

Science, medicine, and the future

Obesity treatment

John Wilding

Obesity now affects 15% of the population, and is an underlying factor in many diseases, yet, surprisingly, it has until recently attracted little medical or scientific interest. The epidemic of obesity is probably a result of increasingly sedentary lifestyles combined with easy availability of palatable, high fat foods. However, not everyone exposed to this environment becomes obese, and there is good evidence that the tendency to develop obesity is inherited—in the vast majority of cases as a complex polygenic trait, with a few rare cases of extreme obesity being due to single gene defects.

Doctors readily accept the need to treat the consequences of obesity, but obesity itself is often ignored because available treatments are considered ineffective or unsafe. Public health measures to prevent obesity are important, but the evidence that even modest weight loss is beneficial, as long as it is maintained, makes a strong case for managing obesity in its own right. In this article I review the mechanisms that control body weight and discuss how understanding these may lead to the development of new, effective, and safe treatments for obese people.

The obesity epidemic

Over half of the British population are now overweight. Between 1980 and 1995, the prevalence of obesity in Britain doubled from 8% to 15%. The myriad medical consequences of obesity make it relevant for most doctors.

Mortality rises exponentially with increasing body weight.¹ The risk of coronary heart disease is doubled if the body mass index (weight (kg)/(height (m)²) is >25 and nearly quadrupled if the index is \geq 29. The risk of developing diabetes increases with increasing weight,

Definition of obesity

- A body mass index (kg/m²) >25 is considered overweight
- In Britain obesity is defined as a body mass index >30
- An alternative to calculating body mass index is to measure waist circumference:
Suggested cutoffs indicating significantly increased risk are >80 cm for women and >94 cm for men
Waist sizes at which intervention is considered necessary are >88 cm for women and >102 cm for men

Possible futures of obesity treatment

Public health measures must remain a priority

New drugs with different modes of action will be developed

Drugs may be used in combination

Surgery will be increasingly used for morbid obesity

Specific treatment may help those with known gene defects

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and people with a body mass index >35 have a 40-fold higher risk of developing the disease than non-obese people. Respiratory disease, particularly sleep apnoea, and osteoarthritis are more common in obese people. They also have higher risks of developing many cancers—for example, the risks of large bowel and endometrial cancers are increased twofold to fivefold. Surgery and anaesthesia are more hazardous, and obesity increases obstetric risk. Psychiatrists may see obese patients because of low self esteem and other problems related to obesity.

Is weight loss a worthwhile goal?

Substantial improvements in associated morbidity occur with successful weight loss. Modest weight loss of about 10% results in clinically beneficial improvements in several parameters, such as blood glucose and lipids, as well as improved physical performance and well-being. Greater loss of weight, for example after surgery, gives greater benefit. Weight maintenance is important once weight is lost, and this is a major limitation of most existing approaches.

How can weight loss be achieved?

Dieting usually results in weight loss, and the initial effect may be greater if very low calorie diets are used. Weight is usually regained, however, although there is evidence that cognitive-behaviour therapy and modest exercise regimens may improve the chances of long term success.^{2,3}

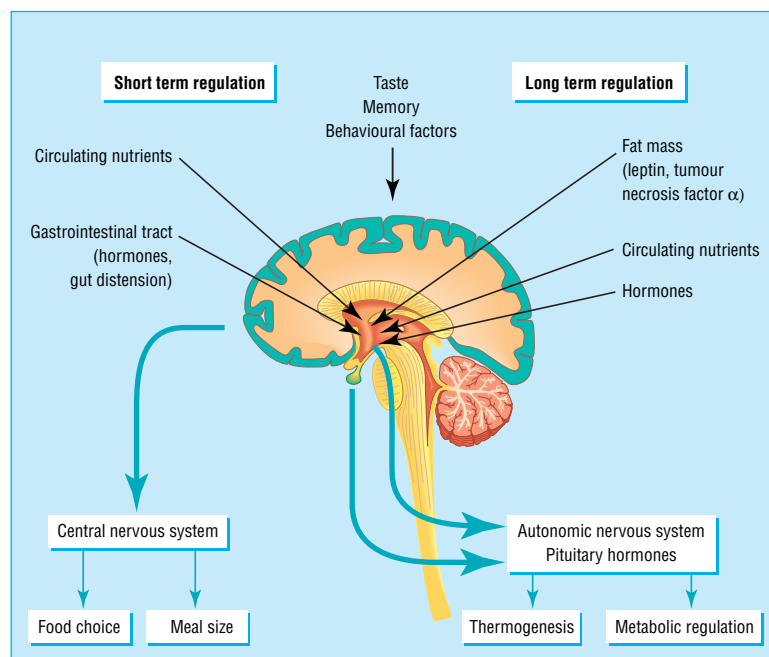


Fig 1 The hypothalamus integrates signals from the gut and circulation to regulate satiety. It responds to long term signals indicating the body's energy stores and is also influenced by higher centres. This information is used to determine how much and what sort of food is eaten, and the regulation of thermogenesis

