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Obesity: genes, appetite and lifestyle

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Obesity – a problem of excess – has escalated rapidly over the past 25 years. Currently, a quarter of UK adults are obese and many more are overweight. Obesity reduces life expectancy and leads to several major diseases, particularly type 2 diabetes, coronary heart disease and certain cancers. Although genes play a role, the modern epidemic of obesity is the result of an 'obesogenic environment' with ready access to palatable, high fat foods and the development of a sedentary lifestyle. Strategies to treat and prevent obesity have been marked to date by a distinct lack of success, and the disease is now a major concern for policy makers and for Government.

Introduction

For many years obesity has been described as the major nutritional disorder in the Western world. This was certainly so 40 years ago in the 'Neuberger Report' on 'Food and Nutrition Research' (HMSO 1974) which was commissioned jointly in the UK by the Medical Research Council and what was then the Agricultural Research Council. If such a view was appropriate in 1974, it is certainly even more true now. This reflects the extent to which obesity has become a major public health problem in the developed world. Indeed, obesity is now also a growing issue in those countries, such as China and Brazil, whose economies are expanding rapidly. It is perhaps ironic that the problem of food shortage has become so quickly overtaken by the challenge of excess. Paradoxically, 'Food Security', in the sense of ensuring an adequate food supply for the population, is now an issue for the UK Government, and for other Western administrations.

In this chapter an overview of obesity is presented – what it is, the scale of the problem, and why it is important for public health. The underlying biological basis for the development of the disorder is summarized and some of the current issues in obesity research are described.

Definition and incidence of obesity

Obesity is characterized by an excess of body fat and this is reflected in an increased

mass of white adipose tissue – the lipid storage organ. But what level of body fat is regarded as obesity? A simple measure is normally used, in the form of the 'body mass index', or BMI, to define obesity (Kopelman 2000; Visscher et al 2010). This is the weight in kg/height in m^2. The cut-off points for normal weight, over-weight and obesity based on BMI for adults of both sexes are usually taken to be:

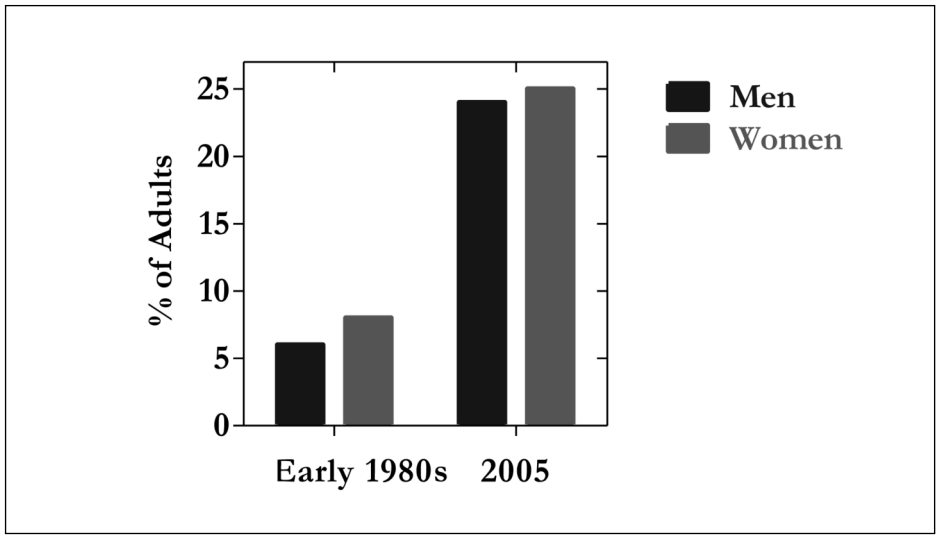
- <18.5 = 'underweight'
- 18.5-24.9 = 'normal weight'
- 25.0-29.9 = 'overweight'
- >30 = obesity
- >40 = severe, or 'morbid', obesity

The principal attraction of BMI as an index of obesity lies in its simplicity, with only weight and height being measured. It is easy, 'low technology' (only weighing scales and a tape measure being required) and rapid. It can readily be measured in the field or in the home, as well as in general medical practice. BMI is particularly attractive for studies on a population basis. However, it does have drawbacks. The central concern is that it is only a proxy for body fat rather than being a direct measure, and as such the changes in body composition that occur in elite athletes and body builders, for example, may suggest a different level of fatness than is implied by the BMI. The increased muscle mass, in particular, of body builders leads to an elevated BMI relative to the amount of fat. Only actual measures of body composition, such as by MRI or by densitometry from underwater weighing, overcome these reservations, but these methods are impractical other than in a clinical or laboratory setting.

