M. M. Ollmann *et al.*, *Science* **278**, 135 (1997).
67. M. F. Dallman, *Trends Endocrinol. Metab.* **4**, 62 (1993).
68. N. Rothwell, *Neurosci. Biobehav. Rev.* **14**, 263 (1990); M. Spina *et al.*, *Science* **273**, 1561 (1996).
69. G. A. Bray, J. Fisler, D. A. York, *Front. Neuroendocrinol.* **11**, 128 (1990).
70. D. P. Figlewicz, L. J. Stein, D. B. West, D. Porte Jr., S. C. Woods, *Am. J. Physiol.* **250**, R856 (1986); C. A. Matson, M. F. Wiater, J. L. Kuijper, D. S. Weigle, *Peptides* **18**, 1275 (1997).
71. J. M. De Castro, *Neurosci. Biobehav. Rev.* **20**, 1119 (1996); *J. Nutr.* **128**, 61 (1998).
72. E. J. Drenick and D. Johnson, *Int. J. Obes.* **2**, 123 (1978); D. D. Stallone and A. J. Stunkard, *Ann. Behav. Med.* **13**, 220 (1991).

73. Supported by grants from the NIH (DK 17844, DK 54080, DK 54890, DK 12829, DK 52989, and NS 32273), the Diabetes Endocrinology Research Center and Clinical Nutrition Research Unit of the University of Washington, and the Merit Review Program of the Department of Veterans Affairs and funds from the Division of Metabolic Diseases, Hoffmann-La Roche, Nutley, NJ.

Strategies and Potential Molecular Targets for Obesity Treatment

L. Arthur Campfield,* Françoise J. Smith, Paul Burn

Obesity is an increasingly prevalent and important health problem. Although treatment is available, the long-term maintenance of medically significant weight loss (5 to 10 percent of initial body weight) is rare. Since 1995 there has been an explosion of research focused on the regulation of energy balance and fat mass. Characterization of obesity-associated gene products has revealed new biochemical pathways and molecular targets for pharmacological intervention that will likely lead to new treatments. Ideally, these treatments will be viewed as adjuncts to behavioral and lifestyle changes aimed at maintenance of weight loss and improved health.

Obesity is an increasingly prevalent, costly, and important health problem throughout the world (*1*, *2*). In the United States, the prevalence of obesity in adults is now 32%, and the prevalence in children has risen by 40% over the last 16 years. Similar trends are being seen worldwide (*1*).

Obesity is a particularly challenging medical condition to treat because of its complex etiology. Body weight represents the integration of many biological and environmental components. The environmental components (*3*) can be modulated through behavioral changes such as healthy eating and physical activity, whereas the biological components are much more difficult to address. Changes in body weight are resisted by very robust physiologic mechanisms that we are only beginning to understand (*4*–*6*). However, the recent explosion of research on the altered biochemical pathways caused by single gene mutations in animal models of obesity has dramatically expanded our knowledge base of these physiologic mechanisms (*6*). As a result, efforts to develop innovative anti-obesity drugs have intensified. Here, we discuss some of the potential drug targets that have emerged from this "new science" of obesity.

The authors are in the Department of Metabolic Diseases, Hoffmann–La Roche Incorporated, 340 Kingsland Street, Nutley, NJ 07110, USA.

*To whom correspondence should be addressed. E-mail: l_arthur.campfield@roche.com

Assessing the Efficacy of Obesity Treatments

Traditionally, the efficacy of a new obesity treatment is assessed by its effect on body weight. By this criterion, a treatment is considered successful if it (i) prevents further weight gain, (ii) induces a 5 to 10% weight loss from the initial body weight, and (iii) allows long-term maintenance of the weight loss once it is achieved (*1*, *7*).

Recently, an alternative, medically based outcome measure for obesity treatment has been advocated by scientists and physicians (*7*). Rather than focusing primarily on body weight, body fat, or the body mass index (BMI = weight/height^2), this measure, called "metabolic fitness," tracks the metabolic health of obese individuals. Metabolic fitness is defined as the absence of biochemical risk factors associated with obesity, such as elevated fasting concentrations of cholesterol, triglycerides, glucose, or insulin; impaired glucose tolerance; or elevated blood pressure. In this school of thought, weight loss is viewed not as a goal but as a modality to improve health (*7*). Many studies have shown that during periods of weight loss there is a uniform improvement in the profile of risk factors (*1*). Interestingly, reductions in the biochemical risk factors may not always be dependent on weight loss. For example, insulin sensitivity and cholesterol levels can be improved by physical activity in the absence of weight loss (*1*, *3*, *8*). The hope is that by using metabolic fitness as a measure of success, health professionals can shift the patient's focus from unrealistic, culturally imposed goals (for example, dress size or belt size), to the more appropriate and achievable goal of better health (*7*).

