. . . Drug effects

Now, a nationwide collaborative study, headed by the San Diego group, reports that long-term and perhaps irreversible organic changes from polydrug use appear to be a concrete danger. The researchers report in the February AMERICAN JOURNAL OF PSYCHIATRY that they examined 151 multiple drug users (some for up to 10 years) and compared them with control populations of other psychiatric patients and nonpatients. The drugs involved included alcohol, depressants, stimulants, heroin and other opiates, cocaine, marijuana and hashish. Patients were rated as either neurologically impaired or unimpaired.

Initially, 37 percent of the polydrug users tested as impaired. After three months of treatment and abstinence or sharply reduced drug intake, 34 percent still showed impairment, reports the research team headed by Igor Grant and Lewis L. Judd. The control psychiatric population's level of impairment also remained essentially constant, but other measures indicated that unlike the drug users, the control group's organic problems were not drug induced. The nonhospitalized group dropped from 8 percent to 4 percent in impairment level after three months.

"Although there is some evidence that such impairment is reversible" among the affected polydrug users, say the researchers, "the condition appears to be of at least intermediate duration and may be long lasting."

Drug types that appear most responsible for undiminished difficulties appear to be central nervous system depressants, including barbiturates, non-barbiturate hypnotics and minor tranquilizers, and opiates. "Specifically, both extensive lifetime and intensive short-term use of CNS depressants and opiates may represent the most dangerous conditions," say the investigators. Particularly surprising, they say, is the apparent relationship between heavy opiate use and neuropsychological impairment. The researchers believe this is the first such link ever reported.

Other high-risk factors for organic impairment identified in the study are increasing age, poorer education, certain historical medical factors and a diagnosis of schizophrenia (about half such patients in the study exhibited neuropsychological deficit). But the most significant findings deal with the correlation between polydrug use and long-term impairment.

"Sedatives and opiates might produce more long-term toxicity than has previously been suspected," the researchers suggest. "If this is so, we need to rethink practices that have led to exceedingly widespread use of sedatives and minor tranquilizers." They also call for a reexamination of "the potential long-term risks of prescribing [opiates] for years, as can occur in rehabilitation programs using the longer-acting narcotics as antagonists." □

Self-styling and the thymus

"Know thyself," counseled Plutarch. His maxim turns out to be a cardinal rule of nature, the cornerstone of immunology. The immune system of mammals is so fine-tuned that it can distinguish a native body component, the self, from a foreign invader, the non-self, when the differences are seemingly infinitesimally small.

How does the body so successfully sort out viruses ensconced in its cells or distinguish between its own berserk cancerous cells and the normal cell cadre? How does it reject skin grafts and tissue transplants? Researchers at the Scripps Clinic and Research Foundation (SCRF) in La Jolla, Calif., and at the Southwestern Medical School (SMS) in Dallas, Tex., have found that the thymus, a pyramid-shaped organ located beneath the breastbone, teaches the immune system how to be self-aware.

More than 15 years ago scientists found that if you remove a mouse's thymus, the mouse loses its cellular immunity. It can no longer reject skin grafts, fight off viruses or destroy tumors. Its bone marrow stem cells no longer mature into killer T lymphocytes that recognize and kill abnormal cells in the body. (T is for thymus-derived.) T lymphocytes are the chief perpetrators of the cellular immune response. Rolf M. Zinkernagel of SCRF has investigated the connection between the thymus and the T lymphocytes.

When a patch of skin or organ is transplanted from one person to another, the graft usually doesn't survive. The killer T cells, recognizing molecules on the grafted cells as foreign, attack and kill the graft. These molecules, histocompatibility antigens, or H antigens, are somewhat like cellular fingerprints — they differ from individual to individual.

Although there are many H antigens — 30 have been detected in the mouse — some are more important than others in mobilizing the killer T cells. In mice one set, the H-2 system, is by far the greatest stimulus signaling the T cells to attack. The researchers have discovered that the bone marrow stem cells must learn from the thymus what their H antigens are before they can become able T cells.

Another wrinkle must also be considered. The body rejects organs and tissue transplants by recognizing foreign histocompatibility antigens. But virus-infected cells or cancerous cells don't have foreign H antigens, they have the afflicted individual's own antigens. So how does the body recognize deranged cells?

In 1974, Zinkernagel and Peter Doherty discovered that killer T lymphocytes could not destroy cells infected with a virus unless the lymphocyte and the cells had at least one H-2 antigen in common.

The researchers infected inbred mice with viruses. After a time they removed the T lymphocytes from the immunized mice and tested *in vitro* what type of infected cells the T cells would attack and kill. They readily killed infected cells from mice of the same inbred strain, but not those of another strain. The researchers concluded that the T cells not only had to recognize the non-self, the antigen to which they were immunized, but the self, their own H antigens, as well.

Now, in reports in the Jan. 19 NATURE and the March JOURNAL OF EXPERIMENTAL MEDICINE, Zinkernagel, Gerry Callahan, Alana Althage and Sue Cooper of SCRF, along with Jan Klein and Wayne Streilein of SMS and Gunther Dennert of the Salk Institute in La Jolla, have discovered more about this programming. They present compelling evidence that T lymphocytes are immunologically incompetent without a thymus because they can't recognize the self.

The researchers irradiated mice with doses large enough to destroy T lymphocytes and bone marrow cells, but not so large as to destroy the thymus gland. They then reconstituted the immune system of the irradiated (A-strain) mice. The mice were injected with stem cells from mice that were the offspring of an A-strain parent and a parent from another (B) strain. Thus, the transferred stem cells have both A- and B-strain histocompatibility antigens on their surfaces.

After infecting the reconstituted A-strain mice with viruses, the investigators removed their "AB" lymphocytes and tested them against virus-infected cells from both A- and B-strain mice. The AB-genetically equipped lymphocytes only killed the cells from the A-strain mice. Virus-infected cells from the B strain were unharmed. Nor did the T lymphocytes act against normal, non virus-infected cells from either strain. Apparently, the lymphocytes couldn't recognize the B part of themselves because the resident A-strain thymus couldn't program them to do so.

Other experiments are even more conclusive. The researchers irradiated AB-strain mice to kill their native lymphocytes and then removed their thymuses. Next, they transplanted A-strain thymuses into the AB mice, and reconstituted their immune systems with immature lymphocytes from other AB mice. Thus, these mice were AB, except their thymuses.

The mice were infected with virus. After the virus-sensitized T lymphocytes had time to mature, they were removed and tested against virus-infected cells. The lymphocytes only attacked the A-strain infected cells, the genetic type of the transplanted thymuses. Since everything about the mice was genetically AB except the thymuses, this seems conclusive evidence that the thymus determines, and in this case limits, the T lymphocytes' ability to recognize self H antigens. □