Obesity and its potential mechanistic basis

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Obesity plays a central role in the development of the thrifty phenotype. The metabolic disturbances of the cardiovascular metabolic syndrome, frequently ascribed to the thrifty phenotype, are rare in the absence of obesity and their expression is generally proportional to the size of the excess fat mass. Thus obesity interacts with early-life programming in the establishment of disease. Surprisingly, the evidence that fetal or infant diet leads to programming of obesity itself is rather weak, though this may be explained by the fact that life-style influences obscure the linkage between metabolic predisposition and maturity-onset obesity. This paper summarises the possible metabolic basis of obesity with special reference to those processes for which there are plausible mechanisms by which long-term programming may operate. It is concluded that the newly-emerging molecular discoveries in body weight regulatory systems point to the need for detailed studies of gene–environment interactions and life-course influences before we will fully understand the aetiology of complex phenotypes such as the metabolic syndrome.

There is a rapidly emerging pandemic of obesity in affluent nations[1]. This is of central importance to the topic of this issue, the thrifty phenotype, since it creates the conditions in which the metabolic disturbances programmed by early-life events find their fullest expression. Obesity seems to play both a permissive role in the emergence of the thrifty phenotype (the metabolic syndrome is rare in the absence of obesity) and an active role (there is a dose-dependent relationship between the level of obesity and its pathological sequelae).

Rather surprisingly, there seems less evidence that the development of obesity is itself a manifestation of a thrifty phenotype, at least in regard to the effects of fetal and early-life programming which are less strong in terms of adipocity than might be expected given the evidence for other metabolic changes[2–4]. This observation might be explained by the fact that obesity is a highly multifactorial syndrome in which social, behavioural and environmental influences might over-ride some of the underlying metabolic pressures entrained as part of the thrifty phenotype.

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Obesity – a complex multifactorial disease

The sharp increase in obesity rates in the late 20th century has been a readily predictable outcome of the major environmental transition that has created an abundant food supply and sedentary life-styles[5]. However, the factors that determine which individuals are most susceptible to the external effects of this new environment are more complex. The schematic in Figure 1 illustrates the interplay of the various factors influencing a person's tendency to gain weight. The innate physiological and metabolic processes regulating energy balance lie at the centre. The blueprint for these is genetically encoded. In rare instances, there are single major gene defects which cause obesity (*see below*). More commonly, obesity arises in individuals who carry a cluster of genes each of which creates only a minor tendency towards energy accretion, but whose combined effects can lead to a pronounced weight gain in an appropriate environmental setting. The term 'thrifty genotype', first coined by Neel in the 1960s, has been widely used to encapsulate the notion of a gene, or set of genes, which assist their carriers to lay down energy more rapidly in times of feasting and to conserve their energy usage during times of famine, thus conferring survival value[6]. The identity of these thrifty genes has proved elusive, but

