F. Letters

August 11, 1978

Prof. J.W. Thompson
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Dear Prof. Thompson,

Having returned from meetings and recovered from the time warp, I have reviewed your questions. I shall try to answer them as best I can. You must realize that the answers are not readily available, nor can I document some of the hunches which I will describe. That is what has sustained our interest in the problems of EEG and drugs since 1958. The meetings in Basle were the most recent of a long series, and you should become acquainted with the citations, as well as the latest publication which Mr. Matejcek will issue at the end of the year.

1. It is clear that there is no reliable relationship between any EEG variable and clinical diagnosis. That is categorical for all psychiatric states described as 'functional'. The only associations are those that are well known-- seizure disorders, post-traumatic states, mass lesions of the brain, post-infectious states, toxic states. For these, there are intimate associations between EEG measures and clinical state. In the toxic states, for example, the association is very high and some authors have used the EEG measures as an index of decompensation, as in hepatic and uremic dysfunctions.

The difficulty with EEG and depression is based on many problems. First, the EEG is a measure of the integrity of the CNS at one moment in time. The diagnosis of depression is a generalization based on historical, experiential, symptomatic factors as well as the training and sensitivity of the psychiatrist. It is the most unreliable of diagnoses with consensual validation less than 50% across cases or studies.It is no wonder that the sensitive EEG measures with careful quantification bear no relation to the presnt diagnostid myths.

2. The question of stability of the EEG reflects some problems with the meaning of EEG measures. The brain is in constant biochemical flux, changing its state for every cell and for the whole brain in patterns that are related to time of day, waking and sleeping, feeding, exteroceptive signals, internal changes (anoxia, for example), etc. It is clear and well demonstrated, that under laboratory conditions, when samples are taken at the same time of day, with adequate attention to food and sleep,

EEG records are highly stable. It is possible to identify the individual patient's or subject's record when we have a few samples as a base. These data are derived from the many placebo controlled drug studies.

With volunteers, the date are excellent. With patients, however, since 1958, there has been a dearth of adequate studies in which placebo controlled EEG records have been taken. We carried out one such study, 1959-1962, in which patients received on a random basis, either imipramine, chlorpromazine or placebo therapy for five weeks. The placebo controlled patient records were remarkably stable, and the data was found to be reliable. However, at the time, our principal interest was in the difference bertwenn the EEG effects of the two active compounds and the pacebo and so did not assess the pàacebo trials independently.

From my experience, I would have to assume that the EEG for a depressed patient will remain stable, from day to day, so long as the behavior, the state of the depression, the feeding and sleep behavior, remain stable. Instability in any of these factors should elicit a variability in the EEG. The issue can be turned about. When EEG records are repeated, and attention paid to time of day and feeding, then any changes in the records are likely due to the changes in mood of the patient.

3. We have not attempted to answer the question about diagnosis, primarily because I have found diagnostic rubrics to be unstable in time and location, highly subjective, wnd of little scientific value. Our emphasis has been on the use of different methods of EEG analysis to measure drug effects, and here the issue is clear. Any quantitative method, carefully applied, is capable of reflecting EEG changes induced by psychoactive drugs. Some methods are more sensitive than others. Thus, the least sensitive measure is that proposed by Goldstein, that of mean integrated amplitude. It is an easy measure, widely applied, with some success in gross studies. The next two methods, period analysis and power spectral density analysis are almost equivalent in sensitivity, although period analysis reflects faster (hmgher) frequencies better than PWRS, and PWRS is a more accurate reflection of the slower frequencies. I tend to teach that period analysis is like the low power of my microscope, and PWRS like the high power. Both are useful and reliable, for different problems.

4. As to the PWRS, we have used principally the classic methods of Tukey using Hanning filter weights.

5. At the present time, it is clear that PWRS examination of the alert EEG in volunteer subjects is the most sensitive measure of drug effects in man. Other methods, like sleep EEG, averaged evoked potential, contingent negative variation, are all less sensitive, less reliable, and less carefully worked out.

For clinical diagnosis, I do not believe any are satisfactory. But others claim that the averaged evoked potential (sensory), the CNV, and

even the sleep EEG are reliable diagnostic tools. I have read much of this literature and find it unimpressive.

6. The evidence from Shagass, Itil, Saletu and others on the merits of AEP for drug assessment indicates that the AEP is an insensitive measure, unreliable and not easily quantified. For clinical diagnosis, the issue is far from clear, but as I said above, I am singularly unimpressed. (In 1964-66, Itil and I worked together on the problem of AEP and drug effects. I found the methods unsatisfactory, and did not proceed further. He went on with a student, Saletu to study the problem up to 1973. I suggest you write to him; from the written evidence, he is unimpressed also.)

7. The only recent report concerning slow potentials that I heard was that of Tecce of Boston, published in the 1978 review of Psychopharmacology (Raven Press). I was chairman of that session and heard Dr. Tecce's report-- it is unimpressive. I have heard that Dongier has found some diagnostic merit in CNV, but I have not seen the published reports.

For the past few years, Fleur-Henry has been publishing reports that depressive and schizophrenic patients differ in the power of the EEG of the two hemispheres. His data is poorm but a number of observers have recently confirmed his observations, making it more important to chack his findings. The issue of diagnosis and its unreliability still remains, but the asymmetry of the brain and its functional significance will be the subject of a symposium in Barcelona at the end of August.

There are also the papers from your laboratory, asserting that the CNV is a realistic and adequate measure of the CNS effects of compounds. I have read the reports of Dr. Ashton and am impressed with the careful attention to detail reflected in them. The measure seems to have the same two-dimensionality of the amplitude integration measure of Goldstein. I was surprised that you Ashton was willing to take on the important issue of EEG dissociation and behavior in a report with five subjects and in which other methods of measurement of brain function were not assessed. After all, the principal argument among pharmacologists regarding brain function measures has been that of 'association' or 'dissociation'. That Dr. Ashton is willing to come out on the side of the issue with such incomplete and imprecise data is disappointing.

Your record is good and I do hope that you will tackle one of the important questions raised by your letter. Good luck !

Sincerely yours,

Max Fink, M.D.
Professor of Psychiatry

June 29, 1978

Prof. J. W. Thompson
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Dear Prof. Thompson,

Thank you for your letter and the reprints, which arrived safely. I have been very busy trying to complete a manuscript before the summer hiatus and so have not spent enough time to answer your questions directly. I will do so within the next two weeks.

The reason for writing today, however, is to suggest that you may be interested in sessions to be held at Basle on the subject of quantitative EEG, from July 17 to 20. The various students of the effects of drugs on brain function in man have met on a number of occasions during the past decade and are constituted in an informal "Pharmaco-EEG Study Group". There are no officers or dues. At the present time, Mr. M. Matejcek (Pharmaceutical Division, Sandoz Ltd., CH-4002, Basle) is the acting executive secretary and has organized a meeting which will be held at the Hotel International. The sessions are dedicated to methodology and technical issues, the effects of drugs, classification, etc. and should interest you.

If you can attend, I think you may find it most useful. I suggest to call or write Mr. Matejcek for further details.

I am glad that you survived our hotels. I trust the accommodation and food is better in Europe -- at least I hope to find out again.

My regards.

Sincerely yours,

Max Fink, M.D.