stimuli Naltrexone is a very safe drug since it has virtually no agonist or side-effects Naltrexone generally fails to maintain treatment participation by lower socioeconomic clients but may be used beneficially with paying drug abuse patients such as health care practitioner abusers Its use by psychologists treating opiate abusers in private practice should be promoted

TOBACCO DEPENDENCE BEHAVIORAL PHARMACOLOGICAL BASIS FOR NICOTINE REPLACEMENT Jack Henningfield, Ph D , Chief The Johns Hopkins University School of Medicine, Biology of Dependence and Abuse Potential Assessment, Laboratory, NIDA Addiction Research Center, 4940 Eastern Avenue P O Box 5180, Baltimore, MD 21224

The fundamental premise of replacement therapy is that the physiologically based feelings of discomfort and disruption of functioning which characterize drug withdrawal, can be therapeutically managed by administration of a chemical which produces cross-tolerance and cross-dependence with the one to which the person is already dependent The chemical may be different in structure, or may be identical in structure but administered in another route or vehicle, or it may even be of identical structure and form but is given according to a prearranged therapeutic schedule The putative replacement chemical should substitute for the abused substance on measures relevant to treatment of the drug-seeking behavior The rational basis for the utility of a replacement approach (vs antagonist administration) to treat tobacco dependence is that nicotine administration produces many of the effects of tobacco that are critical in the dependence process These effects of nicotine include, physiologic dependence which results in withdrawal following tobacco abstinence, and also many of the desirable effects of tobacco such as mood regulation, appetite control, and enhancement of concentration and verbal ("cognitive") performance Although no satisfactory nicotine substitutes have yet been developed, nicotine delivered via different routes of administration (e g , inhaled and IV), and with different vehicles (e g , tobacco smoke, snuff and polacrilex) produce similar effects on a variety of behavioral and physiologic measures However, differences related to the vehicle and pharmacokinetics of each preparation confer various advantages and disadvantages on each as a putative therapeutic nicotine replacement form For instance, cross-tolerance and cross-dependence are obtained for both cigarette smoke-delivered nicotine and polacrilex-delivered nicotine, but cigarette smoke better satisfies the desire to smoke than does the polacrilex Therapeutically managed nicotine replacement for tobacco can currently be accomplished by the administration of nicotine polacrilex (gum) Such administration produces dose-related reduction of withdrawal-related performance impairment and of other signs and symptoms of tobacco withdrawal These beneficial effects are dependent on adequate dose levels of nicotine being administered, and achievement of such levels may require dosing regimens to be specified by the clinician Desire to smoke ("craving") is relatively insensitive to nicotine replacement, however, there is evidence that the reinforcing efficacy of cigarettes is nonetheless reduced by administration of the polacrilex It is plausible that other routes of nicotine replacement would better satisfy the tobacco users desire to use his or her preferred form of tobacco Taken together, these findings are consistent with those regarding replacement therapies in general and confirm that nicotine replacement via polacrilex is well-based on scientific principles

ALCOHOL ABUSE BEHAVIORAL FUNCTIONS OF PHARMACOLOGICAL ADJUNCTS George E Bigelow, Ph D The Johns Hopkins University School of Medicine, Behavioral Pharmacology Research Unit, D-5-West, Psychiatry Department, Johns Hopkins/Key Medical Center 4940 Eastern Avenue, Baltimore, MD 21224

It is in the alcoholism field that the most diverse rationales for pharmacological treatment of substance abuse problems have been articulated and acted upon These rationales have ranged from medical safety (prevention of withdrawal seizures), to subjective palliation (reduction of subjective distress during detoxification), to treatment of presumed underlying disorders thought to cause excessive drinking (prescription of antianxiety or antidepressant medications), to direct efforts to alter the effects of alcohol so as to make drinking less reinforcing (treatment with disulfiram) The last of these approaches—treatment with disulfiram—is the only pharmacological approach currently receiving extensive application in treating the behavioral aspects of alcohol dependence This presentation will review the various approaches and rationales for pharmacological treatment of alcohol abuse but will focus primarily upon disulfiram treatment and upon the use of behavioral procedures to enhance the efficacy of this pharmacological modality Disulfiram is a pharmacologically efficacious agent which has had limited clinical efficacy due to widespread behavioral nonadherence to medication use The action of disulfiram is to cause an aversive reaction if alcohol is consumed thus, its behavioral function is that of a punisher, and its limited self-administration by patients is not surprising Data will be presented illustrating the effective use of behavioral procedures to promote disulfiram use and to enhance clinical outcomes In addition, the presentation will discuss the possibility of utilizing the reinforcing effects of other medications to promote retention and participation in nonpharmacologically-based treatments for alcohol abuse Relevance of these approaches to other aspects of drug self-administration and medication compliance will be discussed

SYMPOSIUM

Conditioned Drug Tolerance Empirical and Theoretical Developments

Friday August 28, 1987 • 10 00 a m –11 50 a m
Marriott Marquis Hotel • Julliard/Imperial Room
Chair *Stephen Tiffany,* Purdue University

ENVIRONMENTAL CUES FOR DRUG ADMINISTRATION ROLE IN TOLERANCE AND RELAPSE Riley E Hinson Department of Psychology, University of Western Ontario, London, Canada

