April 23, 1970

Dr. Ralph Jacobson
Endo Laboratories
1000 Stewart
Garden City, New York 11530

Dear Ralph,

Some months ago, we discussed the possibility of a broad clinical trial of oral naloxone in single large daily doses (2.4 to 3.0 Gms) in opiate dependent subjects. You will recall that we reported our observation that daily doses of 1.2 and 2.0 Gms failed to protect our subjects beyond 18 hours to 25 mg intravenous heroin, but that 2.4 and 3.0 Gms were effective for more than 24 hours.

Upon your reassurance that Mr. David Klein, your vice-president, had personally requested the supplies be made available, we returned our remaining naloxone, so that the larger tablets could be prepared.

During the past 6 months we have received monthly reassurances that naloxone would shortly be available. In your message last week, you stated that prior calls on your supplies, plus difficulties at Mallincrodt Chemical, plus expense and other committments at Endo, made it unlikely that naloxone would be available for clinical trials before September at the earliest, and realistically, probably not until the end of the year.

Meanwhile, the public press indicates (from your release?) that an NDA for Narcan is imminent "with clinical evaluation expected to be completed within 6 to 8 months on the drug's efficacy in heroin and opiate dependence." The report makes erroneous references to the work in this laboratory, and even allowing for reportarial errors, I am concerned that I may be misquoted - not only to the press, but to regulatory agencies as well.

Our findings with oral naloxone in 7 cases have been published. Our subsequent findings with dosages to 3.0 Grams/day are confidential and were reported to you to support our collaboration, and were not available for FDA submission or public reporting.

I hope the misquotation did not result from an Endo release, but did come from an enthusiastic reporter's misquotation of our preliminary reports to the State Narcotic Addiction Control Commission.

I am writing today for the following reasons:

1. To record my understanding of your telephone call - that oral naloxone is not available for clinical trial in opiate dependence in daily doses of 2.4 to 3.0 Grams; and that the earliest date for such supplies may be September 1970.

2. To request that the supplies of naloxone, returned by us during the winter, be made available to us once again. As you recall, we have been able to administer cyclazocine very rapidly, protecting our subjects against the agonistic effects of cyclazocine by oral naloxone. We have found that 300 mg naloxone, 3 to 4 times a day for 3-5 days, is useful in cyclazocine induction. We wish to test this observation in 50 consecutive addicts, and require 4.0 Gms/subject or 200 Gms. Our present supplies are almost exhausted.

We would like to carry out this study as rapidly as possible. Can you return 200 Gms naloxone in 300 mg (or 100 mg) tablets to us within a month?

3. To suggest that we adhere to our understanding, that public statements regarding our work, be made by prior initial consent only. You will recall that our College has subscribed to such an understanding. The enclosed report may reflect a transient lapse of that understanding, and I trust does not set a precedent nor does it represent a change in our understanding. Or does it?

Incidentally, the report of progress in a long acting naloxone preparation was encouraging. You will recall, however, that the figures you quoted, regarding the amounts of naloxone necessary to antagonize heroin in our subjects, seemed out of the range of our experience. I suggest that these figures require review, particularly if the pharmaceutical chemists are using them as benchmarks in their work.

I will call your office in 10 days, if I have not heard sooner, regarding your release of 200 Grams naloxone for a cyclazocine-naloxone study.

Sincerely yours,

Max Fink, M.D.
Professor of Psychiatry

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