The other important caveat in the use of BMI is that it has become evident in recent years that the cut-off points are not universal across cultures and ethnic groups. The standards which have been established and which have been adopted by the World Health Organisation are based on Caucasians from Europe and North America, and they are now recognized to be inappropriate for some other groups. Thus in parts of Asia, such as Japan and China, a lower cut-off in BMI of 27, or even lower, for obesity is now used. This reflects different body frames between Asians and Europeans.

It has become common to use the term 'epidemic' – or even 'pandemic' - to describe the current incidence of obesity. In the UK, approximately 25%, or 1 in 4, of adults are now clinically obese on the basis of a BMI>30, the figures being little different between men and women (Rennie & Jebb 2005). The incidence of obesity in the UK is higher than in other western European countries, but lower than in the United States where one-third of adults are now diagnosed as obese (Ogden et al 2006). These figures reflect a rapid rise in obesity over the past 25 years. In the case of the UK, in the early 1980s just 6% of adult men and 8% of adult women were classified as obese; thus, there has been a three-fold increase in the incidence of obesity in just over two decades (Fig 1) (Prentice & Jebb 1995). This is a remarkable change and has been accompanied by a shift to the right in the distribution of body weight. In other words, not only has obesity been rising but much of the population has increased in weight.

Figure 1: The rise in obesity in the UK over the past 25 years.



The rate of weight gain is such that the Foresight Report on obesity from the UK Government Office for Science (Foresight 2007) has made the somewhat alarmist projection that, on current trends, by 2050 nearly 60% of the UK population could be obese. It is important to emphasize that obesity is not only a concern in adults, but is also a growing problem in children. Present estimates suggest that between 10 and 15% of children in the UK are obese, depending on the precise age group (Rennie & Jebb 2005).

Why obesity matters

For many individuals, overweight and obesity are highly important from an aesthetic point of view and in terms of self-image. Body weight is also of significance in everyday practicality of a quite different sort in relation to issues such as transport policy, with passenger seats on planes and buses being too small for the obese. This has recently led to questions of whether airlines should impose a surcharge on the obese as a consequence of the reduction in space and the increase (albeit marginal) in fuel consumption. However, despite these cultural and economic dimensions, it is the public health consequences of obesity that have led to the disorder becoming a major concern, both for biomedical research and for governments.

Although there has been debate on the effects of obesity on longevity, the consensus is that life expectancy is reduced by several years once BMI reaches 30. Morbid obesity leads to an even greater reduction in life expectancy. Obesity is associated with several major diseases, including type 2 diabetes, hypertension, coronary heart disease and certain cancers (including colon, breast and prostate), as well as with osteoarthritis and sleep apnoea (Kopelman 2000). It is not only the total amount of body fat that matters but also its distribution, with abdominal or visceral fat – what has been described as a 'male' distribution ('apples' as opposed to 'pears',

or female) being particularly linked to type 2 diabetes and the metabolic syndrome. The metabolic syndrome, which is also termed syndrome X, is a cluster of disorders which include abdominal obesity, insulin resistance, hypertension and hyperlipidaemia (Grundy 2007). Abdominal obesity is generally measured by the circumference of the waist or by the waist/hip ratio.

The biggest link between a specific disease and obesity is with type 2 diabetes. Once the BMI has risen to 30, there is an approximately ten-fold increase in the risk of developing type 2 diabetes and the higher the BMI the greater the relative risk. Currently, there are over 2.5 million diagnosed diabetics in the UK, with up to half a million more being undiagnosed (Diabetes UK 2010). Thus 5% of the population – or one person in 20 – is now diabetic. In the United States, the levels of type 2 diabetes are even higher. At least 80% of the increase in the number of type 2 diabetics is considered to be a direct consequence of the escalation in obesity. The implications, both for public health and for healthcare budgets, of the surge in obesity-associated diabetes is considerable – and diabetes is only part of the total social and economic costs of obesity.

