toxicity may explain the two deaths of children from relatively normal doses of the Lomotil Liquid.

Recommendations

The subacute toxicity studies which are supposedly in progress may add more information on the relative toxicity of liquid vs powder and child vs adult.

It would appear that less than weight proportional doses should be prescribed for children and that lower doses of the liquid than the powder should be recommended.

LOUISE L. PHILLIPS, M.D.

MEMORANDUM

DECEMBER 22, 1965.

To: R. J. Robinson, M.D., Chief, Drug Surveillance Branch/DMR.
From: L. V. Pascual, M.D., Medical Officer, DSB/DMR.
Subject: Report of overdose in association with the use of Lomotil.

(G. D. Searle & Co., Chicago, Ill. (A.F. 13-505) NDA 12-462)

This "Drug Reaction Report" from Dr. Miller was submitted by Adverse Reaction Branch/DMI on September 20, 1965. This report as well as two others was submitted by the company to FDA on July 20, 1965.

Lomotil went through the New Drug Application stage without the atropine added.

The marketed drug contains atropine sulfate supportably in sub-therapeutic quantity "to prevent overdosage". We are not aware of any pre-clinical or clinical trials performed with this combination. This combination should be considered a new drug. (Please see Memo of Dr. J. Nestor dated May 14, 1964).

Conclusions

The suggested warning statement pertaining to overdosage should be considered together with a complete revision of the labeling following evaluation of the data submitted in the NDA.

(The supplemental information submitted by Mr. Stetler, subsequently received, follows:)

PHARMACEUTICAL MANUFACTURERS ASSOCIATION,
Washington, D.C., December 12, 1967.

HON. GAYLORD NELSON,
Chairman, Subcommittee on Monopoly Select Committee on Small Business, U.S. Senate, Washington, D.C.

DEAR SENATOR NELSON: I respectfully refer you to pages 2269 to 2272 of the hearings conducted on November 16, 1967, before the Senate Monopoly Subcommittee of the Select Committee on Small Business.

On the cited pages Mr. Benjamin Gordon made certain statements alleging that the G. D. Searle & Co. added the active ingredient atropine sulfate to its drug LOMOTIL without first obtaining the approval of the Food and Drug Administration even though a new drug application covering the drug was, at that time, in effect. Mr. Gordon stated that his allegation was based upon information appearing in "a summary of the NDA. 12-462 Volume II . . ." The "summary" was "signed by John Nestor, Medical Director, FDA" (page 2272).

The document involving LOMOTIL is apparently not "a summary of the NDA." Instead, it appears to be an internal FDA memorandum prepared by Dr. John Nestor, to serve as a critique of the material in the NDA file. G. D. Searle & Co. holds an approved new drug application for LOMOTIL. The company has informed us that this application was originally approved on September 29, 1960, for a product *with atropine*, with exactly the same ingredients as those in the product now marketed. The product originally tested did not contain atropine, but this *was never marketed.* Atropine, in a non-therapeutic quantity, was added to the formula, prior to approval of the NDA, at the request of the Bureau of Narcotics. The Bureau's suggestion was in accordance with a recommendation of an advisory committee of distinguished scientists.

On November 16 you asked Mr. Gordon, "Are you saying that after a new drug application was granted, that the company involved added another active