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Introductory chapter

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Obesity is a global phenomenon, a disease which is spread by increasing urbanization and which causes major morbidity and mortality. Over the last two decades it has reached unprecedented and dramatic levels in industrially developed countries but the rise in prevalence affects almost every part of the world. It is already placing huge burdens on the health systems of many countries. Its potential to cause disability amongst working-age populations worldwide, particularly as a result of complications of diabetes, makes it imperative to work towards both preventative and curative solutions.

Yet, despite the fact that obesity has become such a widespread disease, there remains within the medical community a tradition of stigmatizing individual sufferers. Doctors and other health professionals have tended to provide what is seen as self-evident advice, namely, to consume less food and to expend more energy through physical activity. The subsequent failure of patients to lose weight, despite good advice, and in the face of complications of their condition, is then viewed as evidence of an inability to control lifestyles and to resist urges. At the root of this view lies an historical absence of knowledge of the hugely complex and fascinating innate homeostatic mechanism which controls satiety and energy balance: a mechanism that has evolved over millions of years, has seen humankind through feast and famine, and has run into trouble only since the advent of mechanization. This absence of knowledge, and the resulting lack of effective remedies, has made it convenient for doctors to blame their patients for perceived failings of self-control.

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Nonetheless, the last decade has seen a number of important advances in understanding of the anatomical and molecular basis of the satiety circuits. This knowledge has been translated rapidly into a wide range of drug development programs, offering the prospect that a range of safe and effective antiobesity treatments will become available within the next 10 years. The current chapter aims to set the scene for discussion of these advances by describing the scale, medical consequences and causes of the global obesity crisis, and by reviewing how the development of novel antiobesity compounds may be informed by knowledge of the relative merits of currently available treatments.

1. Definition of obesity

Adipose tissue functions as an energy store, the principal role of which is to improve the chance of survival during prolonged food deprivation. This fact underlies the celebration of obesity as an indicator of health in some rural African cultures and may explain in part the ambivalence of many in Western cultures towards the categorization of obesity as a disease. Nevertheless, an excess of body fat is causally associated with an increased risk of developing diabetes, hypertension, cardiovascular disease, respiratory disease, osteoarthritis and cancer and it is this association which is crucial to the medical definition of obesity.

The World Health Organization (WHO) currently recommends that body mass index (BMI) is used as the standard tool for both clinical and epidemiological assessment of adiposity. This is a pragmatic choice which is acceptable to patients and proven to be robust when performed by trained personnel (WHO, 1995). The association between BMI and total adiposity, body fat distribution and risk of complications is strong but nonetheless varies between populations. In particular, in comparison to Europeans, individuals in some Asian populations tend, at any given BMI, to have greater amounts of total body fat, greater ratios of visceral to subcutaneous fat and, hence, a greater risk of developing complications (WHO Expert Consultation, 2004). In recognition of this, a modification to the previous international classification of obesity has been agreed (see Table 1.1) (WHO Expert Consultation, 2004; WHO Global InfoBase Team, 2005) and work on the utility of waist circumference measurement in addition to BMI is in progress. Recently published epidemiological surveys, such as the INTERHEART study (Yusuf *et al.*, 2005), may hasten the process of incorporating a measure of abdominal obesity into an international classification.

The rapid rise in prevalence of obesity in the developed world is well-documented. In the UK the prevalence in adults almost tripled between 1980 and 1998 (National Audit Office, 2001) and similar increases have been observed in the USA (Flegal *et al.*, 1998, 2002), Canada (Katzmarzyk, 2002;

Table 1.1 *World Health Organization classification of body weight including additional subdivisions of BMI introduced in 2004, intended to provide additional 'public health action points', particularly for Asian populations (WHO Expert Consultation, 2004).*

