SOUTHWESTERN NEWS

Media Contacts: Ione Echeverria
or Ann Harrell
214-648-3404
ione.echeverria@utsouthwestern.edu

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UT SOUTHWESTERN PSYCHIATRY RESEARCHER SAYS GENOME MAP ADDS VALUABLE INFORMATION TO MYSTERY OF DRUG ADDICTION

DALLAS – Feb. 12, 2001 – Knowledge gained from the human genome-mapping project already is leading to a better understanding of how drugs and alcohol act on the molecular and cellular mechanisms and brain pathways to cause addiction, a UT Southwestern Medical Center at Dallas researcher and his colleague say.

Drs. Eric J. Nestler and David Landsman reported on the progress made in the field of drug addiction in a Feb. 12 special issue of *Nature* dedicated to results of genome research and gains to be expected. Nestler, a world-renowned molecular psychiatrist specializing in the mechanisms of alcohol and drugs in the brain, is chairman of psychiatry at UT Southwestern. Landsman is a leading authority on bioinformatics at the National Center for Biotechnology Information, National Library of Medicine, in Bethesda, Md.

In the essay, the authors stressed that addiction represents a biological process caused by the effects of repeated drug exposure on a vulnerable brain and defined it as the compulsive seeking and taking of a drug or alcohol despite adverse consequences.

"The decoding of the human genome will prove incredibly important in all areas of human research, none more so than in alcohol and drug addiction," Nestler said. "In order to understand addiction, it is important to define the types of molecular and cellular adaptations at the levels of neurons and synapses that account for tolerance, sensitization and dependence, terms that are often used to define an addicted state."

The authors explain that genome sequencing – both in humans and in other mammals – will foster an understanding of the biology of addiction by enabling researchers to identify specific genes that contribute to individual addiction risk as well as those involved directly in the addiction process caused by drugs.

Nestler said addiction researchers have come to believe that drugs of abuse act on brain circuits developed at a much earlier time. These circuits are a part of the limbic system, located

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in the frontal lobe and thought to be associated with emotions. Researchers think these circuits regulate individual responses to such things as food, sex or risk-taking activities, all of which may act as "natural reinforcers." Thus, the addict can become "addicted" to things other than drugs.

"The loss of control that addicts show with respect to drug seeking and taking may relate to the ability of drugs of abuse to commandeer these natural-reward circuits and disrupt a person's motivation and drive for normal reinforcers," Nestler said.

He said there is scientific evidence that "natural addictions," such as overeating, pathological gambling, compulsive shopping, and perhaps excessive exercise, may involve analogous mechanisms to the chemical kind.

Nestler said that a major focus in addiction research today is exploring the neurobiology of such addictive conditions. He explained that both the person's intense cravings for the drug, as well as the increased risk of relapse the person experiences, make it clear that major changes have taken place in the brain. "The molecular and cellular adaptations related to tolerance, sensitization (increased sensitivity) and dependence do not persist long enough to account for the more permanent behavioral changes associated with addiction," he said.

He said that this kind of change may well be associated with memory and/or learning behavior, "but little information is available concerning the molecular and cellular basis of essentially life-long memories. Proposed changes in the conversational connections between nerve cells or chromosomal organization remain speculative."

Nestler added that many changes taking place after multiple drug exposure have now been uncovered.

"Because of such major gains like the genome project, today DNA technology makes it possible to investigate thousands of gene products simultaneously after drug exposure. Soon, by combining new genetic tools with increasingly sophisticated models of addiction in animals, it will be possible to identify patterns of altered gene expression that are associated with particular features of the addicted state, such as tolerance, sensitization, dependence, craving and relapse," he said.