Genes and environment

The extent to which obesity is the result of genes or environment has been a matter of continuing debate (Clément 2005; O'Rahilly & Farooqi 2006). Certainly, it has long been recognized that obesity runs in families. The current view is that genetic inheritance accounts for around 60% of the development of obesity. Such a figure should, however, be seen as something of a simplification since the impact of genes will depend upon the environmental circumstances. For example, genetic differences will appear more important when food is abundant, and excess consumption is possible. An analogy is with smoking in that if everyone smoked, lung cancer would be seen as essentially a genetic disease. In essence, the most appropriate description is that of there being a genetic predisposition to obesity with an interplay between genes and environmental factors.

The genetic contribution to obesity is mostly polygenic, with a large number of genes and gene polymorphisms likely to be involved. Intriguingly, a genome-wide siRNA study of the worm *Caenorhabditis elegans* in which each of 16 700 genes was systematically silenced, or suppressed, indicated that >400 inactivations resulted in changes in body fat (Ashrafi et al 2003). In other words, more than 400 separate genes were individually implicated in determining 'fatness' in even a simple worm. Of these, >300 inactivations resulted in reduced fat and >100 an increase. Many of these worm genes are common to, or have homologues, in higher animals, including humans.

Mutations in single genes which lead to overt obesity in rodents have been recognized for more than 50 years. The best known of these is in the obese *ob/ob* mouse in which a mutation in just one gene leads to frank, early-onset obesity whereby body weight becomes 3-4 fold higher than in normal siblings (Trayhurn 1984). A similar phenotype is exhibited in the diabetic (*db/db*) mouse and the Zucker fatty (*fa/fa*) rat (Trayhurn 1984). These obese rodents have been extensively employed in animal studies into the causes and consequences of obesity, and in 1994 the gene that is mutated, or altered, in the *ob/ob* mouse was identified (Zhang et al

1994). The gene encodes a hormone, subsequently named leptin, which is produced primarily in white adipose tissue (Friedman & Halaas 1998). A mutation in the gene encoding the receptor for leptin is responsible for the obesity of both the *db/db* mouse and the fatty (*fa/fa*) rat (Friedman & Halaas 1998). Thus major alterations in the gene for either leptin or its receptor result in obesity.

Mutations in the human homologues of the leptin and leptin receptor genes have been subsequently identified and these too are associated with severe, childhood-onset obesity (O'Rahilly & Farooqi 2006). Such mutations are, however, rare and do not provide an explanation for the generality of human obesity. A mutation in the melanocortin 4 receptor (MC4R) gene appears to be quite prevalent in human obesity of early onset (O'Rahilly & Farooqi 2006), and this is the most common gene linked to human obesity to date. The melanocortin 4 receptor is part of a system in the brain that is involved in the control of appetite and food intake. Overweight and obesity have long been associated with a small number of specific syndromes such as the Bardet-Biedle and Prader-Willi.

Despite the recent emphasis on the underlying genetic basis to obesity, the rapid rise in the level of the disorder over the past two decades cannot be due to changes in the gene pool. The key factors are social and environmental, reflecting the modern Western lifestyle which has led to the establishment of what is termed an 'obesogenic environment'. There is now ready availability of cheap, highly-palatable, energy-dense, high-fat foods. Indeed, food has historically never been cheaper with as little as 11% of average household expenditure in the UK now being spent on it. Social and cultural changes have resulted in food increasingly being consumed outside the traditional context of set family meals. 'Grazing' is commonplace, particularly among the young.

The other key component of environmental change is the evolution towards an increasingly sedentary lifestyle with a marked reduction in physical activity. A number of factors have led to a fall in activity levels, ranging from habitual car use to the time spent passively watching television and sitting in front of computer screens. Labour-saving devices have resulted in household tasks being less physically demanding, while the design of buildings means that the default in moving between floors is either by lifts or escalators rather than stairs. A heightened parental concern with safety means that children are driven to school more and more, and are encouraged to remain in the home rather than playing outside.