Principal categories	Sub-categories		BMI (kg/m^2)	Additional BMI subdivisions for epidemiological reporting
Underweight			< 18.50	
		Severe thinness	< 16.00	
		Moderate thinness	16.00–16.99	
		Mild thinness	17.00–18.49	
Normal range			18.50–24.99	18.50–22.99
				23.00–24.99
Overweight			≥ 25.00	
	Pre-obese		25.00–29.99	25.00–27.49
				27.50–29.99
	Obese		≥ 30.00	
		Obese class I	30.00–34.99	30.00–32.49
				32.50–34.99
		Obese class II	35.00–39.99	35.00–37.49
				37.50–39.99
		Obese class III	≥ 40.00	

Tremblay *et al.*, 2002; Katzmarzyk & Ardern, 2004) and Australia (de Looper & Bhatia, 2001). It was estimated recently that obesity is responsible for 30 000 deaths per annum in the UK (National Audit Office, 2001). This figure is likely to rise as a result of the increasing prevalence of obesity in children and, hence, of the development of complications at ever younger ages (Bundred *et al.*, 2001; McCarthy *et al.*, 2003; Lobstein *et al.*, 2004).

Whilst the prevalence of obesity in developed countries has been systematically studied for several decades, it is only since the introduction of the WHO classification that global comparisons have been possible. The first truly global survey of body weight (WHO Global InfoBase Team, 2005) showed that 75.6% of males aged 15 years and over living in the USA are overweight (BMI $\geq$ 25) and 36.5% of the same population are frankly obese (BMI $\geq$ 30). The corresponding figures for the UK are 65.7% and 21.6% respectively. These results come as no surprise but an unwelcome finding of the report is that obesity is not confined to the developed world but is also becoming prevalent in middle and low income countries (see Figure 1.1).

