fect from a 10-fold to a 1000-fold increase in sensitivity to naltrexone, thus approaching the sensitivity of chronically dependent animals. The presence of a stimulus to which rate suppression became conditioned was implicated. In short, both tolerance and dependence are multi-faceted processes which can be differentially modified. Experimental measurement of qualitatively different effects with quantitatively different sensitivities confounds interpretation. Until the underlying mechanisms are more clearly elucidated, conclusions regarding the dissociation of tolerance and dependence must be carefully evaluated with regard to the considerations discussed.

INVITED ADDRESS
Chair: *Sharon M. Hall*, Psychiatry Service, Veterans Administration Medical Center, San Francisco, CA.

ISSUES IN THE PREVENTION OF WEIGHT GAIN AFTER SMOKING CESSATION. Kenneth A. Perkins, Western Psychiatric Institute and Clinic, University of Pittsburgh, Pittsburgh, PA.

Weight gain following smoking cessation may inhibit attempts to quit smoking and promote relapse if an attempt is made, especially in women. Most of this weight gain appears to be due to increased eating, particularly between-meal snacking. Because of smokers' concern over this weight gain, combining weight control efforts with smoking cessation has received much attention under the assumption that preventing weight gain will enhance ex-smokers' chances of maintaining abstinence. Despite its widespread acceptance, there is essentially no direct support for this assumption. First, prospective studies have not reported that weight gain after cessation directly predicts relapse. Second, behavioral interventions to prevent this weight gain have proven to be ineffective. Pharmacological interventions, which are effective during brief periods of active use, have not been studied beyond several months' duration of treatment. Third, and most importantly, attempting to prevent weight gain after cessation may not improve long-term abstinence. In fact, results of some recent interventions indicate that adjunct weight control treatment may actually *impede* abstinence. Although contrary to common belief, these findings are very consistent with a large body of basic animal research, as well as some human studies, showing that food or weight restriction increases drug intake. It is not clear whether this effect is specific to weight reduction per se, food deprivation, or possibly reinforcement deprivation. Some evidence suggests the converse may also be true, that weight gain (or increased access to palatable food) decreases the reinforcing value of drugs and thus their intake. Therefore, rather than developing intensive strategies for combating weight gain after cessation, a more prudent and fruitful approach for basic and clinical research may be to reexamine the fundamental relationships among smoking, eating, body weight, and perhaps weight-related attitudes. If subsequent research concludes that cessation-induced weight gain is not positively related to risk of smoking relapse in weight-concerned smokers, it may be necessary to consider developing treatments designed to help these individuals accept, rather than fight, weight gain after cessation. Such a strategy may be especially warranted because of the trivial health effects of the typically modest weight gains observed after cessation.

INVITED ADDRESS
Chair: *Lewis S. Seiden*, University of Chicago, Chicago, IL.

ANTISENSE STRATEGIES FOR MODULATING DOPAMINERGIC BEHAVIOR. Benjamin Weiss, Long-Wu Zhou and Sui-Po Zhang. Medical College of Pennsylvania, Philadelphia, PA.

The behavioral and molecular effects of oligodeoxynucleotides antisense to the mRNAs encoding the various dopamine receptor subtypes were examined *in vivo* in mice. The antisense oligodeoxynucleotides were administered intraventricularly to normal mice and to mice with unilateral 6-hydroxydopamine lesions of the corpus striatum. The mice were then challenged with acute injections of dopamine agonists that cause specific behaviors in these animals. The levels of D_1 and D_2 dopamine receptor mRNA were determined by *in situ* hybridization histochemistry, and the levels of D_1 and D_2 dopamine receptors were determined by receptor autoradiography.

In normal mice administering the D_1 antisense produced a cataleptic effect and inhibited grooming behavior induced by the D_1 dopamine receptor agonist SKF 38393 but failed to block the stereotypic effects induced by the D_2 dopamine agonist quinpirole. In 6-hydroxydopamine-lesioned mice, the D_1 antisense blocked rotational behavior induced by SKF 38393, but had little or no inhibitory effects on rotations induced by quinpirole or by the muscarinic cholinergic agonist oxotremorine. Similarly, intraventricular injections of D_2 antisense blocked quinpirole-induced rotations but failed to inhibit rotations of induced by SKF 38393 or oxotremorine.

Continuous intraventricular infusion of D_1 antisense reduced the levels of D_1 dopamine receptors in corpus striatum and nucleus accumbens. Repeated treatment with D_2 antisense significantly reduced the levels of D_2 dopamine receptors and D_2 dopamine receptor mRNA in the striatum. By contrast, D_2 antisense treatment failed to alter D_1 dopamine receptors or D_1 dopamine receptor mRNA in striatum.

These results, showing that *in vivo* administration of dopamine receptor antisense oligodeoxynucleotides selectively blocks specific dopamine receptor-mediated behavior and specifically reduces the levels of the receptors and transcripts encoding the various dopamine receptor subtypes, suggest that the administration of other antisense oligodeoxynucleotides directed at the different dopamine receptor mRNAs may prove useful for uncovering the function of the other subtypes of dopamine receptors. They suggest further that antisense oligodeoxynucleotides targeted toward the transcripts for receptors and receptor subtypes for other neurotransmitters may aid in uncovering their function as well. (Supported by NIMH grant MH 42148).

INVITED ADDRESS
Chair: *James H. Woods*, University of Michigan, Ann Arbor, MI.

BEHAVIORAL INDICES OF DRUG-RECEPTOR INTERACTIONS. Charles P. France, Louisiana State University Medical Center, New Orleans, LA.

