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The Nutrition Society Medal Lecture

Obesity: from molecules to man

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Obesity is now a major public health problem in both developed and developing countries. In the UK over 16 % men and 17.5 % women are obese, an increase of more than 100 % since 1980. However, interventions to prevent and treat obesity are hampered by an inadequate understanding of the aetiology of this condition. The present paper considers the current state of knowledge regarding the causes of obesity, including some of the genetic, metabolic, behavioural and environmental factors which influence energy balance. The present paper comprises The Nutrition Society Medal Lecture and focuses in particular on the research carried out at the MRC Dunn Nutrition Centre in Cambridge. It argues that despite decades of intensive research there is relatively little evidence of genetic or metabolic defects to explain the majority of cases of human obesity. Instead we must look to behavioural and/or environmental factors which may be underpinning the current epidemic of obesity.

Obesity: Energy intake: Energy expenditure: Body fat

Background

Obesity is not a new phenomenon, archaeological evidence of fatness dates back to the Stone Age, but it has never been so common as it is today and across such a large proportion of the world. Currently in the UK 16 % men and 17.5 % women are obese (BMI > 30 kg/m²) and a further 45 % men and 35 % women are overweight (Colhoun & Prescott-Clarke, 1996). This represents a steady increase of more than 100 % since the early 1980s (Fig. 1). The growing recognition of obesity as an important contributor to morbidity and diminished quality of life has intensified the search for a solution to this major public health problem (Fig. 2). The worldwide significance of the problem has been emphasized by the recent publication of a report summarizing the World Health Organization (1998) Consultation on Obesity.

The effective management of obesity requires the prevention of new cases and the treatment of currently-obese individuals. Successful treatment must encompass both a period of acute weight loss and a sustained period of weight-loss maintenance. Weight loss can be achieved using a variety of strategies, including dietary restriction, low-fat diets (Astrup *et al.* 1997), very-low-energy formula diets

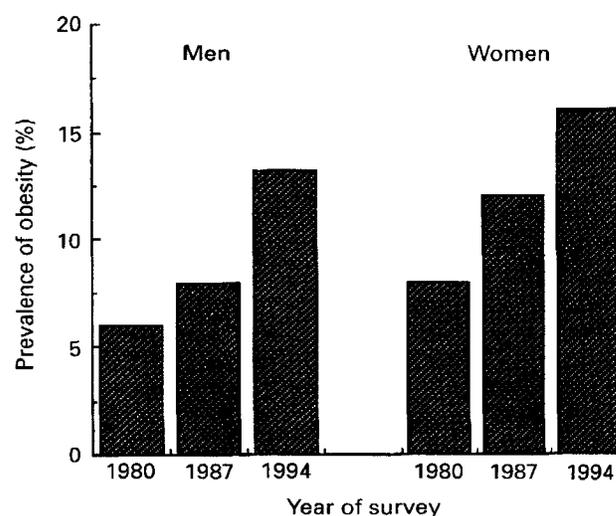


Fig. 1. Secular trends in the prevalence of obesity in the UK. (Data from the Health Survey for England; see Colhoun & Prescott-Clarke, 1996.)

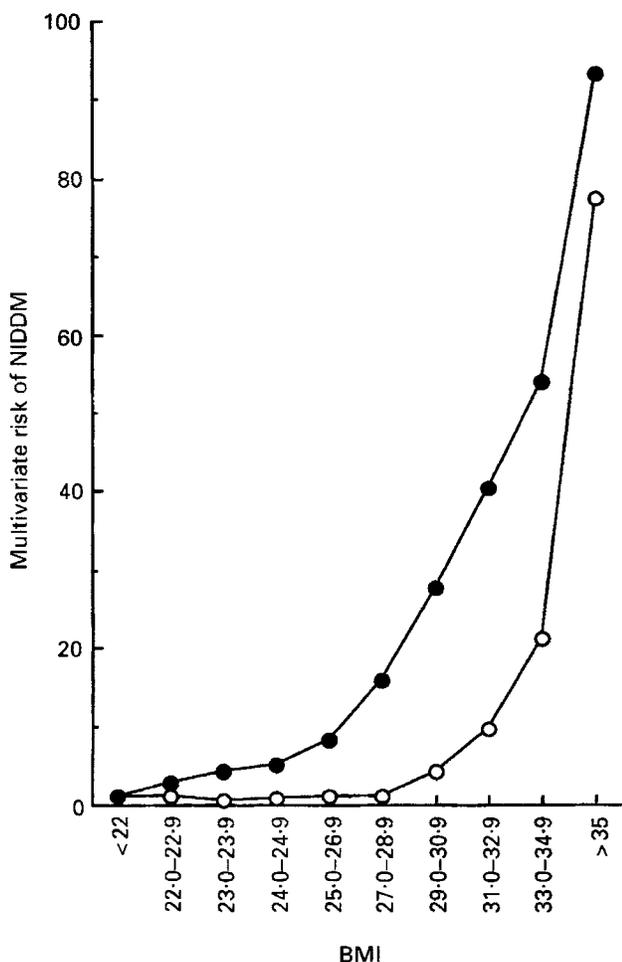


Fig. 2. Relationship between the BMI (kg/m²) and the relative risk of type II diabetes (NIDDM) for men aged 40–49 years (○; Chan *et al.* 1994) and women aged 30–55 years (●; Colditz *et al.* 1995).

(Jebb & Goldberg, 1998), pharmacotherapy (Finer, 1997), or surgery (Kolanowski, 1997). Weight losses of 10 % or greater are relatively common, but most interventions ultimately fail because weight loss is quickly followed by regain. Thus, the prevention of weight gain in lean, obese and post-obese adults can be seen as the first priority in the management of body weight.

Rational interventions to prevent weight gain require a detailed understanding of its development. The present paper will consider the aetiology of obesity from a physiological perspective. It will examine the contribution of genetic, metabolic, behavioural and environmental factors to the developing epidemic through their effects on energy intake, energy expenditure, and hence body fat stores.