Classes of Anti-Obesity Drugs

Anti-obesity drugs can be classified according to their primary mechanism of action on energy balance. When daily energy intake matches daily energy expenditure, body weight remains constant. If intake exceeds expenditure, then a state of positive energy balance is achieved and body weight will increase. Conversely, if energy expenditure exceeds intake, then a state of negative energy balance is achieved and body weight will decrease. The goal of all anti-obesity drugs is to induce and maintain a state of negative energy balance until the desired weight loss is achieved (*4*, *5*, *9*–*11*).

There are four general classes of anti-obesity drugs. (i) Inhibitors of energy (food) intake (or appetite suppressants) reduce hunger perception, increase the feeling of fullness, and reduce food intake by acting on brain mechanisms. As a result, these drugs facilitate compliance with caloric restriction. (ii) Inhibitors of fat absorption reduce energy intake through a peripheral, gastrointestinal mechanism of action and do not alter brain chemistry. (iii) Enhancers of energy expenditure act through peripheral mechanisms to increase thermogenesis without requiring planned increases in physical activity. (iv) Stimulators of fat mobilization act peripherally to reduce fat mass or decrease triglyceride synthesis or both without requiring planned increases in physical activity or decreases in food intake. Importantly, the beneficial actions of all four drug classes can be easily overcome by increased intake of food (especially calorically dense food items) or decreased voluntary physical activity.

The major drugs used to treat obesity are shown in Table 1. Currently, the only drugs approved for use are a small set of centrally acting appetite suppressants that reduce food intake by modulating the concentrations of monoamine neurotransmitters (serotonin and norepinephrine or norepinephrine alone) in the brain. This modulation can occur at the level of neurotransmitter release or re-uptake or both. The identifi-

cation of the specific subtypes of serotonin receptors involved in the regulation of food intake is a major focus of research. Appetite suppressants generally produce an average weight loss of about 10% of initial body weight (*1*).

One of these drugs, dexfenfluramine (Redux), was approved by the Food and Drug Administration (FDA) in June 1996. Although some concerns had been raised about the possible risk of primary pulmonary hypertension and loss of serotonergic neurons, the drug was approved on the basis of its low risk/benefit ratio and extensive clinical experience in Europe and, indeed, was the first anti-obesity drug approved in the United States in more than 20 years. In response to an unexpected cluster of reports of heart valve disease (valve leakage, seen best on echocardiograms) in obese patients who had been treated with dexfenfluramine or a combination of older anti-obesity drugs (fenfluramine and phentermine), both dexfenfluramine and fenfluramine were withdrawn from the global market by the manufacturer in September 1997. It is not yet known if the heart valve leakage observed was due to action of the drugs on the central or peripheral serotonin system or to another unknown mechanism. The National Institutes of Health issued a recommendation in November 1997 that all individuals treated with these drugs, alone or in combination with phentermine, visit their physicians for assessment of their medical condition. Subsequently, the FDA approved sibutramine (Meridia), a combined serotonin and norepinephrine re-uptake inhibitor. In contrast to dexfenfluramine, sibutramine does not stimulate the release of serotonin from nerve endings (*12*).

Orlistat (Xenical), a new drug currently under FDA review, acts by an entirely different mechanism that does not affect the brain. It specifically targets pancreatic lipases, enzymes that digest fat into fatty acids and monoglycerides that can be absorbed into the body. When the lipases are blocked, about one-third of the fat passes through the gastrointestinal tract and is excreted, which reduces the amount of fat absorbed and stored in fat cells (*13*).

Potential Targets for New Anti-Obesity Medicines

Perhaps the most significant new target is the recently isolated hormone OB (the product of the obesity gene *OB*, also known as leptin), which has rapidly become appreciated as a critical signal in the regulation of body fat and body weight. OB is produced by fat cells, circulates in the blood, and enters the brain where it functions to reduce food intake, reduce serum glucose and insulin levels, and increase metabolic rate, ultimately leading to a reduction in fat mass and body weight (6). Mice deficient in OB are obese, and administration of exogenous OB to these mice causes dramatic reductions in food intake and body weight (*14*, *15*). It also causes reduction of food intake and body weight when administered to lean mice, rats, and monkeys (6). OB mediates its effects through a specific receptor, OB-R, which has been cloned and characterized (*16*). A model of the OB signaling pathway is shown in Fig. 1 (6).

