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From the Discussion to the First Symposium:

THE PROBLEM OF ANTAGONISTS TO PSYCHOTROPIC DRUGS

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It has been a privilege and a pleasure to read and to listen to the reports by Drs. GADDUM and DENBER. These authors have approached the problem of antagonists to psychotropic drugs from different vantage points: Dr. GADDUM that of the pharmacologist – theoretician, assessing general issues; and Dr. DENBER, the experimental clinician with a specific problem exemplifying a theoretic principle.

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knowledge of drug action, there was little that could be specified at present. This view, founded on extensive experience, suggests that a critical appraisal is necessary of the many recent fanciful theories on the relation of serotonin, 5-hydroxytryptophan and amine oxidases, amongst others, to human psychoses. If I interpret Dr. GADDUM's review correctly, he is describing basic postulates which must be satisfied before drug antagonisms are established, and such establishment is requisite to the determination of the site of action of such interactions. Dr. GADDUM notes, that for the determination of competitive inhibition, four considerations must be fulfilled, *i.e.*:

1. control drugs are not inhibited;
2. antagonistic actions are demonstrable at several sites or systems;
3. dose relationships are systematic; and
4. agents have a common chemical grouping.

To these I would also add, that for such determinations of competitive inhibition to have significance for human psycho-pharmacology, the antagonisms should not be based on work limited to a single animal species, but should be demonstrated in man.

Dr. DENBER has approached the problem from a specific experiment – the measurement of changes in various blood chemical elements and gross clinical behavior in chronic relapsing psychotic subjects. These patients were studied before and after intravenous mescaline followed by a variety of phenothiazine agents administered as "antagonists". Dr. DENBER confirmed his earlier studies that various phenothiazine derivatives, excepting diethazine, are effective in modifying mescaline clinical affects; and that such effects are related to the halogenation of the chemical ring structure. Parenthetically, we can confirm the observation that diethazine is not an antagonist for hallucinogens, for in our studies diethazine induced illusory states and EEG desynchronization in psychiatric patients, similar to mescaline[1].

The biochemical data indicates the wide range of behaviors altered by these broad acting agents. Like his earlier studies on the changes in the EEG, and the observations from others of the blocking of induced psychotomimetic effects as measured in language, mood, perception, *etc.*, this data must be analyzed from a theoretic framework of the relevance, or imputed causal relations, of such observations to clinical behavior. No such framework is given and the assumed connection between these blood changes and clinical behavior is obscure. Indeed, Dr. DENBER concludes that:

"In all probability, the reactions observed represent part of a total body response to a stress-..."

Assuming this conclusion is a reasonable working hypothesis, we are taxed by the problem of critical experiments to elucidate the body response to psychotomimetic and psychotropic agents. In this task we are faced by a number of monumental problems, and it is here that Dr. GADDUM's principles and Dr. DENBER's experiments approach a common base, albeit tenuous. For what Dr. GADDUM fails to indicate in his principles are the significant behaviors to be studied; while Dr. DENBER selects two aspects of behavior — that of blood chemistry and global clinical interactive behavior — as dependent variables.

It is the selection of significant experimental variables and their quantification that represents a central problem of human psychopharmacologic research today. Assuming that the laws of human interpersonal behavior are the goals of our studies, and that psychopharmacology represents one aspect of the modification of human

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interpersonal behavior, what evidence is there that any single aspect of task behavior is correlated with changes in interpersonal behavior induced by drugs?

I am troubled by the fact that innumerable investigations have selected a single or few variables on the biochemical level and correlated these with a single or few variables on the behavioral level, the selection of which is not designed to elucidate a theoretic framework but rather based on a vague personal notion. Thus, investigator after investigator selects pole climbing, bar pressing, conditioned avoidance, jiggle cage movement, *etc.* as single variables in a wide range of animal studies; and rating scales, self-ratings, psychomotor tasks, EEG, blood pressure, and many others in human studies as single significant variables. Few studies assess the relevance of these tasks for the prediction of the direction or efficacy of drug effects on interpersonal behavior.

Other significant problems include that of generalizing from non-psychopathic populations to our understanding of disordered human behavior. A sub-aspect of this problem is the generalization from one psychopathic population to another without fully taking into account such population factors as genetic predisposition, early organic traumata, varying acculturation processess and sociologic status upon population characteristics. These aspects may so alter the observations obtained with a specific pharmacologic agent as to give varying, and occasionally opposite results when similar studies are done in different settings.

Some years ago, Dr. ABRAHAM WIKLER outlined the problem facing experimental psychopharmacologists[2]. In assessing the relation of psychopharmacology to experimental psychiatry, he recommended:

"In psychiatry we need more properly controlled studies on the comparative effects of a variety of drugs, on the behavior of varied, but selected, homogeneous groups of subjects, under varied but standardized experimental conditions, and with varied but specified activities of the observer."

In this I concur and commend it to the Collegium as the most logical beginning to the resolution of the problems of antagonists to psychotropic agents.

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D I S C U S S I O N

First Symposium - C.I.N.P.

THE PROBLEM OF ANTAGONISTS TO PSYCHOTROPIC DRUGS

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July 4th, 1960, Basle, Switzerland

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