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