Aetiology of obesity

The second law of thermodynamics is one of the few incontrovertible facts in this field. Obesity will only develop if energy intake exceeds energy expenditure over a prolonged period, but the mechanisms underpinning increases in energy intake or decreases in energy expenditure remain elusive (Jebb, 1997a).

Genetics and molecular insights

In recent years there has been considerable progress in elucidating the molecular and genetic basis to many of the animal models of obesity (Beales & Kopelman, 1996). Although a number of genetic syndromes such as Prader-Willi or Bardet-Biedl syndrome are strongly associated with an obese phenotype, there are currently only three single gene mutations which have been reported as directly responsible for cases of human obesity. The first is a single patient with two mutations in the gene coding for prohormone convertase 1 (Jackson *et al.* 1997). Her clinical features are consistent with such a defect, and comparable with those of the carboxypeptidase E mutation in the *fat mouse*. Notably, she has extremely high plasma levels of proinsulin, but very low levels of insulin. She was grossly obese as a child (36 kg at age 3 years), but in adulthood is almost weight stable, with a BMI of 35 kg/m². We are currently involved in further characterizing this patient with respect to some aspects of energy metabolism.

The second affects a handful of individuals with a congenital leptin deficiency associated with a mutation in the leptin gene (Montague *et al.* 1997; Strobel *et al.* 1998), and third a family with a defect in the leptin receptor (Clement *et al.* 1998). The phenotype of these subjects is associated with a normal birth weight but rapid weight gain from about 3 months of age, resulting in gross obesity from early infancy, marked and persistent hyperphagia, and the absence of normal pubertal development. Ongoing treatment of the first child to be identified, using a recombinant leptin preparation, will provide clear evidence of the biological effects of leptin in human subjects. In collaboration with O'Rahilly's team at the Department of Medicine, University of Cambridge, Cambridge, UK, we are monitoring the effects of this treatment on energy intake, expenditure and body composition.

In addition, there has been an ongoing search for obesity genes, usually among familial groups or in morbidly-obese subjects. Towards the end of 1997 the human obesity gene map listed up to three obesity-related loci on each chromosome, except chromosome Y (Chagnon *et al.* 1998). However, the supporting evidence from association and linkage studies is generally weak and inconsistent. Positive associations have been shown between BMI and apolipoproteins B (Rajput-Williams *et al.* 1988; Saha *et al.* 1993) and D (Vijayaraghavan *et al.* 1994), fatty acid-binding protein 2 (Hegele *et al.* 1996), β 3-adrenergic receptor (Kadowaki *et al.* 1995; Fujisawa *et al.* 1996; Urhammer *et al.* 1996), insulin-like growth factor 2 (O'Dell *et al.* 1997), melanocortin receptor 5 (Chagnon *et al.* 1997) and the LDL receptor (Griffiths *et al.* 1995); also between body fat and the leptin receptor (Thompson *et al.* 1997), Na-K ATPase α -2 subunit (Dériaz *et al.* 1994), apolipoprotein B (Pouliot *et al.* 1994), fatty acid-binding protein 2 (Hegele *et al.* 1996), tumour necrosis factor- α (Fernandez-Real *et al.* 1997) and melanocortin receptor 4 (Chagnon *et al.* 1997). Apolipoprotein B (Pouliot *et al.* 1994), fatty acid-binding protein 2 (Yamada *et al.* 1997), glucocorticoid receptor (Buemann *et al.* 1997) and β 3-adrenergic receptor (Kim-Motoyama *et al.* 1997; Sakane *et al.* 1997) have been specifically linked to abdominal fatness. However, the

Table 1. Results of some association studies between genes and indices of obesity (Data from Chagnon *et al.* 1998)

Gene	BMI	Fatness	Abdominal fat	Wt gain	Wt loss
Leptin	+,-	-			+
Leptin receptor		+,-			
UCP 1		-		+	+
β -3 Adrenergic receptor	+,-	+,-	+,-	+,-	+,-
Apolipoprotein B	+	+	+		
Apolipoprotein D	+				
Fatty acid-binding protein 2	+,-	+,-	+,-		
Lipoprotein lipase (<i>EC</i> 3.1.1.34)	+				
LDL receptor	+				
Na-K ATPase α -2 subunit		+,-			
ACP 1	+				
Tumour necrosis factor- α		+			
Insulin receptor	+				
IGF 2	+				
Glucocorticoid receptor	-		+		
Dopamine D2 receptor	+				
	(relative wt)				
Melanocortin receptor 5	+				
Melanocortin receptor 4		+			
3- β Hydroxy- Δ^5 -steroid dehydrogenase (<i>EC</i> 1.1.1.145)			-	+	

+, Association; -, no association; UCP 1, uncoupling protein 1; Na-K ATPase, *EC* 3.6.1.37; ACP 1, acid phosphatase (*EC* 3.1.3.2); IGF 2, insulin-like growth factor 2.

obesity gene map is not clear-cut, and other studies have failed to find any association between some of these genes and indices of obesity. The overall results are summarized in Table 1.

A small number of studies have looked at changes in weight over time. There was a positive association in the Quebec Family Study between weight gain over 12 years and a polymorphism in the gene coding for uncoupling protein 1 (Oppert *et al.* 1994). Studies of the Try64Arg mutation of the β 3-adrenergic receptor gene have yielded mixed results; a positive association between 25-year weight gain in morbidly-obese patients (Clément *et al.* 1995) but no association in an unselected group of Japanese subjects, despite a similar overall frequency of the mutant allele to that found in other populations (Nagase *et al.* 1997).

An alternative approach is that of the genome-wide scan. Two such studies have now been completed in Pima Indian siblings (Norman *et al.* 1997) and a group of Mexican American pedigrees (Comuzzie *et al.* 1997). The first study identified linkage between percentage body fat and a marker on chromosome 3 and two neighbouring markers on chromosome 11, whilst the latter study found linkage only with a marker on chromosome 2.

