The Summer Meeting of the Nutrition Society was held at the University of Surrey on 29 June–2 July 1998

Joint symposium with British Dietetic Association on 'Implementing dietary change: theory and practice' Session 2. Obesity

New understanding in obesity research*

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A public-health approach considers the relevance of nutritional research in the prevention and management of obesity. Well-defined and internationally-agreed definitions based on BMI allow an assessment of the worldwide prevalence of overweight and obesity. There are about 250 million obese adults in the world, and many more overweight. Obesity is emerging in the Third World, first in urban middle-aged women. With economic developments, obesity then occurs in men and younger women. In the West childhood obesity is rapidly emerging, with concern that early-onset obesity is especially hazardous. In Asians the risks of excess visceral fat occur at lower body weights than in Caucasians. The propensity to visceral obesity in Asians may relate to malnourished mothers and low birth weight. The International Obesity Task Force is considering many issues, including the health economics of obesity. It has developed a strategy to define childhood obesity, which in children over 6 years is likely to predict long-term weight and health problems. While the search for genetic markers of obesity continues, with particular interest in the leptin gene, it is clear that societal change, with the decline in physical activity and the passive overconsumption of high-fat diets are major contributors to the global increase in obesity. The public-health aspects of obesity research are therefore challenging.

Public health: Obesity: Overconsumption: Physical activity

It has become traditional when considering obesity research to concentrate on new developments in our understanding of the complex processes which control energy balance. In this field there has been a fascinating explosion in the evaluation of genetic influences, the discovery of leptin and renewed interest in uncoupling proteins. All these fields merit detailed study, but for the present Symposium a broader canvas seems appropriate, and is justified by equally important developments when considered in public-health terms and the relevance of nutritional research to our understanding of how to prevent and manage obesity.

Definitions of obesity

First, there is the simple issue of the definition of obesity. This issue seemed almost settled 15 years ago when the re-analyses of the Metropolitan-Life Insurance tables in terms of BMI and the longevity of young men and women showed that men should have BMI of 20·1–25·0 kg/m^2 and women 18·7–23·8 kg/m^2 (Royal College of Physicians, 1983). This was simplified by Garrow (1981) to 20–25 kg/m^2 for both sexes, with a BMI of 30 kg/m^2 being set as the cut-off point for obesity. This again was an increase in the cut-off point for women, which on the basis of a 20 % increase would have been 28·6 kg/m^2. Later, we extended the lowest range to 18·5 kg/m^2 as a result of considering issues relating to adult underweight or 'chronic energy deficiency' (James *et al*. 1988), this range being accepted by the World Health Organization (1995). Yet it took until this year for the USA to accept the 25·0 kg/m^2 lower limit for overweight and 30·0 kg/m^2 for obesity (National Heart, Lung and Blood Institute Expert Panel on the Identification, Evaluation and Treatment of Overweight in Adults, 1998). This decision followed the major development of a special World Health

*This paper arrived too late for publication with the other papers in this symposium, which appear in Volume 58, no. 1.

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Organization (1998) report on obesity which this year re-affirmed the BMI of 18·5–24·9 kg/m^2 as normal and added a BMI category of 35·0–39·9 kg/m^2 for special treatment with surgery if this severe obesity was accompanied by diabetes, cardiovascular or other serious complications. This change in US policy reflected an intense debate within the USA about the usefulness of having a progressive increase in weight in adult life, this proposition being refuted by data from Harvard (Willett *et al*. 1995) which inferred from long-term prospective studies that BMI values of perhaps 19·0–20·0 kg/m^2 were optimum for reducing risk from CHD. Smokers have higher mortality rates at all levels of BMI; this excess mortality complicates the usual population analyses of BMI and risk in the whole population (Manson *et al*. 1995).

We are now therefore in a position to establish on a systematic basis worldwide prevalence data on overweight adults, i.e. with BMI of 25·0–29·9 kg/m^2, and of the obese with BMI of ≥ 30·0 kg/m^2. It is already clear that there is a pandemic of obesity throughout the world, with obesity emerging in the Third World first in urban middle-aged women. As economic developments occur, men start to become obese, with the incidence of obesity occurring at ever-younger ages in women. We have estimated therefore that there are about 250 million obese adults in the world, with far greater numbers of overweight. In almost all societies women are more prone to obesity than men, as shown in Fig. 1; this situation we believe to be a biological phenomenon which reflects the greater deposition of lean tissue during weight gain in men, and therefore their capacity to compensate better for the excess energy intake due to the rise in BMR as obesity develops, with its accompanying increase in lean body mass (James *et al*. 1978; James & Reeds, 1997).