Weight loss of up to 10% can be achieved with drugs, but since the recent withdrawal of dexfenfluramine—because of reports of a carcinoid-like valvular heart disease with this and the combination of fenfluramine and the amphetamine-like drug phentermine⁴ and a small risk of primary pulmonary hypertension—none is currently licensed for the treatment of obesity in Britain.

The most impressive results come from studies of patients who have had surgical treatment for morbid obesity (body mass index >40) and have lost 30-40 kg. An ongoing prospective controlled study of over 600 patients has shown that vertical banded gastroplasty reduces the incidence of diabetes from 16% to under 1% over 2 years, with improvements in many other risk factors.⁵ While surgery may be used increasingly for the morbidly obese, diet and exercise are likely to remain the cornerstones of any approach and there is a need for better long term treatments.

Control of energy balance

If new treatments for obesity are to be developed it is important to understand the physiological pathways that regulate energy balance (both intake and expenditure), and to identify the factors causing obesity. In the past few years, considerable progress has been made through a combination of physiological research and genetic studies in animals and humans.

The hypothalamus

The nerve centre for regulation of energy balance is the hypothalamus, which integrates neural, hormonal, and nutrient messages from elsewhere in the body and sends signals to higher centres leading to feelings of hunger or satiety. The hypothalamus also controls energy expenditure via the autonomic nervous system

and pituitary hormones (fig 1). The hypothalamus is a complex structure, containing many discrete nuclei, many of which are interconnected and linked to other brain structures. These nuclei contain over 40 neurotransmitters, many of which are implicated in the control of energy balance (see box).

Neuropeptide Y

Of the few neurotransmitters that stimulate feeding, neuropeptide Y has attracted the most interest. Neuropeptide Y is abundant in the hypothalamus of rodents and humans, and in rodents is the most powerful appetite stimulant known. It also suppresses sympathetic nervous system activity, thus reducing energy expenditure. In experimental animal studies, chronic administration leads to weight gain, and non-specific blockade with monoclonal antibodies inhibits food intake. A specific receptor (the Y5 receptor) may mediate these effects of neuropeptide Y. Genetic studies have not shown any association with the genes for neuropeptide Y or Y5 receptor in human obesity.⁶ Studies are under way to assess the therapeutic potential of specific antagonists of the neuropeptide Y-Y5 receptor.

Neurotransmitters that inhibit feeding

These are more numerous, and it has been more difficult to prove specific roles for them as satiety factors. Several anorectic drugs such as phentermine, fenfluramine, and dexfenfluramine act by increasing the release of noradrenaline and serotonin from nerve terminals. Cholecystokinin, released from the gut after a meal, may be one of many peripheral satiety signals. Interestingly, it also acts as a central inhibitor of appetite, and its peripheral release may mediate its release in the central nervous system. Levels of cholecystokinin are normal in obese people, but a physiological role for this hormone in regulating meal size in

Neurotransmitters affecting energy balance

A large number of hypothalamic neurotransmitters affect both food intake and thermogenesis. Those that increase food intake generally suppress sympathetic nervous system activity and thus thermogenesis, whereas the reverse is true for neurotransmitters that decrease appetite

Factors that increase food intake

- Noradrenaline
- Opioids
- Growth hormone-releasing hormone
- Galanin
- Melanin-concentrating hormone
- Neuropeptide Y

Factors that inhibit food intake

- Serotonin
- Dopamine
- Cholecystokinin
- Corticotrophin-releasing factor
- Neurotensin
- Bombesin
- Calcitonin gene related peptide
- Amylin
- Adrenomedullin
- Glucagon
- Glucagon-like peptide 1

humans has been suggested by studies showing decreased meal size after infusions of the hormone to mimic normal postprandial levels.⁷ Glucagon-like peptide 1 (an alternatively spliced product of the proglucagon gene) has been recently proposed to be a satiety factor in rodents that acts centrally.⁸

