> All of us know that we can't get fat people to become slim by suggesting a diet, so we conclude, for the time being at least, that obesity is incurable.

Modell (14) reemphasizes the point in the summary of his report:

> New and logical pharmacotherapy for persons who overeat will more likely come with understanding of the processes involved than through the current practice of developing more variations on old themes which have already been well exploited and have not satisfied the need. There is really nothing new on the scene. There are no "anorexiants" to fit specific disturbances in eating patterns, and there are no useful depressants of the appetite center, wherever it may be. . . . Current pharmacotherapy for persons who overeat has limited use. Insofar as drugs are concerned, at the very best, their potential is secondary to the elimination of the cause of the hyperphagia. Drugs which give assistance along the lines now available provide short-lived symptomatic relief only.

Despite 20 years of extensive use, then, the place of amphetamines in clinical practice is far from established. They represent the treatment of choice for only a small number of those patients for whom they are prescribed. Their effectiveness in treating obesity and depressive reactions is minimal and controversial.

Interestingly, the pharmaceutical industry tells us indirectly that the amphetamines and related drugs offer only a low order of effectiveness by constantly introducing new congeners and combinations. For example, in the 1970 *Physicians' Desk Reference* eight companies have listed nine "new" amphetamine products not listed in the 1968 edition. The industry sends the same message in another more encouraging way; within the last 2 years four companies have voluntarily discontinued their production of amphetamines (Methedrine®, Burroughs Wellcome; Phetobese®, Cole; T.V.D. Formula®, Lambda; Ad-Nil®, Medics).

Hazards of Amphetamines

The irony of the amphetamine situation is that whereas we have been slow to admit the negligible utility of these agents, we have also been slow to recognize their dangers. Their illegal and casual use as stimulants of the central nervous system has grown tremendously. They have become perhaps the most serious drug of abuse in the United States (as in several other countries), except in the large cities, where heroin addiction is widespread. Most physicians are not yet sufficiently familiar with these hazards, which are well documented elsewhere (1, 3, 8, 19-22). Briefly, they fall into all three major areas of concern in psychoactive drugs.

1. Amphetamines are associated with *tolerance* and with an intense *psychological dependence*, which makes it difficult to withdraw from the drug without help. High-dose use may begin in a pattern of illegal experimentation, but it may also begin with a physician's well-intended prescription. The nature of the drug's effects leads easily to progressively increasing dosage in susceptible persons. Prediction of "susceptibles" cannot be made with confidence, but patients for whom amphetamines are prescribed are probably, by the very nature of their illnesses, among those most likely to increase the dose and become dependent. Then begins a prolonged struggle to discontinue drug use, an effort usually attended by intense lethargy and depressive symptoms. The period of depression during the withdrawal (or "crash") is frequently associated with suicidal feelings and actions. The absence of physical dependence in amphetamine abuse may give the impression that it is easier to withdraw from than heroin. This has not generally been the case; in fact, the reverse may be true, although data on this point are lacking.

2. The *behavioral toxicity* of high doses is usually such that the user cannot maintain work, school, or family relationships. With high doses a typical psychosis often develops, characterized by hyperactivity, distortions of reality, impaired judgment, paranoid ideation, and hallucinations. Despite this disturbance, the sensorium is clear, and the individual may appear superficially normal (19).

3. The *physical toxic effects* on the autonomic nervous system and cardiovascular system include sympathetic gastrointestinal and urinary symptoms, occasional systolic and diastolic hypertension, sometimes cardiac arrhythmias (8, 21), and possible necrotizing angiitis (22). In addition, malnutrition, hepatitis, and other serious infections are associated with the intravenous use of these drugs.

These are the major toxic manifestations of illegal, high-dose amphetamine use. But damage also results from the less spectacular adverse reactions to small, legally prescribed amounts and may cause disability for greater numbers of people. These case examples are familiar to most practicing physicians:

Case 1: A 23-year-old male first-year medical student asked his physician for stimulants to help him overcome classroom drowsiness, difficulty in studying, and mild depression. He did not have narcolepsy. Dextroamphetamine, 5 mg daily, was prescribed. He was asked to return but did not. When next seen, he had flunked out of school. Although not the sole factor in this patient's failure, the amphetamine obviously did not help his studying and may have been a critical determinant in his avoiding early, appropriate counseling.

Case 2: To control her appetite a 47-year-old woman had used various amphetamines almost daily for 10