University of Michigan, Ann Arbor, MI.

An important concept in pharmacology is affinity, the attraction that a drug molecule has for a receptor. When measurements are made of the effects produced by an agonist in both the presence and absence of a competitive, reversible antagonist, it is possible to obtain a quantitative estimate of the affinity of the antagonist for a given receptor using pA_2 analysis. A pA_2 value is the negative logarithm of the dose of antagonist which when given in combination with an agonist results in a two-fold increase in the dose of agonist required to produce a given response. The pA_2 method is particularly useful in that it can be used to determine whether or not 1) two different agonists are producing their effects through the same receptor type and 2) a number of different effects produced by a particular agonist are mediated through the same or different receptors. In opioid receptor systems, for example, both mu- and kappa-receptor-selective agonists produce analgesia under certain conditions. In order to determine whether or not these agonists are producing their effects through the same receptor, apparent pA_2 values can be determined for an antagonist with both agonists. If the pA_2 is the same, then it can be assumed that the two agonists are producing the effect through the same receptor, while different pA_2 values indicate that more than one receptor is involved. In addition to producing analgesia, many mu-receptor-selective agonists are self-administered and produce discriminative stimulus effects. In order to determine whether these effects are mediated through the same receptor, pA_2 analysis can also be used. Again, similar pA_2 values indicate that the same receptor mediates the different effects while different pA_2 values suggest multiple receptor involvement. These examples thus illustrate that the pA_2 method can be a very useful tool for evaluating various pharmacological effects.

RELATIVE EFFICACY OF OPIOID AGONISTS: A BEHAVIORAL ANALYSIS. Charles P. France. University of Michigan, Ann Arbor, MI.

Two pharmacological constants, affinity and efficacy, describe interactions among drugs, receptors and receptor-coupled effectors and are unifying principles of receptor theory by which drug actions can be characterized across different biological conditions. Differences in affinity (potency) among agonists are well established at many levels of analysis; however, efficacy has not been widely examined in vivo, despite the well-demonstrated utility of this theoretical construct in vitro both for the classification of drugs and for the classification of receptors. In order to establish efficacy differences among agonists several empirical requirements must be satisfied. First, all of the relevant drugs must produce the measured responses by acting at the same receptor which can be established by showing similar affinity estimates for a competitive, reversible antagonist across all drugs and conditions. Second, compounds of low efficacy must attenuate the actions of compounds with higher efficacy under conditions in which the lower efficacy compounds fail to produce the maximum obtainable response. Presumed differences in efficacy among agonists can be further substantiated under conditions in which receptor reserve is altered, either by administration of irreversible antagonists or by the induction of tolerance. At sufficiently large doses, irreversible antagonists will decrease the maximal response; because low efficacy compounds have smaller receptor reserve, the maximum will be diminished for lower efficacy agonists at doses of antagonists that do not change the maximum produced by more efficacious compounds. The later approach (irreversible antagonism) is critical for differentiating among agonists that have different efficacies but produce maximal responses under all test conditions. To the extent receptor theory has been evaluated *in vivo,* it appears to provide useful and appropriate principles for assessing behavioral effects of drugs. Examples from behavioral studies will be used to demonstrate empirically verifiable hypotheses regarding efficacy differences among opioids. (Supported by USPHS Grants DA05018 and DA00254.)

TOLERANCE AND RECEPTORS. Alice M. Young. Wayne State University, Detroit, MI.

Tolerance to the behavioral effects of repeatedly administered opioids is modulated jointly by pharmacological and behavioral processes. This presentation will examine how pharmacological and behavioral principles can be used to examine the processes underlying the development, characteristics, and persistence of opioid tolerance. Tolerance to opioids is modulated by the opioid employed for repeated treatment, its dose and frequency, the duration of treatment, and the behavioral conditions under which tolerance is developed and assessed. Tolerance to the behavioral effects of the prototypic opioid morphine, for example, can vary directly with the maintenance dose and duration of chronic treatment. Patterns of cross-tolerance suggest that tolerance produced by chronic morphine treatment is limited to μ opioids, and differences in patterns of cross-tolerance among μ opioids suggest that tolerance may result from changes in the receptor populations that underlie opioid effects. Other lines of evidence suggest that development and persistence of tolerance to the behavioral effects of opioids are also modulated by respondent and operant conditioning processes. Tolerance to the analgesic effects of morphine, for example, can be brought under conditional control of the testing environment. Such conditional tolerance is responsive to many of the processes known to modulate respondent conditioning, including blocking, sensory preconditioning, and extinction. Development of tolerance to the disrup-tive effects of opioids on well-developed operant behaviors is also modulated by stimulus control and reinforcement processes. Similar behavioral contingencies modulate tolerance to the discriminative stimulus effects of opioids, with tolerance developing most readily under training conditions that limit transfer of control to lower drug doses. A fuller characterization of opioid tolerance will require both pharmacological and behavioral studies. Both receptor and conditioning theory can provide useful guideposts to studies of tolerance to the behavioral effects of opioids.

SYMPOSIUM

Psychologists in Substance Abuse: Current Activities and Growing Opportunities

Chair: *Joan Ellen Zweben,* The East Bay Community Recovery Project, Oakland, CA.

Discussant: *George DeLeon,* Community Studies Institute, New York, NY.

OPPORTUNITIES FOR PSYCHOLOGISTS THROUGH NIDA. Charles R. Schuster. National Institute on Drug Abuse, Rockville, MD.

