — be they pharmaceutical investors or cancer patients. Reports of near-miraculous tumor shrinkage have been dampened by problems with toxicity (*SN*: 12/13/86, p.373), and all along there have been questions about behavioral changes that appeared to be related to interleukin-2.

Kirk D. Denicoff, David R. Rubinow and their colleagues at the National Institute of Mental Health and Steven A. Rosenberg and his colleagues at the National Cancer Institute are the first to use a battery of psychological tests to measure the degree of psychiatric disturbance that can be directly attributed to interleukin-2 therapy. They find that a number of serious psychiatric disturbances are associated with the drug and are dose-related.

The study is accurate, says Edward Bradley, director of clinical biology for Emeryville, Calif.-based Cetus Corp.—the company holding U.S. patent rights to interleukin-2. But the research can easily be misinterpreted, he told *SCIENCE NEWS*. "What it boils down to is that the patients are often irritable, they can be tired, they can be not quite as sharp as they normally are. . . . That's what Rosenberg means when he says 'neuropsychiatric effects.'"

The study reported more serious behavioral abnormalities than these, however. Of 44 cancer patients studied, 15 were deemed by standardized tests to have "severe behavioral changes," including 12 cases of "severe agitation and combative behavior" that necessitated the use of psychiatric drugs or physical restraints. Seven patients developed delusions, including five with paranoia who were "convinced that at least someone on the staff was trying to hurt or kill them." Severe cognitive changes were identified in 22 patients, with all of them meeting standard psychiatric criteria for delirium. Symptoms included disorientation to time by as much as three days and an "inability to identify correctly the obvious occupations of those in attend-

ance," the researchers report.

Bradley, of Cetus, says that while such findings may sound alarming, "A lot of the words are standard words in psychometric evaluation. I think it would be wrong to say that this is any different from what goes on in lots and lots of common medical situations where a degree of emotional alteration or intellectual impairment is expected." He compares the effects of interleukin-2 to the foggiest or irritability that may accompany the use of antihistamines.

Bradley points out that the researchers, who declined to be interviewed about their work, do note in their article that "every patient studied recovered from the neuropsychiatric side effects." Adds Bradley, "In the context of a patient in the hospital who is being

treated for a life-threatening and otherwise universally fatal malignancy, and when [the psychiatric effect] is self-limited, then as far as the physician goes this is no big deal."

The scientists also found that patient education before treatment, family contact during treatment and sources of stimulation such as television or music were helpful in mitigating negative reactions. Nevertheless, they conclude, "clinically significant neuropsychiatric changes . . . were common and may be treatment-limiting."

They report that the causes of the changes are under investigation and that subsequent research may shed light on the mutual regulatory interactions of the immune and central nervous systems.

— R. Weiss

## Ozone accord draws praise and concern

In the wake of last week's international agreement to dramatically cut the use of chlorofluorocarbons (CFCs), the world's \$2.2 billion CFC-production industry is scrambling to find substitutes for these chemicals, which are used in refrigeration, foam production and the cleaning of electronic parts.

The agreement, officially called a protocol, will force a 50 percent reduction in the use of CFCs by the end of the century. And while both industry and environmental groups criticize aspects of the agreement, all involved have hailed the international treaty as a necessary step to prevent the destruction of the life-protecting ozone layer.

"I think it's a landmark achievement of historical significance," says U.S. Deputy Assistant Secretary of State Richard E. Benedick, who headed the ozone negotiations. Benedick points out that the protocol has managed to balance a number of complex scientific, economic and geographic factors.

Environmental organizations have also lauded the agreement itself as well as the administration's strong push for CFC controls. "It's an amazing accomplishment compared to where we were as short as a year ago," says David Doniger, a senior attorney with the Natural Resources Defense Council in Washington, D.C.

Signed in Montreal by diplomats from 23 nations, the protocol will take effect in 1989 only after 11 countries, representing two-thirds of global CFC consumption, have ratified it. It specifically calls for an immediate freeze on the use of the most damaging CFCs at the 1986 levels of consumption. In 1994, protocol signers

must reduce consumption by 20 percent, and by 1999 they must cut CFC use to half their 1986 levels. The protocol also freezes but does not reduce the consumption of halons, a more destructive but less prevalent class of chlorine chemicals.

Trade provisions in the protocol encourage countries to sign the agreement by prohibiting the importation of CFCs and products containing CFCs from countries that have not signed. The protocol also provides slightly loosened consumption limits for developing nations.

Amid the praise, however, are voices of concern. Doniger cautions that the proposed reductions will slow but not stop the gradual accumulation of long-lived CFCs in the stratosphere and calls the protocol "a major *half-step* forward."

Scientists are finding evidence that chlorine from CFCs and halons is actively destroying stratospheric ozone both on the global scale and — most dramatically — at the poles (*SN*: 9/19/87, p.182). Computer models have shown that an 85 percent reduction in CFC and halon use is needed to simply stabilize the stratospheric levels of such chemicals. So even with the 50 percent reductions, says atmospheric scientist Michael Oppenheimer, chlorine might erode 1 to 2 percent of the ozone layer, thereby increasing the amount of ultraviolet radiation that reaches the ground. Oppenheimer, of the Environmental Defense Fund in New York City, says this increase in radiation might amount to an extra several hundred thousand skin cancer cases in the United States by the year 2025, as well as significant damage to plant and animal life.

At the other end of the political spec-

trum, the CFC industry also praises the diplomatic community for reaching a protective agreement. However, says Kevin Fay, director of the Alliance for Responsible CFC Policy in Washington, D.C., "it goes much farther than anything we think is necessary." Members of the CFC industry think that both the schedule and scale of the reductions are too stringent and do not provide adequate time for the industry to find suitable substitutes for CFCs and halons.

