

F. Letters  
1972

March 10, 1972

Dr. Daniel X. Freedman  
Professor and Chairman  
The University of Chicago  
Department of Psychiatry  
950 East 59th Street  
Chicago, Illinois 60637

Dear Dan:

It was a pleasure to discuss the opiate antagonists as a model for the treatment and prevention of opiate abuse, and it may be useful to outline some issues of interest.

Neither cyclazocine nor naloxone, as now formulated, are practical in the clinical treatment of opiate dependence. At best, we have been able to sustain a select group of opiate users with cyclazocine for up to 5 years, and some are now drug free --- but the number is small, and I believe our success to be as much a result of the dedication of my staff as to any specific pharmacologic activity. But these experiments demonstrate that the antagonists provide effective narcotic blockade; that they are safe; and that tissue tolerance does not develop to the antagonistic actions. They also indicate that drug delivery -- a sustained delivery of weeks or months -- is the immediate hurdle to overcome. As the longer duration of action of methadone and levomethadyl make maintenance therapy feasible, so too, a prolonged acting antagonist would make both deconditioning and prophylaxis clinically realistic.

From this point of view, there are three practical problems: the development of a long-acting delivery system; identification of more potent additional 'pure' antagonists, of greater duration of action; and, biochemical synthesis methods to assure an adequate supply of medication.

Dr. Daniel X. Freeman

March 10, 1972

1) Long-action. There are many routes that can be examined -- substitution of a long-chain fatty acid to delay absorption and degradation (similar to fluphenazine enanthate and naloxone pamoate); modified crystallizations (as utilized by Janssen for a long acting anti-psychotic drug); investment in a biodegradable silastic (as suggested by the Population Council for anti-ovulatory agents); or other novel altered delivery systems as developed by some ingenious chemists for ophthalmic drugs.

We have supported one study of silastic and defined the characteristics of this method using naloxone as the base. The study was discontinued for lack of funds. It warrants continued support, despite the long term nature and potential expense of the investment.

We have also completed initial human assays of naloxone pamoate, observing that 6 cc intramuscular prolongs the duration of antagonism to 25 mg diacetylmorphine/2cc 2 minutes (a 'heroin challenge') to 60 hours -- an increase in duration of at least 15 times. This salutary step demonstrates the feasibility of the approach.

2) A long-acting 'pure' antagonist. Of the tested drugs, naloxone is the 'cleanest' compound, but it has many disadvantages -- its duration of action is 2-4 hours; it is ineffective on oral administration (we required 3.0 grams to extend duration to 24 hours); and it is expensive and difficult to manufacture, limiting its supply. Other compounds warrant testing, and of these M 5050 has the most promise, based on animal trials. To test this compound, it is necessary to first complete adequate animal toxicology. (This step has precluded human assay for more than 2 years, for no agency which we approached was willing to provide the funds. Happily, funds were approved on March 3 for these trials).

In addition to this compound, there are many others that warrant study. Many compounds have been examined by the University of Michigan for antagonist potency, and these data are 'hidden' in the archives of the NRC/NAS. At the request of various agencies, Dr. Villareal has agreed (February, 1972) to undertake a review of the data; and should other compounds be identified, these should be assayed in man, with particular emphasis on their 'purity', degree of antagonism, and duration.

Under the stimulation of Congress, various industrial concerns have returned to their laboratories and examined their files for active compounds. This is true for Merck (levallorphan), Bristol (BC 2605), Sterling Winthrop (*l*-cyclazocine), and Geigy (GPA 2163) -- and these drugs warrant more intensive examinations.

Dr. Daniel X. Freedman

March 10, 1972

Finally, perhaps an interested scientist with experience in analgesics, could be encouraged to visit various laboratories to discuss on an individual basis, the availability of compounds or congeners in their files. When this was recently done with Janssen in Belgium, we were able to identify two possible compounds of interest, and to stimulate their further study.

3) Biochemical synthesis methods. The basic chemicals from which these antagonists are derived are in short supply, apparently because their manufacture is derived from thebaine, a proscribed commodity. Some effort should be made for chemists and botanists to identify other manufacturing methods and other sources of the raw materials.

In this review, I have neglected the need for training psychiatrists and clinical pharmacologists in the special problems of studies in addicted persons (patients usually have a different agenda than the scientist); the need for studies of the extinction of learned patterns; and the need for the studies of the dependence process itself. These general issues are of special concern to the committees of the National Institute of Mental Health, and will surely occupy the attention of the new proposed centers.

In our discussions of the ways in which these studies could attract the attention of scientists in universities and industry, one suggestion may be of special interest. Should an agency, preferably non-governmental, outline the needs for a long acting antagonist, define a reasonable deadline, and offer a prize of significance, would this not stimulate those men who may be unable to visualize the needs of the formulation, to attempt its development? Should an agency offer \$50,000 or \$100,000 for the development of a narcotic antagonist, with a duration of a single administration of 60 days, sufficient to blockade diacetylmorphine 25 mg/2 cc/2 minutes, in man -- would this not stimulate some interest? (An example is the announcement of the Anna Monika Foundation prize).

Two additional needs: support for academic scientists to work directly with industry on a 3-6 month 'fellowship' basis; and support for regular meetings of investigators interested in the narcotic antagonists, similar to the annual methadone meetings. (When we suggested the methadone meetings set aside time for the antagonist workers in New York and in San Francisco, our suggestion was denied. The only special meeting was sponsored by NIMH and the New York Medical College on June 4, 1970).

Dr. Daniel X. Freedman

March 10, 1972

These are some random notes. Should you be interested in the 'back-up', I will provide what I have. Meanwhile, my latest summary as prepared for *Contemporary Drug Problems* is enclosed.

Again, my thanks for lending me your ears. My best regards.

Sincerely yours,

Max Fink, M.D.  
Professor of Psychiatry

MF:ig  
Enc.