The next generation of medicines to treat obesity may target the OB pathway. If OB has all, or even some, of the same biological activities in humans as in mice, a single drug that activates the OB pathway may have multiple therapeutic benefits: It may not only suppress appetite and increase metabolic rate, but may also reduce the amount of body fat.

Obese humans have increased serum levels of OB, suggesting that obesity is due

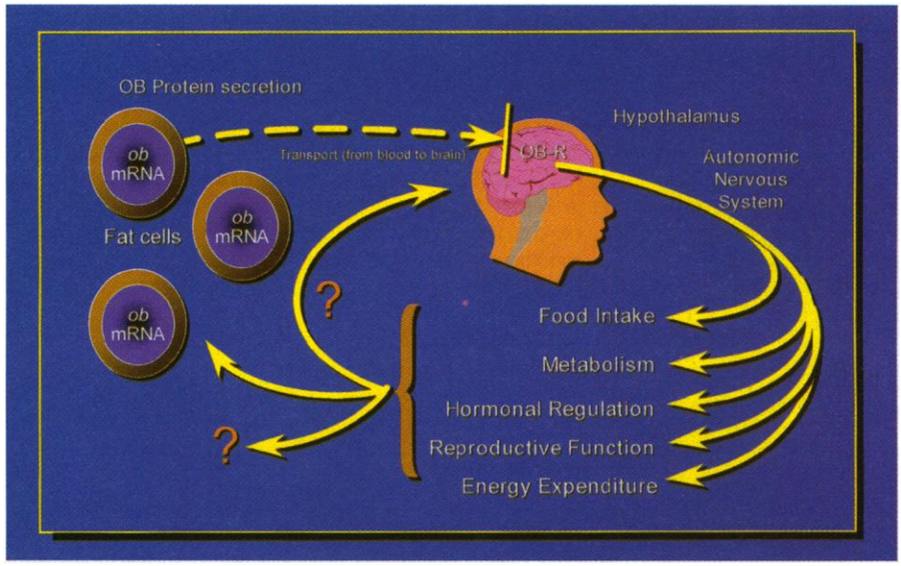

Fig. 1. A schematic model of some of the important elements of the OB signaling pathway that regulates body energy balance [adapted from (6)].

Table 1. Classes of anti-obesity drugs. (There are no current drugs that enhance energy expenditure.)

Drug	Target	Mechanism	Status
	Inhibitors of energy intake (appetite suppressants)		
Fenfluramine	Serotonergic neurons	Inhibits serotonin re-uptake and stimulates serotonin release	Withdrawn
Phentermine	Noradrenergic neurons	Inhibits norepinephrine re-uptake	FDA approval
Fenfluramine and phentermine (Fen/Phen)	Serotonergic and noradrenergic neurons	Inhibits serotonin re-uptake and stimulates serotonin release; inhibits norepinephrine re-uptake	Combination of individually approved drugs (fenfluramine now withdrawn)
Dexfenfluramine (Redux)	Serotonergic neurons	Inhibits serotonin re-uptake and stimulates serotonin release	Withdrawn
Sibutramine (Meridia)	Serotonergic and noradrenergic neurons	Inhibits serotonin and norepinephrine re-uptake	FDA approval
OB (leptin)	OB receptor	Activates OB receptor in brain and reduces food intake	In phase II clinical trials
	Inhibitors of fat absorption		
Orlistat (Xenical)	Pancreatic lipase	Inhibits fat absorption	Under FDA review
	Stimulators of fat mobilization		
OB (leptin)	OB receptor	Mobilization of fat mass	In phase II clinical trials

to a decreased sensitivity to OB, not a deficiency of OB (*6*, *17*). Thousands of obese individuals have been screened for mutations in the *OB* and *OB-R* genes. Thus far, three families have been found to have mutations. Two cousins (male and female) from a large consanguineous family from India have homozygous frameshift mutations resulting in the deletion of a single guanine nucleotide in *OB*, and as expected, they have low or undetectable levels of functional OB. They were both normal weight at birth and then rapidly became severely obese, just like OB-deficient, obese mice (*18*). Three obese members of a Turkish family have recently been shown to carry a homozygous missense mutation in *OB* that is associated with low serum levels of OB (*19*). Finally, three severely obese sisters in a large consanguineous family of Kabilian origin have been found to be homozygous for a splice-site mutation in the *OB-R* gene; the mutant gene is predicted to encode a truncated form of OB-R that lacks both the transmembrane and intracellular domains and, therefore, presumably has no signaling function. There were no signs of pubertal development in two of the adult sisters (*20*), consistent with studies in mice and humans showing that OB also has a role in reproductive development (*21*). These findings strongly suggest that OB plays an important role in the regulation of body fat, body weight, and reproductive function in humans.