The lack of clearer linkage between specific genes and obesity is perhaps not very surprising. Obesity is a complex multi-factorial phenotype whose manifestation is likely to be determined by more than a single gene and modulated by an individual's lifestyle and environment. There is increasing recognition that obesity is a generic term for a family of disorders, each with its own aetiology. A detailed classification system for obesity, based on characteristics such as age of onset, eating behaviour, physical activity or fat distribution, would allow a search for obesity genes in a phenotypically-similar group of subjects.

Alternatively, by studying genetic associations with intermediary phenotypes it will be possible to reduce the biological 'noise' associated with crude measurements of ultimate body weight. Thus, a gene product which promotes satiety (e.g. leptin gene) might be shown to curb intake in standardized experimental settings, a gene product which stimulates thermogenesis (e.g. uncoupling proteins) might stimulate energy expenditure particularly under conditions of excess consumption, a gene product which activates the sympathetic nervous system (e.g. β 3-adrenergic receptor gene) might inhibit lipolysis, whilst others may modulate substrate flux (e.g. lipoprotein lipase; *EC* 3.1.1.34). These functional analyses may prove more fruitful areas of research, but are limited by the constraints imposed by physiological investigations, particularly if they are designed to test dynamic changes such as the response to over- or under-feeding, macronutrient manipulations, temperature stress, imposed exercise or inactivity. In this mode two recent studies have suggested that polymorphisms in uncoupling protein 1 may be related to a susceptibility to weight gain (Oppert *et al.* 1994) and a resistance to weight loss (Fumeron *et al.* 1997). Other studies have shown that the Try64Arg variant of the β 3-adrenergic receptor may also be associated with reduced rates of weight loss (Yoshida *et al.* 1995), but this has not been confirmed elsewhere (Fumeron *et al.* 1997). It is essential that these studies are conducted in highly-controlled environments to truly test metabolic susceptibility to weight gain and/or weight loss rather than behavioural determinants of weight change.

Metabolism

Classical calorimetry is an invaluable tool for assessing whole-body energy metabolism (Murgatroyd *et al.* 1993a). It provides a tightly-controlled environment in which it is

possible to standardize behaviour to provide a reproducible setting in which to compare groups of subjects, e.g. lean *v.* obese (Prentice *et al.* 1986), diabetic *v.* non-diabetic (Totton *et al.* 1995), or to examine the impact of natural or imposed manipulations on a single individual, e.g. different levels of exercise (Murgatroyd *et al.* 1993b), macronutrient manipulations of the diet (Goldberg *et al.* 1998), pharmacological agents (Goldberg *et al.* 1995), acute weight-loss (Jebb *et al.* 1991) or pregnancy (Prentice *et al.* 1989). Measurements of energy expenditure can be made with an accuracy of $\pm 1\%$ over periods as short as 1 h, but potentially lasting for many days, to the limit of subject tolerance (Murgatroyd *et al.* 1987).

These studies have provided a number of important insights into body-weight regulation. Most importantly, it is abundantly clear that increases in body weight are associated with increases in both resting energy expenditure and the energy cost of physical activity (Goldberg *et al.* 1991). On standard activity protocols obese people expend significantly more energy than their lean counterparts. These findings have effectively quashed the myth that obesity is associated with a profoundly-low metabolic rate. However, it does not preclude the possibility that there is a metabolic defect which exists in the pre-obese state and which promotes the development of a positive energy balance. Consideration has been given to potential metabolic defects in resting metabolic rate, diet-induced thermogenesis and the energy cost of exercise. This evidence has been reviewed elsewhere (Jebb, 1997a). Although there is some evidence of minor differences in energy expenditure between those susceptible to obesity and constitutionally-lean individuals, these studies have a number of methodological drawbacks (Prentice & Jebb, 1998). Moreover, the increase in metabolic rate which is associated with a gain in weight should quickly overcome any putative deficit in energy expenditure and hence provide a self-limiting mechanism, but there is little or no evidence that weight gain is finite.

Some of my own research has taken the reciprocal approach, examining whether there may be protective traits which serve to keep some individuals lean, even in the face of an imposed challenge. This is the basis of the *luxus consumption theory* (Miller *et al.* 1967). Lean, young men were confined to a whole-body calorimeter for 12 d and energy expenditure measured minute-by-minute, whilst receiving 50% in excess of their baseline energy requirements (Jebb

et al. 1996). Weight increased progressively from day 1. Although there was a rise in both basal and total energy expenditure, this was consistent with the increase in body weight and thermogenesis associated with the excess food. There was no evidence of any 'adaptive' thermogenesis. These subjects were confined to a calorimeter and were following a prescribed pattern of activity, but in a study in which free-living subjects were similarly over-fed over a 6-week period there was again no evidence of any unexplained increase in expenditure, either in fundamental metabolic rate (measured by indirect calorimetry) or the energy cost of physical activity (measured by doubly-labelled water). This was true for both lean subjects and overweight individuals who described themselves as 'easy weight gainers' (Diaz *et al.* 1992).

