was a two year old child who had ingested approximately 15 Lomotil Tablets of 2.5 mg. each. Dr. Madigan replied to this on October 15, 1963. He requested a copy of the autopsy report on the child. This was submitted with a covering letter dated November 1, 1963. This was acknowledged on February 28, 1964.

In a letter dated December 26, 1963 the firm reported the occurrence of a fatality with Lomotil following the ingestion of 26 tablets of 2.5 mg. or a total of 65 mg. of Lomotil, by 22 month old child. Substantiating data was included.

This was acknowledged by FDA on February 28, 1964. Additionally data was sent in on February 24, 1964. This was acknowledged on March 3, 1964 and additionally data was requested. The firm replied in a letter dated April 6, 1964 stating that the data requested had been furnished. This completes the new drug application.

Although *both of these children died as the result of ingesting a marked overdose of the drug* and not from a recommended dose, nevertheless, review of the new drug application finds it deficient in data to substantiate the safety or efficacy of the drug. All of the animal data were obtained with the one ingredient and without atropine. Apparently all of the clinical studies were done on the same ingredient. The atropine sulfate seems to have been added after all of the studies were done.

In the whole NDA there are only 43 individual case reports of which only one is a child. The remainder of the clinical data is represented by a tabulation in which not even the name of the clinical investigator is listed. It is indicated that more individual case reports were furnished to the firm than were submitted to FDA. At least 1 clinical investigator who did work with children is a man whom I suspect because of his association with Dr. Bennett A. Robins and the general quality of the work I have seen elsewhere from him.

Since the data now in the NDA do not substantiate the safety and efficacy of this drug particularly in children there is no choice but to state that from the strictly medical point of view this drug should not be on the market. My recommendation is that the New drug application be suspended and the drug removed from the market until data are submitted which substantiate safety and efficacy.

JOHN O. NESTOR, M.D.

SUMMARY OF NDA 12-462 VOL. 2

LOMOTIL

(G. D. Searle & Co., AF 13-505)

At the time I reviewed Vol. 1 it was my understanding that it contained all the data pertaining to this new drug. Dr. Ellenhorn has since sent me Vol. 2 with a note to the effect that there may also be another volume.

To begin with, it might be well to state that in the entire NDA I could only find evidence that 84 children were given the drug. I could not find evidence that a single pregnant woman had received the drug.

In general the clinical data consisted mainly of medical testimonials which were obviously uncontrolled studies. Laboratory work was practically nonexistent, that is, such things as stool cultures. In many cases there was concurrent therapy with other drugs such as steroids, sulfonamides, tranquilizers, etc. In many cases it was difficult or impossible to read and interpret the individual case histories which were lacking in significant detail. For instance, in many cases there was no record of the age, sex, name, or weight of the individual.

Side effects consisted of nausea, vomiting, sedation, restlessness, dizziness, vertigo, weakness, dry mouth, ataxia, confusion, hallucinations, angioneurotic edema, giant urticaria, swelling of the gums, malaise, flatulence, and bloating.

Although this NDA pertains only to tablets it appears that many of the children were given the drug in a different dosage form, that is a liquid form

A Dr. Charles N. Brown of the Cleveland Clinic who was one of the investigators mentions a confidential brochure which I have not seen in the NDA. The last item number 38 is a report from the research laboratories of Dr. C. Janssen of October 1, 1959 which is stamped confidential, and refers to the use of R1132 in 830 cases. R1132 is the code assigned to this drug Lemotil which is also known by the generic name of diphenoxylate.

The human pharmacology and investigation of the addictedness of the drug is in section 36 and was worked out at the Public Health Addiction Research