The observation that most obese individuals have elevated serum levels of OB has prompted speculation that human obesity can arise from reduced brain responsiveness to OB. This hypothesis is supported by studies of diet-induced obese (DIO) mice. When lean AKR/J mice are fed a high-fat, energy-dense diet, they become obese and their serum levels of OB and insulin rise (*14*). In comparison to lean AKR/J mice, the DIO mice require higher intraperitoneal doses of OB to alter food intake, metabolism, and body fat. Recent studies indicate that brain responsiveness to OB is reduced in these obese animals and can be reversed by weight loss (*22*). Thus, in terms of OB-based therapy for obesity, a reasonable goal would be to identify the molecular determinants of reduced OB responsiveness and then develop low molecular weight compounds that enter the brain and act on these molecules to increase responsiveness to OB. In principle, a drug that overcomes the weak link or links in the brain pathway that prevent the message conveyed by OB from producing an appropriate response in obese individuals would provide an elegant solution to obesity treatment.

Several additional proteins have been implicated in human obesity and may provide other therapeutic targets. A conceptual representation of the currently known mouse and human obesity gene products and the brain pathways in which they may act is shown in Fig. 2. On the left is the afferent limb of the OB pathway: OB is secreted by fat cells, circulates in the blood, and is transported into the brain. In the middle of the figure is an array of model classes of neurons that are responsive to OB, each producing a specific neuropeptide. On the right is a model neuronal network, the efferent limb of the OB pathway, that controls energy balance through actions on ingestive behavior, the autonomic nervous system, hormones, metabolic rate, and energy expenditure. This network responds to all of the neuropeptides thought to be involved in the control of energy balance: neuropeptide Y (NPY), agouti-related peptides, proopiomelanocortin (POMC) and POMC products including α-melanocyte stimulating hormone (α-MSH) and possibly other melanocortin-4 receptor (MC4-R) ligands, corticotropin releasing hormone (CRH or CRF) and the closely-related urocortin, melanocyte-concentrating hormone (MCH), galanin, orexin (also known as hypocretin), and TUB. The network also responds to the gastrointestinal hormones cholecysto-

