Obesity and affluence: genes, metabolism, behaviour and environment

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Summary

Obesity is frequently described as a multifaceted disease with complex causes ranging from molecular defects to macro-environmental influences on diet and lifestyle. The integration of knowledge across this broad spectrum of disciplines is particularly challenging. Currently there are rapid advances in respect of the molecular genetics of obesity which will greatly enhance understanding of the basic mechanisms regulating energy balance. However there is a need to maintain a balanced approach in obesity research. This paper uses selected examples of aetiologic interactions to illustrate that the development of future preventative and therapeutic strategies will depend as much upon social and behavioural research as on the genetic and pharmacologic areas which are presently attracting most funding and expertise.

Introduction

Most affluent nations are facing an emerging epidemic of obesity which ranks alongside many of the classic infectious epidemics in terms of their public health significance. There are close medico-scientific parallels with the early stages of understanding such epidemics. We still do not understand the aetiology of obesity, and yet are faced with a pressing need to develop better preventative and therapeutic strategies on the basis of pragmatic decisions about the likely causal factors. One of the themes of this paper is to propose a greater cross-disciplinary approach to obesity research with the closer integration of knowledge and expertise from molecular and cellular biology, through whole-body physiology and metabolism, to biopsychology and epidemiology. This integrative approach has been employed by a number of the leading thinkers in the obesity field (1,2), and could usefully be encouraged to percolate further down to influence the design of research programmes especially in these days of increased specialisation.

For a number of reasons there is a particular need to support cross-disciplinary thinking at the present time. For many years obesity has been a cinderella subject which, with notable exceptions, has failed to attract academics or physicians of the calibre that would enter cancer or HIV research. It has also failed to attract comparable funding to these disease areas. This is now changing as a consequence of several factors. Firstly, due to the rapid increase in prevalence rates of obesity which is now forcing governments to take the problem seriously. Secondly, due to the promising and intellectually satisfying developments in the molecular genetics of obesity which are legitimising obesity as a worthy topic of study. The latter developments, together with the fact that obesity is viewed by most pharmaceutical companies as the largest untapped therapeutic area, is drawing significant new financial and intellectual resources into obesity research. However, there is a danger that the commercial imperatives which drive the effort to find profitable therapies are not necessarily in line with the most rational way of tackling the overall public health burden of obesity. Analysis of material presented at recent congresses of obesity reveals a serious mismatch between the resources and competence applied to molecular aspects and those devoted to the psychosocial, behavioural and epidemiological aspects of the problem. The remainder of this paper uses a few examples of etiological interactions across the various scientific disciplines to argue for the maintenance of a broad approach to understanding.

Epidemic or gradual demographic transition

Although it is a useful awareness-raising strategy to describe recent trends in obesity as an epidemic there is a danger that this misrepresents the true picture and hence may impair analysis. Figure 1 superimposes the UK s 70 year secular trends for mean body mass index (BMI = kg/m^2)

and for clinical obesity defined as BMI>30 kg/m². According to the mean BMI there has been a steady rise in the average fatness of the population for many decades (the slight discontinuity in the 1960s is probably a small sample effect and should not be overinterpreted). In contrast the curve indicating the proportion of people who exceed the (arbitrarily defined) clinical cut-off suggests that the problem only originated in the 1970s. The reasons for the difference between these analyses have been described by Rose (3) and relate partly to the fact that as the population average BMI increases the steep section of the distribution curve crosses the 30 kg/m² cut-off, and partly because the distribution curve itself develops a right-hand shoulder as a disproportionate number of people are precipitated into becoming very overweight. Clearly the use of the cut-off approach can be misleading in terms of etiological analysis even if it provides a reasonable picture of the health burden.

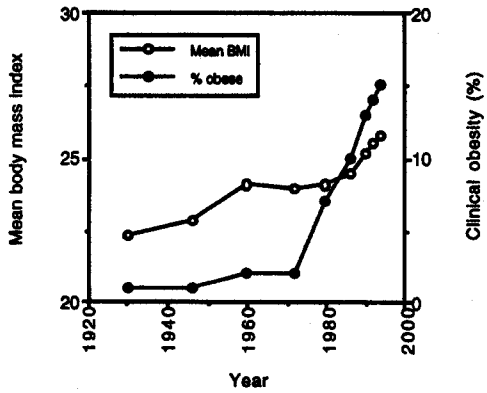

Figure 1. Secular trends in average BMI and in proportion with clinical obesity (BMI>30 kg/m²) in the UK. Data from (4,5).

