October 7, 1970

Dr. Dorothy Dobbs
Food and Drug Administration
18733 Walker's Choice Rd.
Gaithersburg, Maryland 20760

Dear Dr. Dobbs:

I am writing to ask your advice as to the steps necessary to undertake human assays of a new narcotic antagonist, M 5050 - diprenorphine.

Since 1965, we have been interested in treating opiate dependence with narcotic antagonists. This therapy is based on a theoretic model, developed by Wikler and Martin at Lexington, which views opiate dependence as a psychological and physiological conditioning, requiring an active extinction of conditioned responses for successful. therapy. Following their lead, we have assayed cyclazocine and naloxone as therapeutic agents.

A short duration of action of both drugs has led us to seek ways of extending their action, including the development of silastic implants, in which duration is related to the rate of leaching into the tissues and the amount of drug in the implant. Since amount of drug and size of implant are directly related, we are seeking as potent an antagonist as we can find for this purpose.

On June 4 we convened a conference to review the available clinical and pharmacological data, and were heartened by the clinical reports and by the variety of suggestions for developing a long acting formulation.

One discussant led us to M-5050, a narcotic compound produced by Reckitt and Colman of Hull, England. In animal assays, it is a potent antagonist without agonistic properties. Villareal has reported it to be 16-20 times as potent as naloxone. Reckitt and Colman are preparing to market this compound in a package with M-99 - a very potent narcotic - to control large animals in veterinary medicine.

They have no human data, nor are they now interested in developing the compound for human use. They are willing, however, to make supplies available for our assay, both in animal pharmacology and clinical.

Our research program is supported by contracts from the New York State Narcotic Addiction Control Commission, and we believe they will support this project.

I am writing to ask your advice and assistance in formulating the animal toxicology data prerequisite to our proposed clinical assays. We would first determine if M 5050 is an antagonist to heroin, at what dose, and for what duration after a single dose. If antagonism is demonstrated, we would then define the oral or parenteral dose necessary to produce continuous antagonism to heroin. (In this study we would parallel the assays we have made of cyclazocine and naloxone.)

Enclosed are copies of all the data on M 5050 available to us. We also have an initial 10 gramssupply for study.

What additional data are necessary for us to file for single dose assays in man? What toxicology data are needed? What procedures should we follow?

In addition to the M 5050 data, I am enclosing a summary of the June 4 meeting as published in Science; and reprints of our studies of cyclazocine, naloxone and heroin, that will provide the background for our interest in this program.

If useful, I would be pleased to visit your offices to discuss this request with you and your associates.

Many thanks for your help.

Sincerely yours,

Max Fink, M.D.
Professor of Psychiatry

MF:kt

cc: A. M. Freedman, M.D.
H. Meiseles, NACC
M. Luger, NACC