

# 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-