CAS Bids Farewell to Long-Time Researcher Overstreet

Overstreet published nearly 10 manuscripts per year with a primary emphasis on animal models of alcoholism and depression. Overstreet was a key player in the development of the Flinders Sensitive rat line (FSR), a model of depression, and the Flown Hooded rat line (FHR/Wi), a model of comorbid depression and alcoholism, both of which have been extensively used in the study of the behavioral and neurobiological mechanisms of these human conditions. He has published widely on models of anxiety and ethanol withdrawal, novel compounds, cholinergic function, and more. Overstreet will continue to collaborate with close colleagues George Breese, Ph.D., and Darin Knapp, Ph.D. on corticosterone releasing factor (CRF) as well as other mediators of anxiety after alcohol withdrawal. He is also finalizing collaborations with other UNC faculty members on the effects of progesterone and oxytocin on alcohol drinking. Overstreet graduated Phi Beta Kappa with a B.A. in psychology from the University of California, Berkeley. In 1972, he received a Ph.D. in psychobiology from the University of California, Irvine. Overstreet joined the Bowles Center and the Department of Psychiatry in 1990.

“David Overstreet’s retirement will produce a ‘vacuum’ for the laboratory. While we will miss his quick wit, we will miss more the major contributions he has made to the successes our laboratory has enjoyed,” said Breese.

Alcoholics often describe their initial experiences with alcohol in very positive terms. Drinking made them feel happy, expansive, even euphoric; it increased their self-confidence and sense of well-being. It is not difficult to understand why someone experiencing these effects of alcohol might continue to seek it out. While the rewarding effects of alcohol appear to support continued drinking early in the course of alcoholism, they appear to dissipate over time with repeated use of alcohol and are rarely described as reasons for drinking by those with advanced alcoholism. In contrast to the occasional drinker who imbibes in order to experience positive effects, many alcoholics continue to drink even when they experience little positive reinforcement from it. In fact, many alcoholics continue to drink despite experiencing significant negative effects of alcohol. These points are illustrated by the character of Henry Chinaski, the fictional alter ego of his creator Charles Bukowski, the famously alcoholic author known as the “Poet Laureate of Skid Row.” After a night of drinking (writes essayist Adam Cohen in Visions of Bukowski), Chinaski often “awoke in cheaply rented bedrooms, probably independent of outcome. In her memoir Note Found in a Bottle: My Life as a Drinker, Susan Cheever aptly describes the habitual nature of alcoholic drinking: “These were years when I was drinking, but I don’t even remember the drinking. I was acting as if I were a marionette being pulled around by... invisible strings...” Such habitual drinking differs from what behavioral scientists characterize as goal-directed behavior—that is, actions that are dependent on outcomes—drinking motivated by the reward of feeling good, for example.

Dr. Donita Robinson, Assistant Professor in the Department of Psychiatry and the Bowles Center for Alcohol Studies at UNC, believes that understanding the behavioral and physiological underpinnings of habitual drinking could hold keys to curbing the development of alcohol dependence and to preventing relapse. Robinson models both goal-directed alcohol drinking and habitual alcohol drinking in rats trained to press a lever to receive alcohol. To elicit goal-directed alcohol drinking, Robinson uses a fixed-ratio 5 reinforcement schedule in which every five lever presses yields a drink of alcohol. Drinking behavior established on this schedule demonstrates the typical characteristics of goal-directed behavior: alcohol intake is driven by conditioned cues and is independent of outcome. In her memoir Note Found in a Bottle: My Life as a Drinker, Susan Cheever aptly describes the habitual nature of alcoholic drinking: “These were years when I was drinking, but I don’t even remember the drinking. I was acting as if I were a marionette being pulled around by... invisible strings...” Such habitual drinking differs from what behavioral scientists characterize as goal-directed behavior—that is, actions that are dependent on outcomes—drinking motivated by the reward of feeling good, for example.