Asian obesity and syndrome X

There is clearly a tidal wave of obesity sweeping the world, but two features give extra grounds for concern. First, in the West, childhood obesity is emerging rapidly, and the earlier the onset of adult obesity the more hazardous it is (Royal College of Physicians, 1983). Second, in Asia the hazards of even modest weight gain seem more drastic. In native and expatriate Asians the classic complications of obesity, i.e. diabetes, dyslipidaemias, hypertension and CHD, are evident more frequently, even at BMI in the 22–27 kg/m^2 range (Beegom *et al*. 1995; Singh *et al*. 1995). Thus, Singh *et al*. (1995) have called for a cut-off point of 23·0 kg/m^2 as indicative of substantial risk. These worrying complications have been described as syndrome X and linked with abdominal obesity (McKeigue *et al*. 1991). In Asians the risks of excess visceral fat emerge particularly strongly.

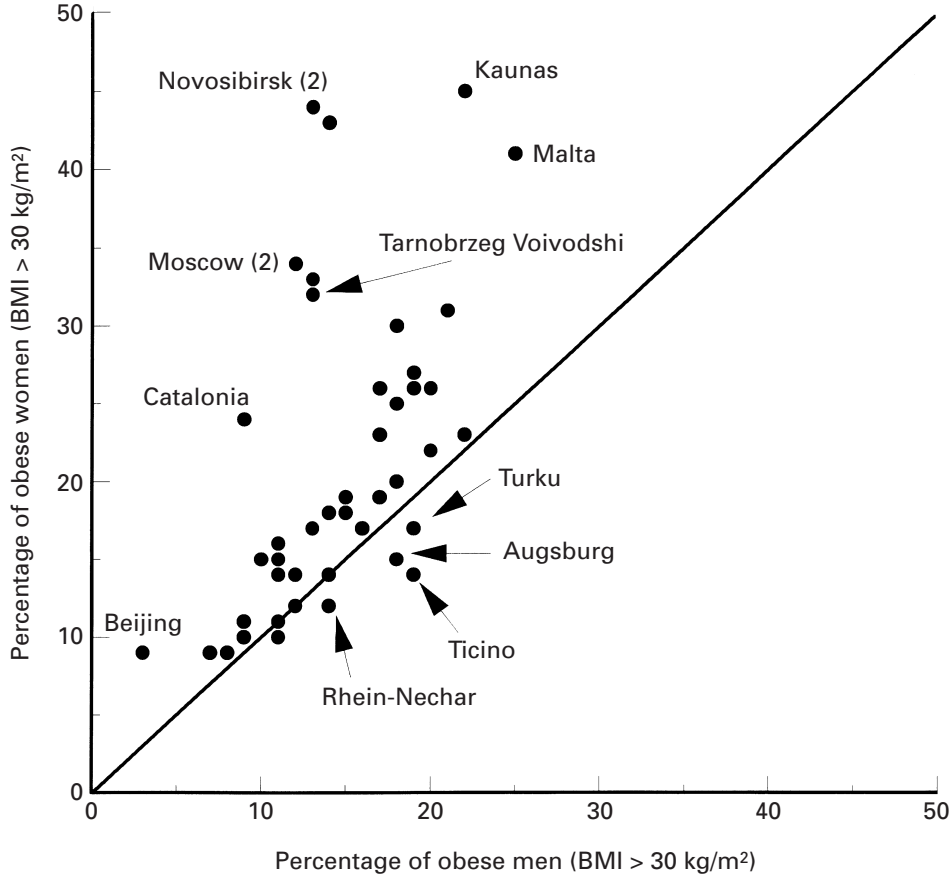

Fig. 1. Comparison of the percentage of men and women aged 35–64 years across the world who are obese (BMI > 30 kg/m^2). (Data from World Health Statistics Quarterly, 1988.)

https://doi.org/10.1017/S0029665199000506 Published online by Cambridge University Press