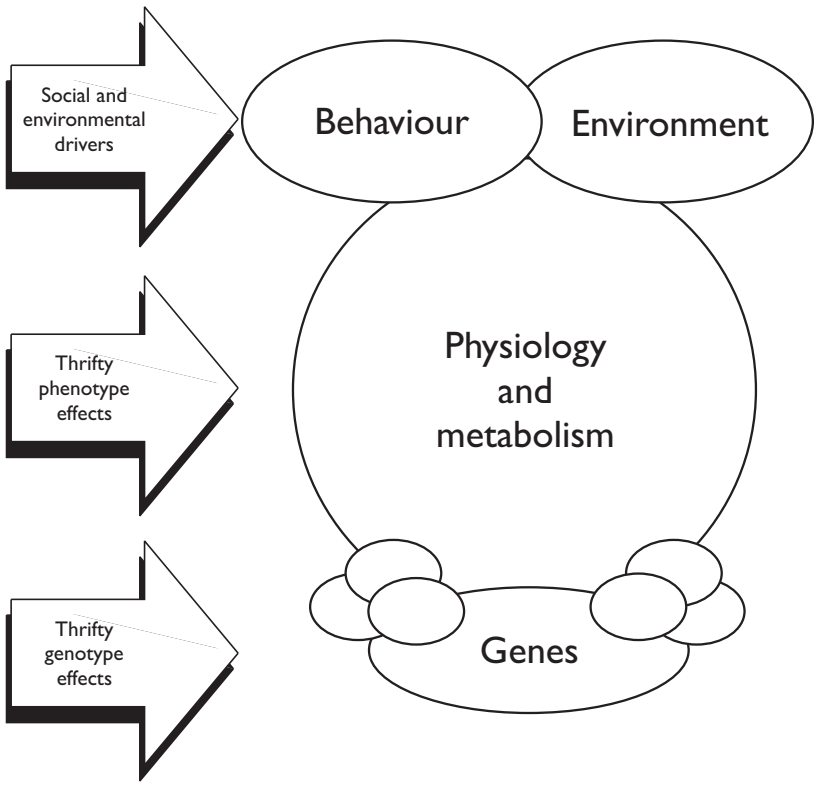

Fig 1 Multifactorial interactions influencing the development of obesity.

the general concept remains useful and it can be demonstrated that famine has been an ever-present selective pressure on human populations and may lie at the origins of modern-day obesity[7].

The readout from the genetic blueprint (*i.e.* the translation of genotype to phenotype) can be permanently modified by an individual's fetal and early-life experiences particularly in regard of placental nutrient supply and infant feeding. Examples of this are known for individual substrates. For instance, baboons that were breast-fed or formula-fed in infancy show altered cholesterol metabolism and lipoprotein levels as adults[8]. The concept of the 'thrifty phenotype' first developed by Hales and Barker[9] extends this idea to suggest that a general shortage of energy-supplying fuels in early life may create a metabolism which is permanently programmed to expect a frugal food supply and, therefore, has difficulty in coping with abundance. In this respect, the thrifty phenotype is analogous to Neel's thrifty genotype[6] – a useful adaptation which has been 'rendered detrimental by progress'.

In a single generation, the levels of obesity in affluent countries have altered so radically as to require a major overhaul of our explanatory paradigms. In Figure 2, the hatched bars illustrate the approximate population distribution of body mass index (BMI) in the UK some 30 years ago. Under such circumstances, any individual exceeding the clinical threshold for obesity (≥30 kg/m^2) would have been at the extreme right-hand end of the distribution and it was highly likely that they carried a pronounced

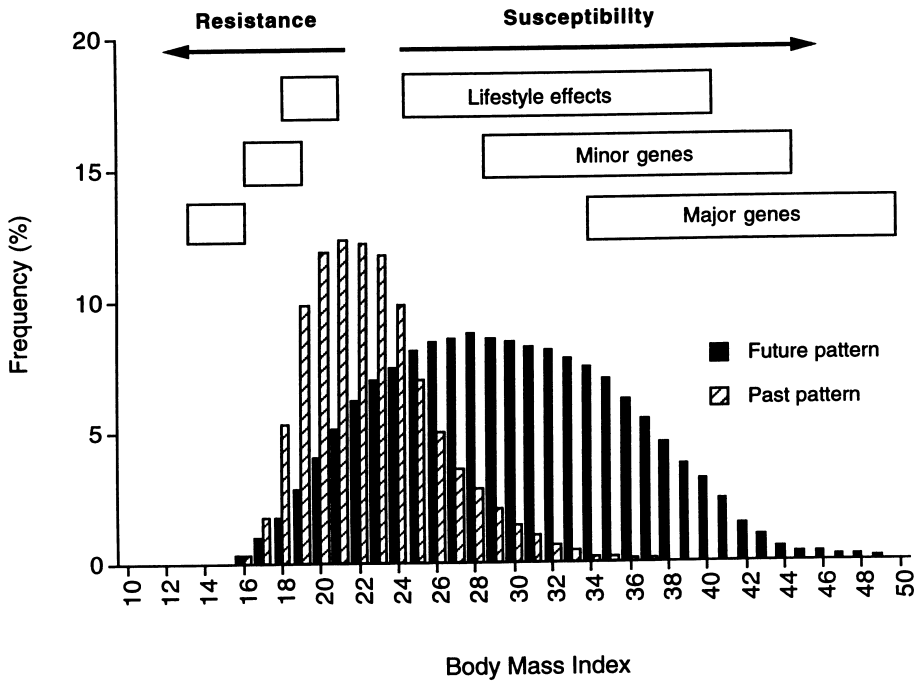

Fig 2 Secular changes in the balance of factors influencing obesity.

genetic propensity towards fat gain. However, the current and projected distributions (solid bars) are shifted substantially to the right by the increasing prevalence of 'life-style' obesity. Under such circumstances, it becomes much more difficult to detect true genetic and metabolic susceptibility. As obesity rates climb still further, the whole concept of genetic susceptibility increasingly loses validity, and as obesity becomes the norm it becomes more interesting to examine evidence for genetic resistance to obesity. It is possible that a similar general argument could explain the relatively weak evidence linking early-life events to later obesity; any underlying association might be obscured by the overwhelming lifestyle influences.