Defining obesity phenotypes

Another oversimplification which is hampering the search for causal linkages in obesity is the use of the global descriptor ≡obesity as if it is a homogeneous entity with a single common cause. Most researchers in the field are well aware that this is not the case and are careful to describe obesity in terms of it being a multi-factorial heterogeneous disease with complex origins. However the lack of a systematic phenotypic classification framework represents a real barrier to progress. This problem has been highlighted by some of the recent searches for human homologues of rodent genetic variants of obesity. For instance, the early demonstration that a small number of obese people showed raised, rather than lowered, leptin (6) was interpreted in many circles as immediately demonstrating that defects in leptin production were not a cause of human obesity. This may prove to be correct, but at the time was a premature assumption which illustrated that many people are still assuming that a single metabolic cause of obesity will eventually be unearthed. In fact it would still have been a major step forward even if only a few in a thousand cases of gross obesity could be explained by a faulty *ob* gene product, and there is some evidence that a subset of cases of human obesity may result from subnormal leptin secretion (7).

Certain morphological characteristics have long been used as a first step in better defining obesity phenotypes. The distinction between abdominal and peripheral adiposity is the prime example which is clearly useful in terms of predicting associated morbidity and is increasingly being used as a means of focusing etiological studies (2). Endocrinological subtypes are also recognised as rare causes of specific obesity syndromes (eg Prader-Willi, Bardet-Biedl, etc). It seems highly likely that in the near future progress in molecular genetics will add further well-defined sub-categories relating to less severe phenotypic manifestations. Likewise there is increasing awareness that many people s obesity has distinct psychological origins such as binge-eating disorder (BED) which in afflicted cases (now estimated at 30% of patients attending tertiary-level

obesity clinics) is a sufficient single explanation of their problem (8). The area which is least well advanced is that of behavioural phenotyping. This may be because it is not academically rewarding to publish papers on clusters of single-origin obesities involving ladies who work in cake shops. Nonetheless such separation of causes would be very useful in refining our current etiological screening programmes. For instance, in our own studies involving detailed and time intensive whole-body calorimetry studies searching for possible etiological clues we are often forced to rely on small sample sizes to address particular questions. It is always possible that a proportion of the sample have non-pathologic causes in spite of all attempts to identify these during subject selection. A refined classification system for obesities is therefore urgently needed and could advance our understanding of causal influences.

Genetics and the current trends in obesity

There can be no doubt that the search for human obesity genes represents the cutting edge of obesity research, and that the study of animal obesities, including the use of transgenic models, is greatly adding to our understanding of the underlying mechanisms regulating adipose tissue mass (9). However it must be stressed that there cannot be a genetic explanation for the recent population trends in obesity. It is true that obesity is more common in certain immigrant and ethnic groups who may be predisposed through evolutionary selection of a ≡thrifty genotype or who may have been programmed through fetal or infant undernutrition, but it is also true that obesity rates are escalating in indigenous populations in whom there has been minimal dilution of the gene pool. Thus, however tempting it is to invoke a genetic explanation for obesity, it is important to be clear that the main causes of the demographic trends must be behavioural or environmental in origin.

To the average non-geneticist trying to keep abreast of the latest developments in the genetics of human obesity it has been confusing to be confronted by a very wide range in the estimates of heritability and by frequent revisions of these estimates (10). It is also difficult to reconcile the claim that demographic trends must be environmentally driven with the finding emerging from many sib-pair studies that most of the variance in body fatness can be explained by genetic effects and that little is explained by shared environment. This latter finding is strengthening with each new twin-pair study (11) although it is reassuring that some cohorts such as the Quebec Family Study still reveal a large component of variance which is attributed to ≡cultural transmission (10). The resolution to this apparent paradox probably lies in the fact that genetic factors play an important role in explaining the variance within any population cluster of BMIs, while environmental and cultural effects determine the mean of the whole population. There are additional complex interactions between the mean fatness of a population and the way in which genetic variances are manifest. These may account for the rapidly changing estimates of genetic heritability, since to reduce the problem to its simplest form there is no genetic transmission of obesity in populations where there is no obesity, and the genetic influence will become progressively uncovered as obesity rates escalate.