Thus, the new developments which we proposed in the Scottish Intercollegiate Guidelines Network (1996) guidelines on obesity management use waist-measurement cut-off points to highlight the health risks of an increase in abdominal girth. These currently apply to Caucasians, but in Asians the same cut-off points have been proposed and occur at lower BMI (Singh *et al*. 1996). Thus, the waist-circumference cut-off points may prove to be more valuable and consistent than BMI. We have proposed that this propensity to abdominal obesity relates not to a genetic predisposition but to a reprogramming of the hypothalamic–pituitary–adrenal axis induced by maternal reprogramming of the fetus when the mother is malnourished, with a low BMI on starting pregnancy (this situation applying to half the Indian population; James, 1995), exacerbated by their low protein intake from a rice-based diet (James, 1997). Bjorntorp and his colleagues (Marin *et al*. 1992) have demonstrated the greater propensity to hypercortisolism in those with visceral obesity, this being manifest under basal conditions but also on formal stimulation of the adrenal with synacthesis, a synthetic adrenocorticotrophic hormone-like compound. Of more general relevance is Bjorntorp's (Marin *et al*. 1992) demonstration that hypercortisolism becomes evident with both physical and psychological stress. Bjorntorp (Marin *et al*. 1992) considers these events may signify a mechanism for the impact of social stress in both Asian immigrants and in those from the lower social stratum in Britain and elsewhere. These individuals have limited control over their lives, as demonstrated in the Marmot *et al*. (1997) studies of CHD, which show that various social and pyschological features are additional risk factors for a myocardial infarct (Brunner, 1997).

Childhood obesity

Our International Obesity Task Force soon recognized that the problem of childhood obesity as well as adult obesity was emerging as an issue of potential importance, and clear definitions were therefore needed. Childhood obesity had been defined as occurring when weight exceeded 120 % of the upper normal World Health Organization (1995) reference limits, i.e. 2 SD of the weight for height-for-age, but this was an arbitrary approach and used mainly data from the USA where childhood obesity was considered to be likely. The International Obesity Task Force, therefore, has developed a new strategy under the auspices of the Chairman of the group on childhood obesity, Dr Bill Dietz from the Center for Disease Control, Atlanta, GA, USA. Using the Cole *et al*. (1990) approach to defining age- and sex-specific BMI curves (which have been accepted already as a reference system for general use by the British Paediatric Association), Cole, with colleagues from Dietz's group (Cole *et al*. 1998), developed a scheme whereby the percentiles of BMI were assessed from a series of modern national surveys of children's growth. Countries such as the USA and Pacific islands were excluded because we needed reference data from societies where both childhood underweight and obesity were considered to be unusual occurrences. The BMI percentile curves were chosen such that at the age of 18 years they correspond to BMI of 25 and 30 kg/m^2, i.e. making these percentiles compatible with the adult cut-off points for overweight and obesity. In practice, the percentiles corresponding to adult BMI of 30 kg/m^2 proved too erratic, since so few children showed the values, but the percentiles corresponding to adult BMI values of 25 kg/m^2 corresponded well. Consistent curves from multiple childhood surveys showed that the 85th percentile value was appropriate for the overweight cut-off point, i.e. corresponding at 18 years to a BMI of 25 kg/m^2. It was assumed that in general children's BMI tracked along the same percentile values with age. It was then possible to define the BMI at each age for boys and girls separately, recognizing that it is the BMI in children of 6 years of age or more which are likely to be predictors of long-term weight and health problems. These reference data are now due for publication (Cole *et al*. 1998).

The health impact of obesity

The World Health Organization (1998) decided to adopt universal BMI cut-off points, although weight gain may be more serious in some societies than in others. The unusual susceptibility of Asians to severe complications was of concern, but the data from Africa were not considered substantial enough to allow distinctions to be made either on a racial or other basis, and no allowance was made for the potentially different psychological, social or economic impacts of grades of overweight in different cultural settings. There is little doubt that in Western societies obese children and adults, particularly women, are stigmatized and suffer greatly from a sense of inadequacy and failure because of their difficulty in conforming to a modern perception of a 'desirable' body weight. These social handicaps or 'intangible costs' contribute to the overall economic impact of obesity, but economic analyses tend to be confined to the 'direct' costs in relation to medical issues. Only a preliminary view had been taken of the 'indirect costs' relating to lost production, to work-related absenteeism or to premature death, but the direct costs alone are estimated to range from 2 to 7 % of total health costs. Thus, even these conservative estimates provide a clear indication that obesity represents one of the largest expenditures in national healthcare budgets. Currently, a further International Obesity Task Force group led by Professor Ian Caterson from Sydney, Australia, is looking at health economics of obesity in greater detail.

