in the United States with perhaps a somewhat lower incidence of side effects.

Section 2 is a paper from the Journal Medicinal and Pharmaceutical Chemistry Vol. 1, No. 4 of 1959 by Paul A. J. Janssen and others concerning the pharmacological properties of R–1132 and related compounds. There was no clinical material included.

Section 3 was a confidential brochure of the Searle Company concerning the pharmacological and toxicological data on R–1132. This section also had to do with 14 day oral toxicity studies in rats.

Section 4 was a report from the Woodard Research Corporation to the Searle Company on the Chronic Oral Toxicity of R–1132.

Section 5 was entitled a Summary of Case Reports of 521 patients to whom Lomotil was administered by 31 clinicians. *This does not make clear whether the Lomotil included the atropine or not.* Furthermore this was merely a tabulation which listed the investigator by number, the number of patients he saw, the age range, the diagnosis, the clinical result, side effects, dosage, and milligrams per day and duration. I presume that is duration of treatment. It is noted that investigator number 5 had 30 patients but only 16 record forms were submitted. Investigator number 6 had 39 patients but only 22 record forms were submitted. It is noted that investigator number 18 had 28 patients of which 14 supposedly ranged from 3 to 21 months of age and 13 ranged from 2–9 years of age. This was probably Dr. Modlin because his location is listed as Laurel, Md. Investigator number 28 had 25 children. Investigator number 29 had 18 children.

The final sheet is a summary of side effects which included nausea, drowsiness or sedation, dizziness, vomiting, skin eruption, restlessness, itching, cramps, headache, swelling of gums, numbness of extremeties, blurring of vision, euphoria, depression, malaise and abdominal distention.

Section number 6 contained some covering letters which were mainly testimonial and a few individual case histories. There were 43 individual case histories which were grossly inadequate as far as details were concerned. Most of them are not legible and in general they add very little to the new drug application.

In this whole original submission there is no explanation of the physiological effect of this drug on the human being except for the gastrointestinal tract where it is supposed to produce hypomobility. Neither are we told anything about its absorption, its metabolism or its excretion.

The receipt of the NDA was noted by a letter dated June 7, 1960. A FDA memorandum dated July 18, 1960 from the Division of Pharmacology to Dr. Madigan in the New Drug Branch who was handling the NDA, which stated "The animal toxicity data are sufficient and satisfactory to suggest safety of *Lomotil* at the recommended dose levels (up to 20 mg. daily for adults and lesser amounts for children); however, because of the limited clinical studies in children less than 3 months old the dose level recommendations for children under 3 months of age should be deleted from the labeling. I recommend that this NDA 12–462 for Lomotil be made effective upon compliance with the labeling changes suggested above."

This was signed by Kent J. Davis and initialed by V. J. Vos.

On July 22, 1960 a letter was written by the firm to Dr. Madigan and Dr. J. William Crosson of the firm stated "In accordance with our telephone discussion on this date, we wrote delete from the labeling reference to administration of Lomotil to children under 3 months of age."

Comment

After reviewing this original submission it is very obvious to me that there was inadequate data on children of all ages under 12 years of age. In the 43 individual case histories there was only 1 child 8 years of age. Furthermore, all of the animal toxicity data were obtained on animals from the diphenoxylate hydrochloride alone which did not include atropine sulfate as the finished formula drug on the market included.

In a letter dated July 29, 1960 Dr. Madigan found the NDA incomplete on 1) manufacturing controls 2) on the basis that the application proposes to make the literature furnishing information for the professional use of this drug available to physicians solely on request.

In a letter dated September 13, 1960 from the firm to Dr. Madigan, this was a covering letter for the final printed labeling. Dr. Madigan acknowledged this in a letter dated September 29, 1960 and stated that the NDA was now effective.

The next item of any significance was a letter from the firm dated September 18, 1963 to Dr. Madigan to report the occurrence of a fatality with Lomotil. This