Much evidence indicates that increasing weight increases health risks (6-8). The relation between increasing body weight and health risks is curvilinear and is often described as J shaped. The minimal mortality from obesity is associated with a body mass index (in kg/m²) of 22 ± 2 whereas increasing mortality with increasing body mass index is related to an increased incidence of elevated blood pressure and serum cholesterol (9).

The risk of obesity is correlated with the amount and distribution of extra body fat (10). The risk associated with increased visceral fat is reflected in an increased risk for diabetes mellitus, hypertension, cardiovascular disease, gall bladder disease, some cancers, and osteoarthritis. High risk is also associated with a waist circumference >100 cm (40 in) (11) and a weight gain of >10 kg after age 18 y (12).

Williamson et al (13) found that intentional weight loss of >9.1 kg (20 lb) in 28,388 women with no preexisting illness was associated with a 25% decrease in all-cause cardiovascular and cancer mortality. Of the 15,069 women in this study with comorbid conditions, any amount of intentional weight loss was associated with a 10% reduction in cardiovascular disease, a 20% reduction in all-cause mortality, a 30-40% reduction in mortality from diabetes, and a 40-50% reduction in mortality from cancers related to obesity.

Obesity and hypertension have many features in common that may guide the future of drug development. Both body weight and blood pressure regulate vascular tone through feedback that involves both the sympathetic nervous system and the angiotensin system. The efferent systems for regulation of body fat may be viewed as the sympathetic system and the secretion of insulin. The controlled system for blood pressure includes the relative amount of body fluids, the tone of the blood vessels, and the function of the heart. By analogy, the controlled system for body fat includes the gut (where food is digested and absorbed), the circulatory system (which transports nutrients for storage or oxidation), adipose tissue (where fat is stored), and tissues that oxidize fatty acids. Afferent blood pressure signals are generated from baroreceptors and from atrial natriuretic peptide. The afferent messages in the weight-regulating system include leptin and the afferent vagal system from gut and liver.

Before the introduction of chlorothiazide in 1958, hypertension had three major treatments: diet, drugs, and surgery. If begun early enough, a low-salt diet was considered beneficial in treating hypertension. When effective pharmacologic therapy was introduced in 1958, however, the use of very-low-salt diets dropped dramatically. Before 1958, drug treatment of hypertension included reserpine, chlorothiazide was introduced. By producing a diuresis, chlorothiazide reduced body sodium stores and the first effective treatment of hypertension appeared. The treatments for obesity analogous to the major treatments for hypertension before 1958 are low- and very-low-energy diets; drugs, which regrettably, have significant side effects; and gastric and intestinal bypass surgery. Orlistat, a pancreatic lipase inhibitor, might be viewed as the analogue of the diuretic. The loss of energy as undigested triacylglycerols could be likened to the loss of sodium with diuretics. The current centrally active norenergic and serotonergic drugs may be analogous to the early drugs used to treat hypertension. Finally, sympathectomy for treating hypertension is analogous to gastric surgery for obesity.

If 1998 is analogous for obesity as was 1958 for hypertension, then we can expect a variety of new and effective drugs. Some of these will act at the level of the brain to modulate feeding. Others will work at the level of the afferent signaling system to modulate feeding. Other drugs are likely to control obesity by modulating metabolic processes in the liver cell, fat cell, or muscle cell, such as drugs that affect the angiotensin system or the nitric oxide system. Finally, there will be drugs that modulate efferent signals and those that regulate food intake. Although the current problems with drug treatment are of concern, we should not throw out the baby (currently available drugs) with the bath water (future potentially effective drugs).

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The treatment of obesity with drugs

Four years ago I (I) commented on a review in this Journal, "Long-Term Weight Loss: the Effect of Pharmacologic Agents,"
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by Goldstein and Potvin (2). At that time there was particular interest in the work of Weintraub et al (3), who had treated obese subjects with a combination of phentermine and fenfluramine for nearly 4 y. These subjects had maintained lowered weight while taking the drug combination and the long-term results led to enthusiastic espousal of drug treatment of obesity. Many likened obesity treatment to that of diabetes and hypertension, urging continuous long-term therapy. I noted that the subjects in Weintraub et al’s study had lost only ~9.1% of their initial body weight 190 wk into the study and furthermore that only one-fifth of those who began the study remained under study. It seemed to me that such treatment was "so little for a disease that is so prevalent and distressing." Nevertheless, in recent years there has been a remarkable interest in these and other drug treatments of obesity. Whether fueled by poor long-term results of combinations of diet, exercise, and behavior modification, including low-fat diets, or the growing belief that there are fundamental biological elements in obesity, probably genetically determined, drug treatment had become the newest fad in obesity treatment, replacing very-low-energy diets, ketogenic diets, and other fads of years gone by.

