the opiates, the tricyclic antidepressants, the neuroleptics, the benzodiazepines, the barbiturates) having been discovered clinically by the 1960's, behavioral pharmacology has acquired particular significance from then onwards because it has produced operational definitions of the actions of these drugs (e.g., tail-flick, reserpine depression, amphetamine-induced stereotypies, conflict, pentylenetetrazol convulsions); it is chiefly these behavioral procedures that have since permitted the industry to improve upon such 'first' molecules as morphine, imipramine, chlorpromazine, chlordiazepoxide and meprobamate. Influences detracting from the behavioral impact on pharmaceutical decision-making have been 1) the fall-out of radioligand binding and the discovery of l-dopa for Parkinson's disease through a biochemical approach, and 2) the abuse of in vivo models of disease and the general slowness of behavioral methods. Among the influences that can enhance the impact of behavioral pharmacology are its coming about as a scientific discipline and the implementation of higher standards, the greater efficiency through data processing technology, the links with other approaches (e.g., through in vivo microdialysis), and, perhaps foremost, the recognition that behavioral pharmacology constitutes a level of analysis of drug action which cannot simply be deduced from or induced into any other level (e.g., biochemical, electrophysiological, endocrinological). But, as the history of the opiates shows, the task of the industrial behavioral pharmacologist remains immensely difficult; unlike other areas and approaches, the behavioral pharmacologist has no apparent access to the dependent variables he proposes to study.

BEHAVIORAL PHARMACOLOGY OF COMPOUNDS THAT ENHANCE MEMORY. Harlon Shannon. Lilly Research Labs, Eli Lilly and Company, Indianapolis, IN.

The continuing increase in the percentage of the population over 65 years old has brought a renewed emphasis on the discovery and development of drugs for the treatment of cognitive deficits which occur in the aged population. The behavioral pharmacology of memory processes has been investigated for more than 25 years, but as yet behavioral pharmacologists have been unable to develop animal models which predict drugs with therapeutic utility. This review will present a brief overview of the history of the behavioral pharmacology of learning and memory and present some thoughts on why the animal models used to date have not been predictive, and what the requirements might be for animal models which might be predictive. The behavioral pharmacology of more recent animal models for learning and memory which appear promising will be briefly reviewed. In addition, data from the author's laboratory will be presented on the behavioral pharmacology of short-term memory in the rat. The effects of selective opioid receptor ligands, cholinergic agonists and antagonists, dopaminergic agonists and antagonists, as well as benzodiazepine agonists and antagonists will be presented. In addition, the effects of lesions of the nucleus basalis and medial septum on short-term memory in the rat will be presented. The results of these studies support a unique role for M_1 muscarinic receptors in short-term memory, although benzodiazepines and kappa opioids also influence short-term memory in the rat.

THE ROLE OF BEHAVIORAL PHARMACOLOGY IN THE DEVELOPMENT OF ANTIANXIETY AGENTS. James L. Howard and Gerald T. Pollard. Burroughs Wellcome Co., Research Triangle Park, NC.

Two decades ago the behavioral pharmacology of antianxiety drugs seemed simple. Anxiety was a unitary concept. Benzodiazepines, propranediol carbamates, and barbiturates were acknowledged to be effective in its treatment, and most other classes were thought to be ineffective. The behavioral pharmacologist had two preclinical tools, the Geller-Seifter conflict test and the Vogel lick suppression test which were sensitive to and selective for antianxiety drugs. Today, the situation is quite different. The nosology of anxiety disorders is complex and changing. Even for the limited category of Generalized Anxiety Disorder (GAD), there are many effective drugs with dissimilar structures and mechanisms of action. Some drugs now recognized as effective in GAD, e.g., buspirone and imipramine, register poorly or not at all in the standard preclinical paradigms. Many new behavioral procedures have been proposed as models of anxiety and preclinical screening methods for antianxiety drugs, but few have been properly validated. The role of the behavioral pharmacologist in the discovery of new antianxiety agents has become more challenging.