It is well established that environmental stimuli affect the display of tolerance and the occurrence of relapse An account of the role of environmental stimuli originally elaborated by Siegel suggests that environmental cues of drug administration elicit conditional responses (CRs) that tend to cancel the drug effect producing tolerance Most of the research on the conditioning model of tolerance has empha-

sized excitatory conditioning This paper will present evidence that inhibitory conditioning also occurs with drugs The "nature" of the inhibitory CR will be discussed Although research has provided evidence of inhibitory-like phenomena, there has to date been no evidence of an inhibitory CR in a placebo test Similarly several studies that have demonstrated environmental-specificity of tolerance have failed to obtain evidence of a CR in a placebo test The difficulty in obtaining placebo CRs will be discussed in relation to inhibitory conditioning The occurrence of inhibitory conditioning will be discussed in the context of alternative accounts of environmental modulation of tolerance (e g , Baker and Tiffany habituation model and Wagner's SOP model of habituation)

MECHANISMS OF CONDITIONED TOLERANCE Christine L Melchior University of Illinois at the Medical Center

Many investigators have shown that tolerance to the hypothermic effect of ethanol can be learned in a classical conditioning paradigm Although substantial efforts have been made to establish that tolerance can follow learning principles, little attention has been paid to determining what is learned Tolerance produced simply by chronic exposure to ethanol is due to functional or dispositional factors In investigating a model of conditioned tolerance in mice we have found that cued changes in the disposition of ethanol occur Notably, the level of ethanol in the brain and blood at various times after administration of ethanol was lower in animals tested in an environment previously associated with ethanol than in animals tested in a novel environment The importance of the central nervous system in modulating the cued alterations in ethanol levels was explored by administering ethanol intracerebroventricularly (ICV) instead of intraperitoneally (IP) during training A conditioned compensatory response was observed in the ethanol associated environment following an ICV injection of CSF and blood ethanol levels after an IP injection of ethanol were lower in the ethanol cued group than in animals tested in a novel environment These findings suggest that exposure of peripheral structures to substantial amounts of ethanol is not critical for the development of cued changes in ethanol levels

STUDIES ON THE ROLE OF LEARNING FACTORS IN HUMAN ALCOHOL TOLERANCE Peter E Nathan Rutgers, The State University

On the basis of animal experiments using both ethanol and morphine, which demonstrated that rats who have developed tolerance will continue to display a high degree of tolerance only if tested under the same environmental conditions previously associated with drug administration Siegel (1978) advanced a classical conditioning model of drug tolerance that accords environmental cues consistently present during prior drug exposure the power to elicit conditioned homeostatic responses that attenuate the systemic effect of the drug Shapiro and Nathan (1986) subsequently tested the generalizability of Siegel's conditioning model to human tolerance to alcohol They found evidence for the influence of conditioning factors for one measure of tolerance to alcohol by humans, coding-vigilance performance, but could not distinguish the role of classical from operant conditioning (drugged practice) in this demonstration Beyond the importance of understanding the basic mechanisms, including learning mechanisms, which may underlie phenomena as central to addiction as tolerance, studies of tolerance are important, as well, because differences in degree and kind of tolerance development in humans may be of etiologic significance for alcoholism (Nathan and Niaura, 1985) In an effort further to explore learning factors involved in tolerance development in humans, Nathan and his colleagues have also reported that factors such as gender (Niaura, Nathan, Frankenstein, Shapiro and Brick, in press), environmental cues (Niaura, Shapiro, Nathan and Brick, in preparation), hormonal factors (Brick, Nathan, Shapiro, Westrick and Frankenstein, in press, Hay, Heermans and Nathan, 1985), drinking history (Niaura and Nathan, 1984), and risk for alcoholism (Guise and Nathan, in preparation) all significantly affect response to alcohol and may influence responses to acute as well as chronic alcohol administration and tolerance in human beings as well The significance of these findings for a comprehensive view of the role of learning factors in human alcohol tolerance will be evaluated and discussed in this symposium presentation

THE RESPONSE COMPETITION MODEL AN ALTERNATIVE ACCOUNT OF DRUG CONDITIONING PHENOMENA David B Newlin Purdue University

Siegel's (1983) classical conditioning model of morphine and alcohol tolerance has spawned a large body of research in which the environmental specificity of tolerance has been found consistently for morphine, alcohol, and other drugs However, although a compensatory hyperthermic response to alcohol cues has been a consistent finding, most authors have failed to replicate Siegel's results showing compensatory hyperalgesic responses to morphine cues The response competition model (Newlin, 1986) is intended to account for these discrepancies The response competition model assumes that there is an inhibitory interaction between concurrent responses due to a limited capacity for response processing Examples of response competition in the visceral domain include *stress response dampening* in which alcohol or nicotine inhibits an autonomic stress response, *UCR diminution* in which the CR inhibits the UCR in eyelid, skin conductance, and heart rate conditioning, *startle modification* in which weak prestimulation inhibits acoustic startle responses, and *drug conditioning* According to the response competition model, drug conditioning represents a special case of response competition because the CR (i e , the response to drug cues) competes with the UCR (i e , the drug effect) for response processing resources Note that the CR may be opposite in direction to drug, in the same direction as drug, or even in an entirely different response system The model challenges Siegel's (1983) assumption that the CR and the UCR combine additively, citing evidence from several different domains in which concurrent responses in the same direction show an inhibitory interaction The response competition model predicts that tolerance will be enhanced by the elicitation of a wide variety of concurrent responses, including CR's to food stimuli, novelty effects, stress responses, and other arbitrary responses Data concerning responses to alcohol in a novel vs a familiar environment in humans are presented that tend to support this prediction