The National Institute on Drug Abuse involves psychologists in a wide range of specialties in the research and related activities it conducts or sponsors. Psychologists currently lead or participate in a wide range of research activities, focusing on topics ranging from the behavioral pharmacology and abuse liability of

drugs, causes and consequences of drug use, and improving prevention and treatment. Others are involved in NIDA's demonstration projects which involve service delivery and evaluation by psychologists. Unfortunately, the demand for psychologists with research skills far exceeds the available pool. In addition to these opportunities in research and research administration, NIDA is making a major effort to build and maintain an alliance between researchers and practitioners. In January 1991, the Institute held a major national conference in Washington, DC to examine and share new methodologies for prevention and treatment programs. The conference was part of a major technology transfer initiative begun in 1990 to ensure that new technologies are adapted by practitioners in the field. Workshop sessions included such areas as risk and protective factors for adolescent drug use, diagnosis and treatment of drug-dependent women, pharmacological advances in drug abuse treatment, and drug abuse funding and abuse treatment, and drug abuse funding and treatment resources. The field of substance abuse is one in which the interplay between the researcher and clinician is often highly collaborative and mutually rewarding. NIDA distributes much of this work in its highly regarded series of Monographs, of which almost 100 have been published since 1975. These are but a few of the areas in which psychologists are making contributions at NIDA and NIDA-supported research and in which significant opportunities remain.

BEHAVIORAL PHARMACOLOGY: RESEARCH WITH HUMAN SUBJECTS. Marian W. Fischman. The Johns Hopkins University School of Medicine, Baltimore, MD.

Laboratory research with psychotropic drugs has provided both the foundation for understanding the behavioral mechanisms of actions of these substances, as well as procedures for evaluating behavioral and pharmacological interventions for treating their excessive use. Such laboratory studies are remarkably diverse, ranging from neurotransmitter systems to multidisciplinary studies that combine physiology and behavior. In addition, laboratory studies can be accomplished with multiple species, providing cross-species generalization of the results collected. Although evaluation of drugs of abuse and treatment of substance abuse disorders has been carried out for more than 50 years, most of the laboratory work has been done with nonhuman subjects. The major exception to this has been in the area of evaluation of subjective effects in humans. A shift in direction began in the 1970's, when investigators began to adapt previously used behavioral procedures and combine these measures with more traditional subjective effects evaluations. Such an approach has provided the structure for behavioral pharmacology research with humans. Laboratory research on substances of abuse with humans is most frequently carried out within an academic environment, often including a medical school/hospital setting. Because medical monitoring can be a part of the design, collaboration with physician-researchers is generally appropriate. This presentation will describe a multiple laboratory approach to carrying out substance abuse research, including both inpatient and outpatient designs, varying from a highly structured residential laboratory in which subjects are monitored 24 hours daily, to experimental designs in which subjects are briefly tested as outpatients at daily or weekly intervals. Human research subjects, under some conditions, are given the opportunity to self-administer specific substances of abuse while under other conditions these substances are administered by the experimenter. A range of measures, including performance and learning, are all repeatedly made, and correlated with blood levels of the drug. This research is under the direction of psychologists, trained in the experimental analysis of behavior using nonhumans, who are extending this laboratory method to testing humans. The research provides data on the antecedents and consequences of substance abuse, necessary in designing and implementing both treatment and prevention strategies.

THE ROLE OF PSYCHOLOGISTS IN VA SUBSTANCE ABUSE TREATMENT AND RESEARCH. A. Thomas McLellan and Arthur I. Alterman. Veterans Affairs Medical Center, Philadelphia, PA.

This presentation examines some representative roles taken by psychologists in the VA and discusses these and other future opportunities for psychologists. The Department of Veterans Affairs (VA) is the largest health care organization in the world and offers quantitatively more treatment, provided in more varieties and more settings, than any other organization in the United States. Historically, psychologists have had leading roles in all aspects of substance abuse treatment within the VA and these often translated into major contributions to treatment and research throughout the field. Three types of contribution will be discussed with representative examples provided in each. First, psychologists within the VA have been developers and providers of innovative treatments within the field of substance abuse (e.g., "relapse prevention," "extinction of conditioned responses," "AIDS awareness and education," etc.) and these have been used extensively throughout other public and private settings. Second, VA psychologists have developed instruments and methods for evaluating the efficacy and costs of substance abuse treatments (e.g., ASI, MAST, RAB, etc., plus a series of representative evaluation studies). Finally, the VA has provided psychologists with opportunities to direct and administer not just treatment programs but treatment policies for substance abusers throughout the system (e.g., director of substance abuse services within the VA, several "Service Chiefs," etc.). These opportunities have been used to great advantage by psychologists in the past and this has, in turn, offered an even greater variety of opportunities in administration, direct care and treatment research for psychologists now working in this area. The presentation will conclude with information regarding the methods for applying to become clinically certified to work within the VA and the procedures associated with applying for research grants within the VA.

TREATMENT RESEARCH IN DRUG ABUSE. James L. Sorensen and Sharon Hall. University of California, San Francisco, CA.

Psychologists have long recognized the value of research with implications for the human services; however, they have not typically availed themselves of opportunities to conduct applied research in the addictions. The decade of the 1990's presents unparalleled opportunities for psychologists to conduct "treatment research" — evaluating the efficacy of substance abuse treatment approaches. The eruption of cocaine abuse in the 1980's, together with the role of intravenous drug use in the AIDS epidemic, have made drug problems a central public health issue. Financial support for addressing these problems is now available from federal, state and local sources. There is an urgent need for behavioral scientists to be involved. This presentation focuses on two roles for psychologists in the public sector: leading treatment programs and organizing treatment research. The first author leads a substance abuse treatment center