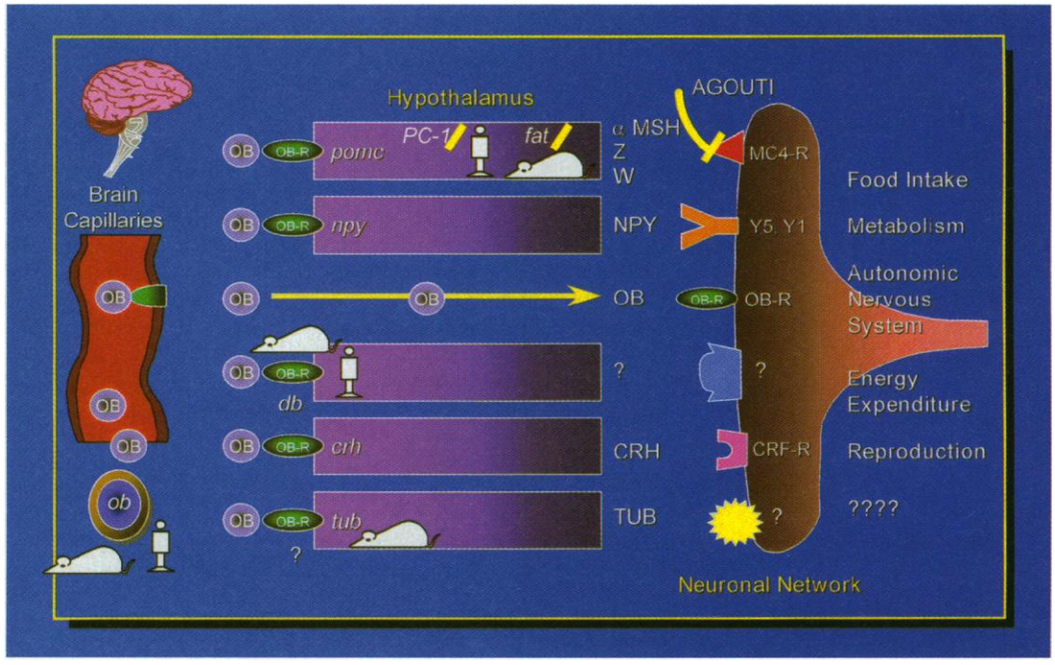

Fig. 2. A conceptual representation of the currently known mouse and human obesity gene products and the brain pathways in which they may act. On the left is the afferent limb of the OB pathway; fat cells (oval with "*ob*", bottom left) secrete OB protein (circles) into the bloodstream and brain capillaries (shown in cross-section), which then enters the brain by a receptor-mediated transport system (half ellipse). The middle diagrams show an array of model classes of OB-responsive neurons (rectangles). OB binds to its receptor, OB-R (encoded by the *db* gene) and alters the expression of the genes indicated (*pomc*, *npy*, "*?*", *crh*, and *tub*), producing the specific neuropeptides shown (on the right side of the rectangles). "Z", "W", and "?" denote presently unknown neuropeptides. The biology of TUB is unknown (*41*). On the right is a model neuronal network schematically represented by the large nerve ending with receptors for the indicated neuropeptides and proteins. This network forms the efferent limb of the OB pathway, through which it controls energy balance by modulating ingestive behavior, metabolism, autonomic nervous system, energy expenditure, reproduction, and as yet unidentified actions ("????"). Note that each of these biological actions is probably determined by multiple neuropeptides or proteins. The mouse or the human character represents mutations in specific genes associated with obesity in mice and humans. The arrow with OB shows that it can also act directly on the neuronal network. According to this scheme, potential anti-obesity drugs can be based on any intervention between the neuropeptide synthesis or release and activation of its receptor.

kinin, bombesin, and glucagon-like peptide–1 (GLP-1), as well as OB, AGOUTI, and growth hormone (GH) (*23*). Mutations in specific genes that are associated with obesity in mice and humans are indicated by the mouse or human character in the figure.

A mutation in the *agouti* gene is responsible for obesity in a strain of yellow mice (*24*). Recent genetic and pharmacological research strongly suggests that AGOUTI causes obesity by blocking MC4-R in the brain (*25*, *26*). Mice deficient in MC4-R develop late-onset obesity and alterations in their peripheral metabolism (*25*). This observation, combined with experiments with MC4-R agonists (which decrease food intake) and antagonists (which increase food intake), indicates that MC4-R is part of a physiological pathway that normally inhibits food intake and fat storage. This pathway may play an important role in late-onset obesity (*26*).

A mutation in the gene *fat* (*27*) causes obesity in mice by decreasing the amount of an enzyme, carboxypeptidase E (CPE), that may be involved in the final stages of processing insulin and POMC and other hormones. Interestingly, an obese person has been identified who carries a mutation in the gene for prohormone convertase–1 (PC-1), an enzyme that catalyzes a reaction preceding that catalyzed by CPE (*28*). These findings indicate that correct processing of certain, as yet unknown, proteins and hormones can be essential for mice and humans to maintain a lean body composition.

Table 2. Potential therapeutic targets for new anti-obesity drugs.

Target	Type of drug
Inhibitors of energy intake (appetite suppressants)	
Serotonin	Re-uptake inhibitors
Norepinephrine	Re-uptake inhibitors
Dopamine	Re-uptake inhibitors
OB receptor	Agonists
NPY receptor (Y5, Y1)	Antagonists
MC4 receptor	Agonists
Agouti-related peptides	Agonists
POMC	Antagonists
MCH receptor	Antagonists
CRH receptor/CRH binding proteins	Antagonists
Urocortin	Antagonists
Galanin receptor	Antagonists
Orexin/hypocretin	Antagonists
CCK-A receptor	Agonists
GLP-1 receptor	Agonists
Bombesin	Agonists
Enhancers of energy expenditure	
UCP2/UCP3	Stimulators of expression/activity
PKA	Stimulators
β-3 Adrenergic receptor	Agonists
Stimulators of fat mobilization	
OB receptor	Agonists
PKA	Stimulators
β-3 Adrenergic receptor	Agonists
GH receptor	Agonists

NPY is the most widely distributed neuropeptide in the brain, and it exerts multiple biological effects. In addition to being one of the most potent appetite stimulators in animals, it appears to be one of the mediators of OB action in the brain (*29*). There is currently much interest in identifying the NPY receptor subtypes that mediate the effects of NPY on food intake and energy balance. Other potential targets are uncoupling protein 2 (UCP2) and 3 (UCP3). These proteins, which are expressed in peripheral tissues, belong to a family of proton transporters that, when activated, may cause increased thermogenesis, leading to reduced storage of fat (*30*).