In recent years there has been a growing interest in the independent balance of each of the energy-providing macronutrients. Within our whole-body calorimeters it is possible to measure changes in substrate balance with a precision of ± 9 g fat/d and ± 20 g carbohydrate/d. The 12 d calorimeter study described previously provides detailed measurements of substrate flux during overfeeding, and in a reciprocal study during underfeeding on a diet providing only 3.5 MJ/d (Jebb *et al.* 1996). In both cases carbohydrate oxidation changed acutely to closely match consumption over a range of intake from 83 to 539 g/d and balance was achieved within 4–5 d. The changes in protein oxidation were extremely small, but tended in a direction to re-establish balance (Jebb *et al.* 1996). However, the changes in fat intake were counter-regulatory. Indeed, there is little or no evidence to suggest that fat oxidation is regulated *per se*, rather it represents the buffer between the energy needs of the subject and the energy supplied by other fuels, principally carbohydrate. This implies that the homeostatic regulation of energy balance is a consequence of the regulation of the individual macronutrients, and we have demonstrated the precise macronutrient oxidative hierarchy which results from these regulatory processes (Fig. 3). This confirms and extends the results from other studies made by our group and others under a variety of conditions, including *ad libitum* diets (Stubbs *et al.* 1993, 1995a; Shetty *et al.* 1994), acute overfeeding (Acheson *et al.* 1982; Flatt *et al.* 1985) and prolonged carbohydrate overfeeding (Schutz *et al.* 1984; Acheson *et al.* 1988). Studies which include alcohol as a dietary component show clearly that this

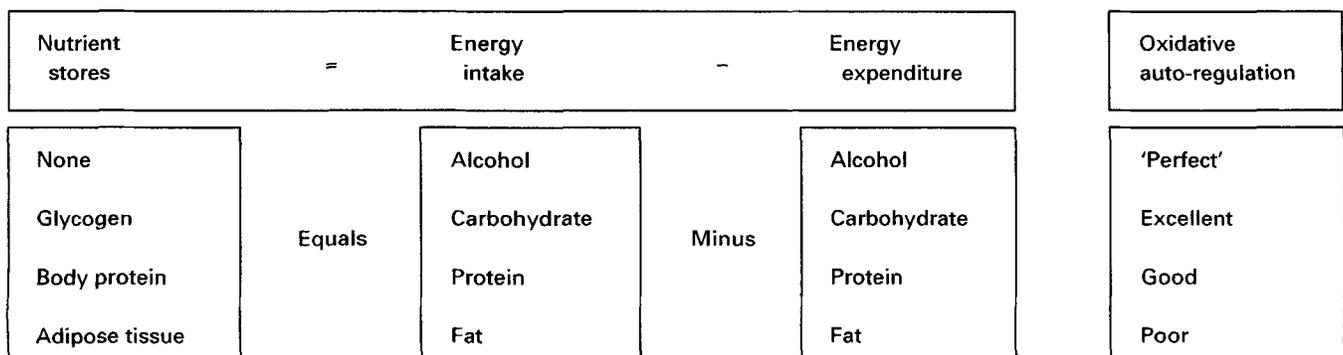


Fig. 3. The oxidative hierarchy of macronutrients. (Reproduced with permission, from Jebb *et al.* 1996.)

dominates even above carbohydrate oxidation, although in most circumstances it is a small component of the energy budget (Sonko *et al.* 1994; Prentice AM, 1995).

Other studies have examined the metabolic processes regulating macronutrient balance in more detail. For example, in a study by Schwartz *et al.* (1995) which included 25 and 50 % increases and decreases in carbohydrate intake, the increase in carbohydrate oxidation during overfeeding could be attributed to an increase in hepatic glucose production, which stimulated moderate hyperinsulinaemia. This in turn decreased lipolysis and fatty acid availability. The net effect was to increase glycogen stores and enhance the delivery of extracellular glucose, favouring carbohydrate oxidation and decreased gluconeogenesis (Schwartz *et al.* 1995). The recent incorporation of facilities for blood sampling within whole-body calorimeters will facilitate a closer integration of these physiological and biochemical effects.

Measurements of substrate balance by whole-body calorimetry are a far more precise method to measure changes in body composition than any *in vivo* body-composition technique. Accordingly, it is possible to examine the precise impact of a variety of interventions over very short periods of time and in much smaller groups of subjects than is necessary when using other methods to measure body fat. For example, recent studies have examined the effect on fat balance of overfeeding with different macronutrients: fat and three different types of carbohydrate (glucose, fructose and sucrose; McDevitt *et al.* 1997). This has shown that net fat balance is extremely similar for all substrates and directly related to the net energy excess. Another study has considered the independent and integrated effect on fat balance of the macronutrient composition of the diet and the appetite suppressant dexfenfluramine (Poppitt *et al.* 1997). This study has shown that a reduction in the fat intake of the diet leads to a far greater reduction in overall fat stores than the independent effect of the drug. However, there is an interaction between diet and drug such that the drug is able to modestly offset the positive fat balance on a high-fat diet, whereas there is no additional drug effect on a low-fat diet. These small differences in fat balance would be almost impossible to detect using *in vivo* body-composition techniques.

Table 2 compares the precision of a range of *in vivo* techniques relative to substrate balance. This demonstrates the limitations of classical two-compartment models, which consider the body as simply composed of fat and fat-free tissue. Multi-compartment models are clearly superior, but

even here the SD in an individual subject is 0.77 kg fat (Jebb *et al.* 1993). In this study the three-compartment model comprised measurements of body weight, volume and water, to account for the effect of hydration on the density of fat-free mass (Siri, 1961), whilst the four-compartment model additionally assumed that bone mineral remained constant over the short duration of this study (Murgatroyd & Coward, 1989). With the advent of dual-energy X-ray absorptiometry (Prentice A, 1995), absolute measurements of bone mineral can now be performed, and we have described a method to calculate fat from weight, volume, water and bone (Fuller *et al.* 1992).

Given the limited accuracy of even the most sophisticated reference methods, it is clear that there is little scope to compromise accuracy or precision for convenience. Although field methods such as skinfold thicknesses or bioelectrical impedance analysis have been shown to provide good group estimates of fatness, there is considerable potential for error at the individual level. In a recent study of 203 men and women across a range of age (16–78 years) and fatness (BMI 16–40 kg/m²) the mean agreement between a four-compartment model and skinfold thicknesses (Durnin & Womersley, 1974) was +0.52 % fat, with 95 % limits of agreement of –8.62 to 9.66 % fat (Fig. 4(a)) and for bioelectrical impedance analysis (Bodystat) a mean bias of –1.46 % fat and 95 % limits of agreement of –10.72 to 7.80 % fat (Fig. 4(b); Jebb *et al.* 1998). Inter-observer error in some methods, especially skinfold thicknesses, will contribute additional imprecision (Fuller *et al.* 1991).

