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Dear Murray:

Your questions are the most significant ones in the field of EEG and pharmacology, and I would be delighted if I could answer them in a fashion which would have scientific significance.

With the demurrer that the following answers are a distillate of my experience, and the knowledge that we are actively working on these problems, the following are the answers as best I can give them:

1. Psychotropic drugs such as imipramine, chlorpromazine, or meprobamate induce changes in the scalp recorded EEG which are characteristic for the compound. The patterns are significantly different on visual analysis and with frequency analysis equipment. (Ref. 1,2). For group data, then, each psychotropic compound seems to have a characteristic spectrum of response.

The responses, however, do depend on the rate and route of administration, and also on the pre-treatment record pattern. We are now working on the problem of whether in an individual case, the drug response can be identified with certainty.

My associate, Dr. Itil, and I believe that with our present quantification method, we can distinguish in an individual subject each psychotropic agent and also separate differences based on rate and dosage. The latter is now under study with pentothal, chlorpromazine, and ditran. We have selected these agents because they represent different classes of drugs.

"Can a blind identification be made?" ... today, with difficulty ... tomorrow, yes, with ease.

(Parenthetically, it has been my conviction that psychotropic drugs may be identified not only for their class of activity, but for their relative potency by acute EEG studies, and I am now in the second year of such a study. [Ref. 3]).

2. It is clear that the EEG response to a drug is dependent on many factors, chief of which are: drug, dose, rate, route, and pre-treatment record. There are some subjects where the psychological state of the individual may also contribute to individual difference, so that responsivity to a drug may be different in schizophrenic, depressive, neurotic, and psychopathic subject.

The work of Shagass, Goldman, Itil and others indicates that the EEG response to a drug may have a classificatory value. Thus, individual differences may be both a limitation, if one is interested in studying the effect of the drug, or an advantage if one tries to classify subject.

The question as to whether alpha rhythm being present or absent being a factor in drug response is not conclusive, since we have learned to describe a drug pattern in 'low alpha records', 'high alpha records', or 'slow wave records', with relative ease.

3. In my studies of convulsive therapy, I have come to the conclusion that induced convulsions are a device to change the cholinergic-anticholinergic-chemical patterns of the brain. I have no respect for the pure psychological explanation of ECT action, nor do I believe that the pure electrophysiological models have any merit. ECT produces systematic, definitive chemical changes in the central nervous system, and it is in response to these biochemical changes that the subject's behavior is altered.

Therefore, drugs which seem to operate by altering the biochemical substrait of the brain and ECT are basically the same mechanism. It is highly probable that a drug or combination of drugs will be found that have the same biochemical patterns as ECT. Indeed, a combination like ditran and chlorpromazine produce EEG changes similar to ECT and as you know, both drugs seem to have an effect in depressive syndromes.

Therapeutic efficacy is directly related to the degree and type of biochemical change of the brain, and to that extent ECT and drug therapy are very similar.

4. "Can we predict the effects of a drug in advance?" ... if we could, we would ... since we can't, we don't.

However, we are working on this problem, and I think the following statements are true: given an individual patient in the EEG laboratory in whom we are able to administer seriatim 2 or 3 compounds intravenously to observe the EEG pattern change, we can say the following:

If the EEG shows a change on acute administration, it will show a similar change on chronic administration. Depending on the type of EEG change, there are certain general predictions which can be made for behavior.

If the EEG shows an increase in synchronization, a shift of frequencies to a slower range and some burst activity, it is likely that the subject will demonstrate behavioral changes of increased sedation, tranquillization, ward participation, and some decrease in the expression of anxiety, hostility, rage and irritability.

If the EEG shows increased synchronization and increased amounts of fast activity, it is likely that socialization, group participation, and general activity level will increase, and anxiety, irritability will decrease.

If the record shows a decrease in synchronization, it is probable that irritability, illusory sensations, hallucinations, thought disorder and anxiety will increase and withdrawal will become prominent.

To the extent that these behavioral changes are maintained by environmental factor, observers will believe that the subject's disease has been altered.

It has been a pleasure to answer your questions, and I am enclosing a few references which may reflect my own views in this area. I am pleased that you are interested.

My associate, Dr. Itil, and I have joined together because we have felt that the role of EEG in psychiatry and clinical pharmacology has been grossly underestimated and largely unexplored - I say this because I have on my desk the galley proof of a bibliography entitled "EEG and Human Pharmacology", consisting as it does of 580 references for the period 1951-62.

Despite this large number of studies, there are only a few that have paid attention to the problems of individual differences in subjects, rate and route and dosage of drug, and the fine points of EEG analysis. It is tragic that most of the articles deal with such simple concepts as "normal - abnormal", and deny the fact that there may be differences in the pre-treatment record which affect the drug response.

Lest you feel that the animal pharmacologists and neurophysiologists have done better, let me remind you that despite such techniques as depth recording, evoked potentials, and implanted electrodes, simple dose response curves, species differences, and individual variability in animals have been largely disregarded.

It has been a pleasure to chat with you in this way, and I would look forward to meeting you and discussing this in person, either here or in New York.

Best personal regards,

Max Fink, M.D.
Director

MF/jb

Enc.