The causes of obesity

This issue presented the International Obesity Task Force with some difficulty, because many physicians are concerned with the diverse nature of obesity and the often marked differences between patients observed in clinical practice. This naturally leads to a great emphasis on the genetic propensity to weight gain, to the selective deposition of abdominal fat, and to assessing the individual responses to adiposity in terms of dyslipidaemias, hypertension, hirsutism etc. Indeed, the search for genetic markers has become intense, as set out by Bouchard (1997), with particular interest being focused on the leptin gene, β_3-adrenergic regulators and uncoupling proteins. There is little doubt that

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there is a genetic propensity to weight gain, but the genes are so far ill-defined (Farooqi *et al*. 1998). In terms of the heritability of total body fat this seems to amount to about 30–40 % of the variation seen in Western societies, with familial environmental factors increasing the background effect to 55 % (Rice *et al*. 1997). The genetic influences on abdominal fat accretion are much stronger, accounting for approximately 60 % of the observed variability, and they operate independently of factors relating to total body fat mass (Perusse *et al*. 1996).

Interest in the metabolic basis of obesity exploded when leptin was discovered, the role of leptin in energy balance having been set out at this year's Winter Meeting of the Society (Andrews, 1998). Changes in the control of leptin secretion or responsiveness are being sought in human subjects, particularly now that two children from a highly consanguineous family have developed obesity within 3–4 months of age and have been shown to have no detectable circulating leptin (Farooqi *et al*. 1998). The obesity is associated with a homozygous mutation of the leptin gene and profound hyperphagia analogous to the observations in the leptin-deficient *ob*/*ob* mouse.

Leptin and peripheral metabolism

Leptin is now seen to have many actions (Trayhurn *et al*. 1998). In tissue terms, rodent studies show that leptin can reduce the triacylglycerol concentration of muscle by increasing lipolysis and fatty acid oxidation (Koyama *et al*. 1997; Shimabukuro *et al*. 1997). Leptin administered *in vivo* to *ob/ob* mice also selectively boosts fat oxidation and energy expenditure (Hwa *et al*. 1997). How leptin alters fatty acid oxidation is unknown, but the newly discovered uncoupling protein UCP-3, present in skeletal muscles of human subjects as well as rodents (Solanes *et al*. 1997), is induced not only by leptin but also by β_3-agonists (Gong *et al*. 1997). The *ob*/*ob* and *db*/*db* mice and *fa*/*fa* rat models of obesity are now known to be either reflecting a mutation in the leptin gene or the leptin receptor gene, and are characterized by a low sympathetic drive (Bray, 1990*a*,*b*), so it seems likely that leptin operates both directly and indirectly through a sympathomimetic mechanism. Given the demonstration by Trayhurn *et al*. (1998) that sympathetic stimuli have a profound effect in suppressing leptin synthesis and release in white adipose tissue, it seems likely that there is a sympathetic–leptin cycle of self regulation which could be of considerable importance.

Leptin also affects peripheral metabolism through insulin-mediated mechanisms, shown by the mimicking of the sympathetically-mediated fall in pancreatic insulin secretion by leptin (Cawthorne *et al*. 1998). Furthermore, the newly recognized minor third pathway of glucose metabolism within cells (involving the generation from fructose-6-phosphate of a glucosamine conjugate, leading through the incorporation of uridine to the production of uridine-N-acetylglucosamine) now seems to lead both to insulin resistance and to leptin induction. This finding would further boost fatty acid metabolism rather than glucose metabolism (Wang *et al*. 1998).

Individual susceptibility to obesity

Given these fascinating developments with leptin, one immediately wonders whether the leptin cycle involving the complex hypothalamic interactions, with effects on glucocorticoid and sex-hormone metabolism as well as food intake, will now be seen as capable of explaining the variety of endocrinological syndromes seen in obese patients. Perhaps of even greater interest is whether changes or differences in the leptin control of appetite and of metabolism can explain the individual susceptibility to weight gain in children and adults. Circulating leptin levels correlate well with total body fat, with women having higher levels than men, so the enhanced leptin levels in obesity are taken to represent leptin ‘resistance’ (Arch *et al*. 1998). Such resistance can be demonstrated in animals, classically where there is a mutation in the leptin-receptor gene. Of greater significance, however, is the demonstration by Campfield & Smith (1998) that diet-induced obesity in susceptible strains of rodents can lead to secondary leptin resistance. This resistance is evident from the limited impact of standardized leptin injections on food intake and metabolism, and on body fat. In man as well as in animals, therefore, there will be a need to distinguish primary from secondary leptin resistance.