Some of the most useful approaches to the use of animal studies in the understanding of human obesities may be those which eschew the single-gene defects in favour of searching for genetic correlates of animals sensitivity or resistance to environmental factors such as a high-fat or cafeteria diet. West s work on the genetics of dietary obesity in AKR/J (diet sensitive) and SWR/J (diet resistant) strains of mice is an example of the type of approach which intuitively seems to be especially useful in respect of human obesities (12).

Possible toxic or infectious causes of obesity

Although there is no solid evidence, prudent scientific method dictates that we must at least consider the possibility that current trends in obesity originate from a toxic or infectious contaminant in the environment which damages the body s autoregulatory mechanisms controlling body weight. There are features of the demographic trends which would attractively fit with such

a hypothesis and there are numerous examples of viral- and chemical-induced obesity in animals (eg 13,14). It is possible to conceive of hypothalamic damage, or of adipocyte hyperplasia (see below), induced by chemical or biological insults. There is currently a lively debate relating to the possibility that atherosclerotic heart disease might be initiated by *Chlamydia pneumoniae*. Such suggestions are usually greeted with hostility since they undermine attempts to build preventative and curative strategies on the basis of existing tenets. They nonetheless remain plausible.

Possible metabolic causes of obesity

Much research effort has been devoted to the search for putative metabolic defects which might explain individual predisposition to obesity. The rationale behind such studies has been that, whatever genetic or metabolic disturbance might exist, obesity can only result from a chronic disequilibrium in the energy balance equation, and therefore the underlying defect should be measurable in terms of differences in variables such as diet-induced thermogenesis, total energy expenditure, or substrate selection. For many years this research was driven by the ≡efficient metabolism hypothesis which originated in the conviction that obese people were not hyperphagic. This in turn was supported by the knowledge that in single-gene rodent models of extreme obesity (such as *ob* mice) the excess adiposity can develop even when the homozygous affected animals are pair-fed to lean littermates, thus proving that metabolic efficiency is greater.

The efficient metabolism hypothesis yielded a rich vein of research into brown adipose tissue as a mediator of energy balance in rodents, and into diet-induced thermogenesis in humans where numerous studies revealed small reductions in DIT in obese people (15). However, it has since been repeatedly demonstrated that obese people have consistently raised 24h energy expenditure when assessed by whole-body calorimetry (16). The advent of the doubly-labelled water method allowed total free-living energy expenditure to be assessed, and hence allowed the combined physiological and behavioural aspects of energy expenditure to be measured. Figure 2 presents a recent analysis of all available data. It indicates markedly raised levels of energy utilisation in over-weight and obese adults compared to their lean counterparts. These findings make it difficult to sustain the argument that any small energy-sparing defects in diet-induced thermogenesis or other compartment of metabolic rate might be an initial predisposing factor in obesity.

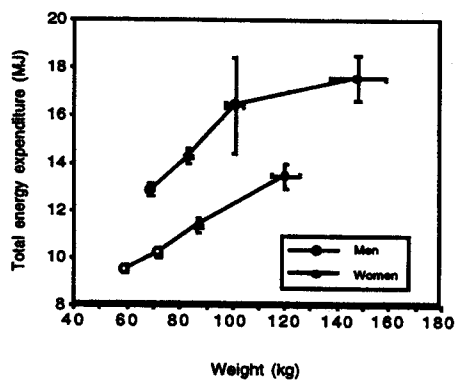

Figure 2. Total-energy free-living energy expenditure in lean, overweight and obese men and women. Analysis of data from 319 subjects in affluent countries. Adapted from (17).

The most significant reason that the efficient metabolism thesis is now waning is the demonstration that obese and weight-conscious people generally under-report their food intake by a highly significant margin (averaging 30% or more) (18). This crucial observation, which has now been replicated in almost every study of the topic (19,20), has removed any need to hypothesise etiological mechanisms which do not involve excessive energy intake since it is now a perfectly

tenable proposition that obesity is caused by transient hyperphagia without decreased energy expenditure.

