fact, it is less stimulating to the CNS. The present recommended dose (maximum) is 40 mgs. 3 times a day. This dose did not disturb sleep in his study patients (Dr. Gagnon's study population consisted of inmates of a psychiatric institution who were taking a psychotrophic drug along with the fenfluramine.)

Conclusion with respect to labeling

The results of the studies thus far presented (Fred, Larson, Itil, and Gagnon) leave no doubt in this reviewer's mind that fenfluramine is less stimulating to the CNS and the automatic nervous system than the amphetamines. A statement to this effect in the labeling is adequately substantiated by the data submitted thus far.

DISCUSSION AND COMMENT WITH RESPECT TO THE EFFICACY OF FENFLURAMINE IN THIS APPLICATION

Guideline criteria for the design of a weight-reducing study

1. 80 to 100 overweight subjects; divided into 2 groups, one on each medication; double-blind, randomized, using placebo and drug, non-crossover; subjects should be 15 to 20% overweight according to the Metropolitan Life Insurance tables.
2. A low calories diet that is the same for all individuals in the study; this would be a maximum of 1200 calories per day. (The following authorities recognize the need for a low calorie diet in any weight-reducing program: Harrison's Medicine, Goodman & Gillman, and the J. American Medical Association New Drugs, and British Medical Association. (Report of Working Party, November 1968 on amphetamine preparations)
3. Two-week, pre-medication baseline period with weight measured at the same time during the day at three weekly intervals.
4. Weight should be measured at the same time during the day at weekly intervals during the study, preferably after breakfast every morning. (In this way, the bowel and bladder habits will be accounted for.)
5. Duration of drug treatment period should be 4 weeks.

Reasons for the above guideline

1. The study should be non-crossed-over with everybody on the same low calorie diet; if a subject is crossed over from drug to placebo, he will have had the benefit of the low calorie diet during the drug period. We know that all patients on reducing diets lose their weight more rapidly early in the study. This would tend to give the impression that the drug was better than the placebo; conversely if the patient is crossed over from placebo to drug he will have had the benefit of the low calorie diet during the placebo period, which could show the placebo to be equal or better than the drug.
2. The determination of how much each patient should be overweight in order to be selected for the study could never be decided unless we arbitarily used a table from Metropolitan Life Insurance Company information or something similar.
3. Proper randomization of 2 groups—one on the placebo and one on the drug—should take care of the possibility of drug and placebo patients cheating on their diets.
4. It would seem to this reviewer that the duration of treatment should not be any longer than 4 weeks in order to establish efficacy for a drug in this category, because in studies lasting longer than 4 weeks, patients tend to lose weight at a slower rate after the first 4 weeks.

VIII. Literature reviewed: 1. Goodman and Gilman; Pharmacological Basis of Therapeutics; 1965

2. Harrison's principles of Internal Medicine (5th Ed.) 1966

3. Report of the Working Party on amphetamine preparations November 1968; British Medical Association

Summary of seven adult-controlled studies

Sub-group A—studies supporting efficacy.—1. Martin S. Roginsky, M.D., East Meadow, N.Y.

Sub-group B—Studies not supporting efficacy for this drug.—1. J. A. Owen, M.D., Charlottesville, Virginia.

2. Solomon Fisch, M.D., Bronx, New York.
3. B. A. Rosenburg, M.D., Brooklyn, New York
4. Robert S. Anderson, M.D., Nashville, Tennessee