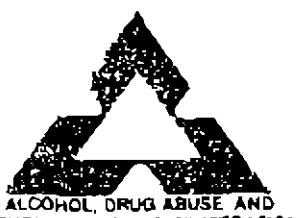
From the Alcohol, Drug Abuse, and Mental Health Administration

Surprisingly Complex Brain Enzyme: Scientists at the National Institute of Mental Health (NIMH) and colleagues at Washington University School of Medicine, St Louis, have deciphered the genetic instructions for tyrosine hydroxylase, the enzyme that makes the neurotransmitter dopamine. Until recently, scientists had assumed the enzyme had only one form. It turns out there are at least five forms, and probably many more, each of which may have distinct functions in different parts of the brain. The NIMH research team, led by Edward Ginns, MD, PhD, and the Washington University team, led by Karen O'Malley, PhD, report on their studies in the Nov 3 issue of *Biochemistry*. Interest in tyrosine hydroxylase has increased recently because the gene that is responsible for it lies in the same area of chromosome 11 as the gene for manic depressive illness in the Amish (*JAMA* 1987;257:2699). The present investigators are using the enzyme's newfound genetic blueprint to probe Amish cell lines, theorizing that the enzyme's dysfunction may in part cause this mental illness. Defects in tyrosine hydroxylase also have been hypothesized to cause such other dopamine-related disorders as Parkinson's disease and schizophrenia. But the discovery of its multiple forms adds new complexity to the search for deficient enzymatic activity, Ginns says, because it is now realized that previous researchers were actually measuring the overall activity of a pool of various forms of tyrosine hydroxylase. If only one of the several forms is defective the defect might barely show up in a gross sample, even though that one might be enough to cause illness. Ginns says investigators now may have to examine each brain area separately, and perhaps at different stages of development, to detect potentially dysfunctional forms of the enzyme.

Cocaine Addiction Brain Receptor: Researchers at the National Institute on Drug Abuse Addiction Research Center have identified in the dopamine system of the brain a specific cocaine receptor site that appears to be responsible for the drug's addictive properties. The receptor is a binding site on the "dopamine transporter," which normally functions to remove the neurotransmitter dopamine from the synaptic cleft so that it is no longer available to act as a bridge for neuronal messages. Cocaine inhibits this process, thereby prolonging dopamine's action. Dopamine has been associated with drug self-administration in animal studies. Although studies have shown that cocaine binds to several sites in the brain, none has identified the specific site associated with its addictive properties. In the new study, reported in the Sept 4 issue of *Science*, Michael Kuhar, PhD, Mary Ritz, PhD, Richard Lamb, PhD, and Steven Goldberg, PhD, correlated the potencies of cocaine and several cocaine-like drugs in inhibiting binding at the dopamine transporter with their known potencies in stimulating drug self-administration in animals. Identifying the site where cocaine initiates its addictive



effect has several benefits: it reinforces clinical use of drugs that interact with dopamine to treat cocaine addiction; it may make it possible to purify the receptor to study its molecular structure and so determine how cocaine acts at that level; and it may help identify the gene for the cocaine receptor, thus enhancing studies of genetic factors in drug addiction.

Brain Cell Destruction From MDMA: Scientists at the National Institute on Drug Abuse Addiction Research Center reported in the September issue of the *Journal of Pharmacology and Experimental Therapeutics* that the drug MDMA (3,4-methylenedioxymethamphetamine)—also called "Ecstasy" in street usage—has long-term toxic effects on the nerve cells that produce the neurotransmitter serotonin. Serotonin is involved in modulating responses to stress and pain, as well as in appetite and sexual behavior. George Battaglia, PhD, and Errol B. De Souza, PhD, have found that MDMA destroys the uptake sites in serotonin-producing brain cells. After administering MDMA to rats for four days, the researchers found drastic reductions in number of uptake sites: a 90% loss one day after the last injection and more than a 50% loss after eight weeks. Six months after MDMA administration, 75% of uptake sites had returned, indicating that nerve cells can recover from the drug, though recovery is much slower than from other toxins. The extent of MDMA-caused damage depended on number and frequency of doses as well as dose levels, suggesting that people who go on drug-taking binges with MDMA, consuming a number of relatively low doses over consecutive days, may risk serious harm.

Surfactant, Alcohol, and Pneumonia: The impact of alcohol (ethanol) on surfactant, the lipid-protein complex lining the internal lung surface, may be a contributing cause of increased risk of pneumonia in alcoholics, reports National Institute on Alcohol Abuse and Alcoholism grantee Gary Roselle, MD, University of Cincinnati Medical Center and Veterans Administration Hospital, in the June issue of *Alcoholism: Clinical and Experimental Research*. Surfactant is important in preventing airway collapse and it has a role in the lung's defense against bacterial infection. It contains opsonins, which are involved in the cell-mediated immune defense against bacteria in the lower respiratory tract. In studies of guinea pigs, Roselle examined the effects of alcohol on level of surfactant in the lung and on variation in surfactant opsonic activity. He injected the animals with alcohol twice a day for six weeks and then collected samples of lung lining by lavage with saline solution. Roselle and coinvestigator Robert Baughman, MD found a 50% decrease in the amount of disaturated phosphatidylcholine, a major lipid component of surfactant, in the lungs of alcohol-treated animals versus controls. The lung lining fluid from the exposed animals also had less opsonic bactericidal activity than fluid from controls. Further research is needed to clarify the relationship between loss of opsonic activity and altered surfactant composition in alcohol-treated lungs.

—by Donald Ian Macdonald, MD
Administrator
Alcohol, Drug Abuse, and
Mental Health Administration

Editor's Note: Inquiries may be directed to Wilfred Austermann, Associate Administrator, ADAMHA Parklawn Building, 5600 Fishers Lane, Rockville MD 20857; telephone (301) 443-3783.