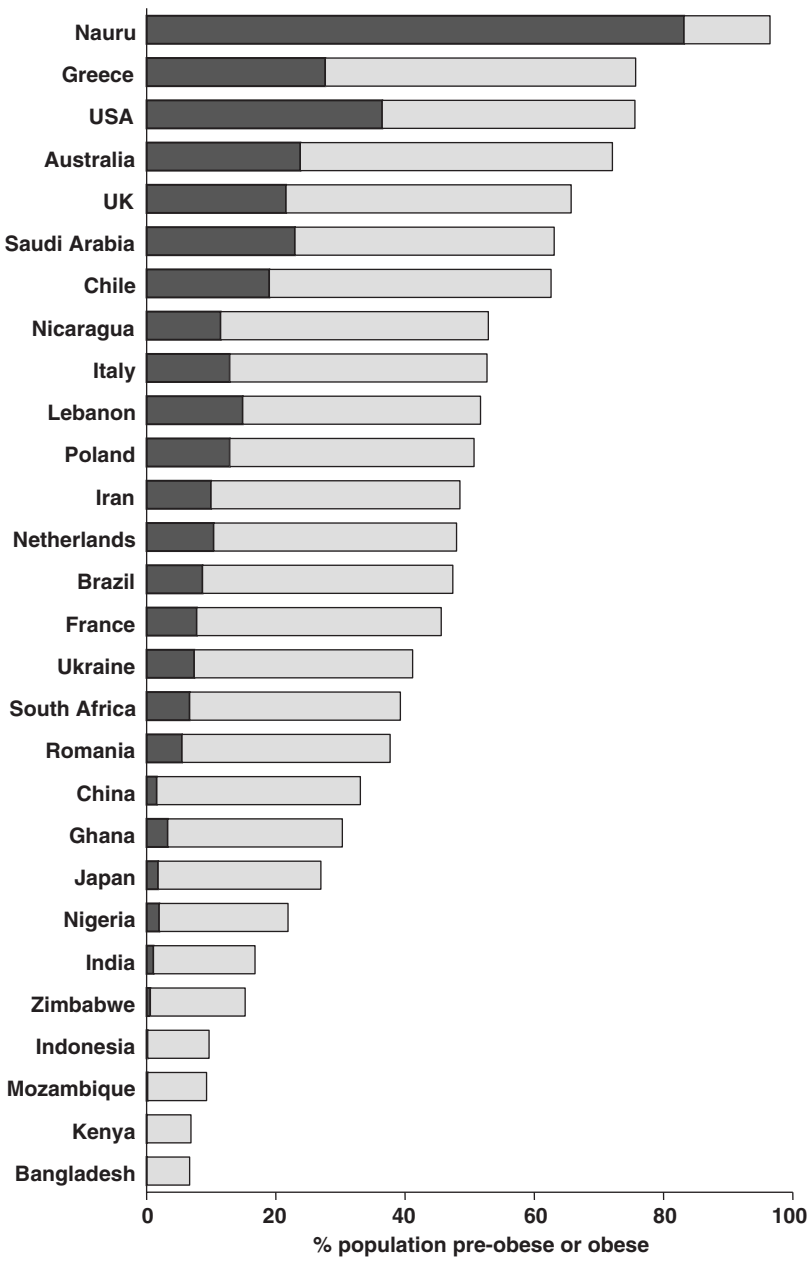

Figure 1.1 Prevalence of obesity (BMI ≥ 30.00; dark grey bars) and pre-obesity (BMI 25.00 to 29.99; light grey bars) in males aged 15 years and above in selected countries. The combined length of the dark and light grey bars is representative of the proportion of each population classified as overweight i.e. BMI ≥ 25.00. Data from World Health Organization SuRF Report 2 (WHO Global InfoBase Team, 2005).

In particular, heavily populated countries such as China and India have experienced rapid changes in recent years. The absolute increase between 2002 and 2005 in numbers of overweight adult males in the two countries combined was almost ten times greater than the increase seen in the USA (WHO Global Infobase Team, 2005). The implication of these findings and of predicted increases in prevalence is that, whilst obesity has until recently been viewed as predominantly affecting developed countries, it is rapidly becoming widespread throughout the world. The inevitable consequence is that huge, global health problems are being stored up for the near future.

2. Complications of obesity

The most devastating human and economic consequences of the rise in prevalence of obesity are likely to arise from an increased incidence of type 2 diabetes mellitus. Obesity is well established as a prime risk factor for the development of insulin resistance and diabetes (Sims *et al.*, 1973; Wannamethee & Shaper, 1999; Stevens *et al.*, 2001). The strength of the association is particularly well illustrated by a prospective cohort study of 114 281 women (Colditz *et al.*, 1995) in which subjects with a BMI between 22.0 and 22.9 had a threefold increase in risk of developing type 2 diabetes compared with those with a BMI less than 22. For individuals with BMIs from 25.0 to 26.9, from 29.0 to 30.9 and in a range above 35.0, the risks were 8 times, 27 times and 93 times greater respectively. Type 2 diabetes mellitus, already a common illness in developed countries, is becoming increasingly common worldwide (Amos *et al.*, 1997; King *et al.*, 1998; Wild *et al.*, 2004). The inevitable consequence of this is that diabetic complications, including retinopathy, nephropathy, neuropathy, peripheral vascular disease, stroke and ischaemic heart disease, will become increasingly common.

Of even greater concern is the fact that obesity and, hence, diabetes are occurring at ever younger ages. Complications of diabetes, which have hitherto been confined mainly to the elderly population, are thus beginning to appear earlier in life. Type 2 diabetes mellitus is increasingly being reported in children (Fagot-Campagna *et al.*, 2000; Ramachandran *et al.*, 2003; Lobstein & Jackson-Leach, 2006) and a recent study of Canadian adults aged 18 to 33 who had developed type 2 diabetes in childhood revealed the devastating damage which may be caused. In a group of 58 patients, seven had died, two of whom had been on dialysis, another three were still alive on dialysis, one had become blind and one had had a toe amputated. The rate of pregnancy loss amongst the women was 38% (Dean & Flett, 2002).

In addition to its role in causing diabetes mellitus, obesity is an important independent risk factor for hypertension and dyslipidemia (Brown *et al.*, 2000; Wilson *et al.*, 2002) and for pro-inflammatory states (Ford, 1999), which together are components of the metabolic syndrome and are implicated in atherogenesis (Ridker *et al.*, 1997; Pickup & Mattock, 2003). It is thus unsurprising that obesity is strongly associated with the risk of developing cardiovascular disease (Fang *et al.*, 2003), acute thrombotic events (Wolk *et al.*, 2003), atrial fibrillation (Wang *et al.*, 2004) and heart failure (Kenchaiah *et al.*, 2002). Indeed, in a 20-year epidemiological study of the inhabitants of two Scottish towns, obesity was associated with 9 additional cardiovascular deaths and 36 additional cardiovascular hospital admissions for every 100 affected subjects (Murphy *et al.*, 2006).