There are particular problems in using two-compartment methods in the obese, since some of the theoretical assumptions of the model are violated (e.g. potential deviations from 'reference man' in the hydration fraction or density of fat-free tissue). The use of simple prediction techniques is further precluded by the paucity of validation studies in the obese population (Jebb, 1998). However, four or more-compartment models are gradually becoming more widely used in both research and clinical practice as the standard for *in vivo* measurements of body composition (Jebb & Elia, 1995). It is possible that this process will be accelerated by the introduction of a commercial whole-body volometer, the BodPod, which has the potential to replace classical underwater weighing procedures to estimate body volume in the majority of subjects (Dempster & Aitkens, 1995; McCrory *et al.* 1995). However, data collected using this method are still too limited to assess its true value. The practical issues involved in the measurement of body composition have been reviewed elsewhere (Jebb & Elia, 1993, 1994).

There is also considerable interest in the measurement of fat distribution, since it is clear that intra-abdominal fat is associated with greater metabolic risks than subcutaneous fat and may have specific aetiological determinants (Bjorntorp, 1993, 1996; Kissebah & Krakower, 1994). Although in an epidemiological context simple anthropometric measurements such as the waist:hip ratio (Ashwell *et al.* 1985) or waist circumference (Lean *et al.* 1995) have been proposed as markers of risk, they are insufficiently precise for most metabolic studies, concealing wide variations in the abdominal fat mass in subjects of similar waist circumference (Ross *et al.* 1996). Some investigators use dual-energy X-ray absorptiometry to provide additional

Table 1. Precision of some models to assess changes in body fat mass and substrate balance (Data from Jebb *et al.* 1993)

Method	Fat (kg)	
	Bias	95% Limits of agreement
Two-compartment models:		
Density	–0.275	–2.25 –1.70
Total body water	+0.330	–2.62 –3.28
Three-compartment model*	+0.045	–1.77 –1.86
Four-compartment model†	+0.008	–1.53 –1.55

* Siri (1961).

† Murgatroyd & Coward (1989).

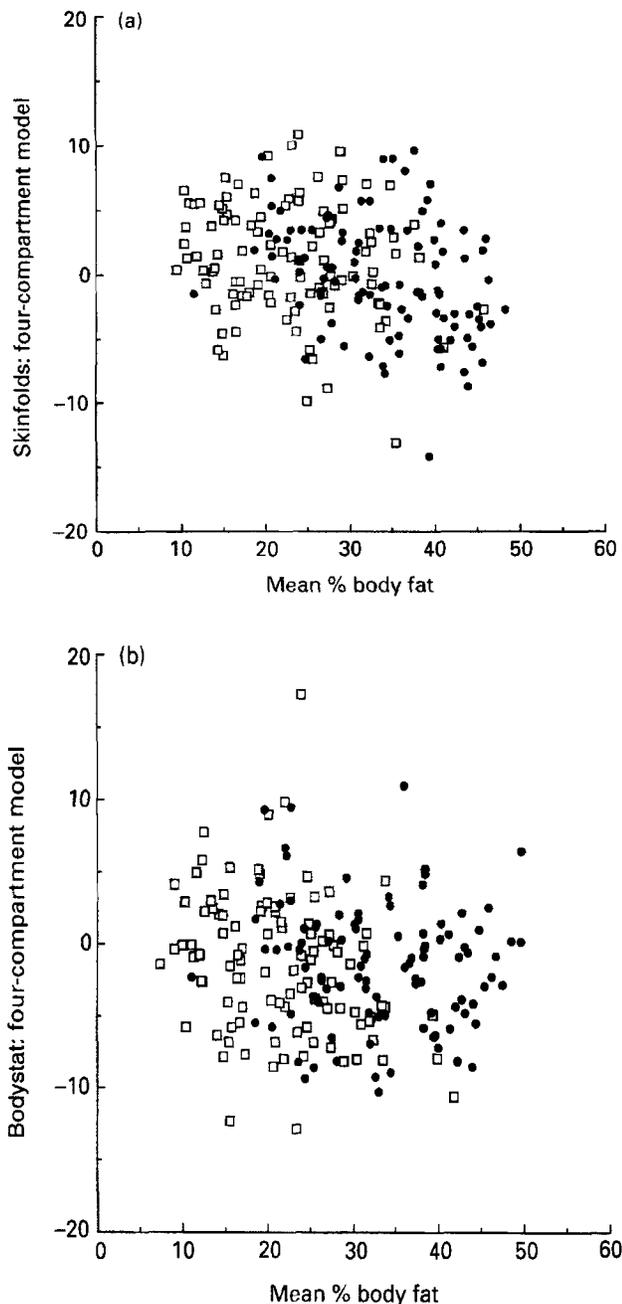


Fig. 4. Individual agreement between a four-compartment model and percentage body fat measured by (a) skinfold thicknesses (Durnin & Womersley, 1974) and (b) bioelectrical impedance analysis (Bodystat; Jebb *et al.* 1998) in men (\square) and women (\bullet).

information on abdominal fat (Svendsen *et al.* 1993; Treuth *et al.* 1995), but imaging techniques such as computed tomography and magnetic resonance imaging undoubtedly remain as the gold standard (Kvist *et al.* 1986; Ross *et al.* 1992), especially for measurements of changes in visceral fat (van der Kooy *et al.* 1993). These methods have been reviewed elsewhere (van der Kooy & Seidell, 1993).

Accurate and precise methods to measure body fat and its distribution are essential in order to study the metabolic and

indeed genetic aetiology of obesity. Much research has been conducted over the last few years to develop and refine the techniques, but there is now a need to apply these methods more widely to address important physiological hypotheses (Jebb, 1997b).

