August 26, 1969

Mr. Herman Weisman
Hoffman La Roche, Inc.
Nutley, New Jersey

Dear Mr. Weisman:

It was a pleasure to have you and Mr. Billig visit my laboratory last week. The questions you raised, whether objective drug specific patterns can be defined for Librium is challenging. Specifically, you asked whether neurophysiologic indices could distinguish Librium (in therapeutic dosages) from barbiturates (e.g., phenobarbital)? Your reference to failures to define such patterns in prior animal studies suggests the difficulty of the problem.

There is some evidence that such a discrimination may be feasible through quantitative EEG measures.

1. In quantitative EEG studies of anesthetics, Belleville in 1956 showed frequency specific responses for different anesthetic agents, including the barbiturates Studies of amobarbital by Shagass and of pentothal by Goldman and Itil showed frequency specific curves for these compounds in mentally ill subjects.

2. Recent quantitative studies of pentothal developed a mathematical expression for the EEG response (see enclosed). This curve differed in patients receiving a phenothiazine from those receiving placebo, suggesting that drug interaction in the CNS may have altered the parameters of the expression.

3. The EEG profiles of Librium and Valium are similar to barbiturates. In our study of diazepam, imipramine and placebo, our techniques classified diazepam, and this pattern differed from imipramine.

The EEG techniques used in these studies represent the best available today. In addition, instead of using a period analysis data reduction model, the more refined power spectrum could be applied for greater resolution. Using power spectrum as a back-up, I believe it should be possible to define EEG profiles in volunteers. This could be attempted with either oral or intravenous preparations. Two courses are suggested.

1. Oral study.

In an oral study, the changes in EEG may be defined during 1-3 hours post-drug using a period-analysis model.- The first step would be a definition of "equivalent" oral dosages of chlordiazepoxide and a barbiturate. The equivalence may be defined by behavioral criteria, either from the literature or in a pilot study.

In a definitive study, volunteers would return for 3-4 sessions, to receive in random sequence chlordiazepoxide - placebo - barbiturate; and a second dose of chlordiazepoxide or barbiturate. Data analysis would follow established univariate (t-tests) for each variable at different times; or, a discriminant function approach for split samples - using 1/2 the sample to define the beta-weights and verification in the second half of the sample.

2. Intravenous study.

These techniques are more adequately tested. The mathematical expression for pentothal has already been defined. A study of the EEG changes in volunteers receiving intravenous pentothal, chlordiazepoxide or saline would allow verification of the pentothal curve, and a statement of the parameters of the chlordiazepoxide effect.

Either study could be undertaken in these laboratories later this fall. The questions you raise are of theoretic as well as practical significance. To my knowledge, no such studies have been undertaken. In part, because EEG quantitative techniques before 1963 were too inexact and unstable to be useful for the fine discriminations required by your question.

Thank you for the opportunity to review this question.

Sincerely yours,

Max Fink, M.D.
Professor of Psychiatry

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