Nonflammable, noncorrosive and non-toxic, these chemicals seemed ideal in almost every sense. They are just too stable in the lower atmosphere, and rise into the ozone layer before releasing their destructive chlorine. The production industry is now looking at CFCs that either lack chlorine altogether or break up in the lower atmosphere.

Several less destructive CFCs are currently on the market and could serve as replacements in a limited number of situations, says Fay. Other substitutes, including the nonchlorinated CFCs, are still in development and will not reach the market for five to seven years.

However, all CFC users may not be able to find replacement chemicals. Says Fay, "the solvents industry and [others] who use [CFC] 113 are very concerned because there really are no substitutes on the horizon." With CFC 113 and the halons, says Fay, the answer to the upcoming limitations may lie in efficient recycling.

— R. Monastersky

### AIDS protein 'computed'

Scientists in England have used a computer to construct the probable three-dimensional structure of a protein that may prove significant in developing new drugs against the virus causing AIDS. In the Sept. 24 *NATURE*, Laurence H. Pearl of the Institute of Cancer Research in Surrey and William R. Taylor of the University of London report their computed structure for the protease enzyme produced by the AIDS-causing HIV virus.

Part of the HIV protease — essential for the production of proteins that make up the virus core — structurally resembles the aspartic class of proteases found in the blood and digestive system. After comparing the amino-acid patterns from both groups, Pearl and Taylor found that the HIV protease is very similar to half of the aspartic protease's structure. Based on this observation, they suggest that HIV protease may in fact be active only when two of these smaller proteases unite. Their computer model of this "double" form and its binding sites may point to the design of drugs that inhibit HIV protease activity, and therefore viral infection, say the scientists. □

## Discounting the threat of acid rain

There is little evidence that acid rain has had a significant impact on lakes and streams in the United States, says a controversial report issued last week by a Reagan administration study group. Even in regions such as New York's Adirondack Mountains, where lake acidification has occurred, it says only a small percentage of lakes have been affected. The report also concludes that most watersheds in the Northeast have reached a steady state, meaning that further acidic deposition is unlikely to increase the number of acidified lakes.

These conclusions are contained in an interim assessment of the causes and effects of acid rain, issued by the National Acid Precipitation Assessment Program (NAPAP), the umbrella organization coordinating federal acid rain research. Originally scheduled to appear in 1985, the report summarizes the current state of scientific knowledge about acid rain after more than five years of study (SN: 7/18/87, p.36).

This document, says NAPAP's Charles N. Herrick, focuses on "what we found out, how we found that out, what we still need to find out, and what we need to do to find it out."

The interim assessment was greeted with strong protests by the Canadian

government, several environmental groups and a number of scientists whose work had contributed to the NAPAP report. Canada's Environment Minister Tom McMillan complained that the report is "voodoo science," designed to prove that the situation isn't serious enough to warrant immediate action. The report, for instance, ignores the potential impact of U.S. emissions on Canadian lakes, a large number of which lie on granite beds, making them more sensitive to acid rain than most U.S. lakes.

Scientists, including James N. Galloway of the University of Virginia in Charlottesville and Michael Oppenheimer of the Environmental Defense Fund in New York City, argue that the NAPAP assessment uses data selectively, ignoring new evidence that doesn't seem to support its conclusions. For example, one recent study shows that some lakes may continue to become more acidic even when the deposition rate of strong acids is reduced. Some researchers also argue that the criteria used by NAPAP to define an acid lake are inadequate. The assessment, they say, excludes a number of lakes where damage has occurred and doesn't take into account the strong pulse of acidity associated with spring snow melts.

— I. Peterson

## Sudden death tied to sickle-cell trait

Black military recruits carrying the abnormal hemoglobin S in their red blood cells are 28 to 40 times more likely to die suddenly during strenuous physical exertion than are recruits without the so-called sickle-cell trait, researchers reported this week. Although scientists have previously reported cases suggesting that people with the trait are more susceptible to death without any known preexisting cause, the current study is the first large-scale look at this phenomenon.

People who inherit hemoglobin S genes from both parents can develop the often-fatal sickle-cell anemia. Those with an abnormal gene from only one parent, however, have sickle-cell trait, ordinarily considered an innocuous disorder. Approximately 8 percent of the black population in the United States has sickle-cell trait, a condition rare among nonblack Americans. Since oxygen deprivation forces cells with hemoglobin S to become sickle-shaped, researchers have wondered about exercise's effect in people with the trait.

Scientists at Walter Reed Army Institute of Research in Washington, D.C., and the Naval Hospital in Bethesda, Md., evaluated all deaths occurring among the 2 million enlisted recruits receiving basic training in the U.S. military from 1977

through 1981. On the basis of detailed autopsy reports, the researchers conclude in the Sept. 24 *NEW ENGLAND JOURNAL OF MEDICINE* that the rate of "sudden unexplained death attributable to [sickle-cell trait]" among black recruits was 31 deaths per 100,000. They also calculate that the risk of sudden death for those with the trait is 28 times that for black recruits without hemoglobin S and 40 times that for all recruits, regardless of race.

The authors suggest that although civilian life is "seldom as stressful as basic military training," studies should be done on sickle-cell trait among others involved in strenuous exercise, such as athletes and heavy laborers. During this study, the Army Medical Corps cautioned recruit training centers in 1982 about the potential risk involved, but a Defense Department spokesman told *SCIENCE NEWS* there is no set policy regarding the issue.

In an accompanying editorial, Louis W. Sullivan of Atlanta's Morehouse School of Medicine notes that, while the study is important, such findings do not show increased risk in ordinary occupations or in daily life. Sullivan says there should be no subsequent discrimination in employment or insurability against those with sickle-cell trait.

— D.D. Edwards