These environmental changes, which have been considerable over the past two or three decades, have been emphasized in the Foresight Report (2007) referred to earlier. However, what the Report has done in its 'obesity systems map' is to risk masking the fundamental point – that obesity can only develop when food (energy) intake is greater than expenditure. In other words, obesity is first and foremost an issue of energy balance. This is the basic biological reality, and the multiple social, cultural, economic and other environmental factors which are given emphasis ultimately impact either on intake, or expenditure – or both.

Energy balance

Energy balance is attained when energy intake exactly equals total energy expenditure (Fig 2). When intake is in excess of expenditure, there is a state of

Figure 2: The energy balance equation.

$$\text{Energy}_{\text{in}} = \text{Energy}_{\text{out}} \pm \Delta_{\text{energy stored}}$$

positive energy balance which if sustained will ultimately lead to obesity. Correspondingly, if expenditure is in excess of intake, the ensuing negative energy balance results in weight loss. A sustained positive energy balance occurs not only during the development of obesity, but also with growth in children and in pregnancy. Some of the energy taken in the food (gross energy intake) is lost in the faeces and in urine, so it is the metabolizable energy intake (gross energy minus the losses in the faeces and urine) that is important in nutritional energetics.

The major macronutrients of the diet vary in their implications for energy balance with high-fat foods being not only very palatable, but also highly digestible. High-fibre diets, on the other hand, have a low digestibility. The consumption of fat has additional energetic implications. It costs only around 5% of the energy contained in fat to digest, absorb and deposit that fat in the adipose tissue stores. However, in the case of dietary carbohydrate approximately 25% of the energy potential is used to process and deposit this macronutrient as fat in adipose tissue. Thus, calorie for calorie, fat is the more 'fattening'.

Appetite

There are multiple inputs into appetite and what determines food intake, and these operate from the behavioural and psychological to the molecular levels. Food choice depends upon factors such as smell, appearance and palatability, and more broadly on the social and cultural context as well as on economics (Rolls 2006; Blundell et al 2010). The hedonic qualities of food are important in terms of short-term consumption. At a physiological level, the stomach signals 'fullness' and there are messages from peripheral organs to the brain which influence appetite. These messages include the hormone ghrelin which is produced from the stomach and stimulates appetite, being released in the fasting state with the levels falling after a meal (Chaudhri et al 2006). Two other important hormones from the gastrointestinal tract that modulate appetite are cholecystokinin (CCK) and peptide YY (PYY)(Chaudhri et al 2006). PYY is produced predominantly from the ileum and colon, and in contrast to ghrelin is released following a meal with the circulating levels being low in the fasted state. PYY inhibits gastric motility, and thus emptying, after a meal. CCK is released from the duodenum and has multiple effects on digestive processes in the gastrointestinal tract, and is a satiety factor.

The peripheral signal to appetite which has received most attention is the hormone leptin which is released primarily from adipocytes within white adipose tissue. Leptin is a powerful satiety factor and its administration to animals that lack it leads to a major (75%) reduction in food intake (Friedman & Halaas 1998). Mutations in the gene encoding leptin and its principal receptor result in profound obesity, both in animal models and in humans (Friedman & Halaas 1998; O'Rahilly

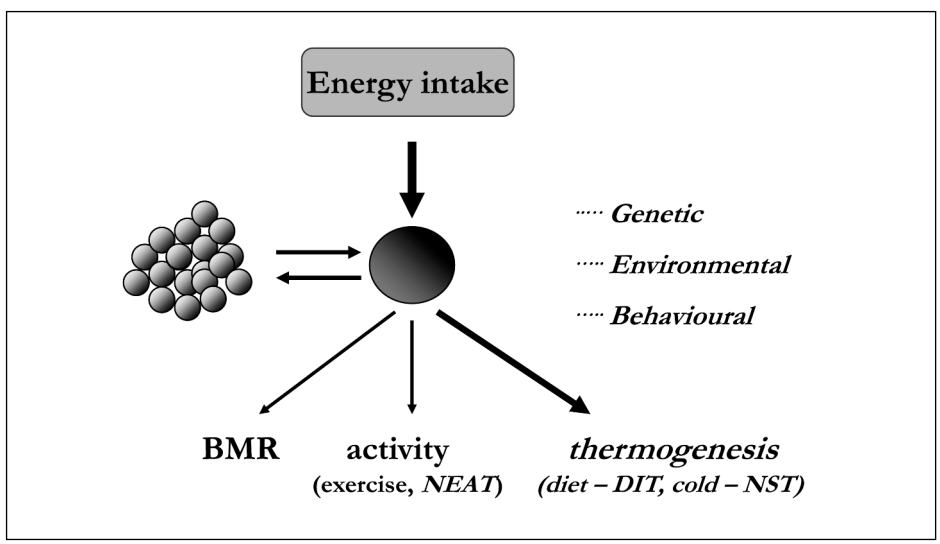
& Farooqi 2006), as noted above. Leptin and ghrelin both affect appetite through the brain, particularly specific regions of the hypothalamus. These peripheral hormones, and others, are transported to the hypothalamus where they interact with the neuroendocrine networks and pathways that modulate and control appetite. The pathways involve specific neuroendocrine factors which are either 'orexigenic' or 'anorexigenic' – appetite-stimulating or suppressing.