Adults with a propensity to obesity are known to have a subnormal sympathetic tone, with lower noradrenaline levels and a tendency to reduce their sympathetic drive and their triiodothyronine : thyroxine values when fed on high-fat diets (Astrup & MacDonald, 1997). They also tend to suppress their fat oxidation when fed on high-fat diets (Buemann *et al*. 1998), this reduced oxidation perhaps relating to a cellular resistance to fatty acid oxidation in the muscles of these individuals (Jenkendrup *et al*. 1998). A low sympathetic drive has also been linked to higher hunger ratings (Raben *et al*. 1996), so the documented greater propensity to weight gain in these individuals may reflect their greater responsiveness in terms of intake as much as their depressed metabolism (Astrup & MacDonald, 1997). All these features highlight the need to assess the leptin system under controlled circumstances, with monitoring of food intakes, sympathetic drive, leptin output and substrate metabolism. Based on the findings of Trayhurn *et al*. (1998), one would expect a low sympathetic stimulation of adipose tissue to allow leptin levels to rise, but the response after feeding is presumably less than expected, and these leptin levels therefore may not reduce appetite and food intake as much as they should.

The determinants of the increasing obesity rates

Geoffrey Rose (1991) nearly one decade ago, highlighted the importance of considering the BMI distribution of the whole of a population when assessing why obesity rates were different in different countries. Using data from the INTERSALT Study, Rose (1991) showed that the average BMI of a population predicted the prevalence of obesity extremely well, so, as with alcoholism, it is the usual behaviour of a society which predicts the proportion in the more extreme category. What this means is that we have to investigate the societal changes that may have caused the

increase in average body weight and, therefore, in the proportion of the population classified as obese.

When looking at this problem from a British point of view (Department of Health, 1995), we realized that as far as total food intake is concerned there seems to have been a marked fall in intake, as judged by national household food surveys. Although more food is being bought outside the home, generous allowances for this did not overturn the conclusion that intakes have actually fallen, in keeping with our general perceptions of the much bigger and more frequent meals of the past. We had also recognized, however, that with ageing there is a substantial fall in intake, amounting (in our recalculations of data from the US Ageing Energy Expenditure Study of Shock *et al.* 1984) to > 4200 kJ (1000 kcal)/d for men measured first when aged 25 years and then again at 75 years of age (James *et al.* 1989). This finding confirms our everyday experience of reducing food intakes with age, thus of course reflecting the remarkable decline in physical activity with age (Health Education Authority and Sports Council, 1992; Bennett *et al.* 1995). In practice, the age-related increase in body weight reflects the small energy imbalance arising because energy intakes had not fallen as much as physical activity. A greater fall in intake is necessary to maintain energy balance as we become physically more inactive. Weinsier *et al.* (1993) predicited (with elegant calculations) slow changes in weight over 5–20-year periods, so that the weight came up to a new plateau. This change occurs with average daily excesses of intake of only 420 kJ (100 kcal). At the new 'plateau' weights the daily maintenance-energy cost of the extra lean tissue deposited finally brings the BMR up to allow energy output to match intake (Jung & James, 1980). These findings also explain why women with an average excess intake of 210 kJ (50 kcal)/d have to put on far more weight than men before they reach a new energy balance; they need to gain more weight to accumulate enough lean tissue to increase metabolism to match the discrepant energy intake (James & Reeds, 1997).

