Toward an Account of Individual Differences in Drug Abuse

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What is drug addiction? It is drug taking on the part of the individual that is usually excessive, harmful to the individual or his/her social environment, and which therefore presents a significant public health problem. The chapters in this technical review deal with the variety of issues of why drug addiction affects only some of us. As documented in these chapters, many of us are exposed one or more times to drugs with abuse potential, yet only a few of us go on to demonstrate drug addiction. Why is this the case? Some believe, as I do, this to be a central, vexing question—addressed often, but not yet satisfactorily answered.

We are offered a rich set of points of view on this question in this monograph. Each is a compelling if different approach to this difficult question. Which of the approaches has the broadest scope and offers the richest avenues for advancing understanding? How can we modify our animal models of addiction to take individual variation into account? How can we best evaluate hypotheses derived from complex epidemio-logically based human studies, and can these hypotheses be tested in animal models? Which of the models is likely to provide the most compelling answer to the central question of individual vulnerability? Which is likely to provide the most testable answer?

Before dealing with specific discipline-related issues, comments should be made on two contributions of epidemiological interest. Dr. Mary McCaul's chapter describes the difficult issue of finding the sources of effect of family history of abuse upon offspring, especially in situations where a host of variables contribute outcome measures. Dr. Ralph Tarter and his colleagues describe an elegant lifespan scheme for elaborating these and other influences where they take a specific measure, DSM diagnosis, as their endpoint. A common problem shared by these types of studies is that single variables that they are measuring, such as unconventional friends or tolerance to deviancy, contributes little per se to the likelihood that drug abuse develops. Dr. Harriet de Wit takes a more experimental approach to human differences in drug abuse by studying normal subjects who may differ in their subjective response to benzodiazepines. She has found that anxious individuals and those with a history of moderate alcohol

consumption show an increased positive response to diazepam and a decreased negative response to diazepam, respectively.

From the perspective of the researcher who has dealt with animal models in which drugs act as reinforcers that control drug taking, discussions of epidemiological issues such as family history may seem unnecessary. When the dose is appropriate, when the behavioral requirements are relatively simple, and when the route of administration assures rapid access of the drug to the brain, drugs come rapidly to serve as reinforcers in animals.

Rodents and primates, without significant individual differences, develop regular, consistent patterns of drug taking. If the opportunity is provided, within weeks, primates develop patterns of drug taking that typically require years of drug taking to develop in human abusers. For example, monkeys become physiologically dependent on intravenously available ethanol within a few days of initiating self-administration; humans may require years of oral ethanol consumption before they show withdrawal signs when they stop drinking. Similarly, monkeys show binge patterns of intravenous cocaine self-administration and the concomitant fasting, insomnia, and self-mutilation, which develops much more slowly in human cocaine abusers.

It is intellectually relevant to the broader problem of individual differences to acknowledge that, under these circumstances, the behavioral arrangements produce drug abuse in all cases! This is vastly different from the findings of other researchers who deal with problems of individual differences in people, only a small percentage of whom ever demonstrate the behavior with drugs that are captured in virtually all cases in rodents and primates. In order to model the problem posed by individual differences in drug abuse, the animal researcher needs to weaken the environmental control of the drug reinforcer to allow other types of variables to exercise influence on behavior. Unfortunately, as suggested by Dr. Marilyn Carroll, the emphasis of animal studies of drug abuse is usually on good baselines of drug-taking behavior, and animals that show reluctance to provide these baselines may be discarded without mention.

Behavioral researchers, however, have begun efforts to study individual differences in drug taking in animal subjects. They have started to evaluate some of the host of behavioral variables that may influence initiation, maintenance, and “relapse” (a reinstigation of drug taking following a period of self- or experimenter-imposed

abstinence) of drug taking. One should not suppose necessarily that there are unique variables that will influence these somewhat artificially imposed distinctions on drug-taking behaviors. Drs. Susan Schenk and Emily Davidson as well as Dr. Carroll note that, in some conditions, simple exposure to the drug of abuse may hasten initiation or relapse. Dr. Michael Nader points to important modulatory behavioral histories that are able to suppress drug taking.

Dr. John Falk takes the novel tactic of examining the discriminative control of excessive drug taking and how the control may be transferred among different consequences (drugs). He makes the important point that this control may change behavior significantly without the drug exerting a reinforcing function. No doubt, in different human situations involving drug taking, variables other than the drug itself may control drug-taking behavior, a point made as well by Dr. Tarter and his colleagues.

The researchers who are interested in the contribution of the biological disposition of the subjects are well represented by the contributions of both Dr. Nick Goeders and Dr. Vincenzo Piazza. These investigators are assessing the influence of stress as expressed through the hypothalamic-pituitary axis on vulnerability to drug abuse. In rodents, it appears that this contribution can be direct and strong.

Dr. Goeders has shown that cocaine is a more potent and stronger reinforcer in animals that have been exposed to noncontingent shock. Corticosterone itself acts as a reinforcer and augments the reinforcing effects of cocaine, and if steroidogenesis is blocked metabolically by administration of metyrapone or ketoconazole, the reinforcing effect of stimulants is reduced or abolished. Dr. Piazza and his colleagues have shown that a rat's locomotor response to a novel situation predicts its stimulant-taking behavior, as well as its likelihood to select a stressful environment. Therefore, human propensity to take drugs may also be related to the amount of stress in their environment, and the individual physiological and behavioral reaction to that stress. Taken together, these studies represent an interesting approach to potential individual variation that will no doubt soon receive attention in primate and human studies. Since the study of steroid effects has taught us in other contexts that long-term effects of steroids should be considered from both organizational and activation points of view, it will be interesting to examine both types of steroid effects in future studies.

From a different "biological" standpoint, Drs. Blake Gosnell and Dean Krahn consider the evidence that vulnerability to drug taking might be considered as appetitive disorders. There is a growing literature, especially in alcohol-related studies, for such differences in animals. For example, animals that consume sweets excessively tend to consume more ethanol. Mechanisms for these effects appear to be elusive at present.

From the genetic perspective, Dr. Frank George's contribution emphasizes the impressive accomplishments that selective breeding studies have made in identifying potential individual differences in sensitivity to ethanol's reinforcing effects. Different aspects of ethanol-related behavior have been bred in mice. Some of them (e.g., serotonin receptor density) are related to, and many of them (e.g., sensitivity to ethanol's stimulant or depressive effects) are not related to the establishment of a reinforcing effect of ethanol in these animals. This approach is likely to continue to be helpful for analyses with ethanol and other drugs. Other genetic approaches that were not represented at the Technical Review but that are very interesting and relevant are those involving transgenic mice that are lacking specific receptors (e.g., dopamine, opioids) and, in addition, those that involve the attribution of effect quantitatively to particular gene loci. What remains to be determined is whether these findings in rodents reflect similar and equally relevant dimensions of human physiology and behavior.

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