The most potent orexigenic neuroendocrine factor is neuropeptide Y, or NPY (Beck 2006). Others include AgRP, or agouti-related protein, and also the endogenous cannabinoids (the cannabis-like lipid substances found naturally in our bodies). These orexigenic agents are balanced by a group of anorexigenic factors, including - melanocyte-stimulating hormone and CART (cocaine- and amphetamine-regulated transcript). Leptin has such a powerful inhibitory effect on food intake because it both stimulates the anorexigenic systems and inhibits the orexigenic (Trayhurn 2005a). Leptin is, however, a longer-term rather than acute signal to appetite.

Energy expenditure

Energy expenditure has several distinct components (Fig 3). The largest in humans is the 'basal metabolic rate' (BMR). This has a rather precise definition involving the measurement of metabolic rate, or oxygen consumption, first thing in the morning after an overnight fast and while lying supine in a warm environment. In practice, it represents the sum of the energy expended on all the normal, basic physiological and metabolic processes such as beating of the heart, breathing, making proteins and the myriad of housekeeping activities that all the cells of the body continually undertake. A second major component of expenditure is physical activity, and this is

Figure 3: A schematic view of the flow of energy ('energy flux') through the body. BMR, basal metabolic rate; DIT, diet-induced thermogenesis; NEAT, nonexercise activity thermogenesis; NST, non-shivering thermogenesis.



clearly highly variable between individuals and during the course of the day. Two components of expenditure have received particular attention in relation to how energy balance may be regulated and body weight maintained. One is termed 'NEAT' – or non-exercise activity thermogenesis. This concept was originally introduced in the late 1990s to reflect the small movements short of overt physical activity that occur during the course of the day, such as fidgeting and the maintenance of posture (Levine et al 1999). Central to the original idea was the possibility that this form of expenditure is reduced in the obese, and indeed may have a causal role in the development of obesity.

The other type of regulatory expenditure is also termed 'thermogenesis', but it relates specifically to adaptive heat production without contraction of the muscles. This type of expenditure occurs as part of the generation of heat to maintain body temperature in the absence of shivering, and is particularly pronounced in small mammals exposed to the cold where it is termed 'non-shivering thermogenesis' (Trayhurn 1993). It also occurs in response to food, as 'diet-induced thermogenesis', which includes both an obligatory component, reflecting the essential costs of digesting and processing macronutrients, and a facultative component (Rothwell et al 1982). Facultative thermogenesis, which has been called by several different names, including 'luxusconsumption', has been the source of much debate. The concept refers to the deliberate burning off of excess energy intake so as to maintain energy balance. The general consensus is that while diet-induced thermogenesis can be an important part of energy expenditure in small mammals, there is no convincing evidence that this is the case in humans.

Linked to the issue of the quantitative importance of thermogenesis to total expenditure is the question of what is the tissue(s) in the body in which it takes place, and what is the core biochemical mechanism. In the late 1970s, a specialized form of fat tissue, known as brown adipose tissue, was identified as the principal site of adaptive thermogenesis in rodents (Cannon & Nedergaard 2004). For several years there was much discussion, not least in the media, centred on the idea that obesity in humans is a consequence of 'inactive brown fat'. However, there was little evidence to support the proposition and brown adipose tissue was thought to be of little relevance to energy metabolism in humans – other than in newborn babies where the tissue is relatively abundant to help maintain body temperature. However, most recently there has been a renaissance of interest in brown adipose tissue in humans and its potential role in energy balance in adults (Nedergaard et al 2007). This was highlighted by a trio of papers on the tissue in the 9 April 2009 issue of the '*New England Journal of Medicine*', the most prestigious weekly medical journal in the world. Active brown fat was unambiguously demonstrated in adult humans and considerable metabolic flexibility observed with a link to obesity (Cypess et al 2009; van Marken Lichtenbelt et al 2009; Virtanen et al 2009).