Obesity results in impaired respiratory function both through mechanical forces, including inhibition of diaphragmatic movement by intra-abdominal fat, and by reducing the capacity of individuals to undertake physical activity. Epidemiological studies have demonstrated a clear association between obesity and asthma (Ford, 2005), obstructive sleep apnea (Resta *et al.*, 2001) and obesity hypoventilation syndrome (Olson & Zwillich, 2005). Both obstructive sleep apnea and obesity hypoventilation syndrome are risk factors for the development of cor pulmonale, diabetes and hypertension. Prospective studies have shown that weight loss results in improvement of symptoms (Avenell *et al.*, 2004; Ford, 2005; Kalra *et al.*, 2005).

Obesity is a major cause of reproduction-related morbidity in women. It reduces the safety of some commonly used forms of contraception, increases the risk of anovulatory infertility (Linné, 2004) and reduces the likelihood of successful in vitro fertilization treatment (Fedorcsák *et al.*, 2004; Lintsen *et al.*, 2005). Fortunately, weight loss improves outcomes in women undergoing treatment for anovulatory infertility (Crosignani *et al.*, 2003). In women who become pregnant, obesity increases the risk of gestational diabetes, hypertension, pre-eclampsia, foetal macrosomia, intrauterine death, emergency caesarean section, wound infection, genital tract infection, postpartum hemorrhage and birth trauma (Sebire *et al.*, 2001; Nohr *et al.*, 2005).

There is also an extensive literature, derived from large cohort studies, describing the increased risk that obese individuals run of developing various cancers, in particular, carcinomas of the esophagus, stomach, colon, rectum, liver, gallbladder, pancreas and kidney and hematopoietic malignancies including leukemia, myeloma and non-Hodgkin's lymphoma. In addition, obese men are at increased risk of developing prostate carcinoma and obese women are at increased risk of cancers of the breast, endometrium, cervix and ovary (Calle *et al.*, 2003; Batty *et al.*, 2005; Hampel *et al.*, 2005). There are several

potential mechanisms by which obesity may result in malignancy. The risk of esophageal cancer is likely to be derived mainly from gastro-esophageal reflux but other alimentary tract cancers have been postulated to occur more commonly as a result of hyperinsulinaemia causing increased mitogenic signalling at the insulin-like growth factor-1 (IGF-1) receptor (Giovannucci, 1995). Postmenopausal breast and endometrial carcinoma, as well as prostate carcinoma, may occur more commonly because excess adipose tissue is a major source of circulating sex hormones (Bianchini *et al.*, 2002; Calle & Kaaks, 2004).

The mechanical stress exerted by obese individuals on their lower limbs is responsible for a large increase in risk of developing osteoarthritis of the knees (Hart & Spector, 1993; Stürmer *et al.*, 2000). Furthermore, weight loss reduces the risk of osteoarthritis (Felson *et al.*, 1992) and, especially in combination with exercise, has been shown to ameliorate symptoms and improve the functional capacity of sufferers (Messier *et al.*, 2004).

Lastly, obese individuals in most societies are disadvantaged socioeconomically and psychologically. They are more likely to take long-term sick leave (Vingard *et al.*, 2005), more likely to be depressed (Heo *et al.*, 2005; Sjöberg *et al.*, 2005; Herva *et al.*, 2006) and have reduced earning potential compared with the non-obese (Baum & Ford, 2004). Whether the latter observation reflects a causal relationship is unclear but further study of trends in the USA may provide useful information since, although it continues to affect lower income groups disproportionately, the prevalence of obesity has increased more quickly over the last 30 years in higher than lower income social groups (Chang & Lauderdale, 2005).