Much of behavioral pharmacology, by virtue of its descriptive approach to drug effects, lacks a strong theoretical frame-

work from which specific hypotheses can be generated regarding the mechanism of drug action. Receptor theory provides one theoretical framework which has proven to be valuable at more molecular levels of drug analysis; however, it is only relatively recently that the principles of receptor theory have been evaluated for their applicability in analyzing and predicting the effects of drugs on behavior. In general, two pharmacological constants describe the effects of drugs that act at receptors: affinity and efficacy. All drugs that interact at receptors have affinity (i.e., the attraction between a drug and a receptor), whereas only agonists have efficacy (i.e., the ability to initiate biological responses by occupation of receptors). Behavioral studies have been used to quantify affinity and efficacy, to estimate fractional occupancy of agonists, to characterize the nature of drug interactions at receptors (e.g., reversible or irreversible), and to ascertain the receptor type(s) through which drugs produce specific behavioral effects. The biochemical and behavioral complexity inherent to drug studies *in vivo* can restrict the conditions under which the assumptions of receptor theory can be satisfied and, therefore, the range of conditions under which this approach can be applied. Nevertheless, it is becoming increasingly clear that the theoretical framework provided by receptor theory can be especially helpful for: interpreting behavioral data; generating specific hypotheses for empirical evaluation of mechanism of action *in vivo;* and directing the development of drugs as well as procedures towards specific pharmacological and behavioral endpoints. This approach to behavioral analyses of drug effects might be particularly useful in the development of pharmacotherapies for drug abuse.

INVITED ADDRESS
Chair: *Jonathan L. Katz*, Addiction Research Center, Baltimore, MD.

BENZODIAZEPINES AND BEYOND: REINFORCEMENT, DISCRIMINATION AND DEPENDENCE. Nancy A. Ator, Johns Hopkins University School of Medicine, Baltimore, MD.

Drugs that enhance the major inhibitory neurotransmitter GABA generally have anxiolytic, anticonvulsant, muscle relaxant, and sedative/hypnotic effects to varying degrees. Initially barbiturates (e.g., Seconal) and then benzodiazepines (e.g., Valium) provided most of the clinically useful drugs of this type. However, chronic barbiturate use rapidly produces physical dependence with a severe and often life-threatening withdrawal syndrome. Furthermore, among those who abuse drugs, a subset have favored barbiturates. Under prolonged dosing conditions, benzodiazepines, too, can produce physical dependence, albeit with a less severe withdrawal syndrome; and they also have been subject to misuse and abuse.

Greater understanding of the structure and functions of the GABA receptor complex has facilitated the development of novel compounds that may show more selective pharmacological profiles (e.g., nonsedating anxiolytics). To the extent that such compounds might have less abuse liability or produce little or no withdrawal syndrome, they could be of great therapeutic advantage.

Laboratory study of abuse liability typically involves study of a drug's ability to serve as a reinforcer under intravenous and oral drug self-administration procedures. Some information on other effects, such as the way a test drug is "classified" under a drug discrimination procedure, also has been interpreted in abuse liability assessment. The extent to which chronic drug administration can produce physical dependence has been assessed separate from reinforcing efficacy. Comparison of barbiturates, benzodiazepine agonists and partial agonists, and of novel nonbenzodiazepine anxiolytics/hypnotics across a range of procedures in the same species is useful not only for assessing abuse liability and dependence potential of novel compounds but also for investigating predictions about variables that contribute to a drug's efficacy as a reinforcer and about the relationship between reinforcing efficacy and dependence. Profiles of recently introduced compounds will be compared with those for established standards from research with nonhuman primates.

INVITED ADDRESS
Chair: *Charles R. Schuster*, Addiction Research Center, Baltimore, MD.

NEW PHARMACOTHERAPIES FOR HEROIN ADDICTION. James H. Woods, University of Michigan, Ann Arbor, MI.

Methadone has been established as a standard of reference for the treatment of heroin addiction since its introduction to medicine in the late 1960s. Naltrexone, a competitive μ receptor antagonist, is also available, but its usefulness appears restricted only to a certain set of addicts. Recently, a long acting μ-agonist, 1-α-acetyl-methadol, was approved for this indication. Buprenorphine, a long-acting, μ-partial agonist, is undergoing extensive trial for treatment of heroin addiction as well. The speaker will describe still another class of compounds, chemically and pharmacologically different in their mechanisms from those above, that may also have potential for the treatment of heroin addiction. These compounds are codeinones that appear to interact irreversibly with the μ receptor; they are converted metabolically to irreversible antagonists. The theory and the behavioral pharmacology of the use of these pharmacotherapies will be discussed.

NEW FELLOWS ADDRESS
Chair: *Warren K. Bickel*, University of Vermont, Burlington, VT.

PRIMING EFFECTS WITH DRUGS AND OTHER REINFORCERS. Harriet de Wit, University of Chicago, Chicago, IL.

Many positive incentive stimuli, including drugs of abuse, produce transient increases in the likelihood or vigor of responding to obtain those stimuli shortly after they are presented. For example, noncontingent presentations of rewarding stimuli such as food, water, rewarding electrical brain stimulation or drugs temporarily increase operant rates of responding to obtain these stimuli. This "priming" effect has been studied in laboratory animals, and, more recently, also in human volunteers. In the context of drug abuse, the priming effect has relevance for our understanding of the determinants of reinitiation and maintenance of drug use, and relapse to drug abuse. Sampling of a small amount of a preferred drug may increase an individual's desire for more of the drug and, relatedly, increase the likelihood that the individual will