

13 February 1974

M E M O R A N D U M

To: Stanley F. Yolles, M.D., for Walton W. Shreeve, M.D.,
Ph.D., Acting Associate Chief of Staff for Research,
VAH-Northport

From: Max Fink, M.D., Professor of Psychiatry

Subject: Proposed Studies of Alcohol Dependence at VAH-Northport

Last summer we were urged to develop studies in alcoholism at VAH-Northport to supplement the ongoing research efforts in the treatment of opiate dependence. In September, we proposed a series of studies to answer three questions:

Does tolerance develop to long-acting benzodiazepines?

Does tolerance to a benzodiazepine provide "blockade" to alcohol (by cross-tolerance)?

If such blockade occurs, can it be put to clinical use in the maintenance of chronic alcohol-dependent subjects by high doses of a long-acting benzodiazepine?

In this project, we proposed to use a new benzodiazepine, ORF-8063. This compound is particularly promising because we have observed a duration of action that is considerably longer than other known benzodiazepines, measured by clinical observations, EEG examinations, and blood level studies. I have extensive experience with this compound, both in the United States and Turkey, where I have found it to be safe to use and clinically active.

Since submitting this proposal, we have been asked many questions by the Research Committee. Most questions are focussed on the legality of our use of ORF-8063, and only occasionally have questions been asked regarding the design or safety of the experiment. I believe we have answered the design and safety questions satisfactorily.

In December the Committee requested that we give them an IND number; I indicated that this would be a study under the IND of the Ortho Research Foundation. When they insisted on written evidence, I requested a copy of the IND letter, and the monitor sent us a letter they had on file. The letter, dated April 8, 1971, referred to studies then approved and indicated single doses were then under study.

Since that time, the Ortho Research Foundation has submitted protocols to the FDA for repeated administration of the drug in man. These studies have not only been undertaken but have been published, and include two reports submitted to the Committee:

"On the Antianxiety Properties of a New Benzodiazepine, ORF-8063." Curr. Ther. Res., 15: 268 (1973). In this study, Sakalis and his co-workers have given ORF-8063 for 21 days from 30-150 mg a day.

"ORF-8063, an Early Evaluation of a New Anti-anxiety Agent." Curr. Ther. Res., 14:664 (1972). In this study, Gallant and his co-workers reported the treatment of 8 chronic alcoholic inpatients for an average of 25 days, from 10 mg to 160 mg daily.

In addition to these two published studies, I have submitted copies of reports of my own work; and indicated that I am personally aware of 20 additional neurotic patients treated for 6 weeks in doses up to 90 mg per day, in a study which I am monitoring in Istanbul. I also attended a conference (June, 1973) at which 7 investigators (including Sakalis and Gallant) presented data on varying dosage schedules in man for extended periods.

The Committee, in requiring a letter from the FDA justifying this study, is asking for a procedure which the FDA does not ordinarily follow. In this request, I believe the Committee is exceeding its charge. Should the Committee persist in this demand--that we obtain prior approval for a study from the FDA--the members would abrogate their responsibility to decide whether a study should or should not be done at the VAH-Northport on the data presented. Continued insistence on IND approval as a prerequisite for studies will not facilitate research at VAH-Northport and will not establish that hospital as a center for human studies.

Yolles/Shreeve

-2-

13 February 1974

I believe that the Committee acted unwisely in its original request for IND data; and that I acted unwisely in attempting to meet their demand. I believe we have submitted sufficient information to warrant the judgment that the study should be approved, and ask your advice as to the next step for us.

MF/cis