Both phentermine and fenfluramine have been available, respectively, as Ionamin (Phentride, Fastin, Obepheh, etc; Medeva Pharmaceuticals Inc, Fort Worth, TX) and Pondimin (AH Robins Co, Richmond, VA) for many years, although their combined use has never been approved by the Food and Drug Administration (FDA). Pondimin is a combination of two isomers of fenfluramine. The d-isomer alone was approved for use only in April 1996 as Redux (Wyeth-Ayerst Laboratories, Philadelphia) or dexfenfluramine hydrochloride. By all accounts, 1996 was a "banner year" for drug treatment of obesity, with 11 million prescriptions for phentermine, 7 million for fenfluramine, and 2.4 million for the newest addition, dexfenfluramine. It is believed that the unapproved but popular "fenphen" combination was prescribed 6.6 million times in 1996 (4).

On September 15, 1997, the bubble burst. The manufacturers, acting on the recommendations of the FDA, removed fenfluramine and dexfenfluramine from the market. However, these drugs were not removed from the market because of their inefficacy. Although these drugs were used by millions of Americans, there were no new reports of efficacy to evaluate the advantages of such widespread therapy. The new problem with drug use is "hazard" of at least three types: primary pulmonary hypertension (PPH), neurotoxicity, and unanticipated cardiac effects.

PPH is a rare but generally fatal disorder. Roughly 30 y ago it became evident that aminorex fumarate, used for obesity treatment, was correlated with an increase in PPH to a level well above the usual baseline of 1–2 cases per million per year. More recently, phentermine and fenfluramine have been implicated in a roughly 20-fold increased risk for PPH when used for >3 mo (5). It was reasoned, however, that even with this additional risk the benefits of drug-induced weight loss were so great as to outweigh the risk of PPH (6).

Physicians using dexfenfluramine have reported to me that some patients experience forgetfulness while taking the drug, an effect that quickly abates when the drug is discontinued. Other neurotoxicities are suggested in a review of the literature by McCann et al (7). They found evidence that "fenfluramines cause dose-related, long-lasting reductions in serotonin axonal markers in all the animal species tested and with all the routes of drug administration used. Doses of fenfluramines that produce signs of brain serotonin neurotoxicity in animals are on the same order as those used to treat humans for weight loss when one takes into account known relations between body mass and drug clearance."

In the summer of 1997, Connelly et al (8) from the Mayo Clinic reported that 24 women who had received the popular fenphen combination developed cardiac valvular abnormalities when examined by echocardiography. The lesions were sufficiently threatening to require surgical treatment in five patients. At surgery, the valves resembled those in carcinoid valvular disease, believed to be a result of excess circulating serotonin. The FDA indicated that it had received additional reports of high prevalence of valvular disease in patients taking the combined drug regimen and in some instances when taking fenfluramine or dexfenfluramine alone. Thus, a report from the distributor (Wyeth-Ayerst Laboratories) issued on September 15, 1997, noted that the FDA had evidence of abnormal echocardiographic findings in 92 of 291 subjects receiving either fenfluramine or dexfenfluramine, usually in combination with phentermine. On the basis of such reports, fenfluramines were removed from the market. It remains unclear why such a remarkable incidence of cardiac toxicity was not evident earlier. This question will undoubtedly be an important one for further investigation as will the fascinating matter of the pathogenesis of this lesion. Is inhibition of serotonin reuptake to be implicated in this unusual form of valvular heart disease? Are there dangers with other widely used selective serotonin reuptake inhibitors? Are there any antecedent conditions, eg, hypertension or mitral valve prolapse, that make drug treatment particularly hazardous?