BEHAVIORAL COMPARISONS BETWEEN COMPETITIVE AND NONCOMPETITIVE NMDA RECEPTOR ANTAGONISTS IN MICE AND PIGEONS. J. David Leander. Lilly Research Labs, Eli Lilly and Company, Indianapolis, IN.

Competitive (e.g., AP-5 and AP-7) and noncompetitive (phencyclidine-like drugs) antagonists of the NMDA receptor have been compared in a number of animal models: NMDA-induced lethality, maximal-electric shock-induced seizures (MES) and neurological impairment in mice; and catalepsy, reversal of NMDA-induced behavioral suppression and phencyclidine-like drug discrimination in pigeons. The NMDA-induced lethality, catalepsy, and reversal of NMDA-induced behavioral suppression are specific for NMDA antagonists (competitive and noncompetitive). In the phencyclidine-drug discrimination, phencyclidine-like compounds are active over the same dose range that they antagonize NMDA-induced behavioral suppression. In contrast, the competitive antagonists are active, if at all, at only much higher doses than are effective in blocking NMDA-induced behavioral suppression. In terms of protection against NMDA-induced lethality and protection against maximal electric shock-induced seizures, both competitive and noncompetitive antagonists provide protection at doses near those which produce neurological impairment. Thus, in the MES model, neither competitive nor noncompetitive NMDA antagonists have protective indexes (ratio of neurological-impairing dose/protective dose) comparable to prototypical anticonvulsants. One phencyclidine-like, noncompetitive NMDA antagonist, dextromethorphan, appears to have a second mechanism of anticonvulsant action, besides the NMDA antagonist action. This action is not present with other phencyclidine-like drugs. These tests can exhibit both similarities and differences between competitive and noncompetitive NMDA antagonists.

SATURDAY P.M.

INVITED ADDRESS

Chair: *Steven I. Dworkin,* Wake Forest University, Bowman Gray School of Medicine, Winston-Salem, NC

THE NATURE OF THE STRESS RESPONSE. Adrian Dunn. Louisiana State University Medical School, Shreveport, LA.

Selye defined stress as the nonspecific response of an organism

to perturbations of its environment. Current evidence suggests that the release of corticotropin-releasing factor (CRF) within the brain may permit the coordination of a whole body response in stress, thus reinforcing Selye's global stress concept. The evidence supporting such a role for CRF is summarized below. CRF administered intracerebroventricularly (ICV) elicits a number of behavioral, physiological, and neurochemical responses characteristic of stress. Behavioral effects include effects on locomotor activity, increased grooming, decreased feeding and sexual activity, decreased exploratory behavior and social interaction, an increased acoustic startle response and shock-induced fighting, and "anxiogenic" actions in conflict tests, and in the elevated +-maze. ICV CRF activates the sympathetic nervous system and the adrenal medulla, and has several effects on gastrointestinal function. Endocrine factors affected include an increase in ACTH secretion, and decreases in LHRH and growth hormone secretion. There is increased firing of noradrenergic neurons in the locus coeruleus, and increased production of the metabolites of norepinephrine (NE) and dopamine, suggesting increased release of these catecholamines. Where tested, these effects are independent of the pituitary, and hence ACTH or glucocorticoid secretion. Each of these effects could indicate merely that ICV administration of CRF is stressful. However, intracerebral administration of a CRF antagonist, α-helical CRF_{9-41} (ahCRF) has been reported to reverse or attenuate the effects of various stressors on LHRH secretion, plasma NE, feeding, exploratory behavior, and aggression. These observations may provide an explanation for the rather widespread distribution throughout the brain of CRF-like immunoreactivity, bioactivity, and CRF-binding sites. The demonstration that CRF can be released from excised brain regions by stimulation with high K^+ in a Ca^{2+}-dependent manner suggests that CRF may act as a neurotransmitter in the brain. Changes in the cerebral concentration of CRF in various brain regions during stress reinforce this idea. The above discussed results support the hypothesis that release of brain CRF may be both necessary and sufficient to characterize stress.

POSTER SESSION

Biological Bases of Behavior

THE CONTRIBUTION OF SUBJECT EXPECTATION ON ANALGESIC EFFICACY FOR CLINICAL AND EXPERIMENTAL PAIN.