3. Causes of obesity

A recent review of genetic studies of obesity concluded that over 600 separate genes, markers and chromosomal regions are linked to obesity phenotypes (Pérusse *et al.*, 2005). A small number of these constitute recently described monogenic obesity syndromes, including leptin and leptin receptor mutations, which are characterized principally by severe early onset obesity. Another small group is known to be responsible for the classical pleiotropic obesity syndromes, such as Bardet–Biedl and Prader–Willi syndromes, in which obesity is just one of several diagnostic characteristics (Farooqi & O'Rahilly, 2005). Although the study of such syndromes sheds considerable light on the pathophysiology of obesity, they are nonetheless exceptional: BMI is a continuous variable within populations and, although obesity tends to run in families, it is not, with few exceptions, inherited in classical Mendelian fashion.

It follows that the vast majority of genes identified by linkage studies may have only small individual effects on body weight. Nonetheless their additive effects, as judged from twin, family and adoption studies, are likely to account for between 40% and 70% of variation in BMI within populations (Maes *et al.*, 1997). This view is reinforced by a prospective study of chronic overfeeding in monozygotic twins which found that the variance in weight gained was three times greater between unrelated subjects than within twin pairs (Bouchard *et al.*, 1990).

If inheritance is such an important factor though, why should there have been an unprecedented increase in the prevalence of obesity over the last 30 years? The most likely explanation is that evolutionary pressure exerted over many millennia of uncertain food supply has favored the survival of individuals possessing 'thrifty' genotypes, a term originally coined by J. V Neel in relation to the risk of developing diabetes mellitus (Neel, 1962). According to the thrifty genotype hypothesis, individuals who were adept at storing excess energy as adipose tissue in times of plenty would have been protected from the worst ravages of famine.

It is only in recent decades that the mechanization of food production and transport, along with a prolonged period of relative peace, has rendered food shortages virtually non-existent for the populations of developed countries. At the same time, marketing pressures have tended to favor the production of highly palatable, energy-dense, cheap, processed foods which are widely available and intensively advertised, especially to children. Fast food has become an increasingly prominent component of modern diets (Nielsen *et al.*, 2002) and seems to play a role in promoting excessive energy intake (Ebbeling *et al.*, 2004). These environmental changes have revealed a widespread predisposition to obesity which has been propagated by the erstwhile evolutionary advantage of the thrifty genotype. Furthermore, there is preliminary evidence that increases in energy intake in pre- and postnatal life may have long-term programming effects on hypothalamic satiety centers, thus enhancing the effect of a pre-existing genetic predisposition to obesity (Prentice, 2005). Within the space of just one or two generations, the thrifty genotype has been rendered not simply irrelevant but positively harmful.

It would be wrong, however, to view technology and prosperity, or, indeed, our genetic inheritance, as the villains of the piece. We are stuck with our thrifty genotypes and would not wish to compensate by returning to a more precarious food supply system. On many levels the situation might be ameliorated by education and re-education: of national and local policy-makers, of schoolteachers, of parents and of children. In particular, progress on prevention may be made by reducing exposure to snacks, confectionery, fast food and

vending machines (Vereecken *et al.*, 2005; Rolls *et al.*, 2006). Such measures are far less expensive than dealing with the medical consequences of obesity. For a rapidly increasing number of people, however, preventative measures will have come too late: the need for effective obesity treatments has never been greater.

4. Treatments for obesity

The current range of choices for treating obesity is limited, the central problem being that appetite must continue to be controlled after initial loss of weight. A combination of dieting and increased physical activity is effective only when pursued vigorously and consistently. There has been a renewal of medical interest recently in the optimum constituents of weight-reducing diets, in part at least because of the commercial success of highly restrictive diets such as that proposed by Atkins (1972). It is likely that diets rich in protein have a greater satiating effect than other forms of weight-reducing diet (Rolls *et al.*, 1988; Barkeling *et al.*, 1990) but this does not necessarily translate into greater weight-reducing efficacy. Furthermore, even patients enrolled in randomized controlled trials have difficulty adhering to weight-reducing diets and typically achieve very modest weight loss (Dansinger *et al.*, 2005).