In an analogous manner to the search for energy-sparing defects there is currently an active search for evidence that predisposition to obesity is associated with impaired fat oxidation in the pre-obese state even though the obese state is clearly associated with raised levels of fat oxidation. Evidence from our own and other laboratories remains mixed. Some studies have demonstrated lower levels of fat oxidation in post-obese women (21), but the differences are small and could easily be over-ridden by small differences in diet selection. Other studies have shown that a low ratio of fat oxidation is a predictor of weight gain in genetically predisposed individuals (22). Of particular interest in this respect is the suggestion by Wade (23), now supported by others (24), that differences in fuel selection might be related to different profiles of muscle fibre types. We have been unable to replicate the Wade findings (25), and suspect that they may be an artefact of different fitness levels. However, the theory remains attractive since it could provide a clear mechanism for genetic transmission of the trait of impaired fat utilisation.

Both the energy-sparing and impaired fat oxidation hypotheses have to try to resolve the fact that once obesity has developed affected subjects display very high levels of energy expenditure and fat oxidation. These are combined with a number of other metabolic perturbations, such as insulin resistance, which should logically all act in an auto-regulatory manner to bring body weight and adiposity back down. The fact that obesity is sustained, and in some cases continues to develop further, in spite of this constellation of corrective influences indicates that the drive towards positive energy balance is extremely powerful. This suggests that some sort of positive feedback cycle must at some stage switch in, and must override the autoregulatory processes. Much of our own current work centres on the search for this self-sustaining positive feedback cycle. It should be noted that positive cycles of this nature need not necessarily be metabolic in nature. They might be psychological, as in the case of the vicious cycle which can develop between depression and binge eating.

Behavioural and environmental causes of obesity: diet

The case has already been argued above that the primary causes of the current increasing levels of obesity in affluent nations must be behavioural or environmental in origin. The two leading candidates are excessively fatty diets and sedentary lifestyles (26).

The evidence that high-fat diets are especially adipogenic is extremely strong at the physiological level. In experimental studies involving covert manipulations of the fat-to-carbohydrate ratio of diets it can readily be demonstrated that high-fat diets lead to spontaneous hyperphagia (27), sometimes described as ≡passive overconsumption because the excess energy is consumed without any increase in the bulk of food eaten. This is in line with the observations using classic pre-load experiments that fat has a lower satiating power than the other macronutrients (28). The ease of fat deposition on high-fat diets also fits with the fact that, in contrast to alcohol, carbohydrate and protein, dietary fat exerts virtually no auto-regulatory control over the rate of its own oxidative disposal placing fat at the bottom of the oxidative hierarchy (29). Current thinking is that high-fat hyperphagia is not nutrient specific but is related to the high energy density of fatty diets (30), and that any energy-dense diets will lead to similar hyperphagia.

It can be shown that the physiological aspects of high-fat hyperphagia interact with psychosocial variables at a number of levels. For instance, one of the most reproducible findings in our own experiments designed to assess dietary effects on appetite is that people exert very strongly ingrained cognitive control over when and how much they eat (27). This is the cause of passive overconsumption since subjects continue to eat a similar bulk of food irrespective of its energy content suggesting that inbuilt satiety signals are rather weak and in many people fail to down-regulate food intake even under conditions of rapid fat storage. This is surprising in view of the known effects of fat on short-term mediators of satiety (28), and provides another example of

where much work needs to be done to reconcile the behavioural and biochemical observations. At the psychological and sociological levels, obesity appears to be associated with an innate preference for high-fat foods (31), and there is considerable edipemiological evidence to suggest that people who choose to consume diets with a high fat-to-carbohydrate ratio are much more likely to develop obesity (32). This latter evidence is now being questioned on the basis that the fat content of diets in several affluent countries now appears to be falling gradually and yet obesity continues to escalate, and on the basis that dietary data are unreliable especially when relating to obese and overweight people. Nonetheless, the weight of evidence accrued at various levels still supports the view that high-fat diets are likely to be especially adipogenic.

With respect to possible dietary causes of obesity most research has focused simply on the total amount of energy and on the major macronutrients in a quantitative rather than a qualitative way. It is worth noting that specific dietary components might precipitate obesity through diverse possible mechanisms. To give just two examples: firstly, it appears that the pre-adipocyte nuclear receptor PPAR-gamma which stimulates adipocyte hyperplasia is activated by a prostaglandin ligand whose concentration might be influenced by specific dietary fatty acids (33,34); secondly, it can be shown that fatty acid profiles can influence insulin sensitivity, which in turn may influence adiposity (35).