'Passive overconsumption' of fat

Our original perspective on intake–output measures in relation to the British epidemic of obesity was dominated by the emerging linkage between the tendency to overeat unwittingly on high-fat diets and the importance in relation to energy imbalance of physical activity (Stubbs *et al.* 1995). The work of Blundell & Stubbs (1997) highlighted the many ways in which dietary fat seemed to lead to 'passive overconsumption', with evening fatty meals not allowing even the relatively poor fat compensatory mechanism to be invoked until perhaps lunchtime the next day, at which time compensation for the evening's excess intake was poor (Blundell & Stubbs, 1997). Since then, Stubbs (1998) has re-emphasized the importance of energy density *per se* in determining at least short-term effects on energy intake, thus raising the issue of how best to express and then assess the energy density of intake. This factor has many implications for an optimum dietary composition in relation not only to fat but also to sugars and maltodextrose in snacks and drinks as well as meals. Given the major vested interests in this topic, however, there will be a need to obtain very clear evidence before we can consider how best to limit the development of obesity by measures other than restricting fat intake and promoting physical activity.

Fatty foods are an ideal way of inducing obesity in experimental animals, with some strains being much more susceptible than others (York & Hansen, 1997). In human subjects, Heitmann *et al.* (1995) observed a link between high fat intakes and excess weight gain in those with a family history of obesity. Astrup *et al.* (1996) have also extended our original findings that the post-obese, i.e. obesity prone, have different metabolic responses to altered dietary carbohydrate : fat values, with a boost in their metabolism observed on feeding low-fat high-carbohydrate diets (Lean & James, 1986; Astrup & MacDonald, 1997). Toubro & Astrup (1997) have also noted the tendency of obese individuals to eat a fattier diet than non-obese individuals; in practice they need low-fat diets to prevent weight regain. McDiarmid *et al.* (1996) also showed in a re-analysis of the British National Survey that adults on fat intakes of > 45 % energy from fat had a higher distribution of BMI that those on intakes < 35 % energy from fat. Our own analyses suggested a progressive increase in BMI with increasing fat intakes from 15 % energy upwards, at least in men (Francois & James, 1994), and new data from Malaysia (Ismail *et al.* 1995) confirm the increasing propensity to obesity, especially in women on average fat intakes of as little as 20 % energy. However, young men on *ad libitum* intakes of 20 % energy from fat manage to maintain energy balance even when they are in the sedentary state (Stubbs *et al.* 1995). It is also this 20 % energy level which is now suggested as an upper dietary value in proposals for preventing obesity made by the International College of Nutrition in India (Singh *et al.* 1996).

These observations on dietary fat intake, with its implications that the British goal of 35 % energy from fat is far too high, do not in any way conflict with the new evidence on the profound importance of physical activity. Prentice & Jebb (1995), in their elegant extension of the Department of Health's (1995) analyses, showed that the secular increase in obesity rates relates powerfully to declining physical activity. These new sedentary lifestyles stem from greater car use, work- and home-based mechanical aids in a computer-based society, and also from television watching. This last feature has been found by Dietz (Gortmaker *et al.* 1996) to be a powerful predictor of weight gain in children. Prentice & Jebb (1995) also linked the higher obesity rates in the lower socio-economic classes to their sedentary lifestyles. These findings and those from Stubbs *et al.* (1995), Blundell & Stubbs (1997) and Astrup *et al.* (1996, 1997) simply demonstrate the powerful interplay between physical inactivity and the fat content of the diet. A diet containing 40 % energy from fat (even if from olive oil!) is only compatible with energy balance and a normal body weight in both the average and obesity-prone individual if accompanied by sustained physical activity every day. Thus, the much-cited Cretan men in Keys (1980) Seven Country Study ate a diet containing 38 % energy from fat (dominated by olive oil), but they were walking for 15–30 km daily in the hills of Crete. This is a rather impractical prescription for every adult throughout life, as sometimes implied by the rejection of the importance of

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dietary fat in determining the prevalence of obesity (Katan *et al*. 1997; Willett, 1997).

A distinction needs to be made between those factors which induce obesity and the most effective ways of slimming. As Astrup & MacDonald (1997) showed, obesity-prone subjects with low sympathetic drives are those most likely to do poorly on weight-loss and weight-maintenance regimens, and there is now powerful evidence for what is in effect a resetting of the body's regulatory 'set-point' once weight gain has occurred (Rosenbaum *et al*. 1997).

The data on physical activity need to be amplified, but it is already clear that quite modest increases in activity can have marked benefits in preventing diabetes, coronary events and hypertensive-related strokes, independently of body weight (Blair, 1993). A physical activity level of about 1·75 is also the level above which risk of some cancers, e.g. large-bowel cancers, may be prevented (World Cancer Research Fund, 1997). To achieve more than these physical activity levels should also prevent obesity (Ferro-Luzzi & Martino, 1996), but we will need a transformation of approaches to everyday life rather than concentration on leisure time and sports activities to achieve this (World Health Organization, 1998).