Unexpected adverse effects have led to the withdrawal of several antiobesity drugs in recent years, including phentermine, fenfluramine and dexfenfluramine, and regulatory scrutiny has thus become particularly stringent on potential newcomers to the market. This approach is entirely justifiable, particularly since patients may need to continue treatment for several decades. Of the treatments currently available, orlistat (Xenical, Roche Products Ltd), a pancreatic lipase inhibitor which works by reducing intestinal absorption of dietary fats, has been shown to cause an additional 3–4% weight loss over and above that achieved by diet alone in a 2-year period but at the expense of adverse effects which include anal leakage of oily faeces. Rebound weight gain occurs after cessation of treatment (Foxcroft & Milne, 2000). Sibutramine (Reductil, Abbott Laboratories Ltd), an inhibitor of serotonin and noradrenaline reuptake in the central nervous system (CNS), which reduces appetite and increases energy expenditure (Hansen *et al.*, 1998), has been shown to result in a similar amount of weight loss (Finer, 2002). Its use is limited by side effects including tachycardia and hypertension and it is licensed for a maximum of one year's treatment in the UK. Again, rebound weight gain occurs after cessation of treatment (Wirth & Krause, 2001).

Apart from the licensed antiobesity medications, a number of currently available drugs, including fluoxetine, sertraline, buproprion, zonisamide and topiramate, are used on an unlicensed basis. A recent meta-analysis of

published trials (Li *et al.*, 2005) found that there was little evidence to support the use of either fluoxetine or sertraline but that buproprion and topiramate have weight-reducing effects broadly similar to both sibutramine and orlistat. The same may also be true for zonisamide but the supporting data comprise only a single randomized controlled trial at present (Gadde *et al.*, 2003).

Bariatric surgery is the only treatment currently available which routinely results in substantial, permanent weight loss. Procedures may be purely restrictive, for instance gastric banding or gastroplasty, or use a more complicated reconstructive technique incorporating gastric bypass, for instance Roux-en-Y gastric bypass or biliopancreatic diversion. The latter operations are more efficacious in terms of initial weight loss, sustainability of weight loss and resolution of pre-existing metabolic conditions such as type 2 diabetes mellitus and hyperlipidemia (Biertho *et al.*, 2003; Sjöström *et al.*, 2004; Scopinaro *et al.*, 2005). The perioperative mortality rate in experienced centers for Roux-en-Y gastric bypass is typically about 0.5% (Buchwald *et al.*, 2004). A recent study has raised concern about hospital readmission rates after Roux-en-Y gastric bypass (Zingmond *et al.*, 2005) but the procedure is nonetheless considered by many to offer the most appropriate compromise between efficacy and operative safety (Sjöström *et al.*, 2004; Haslam & James, 2005; le Roux & Bloom, 2005).

The mechanism by which Roux-en-Y gastric bypass cause sustained weight loss are intriguing. The reduction in gastric volume required for a successful result is less than that required for purely restrictive procedures. Furthermore, post-operative malabsorption is usually transient because of gut adaptation. Nonetheless, not only does Roux-en-Y gastric bypass result in a dramatic reduction in appetite, as assessed by meal frequency and preference for calorie-dense substances (Halmi *et al.*, 1981; Kenler *et al.*, 1990; Brolin *et al.*, 1994), it also causes rapid resolution of hyperglycemia and hyperinsulinemia, typically within a few days of the operation and well in advance of significant weight loss (Kellum *et al.*, 1990; Schauer *et al.*, 2003). It is likely that these advantageous metabolic changes are caused by profound alterations in gut hormone secretion which occur as a direct result of the procedure (Cummings *et al.*, 2004; le Roux *et al.*, 2006). A greater understanding of these changes will be vital to the ongoing search for novel treatments.

The development of novel antiobesity medications has become a very active research area over the last decade, propelled by a recognition of the growing scale of the clinical problem, by the current lack of safe and effective treatments, and by the discovery of leptin, which invigorated the whole field and led to an understanding of the molecular basis of the hypothalamic satiety circuits. The targets of compounds currently under development include