Genetic models of obesity

In mice α melanocyte-stimulating hormone is a centrally acting appetite suppressant. A genetic model of obesity, the agouti mouse, is characterised by a yellow coat colour, which is due to failure to promote production of melanin. Agouti protein is made in excess in this model, and this protein is an antagonist of the melanocortin 2 receptor in the skin and melanocortin 4 receptor in the hypothalamus (fig 2).⁹

Another genetic model of obesity, the *fat* mouse has a defect in the enzyme carboxypeptidase E, which is involved in the post-translational processing of many peptide hormones, including insulin.¹⁰ It seems likely that obesity in these animals develops because of failure to produce one or more appetite inhibiting substances. Human obesity has been reported in association with a mutation in a different processing enzyme, prohormone convertase 1, which is involved in the synthesis of many peptide hormones and neurotransmitters, including insulin and glucagon-like peptide 1.¹¹

Long term regulation of body weight

Body weight is very tightly regulated, as only a small imbalance is necessary to produce weight gain, for example a daily excess of 100 kcal (418 MJ) (equivalent to a small chocolate bar), would result in a 4 kg weight gain in a year. There are many possible factors that might signal the state of the body's energy stores to the hypothalamus (see fig 1) so that intake and energy expenditure can be adjusted accordingly. There is evidence that hormones such as insulin and the concentrations of nutrients such as glucose and amino acids all play a role, but the recent discovery of leptin has transformed understanding of this aspect of weight regulation.

Leptin

Leptin is the product of the gene that is defective in the obese *ob/ob* mouse.¹² Leptin is a 16 kDa peptide hormone synthesised in fat that acts in the hypothalamus to suppress food intake and increase energy expenditure. *ob/ob* mice have increased expression of neuropeptide Y in the hypothalamus, and, if given leptin, their neuropeptide Y levels fall and food intake and energy expenditure are normalised.¹³ Two other rodent models of obesity, the *db/db* mouse and the *fa/fa* rat, have defects in the leptin receptor; exogenous leptin is ineffective in these animals.

Leptin concentrations seem to be high in nearly all obese people, and they fall with weight loss, possibly suggesting some resistance to the central effects of leptin in obesity. The leptin and leptin receptor genes are normal in most cases of human obesity, so any defect is likely to lie beyond the receptor. The importance of leptin in humans was recently established with the description of two cousins with morbid obesity of early onset who had a mutation in the leptin gene.¹⁴ Interestingly, a transgenic mouse that does not make leptin or

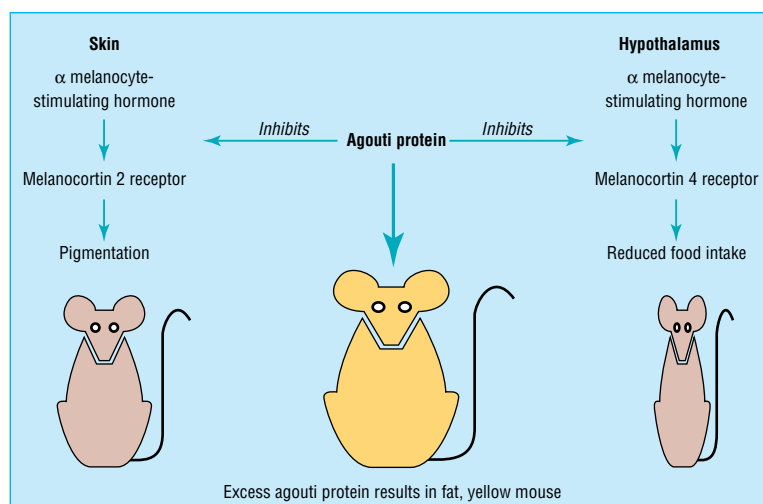


Fig 2 The yellow obese mouse produces excessive amounts of the agouti protein, the normal function of which is to inhibit the melanocortin receptor in skin. Agouti protein also inhibits the hypothalamic melanocortin 4 receptor, which may normally have a restraining influence on food intake

neuropeptide Y is midway between a normal mouse and the *ob/ob* mouse in weight, indicating that multiple systems are involved and clearly showing the considerable redundancy in the systems of weight control.¹⁵

Energy expenditure

A common complaint made by obese people is that they have a "slow metabolism." In fact, obese people generally have higher metabolic rates than usual, although it is possible that a slightly slower metabolic rate may have contributed to their weight gain. This is supported by a twin study that suggested that there is an inherited component to the tendency to gain weight when people are overfed, which can be explained only by differences in energy expenditure.¹⁶

