ing data in the NDAs revealed such a limited degree of efficacy. Although we customarily do not include such information in package inserts, the amphetamines constitute a special case and must be dealt with accordingly.

2. I urge that the labeling of these compounds be revised to include, in each case, a factual tabulation of the actual amounts of weight loss which have been reported by the various investigators, to include the duration of therapy, so that the physician will be in a better position to decide as to whether or not use of a sympthomimetic amine is warranted. The common practice of expressing results in terms of rate of weight loss per week is particularly objectionable and should be discontinued.

3. The duration of therapy to be recommended in the package insert is very important. Various recommendations have been made, e.g.:

a. Use short-term therapy as initial treatment only, with the purpose of re-educating the patient's eating habits, etc.

b. Use long-term therapy in spite of the fact that tolerance is known to develop to the sympathomimetic amines.

c. Use intermittent therapy so as to allow the patient an opportunity to regain sensitivity to the drug.

Only limited results have been demonstrated with the first two methods, and the third method is merely a variation of the second. I suggest that unless long-term therapy can be demonstrated in controlled trials to be significantly effective, only short-term therapy be allowed. The development of tolerance figures prominently in this decision.

4. NDAs which are now under review in the OND pertaining to antiobesity drugs should not be approved unless:

(1) a clinically significant amount of weight loss is shown by controlled trials, and

(2) the package insert conforms to the above suggestions.

MEMORANDUM

APRIL 8, 1970.

To: John J. Jennings, M.D., Acting Director, Bureau of Drugs.
From: Robert O. Knox, M.D.
Subject: A suggested tabulation of therapeutic results to be incorporated into the package insert of a sympathomimetric amine.

1. In accordance with your request of March 24, 1970, for an example of a tabulation that could be incorporated into the package insert of a sympathomimetic amine in order to present the physician with some quantitative results which had been demonstrated by the investigators, the attached model is submitted for preliminary consideration.

2. Some of the points shown by this tabulation are:

(a) the almost total lack of a dose-response relationship.

(b) the fact that most of the studies reveal less than 5 lbs. of total net weight loss.

(c) Dr. Hollingsworth reports greater weight loss following placebo than most of the other investigators reported with fenfluramine—even using the high dose of 120 mg. per day. His results largely depended on whether fenfluramine or placebo was given first.

3. Some relevant excerpts from "Drugs of Choice" by Walter Modell, M.D., The C.V. Mosby Co., 1970, are appended:

"The long-term results of anorexiant therapy are very poor at present. . . . an anorectic agent is likely to have as little effect on the overall problem of obesity as disulfiram (Antabuse) has had on the overall control of alcoholism. . . . none of the anorexiants are effective unless food intake is controlled as well; hence, it is obvious they really are not very effective against this force."

". . . even when the double-blind technique is used to start, after 30 minutes some patients know which is medication and which is placebo, and only the physician remains blind. All the psychic impact of the knowledge that an effective drug is being taken is thus exerted in favor of the drug being tested. From this point of view, therefore, a difference between the effects of the placebo and the drug in these studies may well result from the detection of this difference by the patient as well as from the action of the drug itself."

". . . it is by no means definite that these drugs have any primary effect on appetite at all."