Although fenfluramine and its isomers are not likely to be used for treatment of obesity in the near future, the prospect of using other drugs still kindles great enthusiasm. On September 16, 1997, the day after fenfluramines were removed from the market, the Wall Street Journal reported on "Future Fat Fighters," which included a lipase inhibitor, a "booster" of brain chemicals, leptin, leptin mimics, urocortin mimics, and brain neuropeptide Y receptor blockers (9). Have we learned anything in the past 5 y that might help us in the evaluation of such future drug possibilities? The following simple analysis of three categories of the desirable effect (DE) of drugs may help order our thoughts as we consider each new possibility.

1) A DE of any drug or other therapeutic intervention in obesity is directly proportional to drug-induced weight loss leading to reduction in mortality and morbidity and indirectly proportional to the hazard of the intervention. A simple expression for this relation is DE = (1 + M)/(1 + H), where M is the fractional decrease in mortality and morbidity (ie, a 20% decrease would be 0.2) and H is the fractional increase in the same index (eg, mortality or morbidity related to the use of the drug). The calculation of M might use data obtained when obese individuals lose weight while following an acceptable dietary regimen, presumably the least hazardous of all interventions. A decrease in mortality or some specific comorbidity of obesity (diabetes, hypertension, etc) achieved by diet-induced weight loss would be considered equal to the reduction of mortality or morbidity with equal weight loss induced by drug use. The hazard of drug use would be adverse effects on mortality or morbidity, measured in obese individuals who took the drug and did not lose weight as well as in those who did lose weight, to determine any interaction of hazard and weight loss.

2) The DE is most likely to increase when the therapeutic intervention is specific for the abnormality that caused the obesity. Ideally, one would ascertain the exact biochemical or
behavioral events that initiate obesity and treat only with agents that specifically aim at a reversal of these events. A full understanding of the pathogenesis of human obesity is not yet available and it is difficult to study subjects in depth before their development of obesity. One way to approximate the preobese state is by examining the weight-reduced obese, who often become obese again, to uncover biochemical or behavioral differences between them and those who have never been obese. Any intervention that is specifically aimed at correcting such differences could, most likely, increase the DE with vanishingly low hazard. Drug treatment removes the offending abnormality of obese individuals, thereby rendering them "normal." This is the equivalent of replacement therapy for avitaminoses or endocrinopathies. This is not always achieved with drug therapy for most diseases, but is surely the "ideal" treatment.

3) The DE is less likely to be increased when therapeutic interventions are not specific for the abnormality that leads to obesity. Fat storage is maintained by a balance of energy intake and output. The systems that maintain energy balance are of fundamental importance for survival and therefore are coupled with each other and have redundant loops to ensure that an aberration in any part of the system will be compensated for by changes elsewhere. Thus, any intervention in the various regulatory loops of these systems that is aimed at reducing food intake or increasing energy output is likely to be compensated for by changes elsewhere in the system. Although multisystem involvement of the intervention across several loops reduces the likelihood of compensation, it also increases the likelihood of unwanted hazard. Obviously, the arrow that strikes the bull's-eye travels the shortest course. The wider the arrow is from the mark, the greater the likelihood of injuring passersby and spectators.

The first thing to be said about the above considerations is that the calculation of the DE may not be possible for a given intervention because of the lack of sufficient precise information. I argue that in this circumstance the drug should not be used. What about the DE of therapies now under development?

Because the exact nature of the defects that lead to human obesity have not yet been determined, all treatments in development are nonspecific and fall into category 3. Therefore, hazards would be expected to be relatively high for any given level of benefit. Thus, there is no current evidence that fundamental differences in the mechanisms of serotonin reuptake are a cause for obesity. Likewise, there are no definable abnormalities in the functioning of pancreatic lipase, urocortin, neuropeptide Y, or leptin that have been shown to cause obesity in humans. Use of such agents for pharmacologic interventions, like surgery of the gastrointestinal tract, may lower body weight, but at a cost that is unacceptable except in those with severe obesity that is immediately life threatening. The decision to use a drug can be made more intelligently by calculating the DE or some similar index. Given the uncertainties of most epidemiologic measures, one would want the DE to approach 1.5 before recommending the use of the intervention under consideration. (A DE = 1.0 indicates no beneficial effect.)

If one subscribes to the above analysis of drug treatment of obesity and its hazards, it becomes evident that what is most needed is a deeper understanding of the subtle ways in which the genetic makeup of the organism is shaped by developmental events and tuned by those psychosocial aspects of life that shape behavior. When the intricacies of these complex systems are clarified by scientific inquiry, treatments (and preventive strategies) with few associated hazards are likely to be found.

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