When rodents are given a choice of highly palatable foods (a "cafeteria diet") they develop obesity, but the amount of weight gained is limited by generating heat (thermogenesis). This occurs through "futile" metabolic cycling, achieved by uncoupling oxidative phosphorylation in mitochondria. In rodents thermogenesis mainly occurs in brown adipose tissue, which responds to activation by the sympathetic nervous system via the β_3 adrenoceptor. A possible role for this system in adult humans, who have little or no brown fat, is uncertain. Some studies have reported a polymorphism in the β_3 adrenoceptor gene to be associated with an increased prevalence of obesity.¹⁷ The genes for two previously unknown mitochondrial uncoupling proteins have recently been cloned. These genes are expressed mainly in fat, muscle, and liver, and their discovery has rekindled interest in the regulation of energy expenditure, but their possible role in obesity is yet to be determined.^{18 19}

Future drug targets

Two new drugs are currently under review. These are sibutramine, a serotonin and noradrenaline reuptake inhibitor, and orlistat, a pancreatic lipase inhibitor which inhibits triglyceride digestion and therefore decreases fat absorption in the small intestine. These

drugs have similar efficacy to dexfenfluramine and result in weight loss of up to 10%, followed by maintenance of lost weight for up to two years if treatment is continued. Side effects include a small rise in blood pressure (2-3 mm Hg) with sibutramine and predictable effects on the gut related to malabsorption of fat with orlistat.

There are many possible new therapeutic targets, and combinations of drugs with different modes of action may be required, as is currently the case with hypertension. Peripheral satiety factors such as cholecystokinin are promising, and specific cholecystokinin agonists are being developed. Leptin is an obvious choice, and trials of recombinant human leptin are under way. Peripheral energy expenditure could be increased by means of β_3 adrenoceptor agonists, or by targeting the uncoupling proteins more directly. Finally, the development of new, highly specific and effective, centrally acting agents remains an attractive option. Possibilities include agonists of glucagon-like peptide 1 and melanocortin 4 receptors. Neuropeptide Y-Y5 receptor antagonists are the current leaders, but many other potential targets are waiting in the wings.

Conclusions

The obesity epidemic is not going to go away. Although public health measures to alter lifestyles are vital, they do little to help people who are already obese. Epidemiological and clinical studies have made the hazards of obesity clear and shown the benefits of weight loss. A combination of genetics and physiological studies is improving our understanding of the complex mechanisms that control appetite and energy expenditure, and this should lead to new, more effective treatments for obesity that will transform its management in the future.

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Lesson of the week

Subjective change in ejaculate as symptom of infection with *Schistosoma haematobium* in travellers

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Schistosomiasis should be suspected in travellers who report subjective changes in their semen and have recently returned from endemic areas

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Several published papers have highlighted increased reporting of schistosomiasis in developed countries.¹⁻³ Once considered a rare tropical disease, it has become an important differential diagnosis in those who have travelled in endemic areas and who have haematuria, haemospermia, or acute neurological symptoms; swimming in freshwater lakes in Africa is the principal risk factor.

Nineteen travellers returned to Christchurch, New Zealand, with schistosomiasis over three years.² Seven of them were men who attended a sexual health clinic with changes in their ejaculate as their principal symptom. We report these cases in detail as the clustering of cases with this presenting symptom is unusual.

Case reports

The median age of the seven men was 27 years. Before diagnosis all had noted changes in their ejaculate over time (range 2 weeks to 8 months). Four had consulted other medical practitioners before attending the sexual health clinic. Another two were referred to our department by their general practitioners for further investigation of semen abnormalities. One attended because his travelling companion had been diagnosed in London as having schistosomiasis. All of the men had swum in Lake Malawi during the preceding 12 months. In one case (number 7) exposure had been only a few hours of swimming at the water's edge. No patient

Symptoms and laboratory findings in seven patients with schistosomiasis who presented with changes in ejaculate