According to the scheme shown in Fig. 2, potential anti-obesity drugs can be based on any intervention between the neuropeptide and its receptor that would alter the biological responses mediated by the neuronal network—in particular, food intake, metabolism, and energy expenditure. These potential drugs, listed in Table 2, can be classified as inhibitors of energy intake, enhancers of energy expenditure, and stimulators of fat mobilization.

Many pharmaceutical companies have large programs directed at the development of new modulators of monoamine neurotransmitters and neuropeptide receptor agonists or antagonists. In addition to the well-documented effect of serotonin modulation on food intake, there is strong evidence that modulation of dopamine or norepinephrine has an effect (*31*). There is also a large effort to develop antagonists for specific NPY receptors (Y5, Y1) that have been associated with food intake (*32*). Among the newer targets, MC4-R has attracted a lot of attention. Selective MC4-R agonists could inhibit food intake, and because AGOUTI inhibits MC4-R, analogs of the agouti-related peptides may also serve as appetite suppressants. It is widely believed that the endogenous ligand of MC4-R is α-MSH or another product of POMC processing; thus, compounds that increase POMC levels may also reduce food intake (*33*). Other potential neuropeptide targets for appetite suppressants include receptors for MCH, CRH (and the closely related urocortin), galanin, opioid peptides, and the recently discovered orexin (hypocretins) (*23*, *34*).

Receptors for three well-known gastrointestinal hormones are also targets for the development of appetite suppressants. Cholecystokinin (CCK) is released from the intestine in response to meals and plays an important role in meal termination. CCK-A receptor agonists reduce meal size and food intake in animals (*35*). Bombesin reduces food intake when injected into rodents; thus, bombesin receptor agonists may be useful as appetite suppressants (*36*). Although GLP-1 has been under study as an endogenous stimulator of insulin release from the pancreas in humans, it was recently shown that brain administration of GLP-1 to rats reduces food intake (*37*). If gastrointestinal and other side effects can be avoided, GLP-1 receptor agonists may also be useful for reducing food intake.

New targets for drugs that enhance energy expenditure include the aforementioned uncoupling proteins (UCP2 and UCP3) and the well-characterized enzyme protein kinase A (PKA). Mice in which PKA is dysregulated (by inactivation of the PKA subunit RII β) are lean and resistant to diet-induced obesity (*38*). Thus, in theory, pharmacologic stimulation of PKA may cause increased thermogenesis and fat mobilization.

Another drug target in this category is the β-3 adrenergic receptor, which has been extensively studied. Large development programs have identified several agonists. Early nonselective compounds that were β-adrenergic receptor agonists increased thermogenesis in obese humans, but they had unwanted side effects including increased heart rate or tremor (*39*). These drugs also increase fat mobilization in animals. Newer, apparently selective, β-3 adrenergic receptor agonists have not increased thermogenesis in humans, and the search for more effective agonists continues.

Drugs that would potentially stimulate fat mobilization include growth hormone (GH) receptor agonists, OB, PKA stimulators, and β-3 adrenergic receptor agonists. In animal studies, administration of GH increases lean muscle mass and reduces fat mass. The role of GH in the treatment of obesity is currently being evaluated in clinical trials (*40*).

Conclusions

Complementary investigations at the pharmacologic, physiologic, and behavioral levels will be critical to the evaluation of all new anti-obesity drugs. The most effective pharmacologic treatments are likely to be those that involve the use of a combination of drugs, each with a distinct mechanism of action, or a single drug with multiple activities. Indeed, if OB is found to have the same biological activities in humans as in rodents, a drug targeting this pathway could theoretically have multiple beneficial activities.

Obesity is a chronic disease, and the possibility of long-term treatment—either

continuous or intermittent treatment throughout adult life—is a concept that is receiving more attention. In this context, the risk-benefit and quality-of-life analyses of pharmacologic treatment become increasingly important. Vigorous dialog between health care professionals, patients, the research community, and regulatory authorities is needed to define, in objective and quantifiable terms, the minimum efficacy required to justify long-term treatment. Safety considerations are critical. For example, because women make up the largest group seeking treatment for obesity, potential drugs must be tested in long-term studies for possible undesired effects on reproductive function and hormonal status.

Innovative drugs will be most effective when they are used as adjuncts to, rather than substitutes for, lifestyle changes to improve the metabolic fitness, health, and quality of life for obese individuals. Such drugs will likely be part of sequential or combined treatment programs tailored to individual patients. In summary, although the path to innovative medicines for obesity is strewn with many obstacles, the recent progress in the "new science" of obesity provides hope that the future of obesity treatment will be bright.

