May 30, 1974

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Dear Henk:

First, let me apologize for not having reported earlier; but, after visiting Joyce two weeks ago, I was concerned that my impressions may have been in error, and knowing that she would be at the ECDEU meetings, I waited to confirm my observations with her. Following are some notes concerning our projects.

1. Joyce Small. I visited Indianapolis on May 7. Joyce showed me through the laboratories and we were accompanied by Victor Milstein who is directly involved with these studies. Their optimism in studies of OI-63 was in marked contrast to their pessimism with GB-94.

a. GB-94: They have completed nine subjects in the series, and in no instance have they been able to avoid ECT. While none of the patients exhibited a clinical worsening, none improved sufficiently to provide any feeling of optimism. When I enquired about side effects, she called her nurse-monitor who seemed comfortable with the drug and unable to identify symptoms that were problems to the patients. There were no "anticholinergic" symptoms. But Joyce's questions were sharp and her statements stronger than the data seemed to warrant. I became concerned that we may be seeing the development of a halo effect, i.e., the failure of the first few patients to improve markedly has set the stage for a negative evaluation. She asked me whether she could discontinue the study after ten subjects without 'breaking her work' to you. (In discussing this in Florida, she was more negative than the data warranted, considering the very severe test to which the drug was put).

I suggested she complete ten subjects, summarize her observations, send the reports to you (me), and not induct any new patients into this study until these data have been digested.

b. OI-63: This study is progressing well. Enclosed is a data sheet summarizing her observations in nine subjects to the end of April. She finds OI-63 to have little effect in the immediate post-seizure recall period, but may improve recall at twenty-four hours. She is anxious to go to the next group of subjects, in the same design, but at the higher dosage of 30 mg. I found this suggestion reasonable, and encouraged her to proceed.

She and Dr. Milstein indicated that they were also re-assessing the memory tests and they seemed pleased that some of the methods they have developed had shown differences in OI-63 effects. Some additional tasks are being tested at the same time as these studies are in progress.

Both she and Dr. Milstein were somewhat depressed, however, about their local funding and space problems, reporting that some of their grantgs had not been approved, and that she was anxious to obtain additional industry support for studies.

Joyce has collected tapes of EEG data with OI-63 and GB-94. Her tape recorder is a unique 8-channel, 1/4 inch, General Precision instrument which is no longer made. Failing to find one in New York, I decided to send a member of my staff (Peter Irwin) with one of my 4-channel recorders to Indianapolis to transcribe the data from her tapes to mine; and we will then analyse the data here (unless you prefer to use these tapes to test your system in Oss?). I have set a date for June 13-14 for the transcription.

(Joyce gave me a little visitor's packet of her programs; I have had these copied and send them to you for your information.)

2. ECDEU: The meeting was well attended, and the presentation "Effects of ACTH Peptides on Memory and Brain Function" was well received. A copy of the report is enclosed. (Please edit it and I would be grateful for any corrections of fact or nuance that you may suggest.) The discussion was started by Joyce, who reported that she completed nine subjects in the ECT paradigm; that there was improved recall of learned material twenty-four hours

after the seizure; and that the effects were not evident in the immediate post-seizure recall. She was encouraged by the findings, and said she was extending the sample at a higher dose of 30 mg. Others enquired about the similarity of OI-63 to UCB (pyracetam) and to Unger's compound (scotophobin), and to the availability of the materials.

The presentation was timely because the next afternoon was devoted to reports of TRF (TRH) in depression and schizophrenia. The data was sparse, with the usual N of four to ten in each study. Hoechst was well represented (six visitors) and Dr. Alan Gordon summarized the findings of European studies as equivocal or negative in depression. He reported sleep EEG studies which failed to show an effect of TRF. Drs. Prange, Lipton, Hollister and Huey individually reported small studies without consistent findings in depressed and schizophrenic patients. Yet, each reporter apologized for the paucity of the results; described some anecdotal, single cases that were remarkable; and suggested that some findings were there, although they did not know how to extract them. Itil presented EEG and the clinical data from Turkey, and his report was optimistic and constructive. He reported well defined EEG changes, similar to dextroamphetamine, with clinical effects in depressed patients of short duration, with self reports more positive than observer ratings. There was some criticism of his report, notably the question by Gordon that since he could not find EEG effects of TRF in the sleep record, how did Itil explain his findings in the alert subject. This gave Itil an opportunity to describe the differences in methodology, the problems with sleep assays, and the necessity for quantitative methods.

I was left with the impression, both by the interest of the reporters and the audience, that the peptides were now among us, and that much study will have to be done in the next few years defining their activity and developing new methods of analysis. A few investigators (N. Kline, D.F. Klein, J. Simeon, L. Hollister, R. Shader) asked about the report and OI-63, and I will send copies of the report to them, hoping that their interest has been aroused.

I am sending a copy of the report to the editor of Psychopharmacology Bulletin for her consideration for inclusion in a forthcoming issue.

3. FDA Report and Dr. Kastin: I have decided to send the FDA the report I have given to the ECDEU, as well as a covering letter describing the data of the Miller and the Fink studies. I will omit reference to the recent Kastin and Sandman reports. Abba sent me the latest report with a covering letter that seemed unnecessarily harsh. However, I am willing to serve in the relationship with him being acutely aware of his idiosyncratic and irritating behavior, but accepting these as necessary accompaniments of the program.

In reading Kastin's letter to you of April 29, I found references to a study of ? OI-63 in schizophrenic patients. I have not heard from Kastin regarding this study. Should he wish to file an amendment again, and to avoid the criticism that we are holding him up, I am writing to him directly (enclosed).

4. Essman: I read the Essman letter and the two scales. Because I found these confusing, I called him, and he explained that the tasks were derived from some studies by Squire. He asserted that the tests have had some reliability testing (two forms) and at least two applications. It should be interesting to read these reports and if they are sensitive to memory loss (recent and remote), then the application of the tests may be useful.

5. Klein, D. F.: We met in Florida (although we live in the same community, I tend to see him in far-away places) and began a discussion of OI-63. He wished to read the reports which were the basis of my peptide summary, and I gave him a duplicate set that I had with me. I shall send him a copy of the ECDEU report and try to meet with him in Great Neck in the next two weeks.

I have received a letter from Jack regarding the visit to the U.S. for a review of the data analyses of GB-94, and I have made arrangements for Drs. Bonato and Guy of the Biometric Laboratory in Washington to assist us.

I have become even more interested in the peptides since writing the summary, and I look forward to listening at Utrecht in July.

My best regards.

Sincerely yours,

Max Fink, M. D.
Professor of Psychiatry

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Enclosures