Eating and exercise behaviour

Eating and exercise represent two discretionary activities which can exert a profound influence on energy balance. However, it is almost certain that they are each also subject to some physiological regulation, presumably with a genetic basis. Observed eating and exercise habits represent the sum of both genes and lifestyle, which are not easy to disentangle. Moreover, research into eating and exercise behaviour has been confounded by measurement difficulties.

The inaccuracies and limitations of self-reported food intake were first highlighted by studies of energy expenditure which revealed high levels of energy expenditure in weight-stable obese people despite remarkably low reported energy intakes (Prentice *et al.* 1986; Lichtman *et al.* 1993). We have proposed a system to identify datasets which are characterized by significant under-reporting of food intake based on fundamental principles of energy metabolism, with appropriate allowances for day-to-day variability in both intake and expenditure (Goldberg *et al.* 1991). Today some progress is being made towards understanding the characteristics of under-reporters; the prevalence of under-reporting increases throughout childhood and adolescence (Livingstone *et al.* 1992b), is more common in women than men (Johnson *et al.* 1994), in smokers relative to non-smokers (Pryer *et al.* 1997), among those of low literacy and/or income (Johnson *et al.* 1998; Krebs-Smith *et al.* 1998) and in obese subjects (Prentice *et al.* 1986), post-obese subjects (Black *et al.* 1995) and restrained eaters (Macdiarmid & Blundell, 1997) relative to constitutionally-lean subjects with low levels of dietary restraint (Black *et al.* 1993). Marked differences in the quality of the diet are also observed between apparently-accurate reporters and low-energy reporters. The latter are variously shown to record fewer food items (Krebs-Smith *et al.* 1998), smaller portions (Krebs-Smith *et al.* 1998) and fewer snacks (Heitmann & Lissner, 1995; Poppitt *et al.* 1998), such that the macronutrient composition of their diet appears to contain a higher proportion of protein (Heitmann & Lissner, 1995; Price *et al.* 1997; Pryer *et al.* 1997; Voss *et al.* 1998), a lower proportion of fat (Briefel *et al.* 1997; Voss *et al.* 1998), and lower added sugars (Poppitt *et al.* 1998). Although greater awareness of the problem of under-reporting has prompted the design of more sophisticated methods of data collection and analysis (Lissner *et al.* 1998), it is still easy to draw incorrect conclusions regarding the aetiology of obesity on the basis of apparent differences in both the quantity and quality of food consumed by lean and obese individuals. This remains one of the most critical limitations in integrating biobehavioural factors into aetiological analyses.

In spite of these difficulties there have been numerous studies into appetite and eating behaviour in obesity, and a broad consensus has emerged with respect to the quality of

the diet. Epidemiological studies tend to show a positive relationship between fat intake and obesity (Hill & Prentice, 1995; Lissner & Heitmann, 1995). In global comparisons the analysis is dominated by developed–developing country differences which may be misleading, but within-country analyses also broadly support the link between high-fat diets and obesity (Bolton-Smith & Woodward, 1994). In addition, secular associations between the increase in the proportion of dietary energy from fat and the prevalence of obesity have been reported (Lissner & Heitmann, 1995).

Controlled experimental studies in metabolic units or calorimeters allow the precise documentation of intake. Here energy intake can be measured to within $\pm 2\%$ as compared with the chemical analysis of duplicate diets, which is beyond the remit of most field studies. Some aspects of eating behaviour can also be measured, e.g. eating frequency. These physiological studies have shown that high-fat energy-dense diets consistently induce profound overconsumption, even in constitutionally-lean subjects, relative to less energy-dense diets, usually rich in carbohydrate, due to an increase in energy intake per meal (Prentice & Poppitt, 1996). This was powerfully demonstrated in the studies of Stubbs *et al.* (1995a,b) in Cambridge where over three 1- or 2-week periods subjects were exposed to covertly-manipulated diets with a fat content of 20, 40 or 60% dietary energy and allowed to eat *ad libitum*. Since the dietary manipulation was covert, cognitive adaptations in consumption can be assumed to be small and random. On the high-fat diets subjects consumed more energy, yet expenditure was virtually unaltered, and hence weight (mostly fat) was gained. The positive energy balance was not attenuated over the course of the studies, suggesting the absence of any physiological cues to detect the increased intake and restore energy balance.

One interesting finding of these studies was that energy and fat balance at each of the three levels of fat intake was significantly more positive when subjects were confined to a calorimeter, relative to the free-living state. This implies that subjects failed to compensate for the imposed inactivity (and hence reduced energy needs) by down-regulating their intake. However, before seizing on a physiological defect in energy regulation to explain this finding it is important to remember that the cognitive cues to eating in a calorimeter are very different from those in the free-living situation. Subjects may eat abnormally in this unusual environment, and there may be a tendency to overeat out of boredom or other psychological factors.

There are good reasons to suppose that increased levels of physical activity, or activity above a critical threshold, may be a crucial factor in the control of energy intake, thus providing a homeostatic system to respond to the changing energy needs of the individual. This hypothesis was first proposed by Mayer in the 1950s. He observed that rats who exercised regularly at progressively higher levels increased their food consumption, suggesting a close link between energy intake and energy requirements (Mayer *et al.* 1953). However, animals forced to be inactive overate relative to their reduced energy needs. In a survey of the Indian population he demonstrated a similar phenomenon; in all but the most sedentary occupations there was a good relationship between the increased occupational energy demands and

increased energy intakes, such that body weight was not significantly different (Mayer *et al.* 1955). However, sedentary employees ate similar quantities to those in physically-active jobs and were heavier.

