Center in Lexington, Kentucky by H. F. Fraser and H. Isbell. This was quite a thorough work and naturally I can only summarize the high points. It seems that diphenoxylate is a congenar of meperidine and it produces euphoria in somewhat the same fashion as morphine and codeine. It is about ½ as potent as morphine and 1 and a half times as potent as codeine. The main difference from the codeine effect was the time of effect the codeine took from one to two hours, and R1132 which is the diphenoxylate took from four to six hours. R1132 is an effective suppressor of abstinence from morphine. It induces constipation similar to that of the opiates such as morphine and codeine. It also depresses the respiratory rate, is addicting, constricts the pupils, produces euphoria, and when administered in large doses orally and intravenously in subject to abuse liability. It has no advantage over codeine in physical dependence. Addiction to it is similar to that of morphine and codeine.

The final clinical study was done by a group of three men from the Department of Internal Medicine at the University of Louvaine in Belgium. The clinical pharmacology was included in section number 37 and in section number 38 there is a tabulation of 830 cases. This is strictly a tabulation giving the case numbers, sex, age, weight, daily dose, duration of treatment, the doctor who treated, side effects, results, and diagnosis. No mention is made of laboratory work and there are no individual case histories. In this particular study there were supposedly 51 children of which 23 were cases of acute diarrhea, and 28 cases of chronic diarrhea.

This drug does have a constipating effect but also it is like opiates in that it can produce addiction. There are fewer than 100 children in the two volumes of the MDA reviewed to this point, and there are no pregnant women. Except for the excellent study in human pharmacology done by Fraser and Isbell in a relatively small number of the total number of patients, the clinical data is testimonial in character and does not represent well controlled studies. Laboratory data is practically nonexistent.

Since to this point I have not run across any labeling in this volume, I must conclude that the small amount of labeling in volume 1 constitutes the total at the present time.

The additional clinical data submitted in this volume 2, despite its inadequacies, do seem to indicate that the drug can produce constipation and control diarrhea. The data also indicate that it produces a significant number of adverse toxic effects. Certainly the data do not substantiate the safety and efficacy of this drug for use in children under 12 years of age and in pregnant women.

Until the additional volume of the MDA is found I will be unable to draw any final conclusions.

I had previously pointed out that it had not been used at all in pregnant women during the investigative stage as far as the MDA showed, and that there were very few individual case histories pertaining to its use in children although there was one long tabulation of children from a study done in Belgium. However, this was merely a tabulation and did not contain any significant details of the medical history and laboratory work. There were a total of only 40 very brief completely inadequate individual case histories submitted in children. 21 of these were for children under the age of 2 years 14 for the ages between 2 years and 6 years, and five between the ages of 6 years and 12 years. The sum total of all of the children mentioned in this MDA whether it applies to the 40 individual case histories or to the tabulations amounted to a total of 235. Obviously, this was grossly inadequate to substantiate the safety and efficacy of the use of this narcotic drug in infants and children. Obviously also there was no demonstration whatever of the safety or efficacy of this in regard to the fetus of a pregnant woman.

Since the best study in the NDA was the study performed by Dr.'s Fraser and Isbell of the National Institute of Mental Health Addiction Research Center in Lexington, Kentucky I will review that work in more detail. The title was, "The Human Pharmacology and Addictedness of Diphenoxylate or R1132."

These authors pointed out that this drug is a congener of meperidine which is Demarol. They stated that it had a pronounced constipating and antidiarrheal effect in man and many species of animals. Small doses of 2.5 to 5.0 mgs. daily with a maximum dose of 30 mgs. are effective for this purpose. Because of the potential use of the drug for this purpose they decided to study this human addiction liability. They performed a series of very careful studies and came up with the following information.