Manon Houle, S. Kogon, P. A. McGrath and G. Moran. University of Western Ontario, London, Canada.

The study aims to quantify the contribution of expectation for pain relief on analgesic effectiveness for both experimental and clinical pain. One hundred patients scheduled for extraction of impacted third molars used visual analogue scales to rate the intensity and the unpleasantness of experimental pain (thermal stimuli 45–51°C) before and after double-blind administration of Tylenol 3 or placebo. Subjects were divided into four groups of a balanced placebo design in which the traditional placebo design—expect analgesic/receive placebo and expect analgesic/receive analgesic is complemented with two groups—expect placebo/receive analgesic and expect placebo/receive placebo. These expectancy manipulations allow for the determination of what portion of the overall experimental pain reduction (both intensity and unpleasantness) is due to the independent effects of the expectation of receiving an analgesic and what portion is due to the pharmacological effect of the analgesic. Subjects also used visual analogue scales to rate the intensity and unpleasantness of postsurgical dental pain both before and after treatment administration. Although all subjects received the analgesic for postsurgical pain, expectancy was manipulated by telling subjects that they received the same drug as they had received during the experimental session. It is expected that subjects' expectancy will be a major determinant of subjects' analgesic responses to placebo and significantly modulate subjects' ratings of the efficacy of the analgesic.

SENSORIMOTOR REPLACEMENT AS A STRATEGY FOR SMOKING CESSATION.

Jed E. Rose, F. Behm, C. Schur, N. Comfort, E. D. Levin and D. P. Tashkin. University of California, Los Angeles, CA.

In a three-week smoking cessation program, we tested an inhaler that delivered an aerosol containing citric acid and smoke flavor. The goal was to simulate the taste and tracheobronchial sensations produced by cigarette smoke. The active inhaler was compared with a placebo inhaler in a randomized double-blind design. Relative to placebo, this treatment significantly reduced smoking and self-reported craving for cigarettes in subjects with baseline CO values higher than the mean. These results suggest that sensorimotor replacement, alone or in combination with nicotine replacement treatments, may be useful as a smoking reduction or cessation aid.

SMOKELESS TOBACCO DEPRIVATION, NICOTINE AND PERFORMANCE.

Dorothy K. Hatsukami, Robert M. Keenan and Deborah J. Anton. University of Minnesota, Minneapolis, MN.

The purposes of this study were to 1) examine the effects of smokeless tobacco deprivation on performance, and 2) determine the effects of nicotine gum dose on performance during deprivation. Male Copenhagen smokeless tobacco users underwent 3 days of baseline measurement while continuing to use smokeless tobacco ad lib. They were then randomly assigned to one of five groups for the next five days: 1) continuous smokeless tobacco users; 2) discontinuous users; 3) 0 mg nicotine gum; 4) 2 mg nicotine gum; or 5) 4 mg nicotine gum. All groups except the continuous smokeless tobacco users were asked to quit using smokeless tobacco during this experimental period. The results were as follows: 1) There were significant increases in reaction time and variability of reaction time (S.D.) during the experimental period among the discontinuous users when compared to the continuous users group. 2) There were no nicotine gum dose-related effects on reaction time performance after smokeless tobacco deprivation. 3) There were significant increases in reaction time and variability of reaction time (S.D.) among the discontinuous users when compared to the placebo group. Those findings replicate previously published results regarding the effects of smokeless tobacco deprivation on performance. They also indicate that among smokeless tobacco users, there is a significant placebo effect which masks the effects of nicotine gum.

EFFECTS OF SMOKING AND SMOKING ABSTINENCE ON FINE MOTOR PERFORMANCE.

Michael J. Klitzke, Thomas W. Lombardo and Stephen C. Fowler. University of Mississippi, University, MS.

Data regarding the effect of smoking and abstinence from smoking on fine-motor task performance are rarely encountered in the literature. However, precise spatio-temporal force regulation is important for professionals such as pilots and surgeons. In a laboratory setting, the performance of nonsmokers, abstinent