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schedule is easily extinguished such that when a rat is no longer given the alcohol when after lever presses, the rat soon ceases to press the lever. Under this reinforcement schedule, the rat unable to achieve the “goal” of the drink of alcohol no longer performs the goal-directed behavior of lever pressing. To elicit habitual alcohol drinking, Robinson uses a variable-interval 30-second reinforcement schedule in which a variable amount of time (on average 30 seconds) must go by before a lever press will earn a drink of alcohol. The variable-interval 30-second reinforcement schedule produces behavior that optimizes habitual drinking of the human alcoholic in that it is resistant to extinction and not influenced by reward devaluation. Resistance to extinction is demonstrated by the finding that, even when lever presses no longer yield alcohol, the rat continues to press the lever. Reward devaluation is demonstrated by the finding that, even when the alcohol is made less rewarding by pre-exposing the animal to as much alcohol as it cares to drink before the lever-pressing task, the rat continues to press the lever to obtain alcohol. This resistance to extinction and to the effects of reward devaluation resembles the behavior of the alcoholic who continues to drink even when drinking no longer elicits good feelings.

What changes in the brain mediate the transition from goal-directed drinking to habitual drinking in the alcoholic? Robinson was recently awarded a five-year grant from the National Institute of Alcohol Abuse and Alcoholism to address this question by using two-state-of-the-art techniques to study the activity of nerve cells (neurons) in rats trained to press a lever to receive alcohol. First, Robinson uses the technique of extracellular recording at multielectrode arrays to characterize the electrical activity of small groups of neurons. Second, Robinson uses the technique of fast-scan cyclic voltammetry to gauge release of dopamine, a neurochemical that (among others) is important in mediating the function of the brain’s reward circuit. These measurements are made in real time while the animal is seeking and drinking alcohol. Robinson is focusing her efforts on understanding changes in neuronal firing before and after lever presses that are reinforced with an alcohol reward. Dorsolateral striatum—areas that form part of the brain’s reward circuit and that have been implicated in goal-directed and habitual behaviors—will be studied. Previous data in animals suggest that the dorsomedial striatum is involved in goal-directed drug-taking behavior whereas dorsolateral striatum is involved in habitual drug-taking behavior. These data and other results are consistent with the possibility that the transition from goal-directed alcohol drinking to habitual alcohol drinking is associated with an anatomical shift of information processing from the dorsomedial striatum to the dorsolateral striatum. Robinson will explore how dopamine signaling changes in rats trained on the fixed-ratio 5 reinforcement schedule (to produce habitual drinking) with that in rats trained on the variable-interval 30-second reinforcement schedule (to produce habitual drinking). She hypothesizes that the neurons in the dorsomedial striatum will be preferentially active during goal-directed alcohol drinking whereas neurons in the dorsolateral striatum will be preferentially active during habitual alcohol reinforcement. Neural activity and dopamine release in these two brain areas will be assessed during alcohol self-administration; during extinction, in which alcohol delivery is ceased in animals previously trained to press the lever for alcohol; and during reinstatement, in which alcohol delivery is reinstated in animals that had previously undergone extinction.

“Our work should provide the most complete picture to date of how the brain encodes alcohol-related habit formation,” says Robinson. “The disconnection of the drinking behavior from negative consequences is a major factor that makes alcoholism so difficult to treat. Alcoholics continue to drink despite negative consequences and devaluation of alcohol by tolerance. If we can understand how the brain wires itself or changes its coding to support this maladaptive behavior, we can begin to investigate therapeutic approaches that can control habitual drinking.”

In fact, Robinson was recently awarded a supplemental two-year grant to study the effects of drugs in her model. Animal models previously used to screen drugs for potential usefulness in human alcoholics have almost exclusively employed goal-directed reinforcement schedules. Robinson, on the other hand, screen drugs under both goal-directed reinforcement schedules and habitual reinforcement schedules. She hypothesizes that naltrexone, a drug that appears to make alcohol less rewarding, will be less effective in reducing alcohol drinking under habitual reinforcement schedules (i.e., variable-interval schedules) than under goal-directed reinforcement schedules (i.e., fixed-ratio). Further, she hypothesizes that topiramate, a drug that stabilizes neurocircuitry, will be less effective in reducing alcohol drinking under the habitual reinforcement schedule. By opening the door to studying drug effects in habitual drinking, these experiments could lead to improved preclinical animal models of alcohol drinking and relapse-like behavior.
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**CONGRATULATIONS to Dr. John J. Lemasters on Receiving the 2009 Thurman Lectureship Award**
Breaking the Habit: Scientist’s Research Will Reveal Mechanisms of and Potential Targets for Maladaptive Alcohol Drinking

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