Case No	Age (years)	Year of diagnosis	Presenting symptoms (duration)	Time from probable contact to diagnosis (months)	Retrospective symptoms		Analysis of urine	Results of:			Prostate specific antigen
					Cercarial itch	Katayama fever		Urine microscopy	Stool microscopy	Blood eosinophilia	
1	31	1993	Genital tingling and watery semen (3 months)	9	No	Yes	Microscopic haematuria	<i>S. haematobium</i> ova	<i>S. haematobium</i> ova	Yes	Not tested
2*	28	1993	Yellow semen (8 months)	14	No	No	Negative	Negative	Negative	No	Normal
3	28	1993	Yellow semen and testicular pain (8 months)	12	No	No	Microscopic haematuria	<i>S. haematobium</i> ova	Negative	No	Not tested
4	27	1994	Yellow semen and testicular ache (2 weeks)	1	No	No	Negative	<i>S. haematobium</i> ova	Negative	Not tested	Normal
5	24	1995	Watery semen (1 month)	4	No	No	Microscopic haematuria	<i>S. haematobium</i> ova	Negative	No	Not tested
6	23	1996	Absent semen (2 weeks)	5	No	No	Microscopic haematuria	<i>S. haematobium</i> ova	Negative	No	Normal
7	25	1996	Reduced volume of semen (2 weeks)	6	No	No	Microscopic haematuria	<i>S. haematobium</i> ova	Negative	No	Normal

*Diagnosed by microscopy of semen.

recalled a cercarial itch; this is in keeping with the concept that previous sensitisation is required for the itch to occur.

The alteration in ejaculate included change to a yellow colour (cases 2-4), a reduction in volume (cases 6 and 7), and a reduction in viscosity to the consistency of water (cases 1 and 5) (table). Analysis of seminal fluid from three of the men showed a polymorph infiltrate and *Schistosoma haematobium* ova. The number and motility of spermatozoa were unaffected. None of the patients recalled that their ejaculate had turned brownish in colour (haemospermia).

Three patients described an associated testicular ache or urethral tingling, and they had been treated for non-gonococcal urethritis. Examination of the prostate gave normal results in all cases.

Three female partners of the affected men were also seen. A complete sexual health examination and screen

for parasites gave negative results, but two women were positive for *S haematobium* on serological testing.

All patients were treated with praziquantel 40 mg/kg and followed up for several months. All seven men reported that their ejaculate returned to normal, and analysis of semen was normal on testing after treatment.

Discussion

A reported alteration in semen is an unusual presenting symptom, even in sexual health clinics. The pattern of change in ejaculate in these cases was quite specific for schistosomal infection.

The site of infection was presumed to be the prostate or seminal vesicles,⁴ but why an inflammatory reaction with yellow or watery semen occurred rather than haemospermia is unknown. We have found no reference to the symptoms our patients described in the medical textbooks, although there was a case report of schistosomiasis affecting ejaculate in an Australian traveller in 1992.⁵ A recent report on a series of 10 Spanish travellers recorded haemospermia and clinical prostatitis after freshwater exposure in Mali, but the authors did not comment on other changes in ejaculate.³

The delays in diagnosis and the presumptive diagnosis of and treatment for a sexually transmitted disease by primary care practitioners are not surprising. A high index of suspicion of schistosomiasis should be maintained for any traveller who has visited an endemic area and who complains of an alteration in ejaculate.

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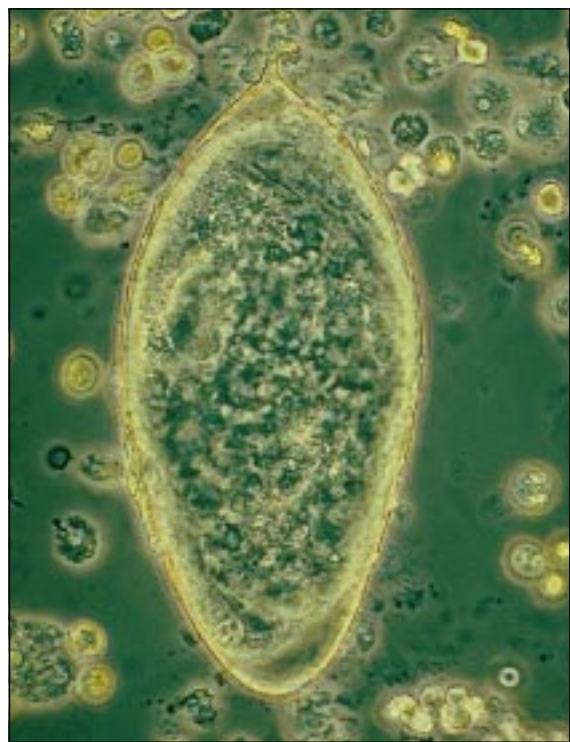
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Light micrograph of *Schistosoma haematobium*

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