Research in this area is hampered by the difficulties in obtaining reliable measurements of physical activity as well as intake. Measurements made in the confines of a calorimeter do not reflect the usual habits of free-living individuals. The development of labelled-isotope techniques (doubly-labelled water and the labelled bicarbonate–urea method) to measure total energy expenditure has overcome many of these problems, and when combined with measurements of resting metabolic rate, can be used to calculate the energy cost of physical activity (Coward, 1988; Elia *et al.* 1995). These techniques also have the advantage of allowing measurements over many days, thus increasing the probability of measuring habitual energy expenditure (Black *et al.* 1996). An assimilation of the available data on total energy expenditure measured by doubly-labelled water has failed to find any evidence that obese subjects are less physically active than their lean counterparts, when activity is expressed as a multiple of BMR; indeed the total energy cost of activity is higher as a function of their greater body size (Prentice *et al.* 1996). Exceptionally, in the grossly obese there is some evidence of an attenuation of activity, presumably because their body size becomes physically incapacitating.

Although these findings provide useful information for large groups of subjects, the inter-individual variability demonstrates the need for individual measurements in studies of the aetiology of obesity. Questionnaires have been widely employed, but tend to emphasize specific periods of exercise rather than the many small aspects of habitual lifestyle, such as stair-climbing or prolonged periods of standing rather than sitting, which can make a significant contribution to habitual energy expenditure. Heart-rate monitors have been validated against calorimetry (Spurr *et al.* 1988; Ceesay *et al.* 1989) and doubly-labelled water (Livingstone *et al.* 1992a). Whilst they can make a useful contribution to population-based studies (Wareham *et al.* 1997), they lack sufficient precision for the individual assessment of physical activity. Actometers have also been tested, but to date they are less useful (Greene *et al.* 1998). We are currently developing a combined monitor and have completed a preliminary validation study which demonstrates improved precision relative to each individual technique (K Rennie, NJ Wareham and SA Jebb, unpublished results).

Despite these measurement difficulties there is indirect evidence from diverse sources to support a role for physical activity in the prevention of obesity. Data from the Health Survey for England (Bennett *et al.* 1995) demonstrate that there is an inverse relationship between the level of physical activity and obesity. Fig. 5 shows that there is a significantly greater prevalence of obesity in the most inactive group relative to the mean. Even minor activity reduces the risk of obesity, and there is little further reduction in risk in those in the higher categories of physical activity. Prospective studies of physical activity and obesity have been inconclusive (Williamson, 1996), although the largest of these studies (n 12 669) found that men

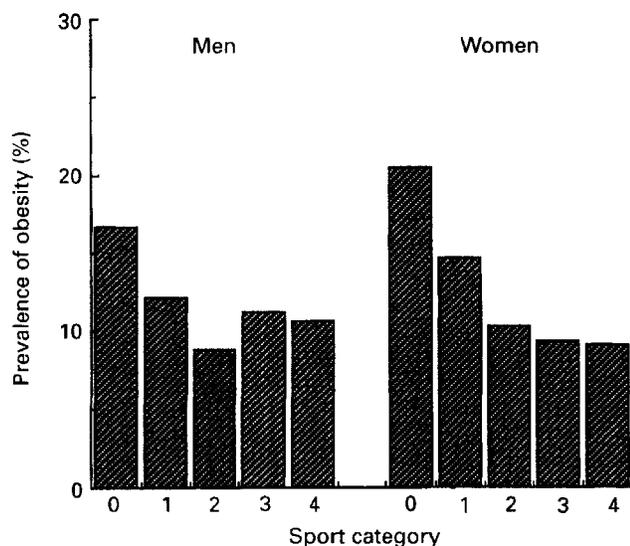


Fig. 5. Relationship between sports participation (sport category 0–4, where 0 is sedentary and 4 is most active) and the prevalence of obesity. (Data from the Health Survey for England 1993; Bennett *et al.* 1995.)

who reported 'rarely' participating in leisure-time physical activity had a relative risk of 1.9 (1.5–2.3) of gaining in excess of 5 kg relative to 'regular' exercisers, and for women the comparable relative risk was 1.6 (1.2–2.2; Rissanen *et al.* 1991). Changes in habitual activity can be particularly significant. Many people recognize that they have gained weight after giving up a regular activity, and in a prospective study men who decreased their level of activity had an odds ratio of 1.96 (1.39–2.75) for weight gain in excess of 5 kg over 10 years compared with those who remained active throughout the follow-up period, and for women the corresponding odds ratio was 2.49 (1.72–3.60; Haapanen *et al.* 1997). There is also very clear evidence that physical activity can help to prevent weight regain following successful weight loss. This is illustrated clearly in the study of Boston policemen, where those who continued their exercise programme maintained their weight loss, whilst those who did not exercise, or ceased to exercise, rebounded to their starting weight (Pavlou *et al.* 1989).

Intriguingly there are also epidemiological data which support a role for an interaction between diet and activity in the aetiology of obesity (Lissner *et al.* 1997). Here, analysis of the data, stratified for differences in leisure-time physical activity, showed that a high dietary fat intake was predictive of subsequent 6-year weight gain only in the most sedentary group, and not in the two groups reporting more leisure-time physical activity.

We have investigated the interactions between appetite and activity at the physiological level within whole-body calorimeters. In this controlled environment internal and external eating cues can be standardized to allow a clearer assessment of the metabolic control system. The regulation of food intake is tested by covertly manipulating

the fat content of the diet, and the interactions with activity investigated by imposing periods of exercise or inactivity. Subjects consumed more energy on the high-fat (60 % energy) diet relative to the low fat (35 % energy) diet, and not surprisingly energy expenditure was greater in the high-exercise protocol, relative to the sedentary protocol. However, the key finding was that on the low-fat diet, energy intake was independent of activity, whilst on the high-fat diet, energy intake was significantly greater on the sedentary protocol. Thus, energy balance was preserved on the high-fat diet high-exercise protocol, both by the increased energy costs of the imposed exercise and the attenuation of energy intake (PR Murgatroyd, F Leahy, GR Goldberg and AM Prentice, unpublished results). On-going studies are examining the mechanism underlying this apparently important interaction.

