Animals given fenfluramine in appropriate doses differ from those given amphetamine by exhibiting decreased motor activity, suppressed conditioned avoidance responding, increased total sleep time, and EEG changes of increased slow-wave sleep time, slowed electrocortical activity, and depressed reticular-formation activity.

In humans, sedation is the most prominent side effect of fenfluramine, in contrast to amphetamines. EEG changes correlating with sedation were observed. Amphetamine addicts could not distinguish between fenfluramine and placebo, and rated fenfluramine as less euphoriant than placebo.

These observations generally suggest strongly that fenfluramine should not be considered equivalent to other anoretics with respect to dependence potential of this class of agents.

5. Pulmonary hypertension

A European anorectic drug aminorex (Menocil), pharmacologically related to amphetamines but structurally somewhat different, has been associated with potentially fatal pulmonary hypertension. Congeners have been neither convicted nor exonerated of similar effects, although recent German reviews have publicized the possibility of similar effects. German regulatory authorities have just required warning labeling in this regard, which we are to receive and review.

ASSUMPTIONS

Following this section are the alternative courses of action which we believe may reasonably be considered with respect to anorectic drug policy. Before discussing them, certain assumptions should be made explicit. (As is appropriate to the format of a memo like this, these assumptions are discussed in the DISCUSSION section on page 17, to which the reader may wish to turn before proceeding.) The assumptions are:

1. Actions are best taken with respect to the whole class of anorectics.
2. Actions should not be taken with respect to pharmacologically related agents of different therapeutic classes, but should be restricted to anorectics.
3. Actions should not be deferred.
4. The two indications for amphetamines other than obesity are basically accepted (minimal brain dysfunction in children; narcolepsy).
5. Efficacy demonstrated for some amphetamines can be extended to all amphetamines generically.

ALTERNATIVE COURSES OF ACTION

In implementing policy for an entire class of drugs, indicated in an extremely widespread condition, actions will be numerous, and alternative choices correspondingly numerous. In the interests of clarity, we present here only the major decisions, as we see them, with viable alternative courses of action.

A. With respect to the approval of anorectics in general

The first major area in which alternative courses of action should be distinguished is the area of criteria for demonstration efficacy of anorectic drugs in general. The three alternatives are considered mutually exclusive.

1. Base judgments on the efficacy of anorectic drugs on the currently available substantial evidence derived from short-term studies (up to 3 months). This would be coupled with a requirement for further testing with respect to abuse potential (see D.1 below).

PRO: This is the recommendation of FDA consultants. (See Tab C) Several past attempts to gain support from experts for longer-term trials or for a more "clinical" definition of efficacy (e.g., loss of 50% of excess weight) have failed. Trials of this sort reflect the current state of the art. To increase requirements now would mean that all NDA anorectics are non-approvable for an indefinite period of time. No better alternative drugs exist.

CON: Approval based on short-term trials leaves unanswered questions as to the long-term effect of drug therapy on the natural history of obesity, as well as on morbidity and mortality associated with obesity.

2. Require that the efficacy of anorectics be based on substantial evidence that the use of these drugs results in achievement and maintenance of weight loss and in improved morbidity or mortality.

PRO: Fulfillment of criteria along these lines would provide evidence that these drugs are medically useful in undeniably important ways.