REFERENCES AND NOTES

1. P. R. Thomas, Ed., *Weighing the Options: Criteria for Evaluating Weight-Management Programs* (Food and Nutrition Board, Institute of Medicine, National Academy Press, Washington, DC, 1995); D. B. Allison and F. X. Pi-Sunyer, Eds., *Obesity Treatment: Establishing Goals, Improving Outcomes, and Reviewing the Research Agenda* (Plenum, New York, 1995).
2. P. Bjorntorp and B. N. Brodoff, Eds., *Obesity* (Lippincott, Philadelphia, 1992).
3. J. Hill, *Science* **280**, 1371 (1998).
4. C. Bouchard and L. Perusse, *Annu. Rev. Nutr.* **13**, 337 (1993).
5. R. L. Leibel, M. Rosenbaum, J. Hirsch, *N. Engl. J. Med.* **232**, 621 (1995).
6. L. A. Campfield, F. J. Smith, P. Burn, *Horm. Metab. Res.* **28**, 619 (1996); *Endocrinol. Metab.* **4**, 81 (1997).
7. L. A. Campfield, in *Overweight and Weight Management*, S. Dalton, Ed. (Aspen Press, Gaithersburg, MD, 1997), pp. 466–485; in *Obesity Treatment: Establishing Goals, Improving Outcomes, and Reviewing the Research Agenda*, D. B. Allison and F. X. Pi-Sunyer, Eds. (Plenum, New York, 1995), pp. 93–95; G. L. Blackburn, D. Miller, S. Chan, *Nurs. Clin. North Am.* **32**, 831 (1997).
8. J. O. Hill, H. J. Douglas, J. C. Peters, in *Physical Activity, Fitness, and Health: International Proceedings and Consensus Statement*, C. Bouchard, R. J. Shepard, T. Stephens, Eds. (Human Kinetics, Toronto, Canada, 1994).
9. J. Le Magnen, *Behav. Brain Sci.* **4**, 561 (1980).
10. C. Bogardus *et al.*, *N. Engl. J. Med.* **315**, 96 (1986).
11. M. Rosenbaum, R. L. Leibel, J. Hirsch, *ibid.* **337**, 396 (1997); M. Rosenbaum and R. L. Leibel, *Pediatrics* **101**, 525 (1998).
12. D. H. Ryan, P. Kaiser, G. A. Bray, *Obes. Res.* **3**, 553S (1995); M. J. Stock, *Int. J. Obes.* **21**, S25 (1997).
13. M. L. Drent *et al.*, *Int. J. Obes.* **19**, 221 (1995).
14. L. A. Campfield, F. J. Smith, Y. Guisez, R. Devos, P. Burn, *Science* **269**, 546 (1995).
15. M. Pelleymounter, et al., *ibid.*, p. 540; J. L. Halaas *et al.*, *ibid.*, p. 543; T. W. Stephens *et al.*, *Nature* **377**, 530 (1995).
16. L. A. Tartaglia *et al.*, *Cell* **83**, 1263 (1995).
17. R. V. Considine *et al.*, *N. Engl. J. Med.* **334**, 292 (1996); M. Maffei *et al.*, *Nature Med.* **1**, 1155 (1995).
18. C. T. Montague *et al.*, *Nature* **387**, 903 (1997).
19. A. Strobel, T. Issad, L. Camoin, M. Ozata, D. Strosberg, *Nature Genet.* **18**, 213 (1998).
20. K. Clement *et al.*, *Nature* **392**, 398 (1998).
21. F. Chehab, M. Lim, R. Lu, *Nature Genet.* **12**, 318 (1996).
22. L. A. Campfield *et al.*, *Soc. Neurosci. Abstr.* **23**, 815 (1997).
23. S. C. Woods, *Science* **280**, 1378 (1998).
24. S. Bultman, E. Michaud, R. Woychik, *Cell* **71**, 1195 (1992).
25. D. Huszar *et al.*, *ibid.* **88**, 131 (1997).
26. W. Fan, B. A. Boston, R. A. Kesterson, V. J. Hruby, R. D. Cone, *Nature* **385**, 165 (1997).
27. J. Naggert *et al.*, *Nature Genet.* **10**, 134 (1995).
28. R. S. Jackson *et al.*, *ibid.* **16**, 303 (1997).
29. J. T. Clark, P. S. Kalra, W. R. Crowley, S. P. Kalra, *Endocrinology* **115**, 427 (1984); H. M. Frankish, S. Dryden, D. Hopkins, Q. Wang, G. Williams, *Peptides* **16**, 757 (1995); F. J. Smith, L. A. Campfield, J. A. Moschera, P. Bailon, P. Burn, *Nature* **382**, 307 (1996).
30. R. E. Gimeno *et al.*, *Diabetes* **46**, 900 (1997); O. Boss, et al., *FEBS Lett.* **408**, 39 (1997); C. Fleury *et al.*, *Nature Genet.* **15**, 269 (1997); A. Vidal-Puig, G. Solanes, D. Grujic, J. S. Flier, B. B. Lowell, *Biochem. Biophys. Res. Commun.* **235**, 79 (1997).
31. J. Blundell, *Trends Pharmacol. Sci.* **12**, 147 (1991).
32. C. Gerald *et al.*, *Nature* **382**, 168 (1996).
33. M. W. Schwartz *et al.*, *Diabetes* **46**, 2119 (1997).
34. T. Sakurai *et al.*, *Cell* **92**, 573 (1998).
35. T. H. Moran, P. J. Ameglio, H. J. Peyton, G. J. Schwartz, P. R. McHugh, *Am. J. Physiol.* **265**, R620 (1993).
36. H. Ohki-Hamazaki *et al.*, *Nature* **390**, 165 (1997).
37. Z. Wang *et al.*, *J. Clin. Invest.* **95**, 417 (1995).
38. D. E. Cummings *et al.*, *Nature* **382**, 622 (1996).
39. E. Danforth Jr. and J. H. Himms-Hagen, *Eur. J. Endocrinol.* **136**, 362 (1997).
40. G. Johannsson *et al.*, *J. Clin. Endocrinol. Metab.* **82**, 727 (1997).
41. P. W. Kleyn *et al.*, *Cell* **85**, 281 (1996); K. Nobentrauth, J. Naggert, M. North, P. Nishina, *Nature* **380**, 534 (1996).