Obesity management

Much has been made of obesity management since we publicised our Scottish Intercollegiate Guidelines Network (1996) guidelines in Scotland. These guidelines benefited from the US analysis of optimum treatments (National Institute of Medicine, Committee to Develop Criteria for Evaluating Outcomes of Approaches to Prevent and Treat Obesity within the Food and Nutrition Board of the National Institute of Medicine, 1995) and helped to ensure that US guidelines were compatible (*Shape Up America 1997*; American Obesity Association, 1997). These guidelines then led to coherent analyses of management strategies by the International Obesity Task Force, and then by the World Health Organization (1998), which set out the need for a staged scheme of patient recruitment, assessment of family history and other factors, then a risk-factor assessment for dyslipidaemias, hypertension and other problems. The weight-management strategies were transformed into long-term weight-management schemes with an emphasis on weight maintenance. There was also an emphasis on modest weight losses of 5–10 %, and ensuring a reduction in the risks associated with obesity. Gone, therefore, are the concepts of 'ideal goal weights' and crash diets which did little for the long-term benefit of the patients.

This new approach is being taken very seriously in most countries, despite the lukewarm approach of the general practitioners in Britain, who are suddenly confronted by a huge case load and the need to think about long-term health management rather than dispensing prescriptions for arthritis, hypertension, breathlessness, diabetes or other numerous complications of obesity. Paradoxically, doctors' attitudes may be changed by the advent of two new drugs, i.e. the lipase (*EC* 3.1.1.3) inhibitor orlistat and the combined noradrenaline and serotonin re-uptake inhibitor sibutramine. The original Scottish Intercollegiate Guideline Network (1996) guidelines and the more recent World Health Organization (1998) report only had the fenfluramine and dexfenfluramine efficacy data to assess, but the principles applied to any effective drug for inducing long-term weight loss. We have, for a long time, prescribed drugs for dietary-induced diseases such as non-insulin-dependent diabetes mellitus, CHD, hyperlipidaemia and hypertension. With obesity now recognized as a disease resistant to treatment by diet and exercise, a new consensus has emerged on the use of drugs. When BMI exceeds 30 kg/m^2 and when risk factors persist despite attempts at careful dietary, activity and behavioural modifications, then the use (potentially extended use) of appropriate and efficacious drugs is warranted. These drugs must be used in conjunction with dietary therapy, which in all the recent and current Roche and Knoll (Roche Pharmaceuticals, Nottingham, UK and Welwyn Garden City, Herts, UK) company trials is based on our 2090–2500 kJ (500–600 kcal)-deficit diets (Lean & James, 1986). This approach has led to an astonishing international consistency of response in the placebo component of the different drug trials (for example, see Sjostrom *et al*. 1998).

The most severe forms of obesity are now to be managed by surgery, for which there is increasing evidence of cost-effectiveness (Karlsson *et al*. 1998). What these pharmaceutical studies also show, however, is the profound importance of maintaining weight loss and the benefits of preventing weight gain. These new therapies, therefore, are highlighting the overwhelming need to incorporate preventive strategies into medical practice. Until this is done we will have an escalating burden of clinical care for doctors to cope with throughout the globe.

Conclusions

Obesity has not only become a major public health problem around the globe, but is intellectually a very challenging research area. To engage in studies on the control of energy intake or of substrate metabolism and energy expenditure, measured in well-defined groups of children or adults with or without an intrinsic tendency to weight gain, is a formidable challenge. It requires sustained effort, with excellent facilities and a capacity to design research protocols to answer carefully-constructed questions. The explosion in neurochemical studies on the control of food intake and the control of selective macronutrient intake, on the hypothalamic–pituitary–adrenal axis and the autonomic nervous system, now need to be matched by studies to test the intriguing suggestion that peripheral metabolic events may feed back to appetite control by systems other than leptin. The whole field of energy imbalance and its societal significance is therefore at last a major (and respectable) subject for investigation in Britain as well as elsewhere. These developments come at a time of great changes in the British resources and personnel dealing with these endeavours, so this area of research presents the British nutritional community with real challenges.

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https://doi.org/10.1017/S0029665199000506 Published online by Cambridge University Press