Fat storage

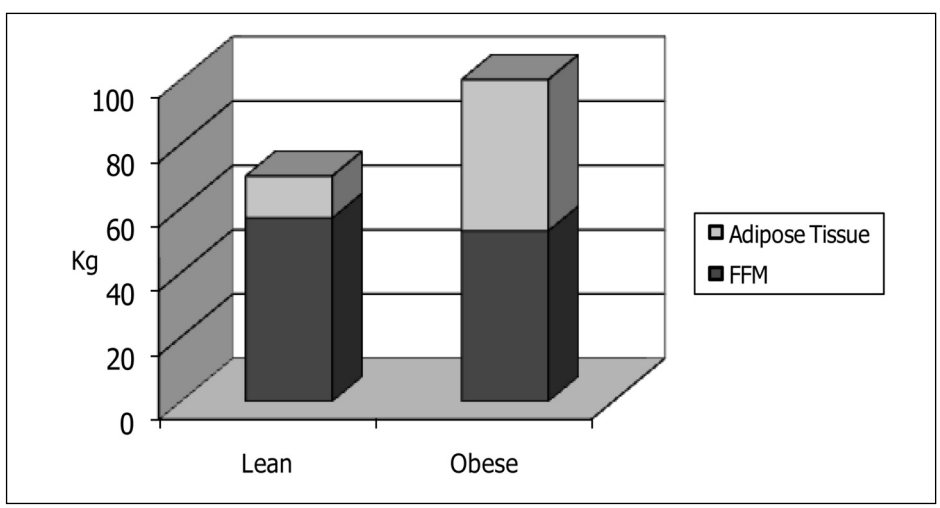
Obesity has been discussed so far in the relative terms of BMI without reference to the actual amounts of body fat. Fat is stored in a specialized organ, white adipose tissue (also known as white fat). While the primary function of brown adipose tissue is to produce heat, the central role of white adipose tissue is to provide fuel storage

– although it has other important roles as well. Fat is stored in adipose tissue in the form of triglycerides, and this is highly efficient since storage takes place with minimal water and the energy content of lipid is twice that of carbohydrate. In contrast, the other major form of stored fuel, glycogen, is present in association with considerable amounts of water, so that overall many more calories can be deposited per gram of tissue in the case of triglycerides than with carbohydrate.

White adipose tissue, which occurs in multiple sites in the body, both internally and subcutaneously, constitutes as much as 15 to 20% of total body mass in a lean individual with a BMI of 22 (Fig 4). Thus, even in someone of ideal body weight fat tissue is a considerable part of the overall composition of the body, dwarfing major organs such as the heart, liver and brain. The amount of body fat rises markedly, of course, in obesity and once a BMI of 30 is reached, adipose tissue accounts for 45-50% of body weight (Fig 4). For individuals who are morbidly obese, adipose tissue is well over half of total body composition. In the obese, therefore, white adipose tissue is by far the largest organ in the body. One of the implications of this is that even though white fat is not as metabolically active as most other organs, small changes in what it does may have considerable impact on the metabolism and physiology of the body as a whole.

White adipose tissue has other functions in addition to the central role of fuel storage. It can act as a thermal insulator, particularly in the form of blubber in marine mammals, and provide mechanical protection to other organs. However, one of the most exciting developments in obesity research over the past 15 years has been the recognition that white fat is itself a major endocrine organ, secreting several key hormones (Trayhurn 2005b). Indeed, in the overweight and obese, it is much the largest endocrine organ. The pivotal development that changed the way in which the fat storage organ is viewed was the discovery of leptin. This was in 1994, and it was

Figure 4: Body fat as a percentage of total body weight in lean (BMI≈22) and obese (BMI 30) people. FFM, fat-free mass.



followed by the identification of another adipocyte hormone, adiponectin, a couple of years later (Trayhurn 2005b). Subsequently, many protein factors and signals have been shown to be released from fat cells, and the current view is that adipose tissue converses extensively with a range of other tissues, including the brain, skeletal muscle and the liver. The various protein factors secreted from fat cells have been termed adipokines, and through their release it is apparent that adipose tissue is involved in processes as diverse as blood clotting, the control of blood pressure, the regulation of appetite and the modulation of insulin sensitivity (Trayhurn 2005b; Rosen & Spiegelman 2006).