42. We thank J. F. R. Curtis for assistance with the artwork; K. Yagaloff, S. Fisher, W. Danho, J. Kochan, D. Hartman, J. Grippo, R. Sarabu, S. Wertheimer, A. Olivier, R. Garippa, J. Coffey, B. Oemar, and J. Guenot for insightful discussions; I. Rivera, J. Yu, M. Renzetti, and G. Mackie for technical assistance; and D. Loh for support, encouragement, and helpful comments. Because of space limitations, it was not possible to include a comprehensive list of references for all of the work discussed.

Eating Disorders: Progress and Problems

B. Timothy Walsh* and Michael J. Devlin

Recent research on Anorexia Nervosa and Bulimia Nervosa has yielded an increasingly detailed understanding of the range of biological and psychological abnormalities associated with these eating disorders. Inherited vulnerabilities, cultural pressures, and adverse individual and family experiences all appear to contribute to the onset of extreme dieting, binge eating, and purging. Once initiated, these behaviors give rise to multiple physiological disturbances, some of which may serve to perpetuate the illness. Although there have been substantial advances in the management of Bulimia Nervosa, the goal of offering effective treatment to all individuals with eating disorders remains elusive. This article reviews current thinking on the etiology and treatment of the two major eating disorders and a related syndrome, Binge Eating Disorder.

Over the past 25 years, Anorexia Nervosa (AN) and Bulimia Nervosa (BN), the two officially recognized eating disorders, have become a major focus of attention among both the research community and the general public. Together these illnesses affect about 3% of women over their lifetime, and BN, the more common disorder, appears to be increasing in incidence. The causes of AN and BN remain enigmatic. Cultural and environmental factors are thought to play a role, as eating disorders are generally more common in industrialized than in developing nations. The possible etiologic role of biological factors has been difficult to study because the disorders are relatively rare and because good animal models do not yet exist. Although significant strides have been made in developing effective treatments for BN, AN remains difficult to treat, especially over the long term. Here we provide an overview of recent progress.

The authors are with the New York State Psychiatric Institute and the College of Physicians & Surgeons, Columbia University, 722 West 168th Street, New York, NY 10032, USA.

*To whom correspondence should be addressed. E-mail: btw1@columbia.edu

Anorexia Nervosa: An Old Enigma

AN is among the most disabling and lethal of psychiatric disorders. Although it is sometimes attributed to the widespread practice of dieting among women in the late twentieth century, the first case of AN was reported 300 years ago and by 1874 the syndrome was already well described (*1*).