BEHAVIORAL MODELS IN DRUG DISCOVERY. James E. Barrett. Lederle Laboratories, Pearl River, NY.

The use of animal behavior models to aid in the discovery and understanding of new drugs for the treatment of psychiatric disorders has often been questioned or criticized. Since so little is known about the pathophysiology and etiology of most psychiatric disorders, it is difficult to experimentally induce the disease and, as a consequence, many drug effects are evaluated relative to known pharmacological standards. Clearly, this poses certain difficulties when there are either no known standards for validating a behavioral procedure (e.g., in the area of "cognition enhancer") or when compounds are being evaluated that could be clinically effective but, because they function through different neuropharmacological systems, might not be detected. In this case, the procedure is compound specific rather than a general procedure for that particular disorder. Despite these and related concerns, this paper emphasizes an alternative viewpoint and draws from the extensive literature on the successful use of behavioral models with animals as a fundamental method in drug discovery and in the clarification of the neuropharmacological mechanisms underlying drug effects. Although there are acknowledged limitations with any type of animal model, behavioral techniques offer the distinct advantage of being nondestructive indices of integrated CNS activity. Significantly, the actions of drugs on behavior can also be studied when the environmental conditions that control behavior are manipulated, an action that presumably also modifies the neurobiological substrates contributing to the pharmacological actions of the drug. Thus, it is possible to study and understand drug action at many different levels and as a function of several different variables. It is becoming clearer that many pathological conditions do not reflect deficits in a single neurotransmitter system and that therapeutic drugs of the future may require compounds targeted at several receptor sites. These directions pose new challenges for the selection and refinement of suitable behavioral models with which to evaluate these possibilities. Several models are now available that provide essential information on these issues and will be used to illustrate the point that behavioral models are critical for the development of new drugs with multiple targets. Progress in the area of animal models in behavioral neuropharmacology has been considerable. Continued refinement of these procedures is essential for understanding the behavioral bases of the bioassays that are currently used and to direct the design and development of newer, more effective, and safer therapeutic agents.

ANIMAL MODELS OF DRUG SELF-ADMINISTRATION. *Marilyn E. Carroll.* University of Minnesota Medical School, Minneapolis, MN.

Several animal models of drug abuse are reviewed; a rat model in which IV cocaine is self-administered and a primate model in which rhesus monkeys are trained to smoke cocaine base or self-administer orally delivered drugs, as well as models of acquisition, maintenance, and withdrawal. The effects of nondrug alternative reinforcers and pretreatment with potential therapeutic drugs are discussed. For instance, a recent study has shown that only 50% of a group of rats that had access to a glucose and saccharin drinking solution (nondrug reinforcer) acquired cocaine self-administration within 30 days, while 100% of controls acquired within 5-23 days. During the stable maintenance phase of drug self-administration with many drugs, routes of administration and species, the effectiveness of alternative nondrug reinforcers depends on how hard the animal works for each mg of drug delivered. The higher the unit price of the drug (responses per mg), the greater reduction in drug-reinforced behavior due to nondrug reinforcers. Pharmacological treatments also produce greater reductions in drug-reinforced behavior when the unit price of the self-administered drug is high. Drug withdrawal studies have been conducted using food-reinforced responding as a measure of behavior that is disrupted due to drug abstinence. Food-reinforced responding is diminished when a self-administered drug is replaced by water, and responding is readily reinstated when drug access is restored. Recent work has shown a biphasic economic effect, the severity of the withdrawal effect increases as the price of food increases, but as body weight begins to decrease, the drug withdrawal effect is diminished. These animal models indicate that alternative reinforcers and drug treatments may alter many aspects of drug dependence. Behavioral and drug treatments interact with the behavioral economics of procuring the drug. It is important to establish models for evaluating the potential treatment at several phases of the addiction process; such as acquisition, maintenance, withdrawal and relapse, as treatments may be differentially effective at different stages.

ADVANCES IN UNDERSTANDING THE NEURAL BASIS OF THE BEHAVIORAL EFFECTS OF DRUGS. Steven I. Dworkin. Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, NC.

An evaluation of current research endeavors investigating the neurobiology of substance abuse will be provided. The presentation will focus on the design and implementation of integrated approaches combining neurochemical techniques with operant conditioning methodologies to further our understanding of the basic neurobiology of reinforcement, concentrating on the neuronal systems involved in the reinforcing effects of self-administrated drugs. Data will be presented from studies evaluating the behavioral and neurochemical consequences of response-dependent versus response-independent presentations of cocaine. The strategic approaches that will be highlighted include the use of 2-dg autoradiography, neurotransmitter turnover, receptor binding, in vivo microdialysis, electrophysiology, and medicinal chemistry. The use of these neurochemical procedures in different behavioral models will be discussed. The 2-dg autoradiography procedure has been used to identify CNS sites that are potentially involved in the reinforcing effects of self-administered drugs. The specific neurotransmitter pathways connection of these regions have been identified using neurotransmitter turnover methodologies. Verification of the role of these neurotransmitter systems have been obtained by monitoring the dynamic changes in neurotransmitter overflow using in vivo microdialysis and determining the effects of site and neurotransmitter specific lesions using selective neurotoxins. Data on the involvement of individual neurons in the reinforcing effects of cocaine identified through the use of electrophysiological techniques will also be presented. This presentation would demonstrate how the integration of behavioral analysis with neurochemistry can increase our understanding of behavior and its neurobiological correlates.