Behavioural and environmental causes of obesity: sedentary lifestyles

The evidence that physical inactivity may be the key explanatory variable behind the population trends in obesity is rapidly gaining ground, and it is already accepted that promoting activity must play an important role in any preventative strategies especially as active lifestyles have many other health benefits. On the basis of time-trend and social-class analysis of associations between obesity and dietary or activity variables in the UK (Figures 3 and 4) we have concluded that physical inactivity is at least as important as diet and possibly the dominant etiological factor (26). This type of analysis, though crude in itself, is supported by several prospective studies of weight gain (eg 36).

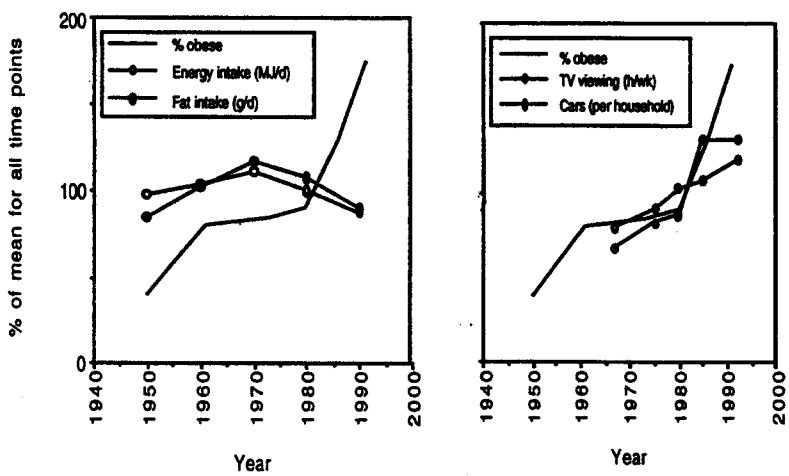

Figure 3. Secular trends in obesity compared to dietary and activity variables. Reproduced with permission from (26).

The mechanisms by which activity protects against weight gain are not readily apparent. Simple energy balance calculations based on the energy used in activity do not indicate a ready solution especially under conditions of abundant food supply. Likewise putative effects in terms of increased fat oxidation are difficult to identify. Much current thinking stresses the possibility that a raised energy flux enhances metabolic control and the regulation of appetite. Once again this is a fertile area for integrative research across all disciplines from molecular genetics to behavioural science.

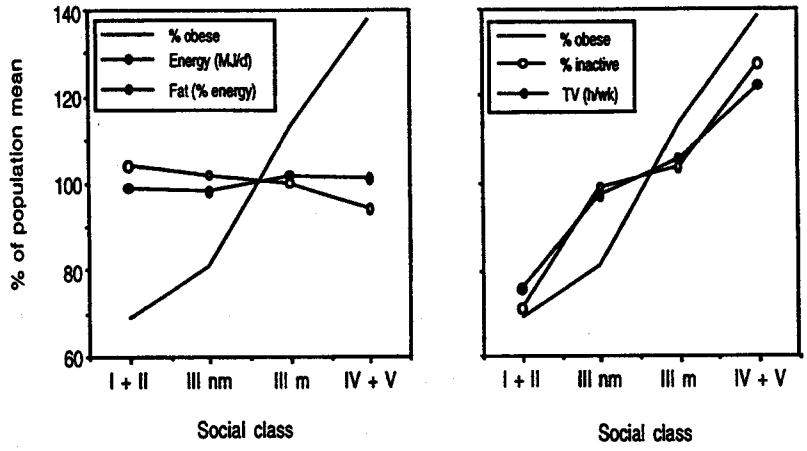

Figure 4. Social class trends in obesity compared to dietary and activity variables. Reproduced with permission from (26).

Conclusions

This highly superficial survey of a few of the factors which impact on the regulation of body weight is probably sufficient to demonstrate that obesity must be amongst the most complex of diseases in terms of its aetiology. Commercial interests are ensuring that the molecular genetic and pharmacological aspects of the problem are being addressed vigorously. This effort should be balanced by a greater investment in the behavioural aspects of the problem if we are to achieve affordable solutions to the public health burden of obesity in the foreseeable future.

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