What was formerly a 'Cinderella organ' has become a focus of intense biomedical research attention. This is not just because of the range of biologically-active proteins, peptides and other factors that it releases, but because the changes in the tissue that occur in obesity are now seen as being directly linked to the development of the major obesity-associated diseases (Rosen & Spiegelman 2006). The production and release of many protein signals change in adipose tissue in obesity, most increasing, and the critical factor is that an inflammatory state is established (Trayhurn 2005b). Inflammation is increasingly seen as being part of a number of diseases, including diabetes, and obesity is now one of this group (Hotamisligil 2006). Indeed, the discovery a few years ago that chronic, mild inflammation is a characteristic of obesity was an important advance, opening the door to unravelling the link with the associated diseases.

Coda – treatment and prevention

The continuing rise in obesity is a potent indication of the lack of success of both past and current strategies for treatment and prevention. Conceptually, treating (and preventing) obesity is simple – as simple as the energetic basis for the cause of the disorder. All that is required is for energy expenditure to exceed energy intake and for negative energy balance to be sustained over a prolonged period. There are a plethora of approaches that have been, and are being, employed to reduce intake. These include a variety of specialized diets, many of which, such as the 'Atkins', will be familiar from magazines, books and television, and may well be promulgated by 'celebrities' rather than scientists or clinicians. However, any diet will only work if it reduces intake and the individual maintains a commitment to being in negative energy balance over many months. The overall success rate is, however, poor, and relapse is high, even when combined with behavioural modification. Similarly, activity regimens have limited success, whether used alone or in combination with dietary restriction.

Effective drugs as a key therapeutic tool have long been a goal for the pharmaceutical industry and for many clinicians. However, while several agents have been tried over the years they have not proved successful and have not remained on the market for long. This is generally because of unacceptable side-effects. At present, only the lipase inhibitor Orlistat ('Xenical') has continuing regulatory approval, and this prevents the breakdown and absorption of fat from the diet. Orlistat has been available for several years, and although there are gastrointestinal side-effects they are not of a serious nature. The weight loss is, however, modest. There is much interest in developing selective appetite-suppressants and there is a periodic concern with thermogenic agents which would stimulate energy

expenditure. The threshold for a successful anti-obesity drug is, however, high; there must be an appropriate rate of weight loss (neither too little nor too much) which is sustainable, patient compliance should be high, any side-effects must be minimal and acceptable, and cost should be deemed proportionate. In practice, only moderate weight loss is necessary to reduce the medical risks of obesity-associated disease, but the patient generally desires a substantial rather than modest reduction in weight.

Bariatric surgery, in which the size of the stomach is reduced, or part of the gastrointestinal tract bypassed, is an alternative approach. Weight loss is substantial and with the procedures now used mortality in the best centres is well under 0.5%. This is, of course, still significant and would be unacceptable if it were a drug. Bariatric surgery is in practice unlikely to be available for more than a small minority of the obese – the logistics are complex and such surgery would not be possible on an extensive scale. In the UK, for example, in 2009 just over 4000 operations were performed and even a 10-fold increase would be a very substantial challenge.

There is now a developing focus on anti-obesity initiatives by policy makers and governments. Although measures to reverse or minimize the obesogenic environment can be introduced, whether through changes in planning laws, the design of buildings and towns, the nature of school meals, or taxes on fat, obesity is essentially a challenge for the individual. In many ways this may seem obvious, but what 30 years ago was seen in puritan terms as a matter of personal 'gluttony and sloth' has become viewed as primarily a societal issue where the responsibility of the individual is limited. This change parallels the broader social and cultural shift in the balance between individual and collective responsibilities.

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