There is a growing body of evidence relating to eating and exercise behaviour to suggest first, that the fat content and/or energy density of the diet may undermine (or fail to initiate) appropriate physiological controls of energy intake, and second, that low levels of physical activity contribute to the creation of positive energy balance, both through a reduction in absolute energy expenditure and through interactions with appetite. There is now a need to try to integrate these whole-body physiological observations with a more detailed evaluation of the mechanism of these effects.

There has been a considerable amount of research into the neurobiology of energy regulation, but to date this has largely been confined to animal studies. Most of the neurotransmitters which have been identified act on appetite, with lesser effects on thermogenesis (Wilding *et al.* 1997). Most are inhibitory, e.g. serotonin (Shor-Posner *et al.* 1986), cholecystokinin (Gibbs *et al.* 1973; Ballinger *et al.* 1994), glucagon-like peptide-1 (Turton *et al.* 1996) and corticotrophin-releasing hormone (Glowa *et al.* 1992), although there are a few potent stimulators of intake, e.g. neuropeptide-Y (Stanley *et al.* 1986), galanin (Tempel *et al.* 1992) and orexins (Sakurai *et al.* 1998). This is a major research area with regard to the fundamental control of appetite, and there is clearly the potential for an interaction with the energy needs or physical activity level of the subject. Understanding the integration of these neuropeptides in the overall regulation of energy balance in man is a particular challenge, and requires innovative research strategies. For example, positron-emission tomographic scanning may provide further detail regarding the site, initiation and duration of the central actions of these neuropeptides, whilst the use of pharmacological modulators may indicate the relative importance of some of these peptides in the *in vivo* control of energy balance in man.

In any consideration of the influence of human behaviour on the susceptibility to obesity it is important to note the potential for effects of genes on behaviour. This has received less attention than the genetic influences on metabolism and physiology. The genetic programming of food preferences, snacking habits or habitual physical activity is an important area for future research. However, it will require new methodologies to objectively document these characteristics in order to produce integrated analyses of the effects of genes, metabolism and behaviour.

Environmental influences

The secular changes in the prevalence of obesity, even over relatively short periods of time, provide clear evidence that environmental influences exert a profound influence on the likelihood of weight gain. This is true in both developed and developing countries. There are numerous examples throughout the world of regions in which economic development, and in particular urbanization, have led to a rapid increase in obesity (James, 1996). In developed countries such as the UK and USA the recent increases in obesity have been all the more remarkable since they have occurred at a time of unprecedented information and advice regarding the avoidance of weight gain (Seidell & Rissanen, 1998). Furthermore, our analysis of trends in obesity in the UK over the last 50 years has demonstrated that since 1970 mean per capita food intake has been declining (Prentice & Jebb, 1995a). The extent of the reduction varies depending on the source of the dietary data, but the decrease seems indisputable (Prentice & Jebb, 1995b).

The paradox of increasing obesity at a time of decreasing food consumption can only be reconciled by an even sharper decline in energy requirements. Direct evidence of changes in energy needs is scanty, but sociological trends in lifestyle provide compelling support to this proposition; the proportion of manual occupations has declined, car ownership has increased and cars are widely used even for short journeys which were previously made on foot or bicycles, electric gadgets have reduced many of the labour-intensive tasks in the home, and leisure-time is dominated by sedentary pursuits, predominantly watching television and videos. Incorporating physical activity into our contemporary lives requires a specific commitment in terms of time and/or money, whereas it was previously an integral part of every day. For large sectors of the population sedentary lifestyles have become the norm.

Although we believe that low levels of habitual activity are a key component underpinning the epidemic of obesity (Prentice & Jebb, 1995a), it is again necessary to reflect on the apparent inability of the body to down-regulate its intake to meet these low energy needs. Physiological studies have provided some evidence of a metabolic interaction between activity and appetite, but it is clear that there are environmental influences on food intake which tend to promote overconsumption. Although mean energy intakes are declining, there are inevitably significant differences within the population. Today people in the developed world have access to an abundance of food, with more variety available and at lower relative cost than ever before. Portion sizes are increasing across a range of items, from confectionery to fast-food; regular snacking is replacing meal-eating, and marketing strategies promote consumption rather than restraint. Environmental influences conspire to simultaneously encourage overconsumption and inactivity. The 'couch-potato' is one of the symbols of the decade.

The modern environment does not make obesity inevitable, but does increase the likelihood of inducing a positive energy balance (Prentice, 1997). However, some individuals remain slim. In most developed countries a marked social class gradient has developed in which professional groups, especially women, are much less likely to be

obese than their counterparts with lower educational or occupational status (Jebb *et al.* 1997). This suggests that it is possible to develop behavioural strategies to defend body weight from these external influences. This may be achieved either by a low-fat diet and/or habitual physical activity, which allow the physiological systems to operate effectively, or alternatively through cognitive controls over eating, including the imposition of dietary restraint and/or prescribed exercise sessions.

Summary

Undoubtedly research into the genetic and metabolic basis of obesity has been enhanced by methodological advances with respect to the measurement of energy balance. However, in the overwhelming majority of cases there is still no clear evidence of a genetic or metabolic defect responsible for obesity. The developing epidemic of obesity suggests that the capacity to gain weight is not limited to a few individuals and the concept of a genetic or metabolic predisposition to obesity is gradually becoming redundant. It may eventually be easier to search for protective traits rather than susceptibility factors in order to understand the physiological basis of body weight regulation.

In any group of similar subjects there will be a variation in energy needs; however, obesity will only develop if individuals fail to match their energy intake to their energy needs. We therefore propose that the primary defect in obesity lies in the integration of energy intake with energy expenditure. Whilst in the long term gene therapy may be used to modulate aspects of both energy intake and expenditure, in the short and medium term there is a pressing need to find effective ways to encourage both individuals and society at large to make the necessary changes in lifestyle which can, and will, reverse this threat to health. Obesity may have a molecular or metabolic basis, but is ultimately determined by the behaviour of man in the modern world.

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