Genetic factors

The very rapid increase in obesity in populations in which there has been a minimal infusion of new genes through immigration and inter-marriage provides unequivocal proof of the importance of environmental factors. This, however, does not diminish the importance of understanding genetic susceptibility to obesity. Indeed, it is work in the latter domain that has recently provided a quantum leap in our knowledge of the mechanistic basis of obesity.

Monogenic disorders

Certain discrete (probably monogenic) disorders in which severe obesity is one part of a pleiotropic clinical picture have been known for many years (*e.g.* Prader-Willi and Bardet-Biedl syndromes)[10]. In such cases, the obesity is usually viewed as just one of many symptoms and usually has a clear aetiology, as in the case of the voracious and seemingly unquenchable appetite typical of the Prader-Willi patient. More recently, there has been a series of discoveries of monogenic mutations in which obesity appears to be one of the most prominent aspects of the symptomatology and was the basis of the initial genetic screening for mutations[11]. Several of these new Mendelian causes of human obesity appear to be directly homologous to mouse mutations that have been known and studied for decades, thus providing additional insight into the biology underlying the effects of each mutation (*see* Table 1). A recent *Nature Insight* publication provides an excellent series of reviews for readers interested in a detailed coverage of these new genetic discoveries and of the understanding they provide about the regulation of energy balance[12]. In the present context, a brief description of two of these mutations will suffice to put the monogenic disorders into perspective in relation to the overall problem of obesity.

Table 1 A selection of genetic mutations causing homologous obesity in mice and humans

Mutation	Mechanism
obese	Absence of functional circulating leptin leads to absence of feed-back signal from adipose tissue stores
diabetes	Loss of function of leptin receptor in hypothalamus
fat	Loss of function of carboxypeptidase E responsible for processing receptors for endocrine and neuroendocrine prohormones
MC4r	Loss of function of brain receptor for α-MSH and agouti-related protein
POMC	Loss of function of precursor of brain α-MSH and β-endorphin
A^y	Ectopic expression of agouti protein: antagonist of melanocortin receptors

Cited in Barsh *et al*[11].

In 1994, Friedman and colleagues used positional cloning to identify the gene defect responsible for the severe obesity of the *ob/ob* mouse[13]. The gene encodes an adipocyte-derived hormone, leptin, which is secreted into the circulation in proportion to the size of the adipose tissue mass. Leptin crosses the blood–brain barrier and signals to the central nervous system through leptin receptors in the arcuate nucleus of the hypothalamus[14]. In the *db/db* mouse, obesity is caused by a mutation leading to non-functioning leptin receptors[15]. The circulating plasma leptin signal correlates both with the size of the adipocytes and with their energy flux. It thus provides the brain with a very effective fuel gauge that integrates information on both the long-term and short-term energy status of peripheral tissues. A complex series of neural circuits activated by leptin act to modulate appetite, energy expenditure (at least in mice), reproductive function and immunity (again in mice)[14,16]. This energy regulating system is sometimes termed an 'adipostat'.

Human homologues with defects in leptin and in the leptin receptor have now been traced but are extremely rare, having been identified in just a handful of in-bred families throughout the world[11,17]. Nonetheless, these discoveries provide unparalleled insight into the biology of body weight regulation by showing that a defect in either the signal or the receptor can lead to increased appetite and subsequent hyperphagia leading to morbid obesity. In leptin-deficient patients, substitution of the defective natural leptin by regular injection of human recombinant leptin has also been shown to suppress appetite and lead to impressive weight loss[18]. Other cases of human obesity arise from mutations involving some of the signalling steps downstream of leptin, but all are extremely rare. In spite of a world-wide search for such mutations by numerous research teams, there were only 22 individuals affected by these monogenic mutations listed in the latest update of *The Human*

Obesity Gene Map[17]. Thus it can be safely concluded that, however informative they are, the monogenic human obesities do not make a significant contribution to the global burden of disease. Despite much initial excitement, defects in the leptin gene have not turned out to be a wide-spread cause of obesity[17], and leptin so far shows very limited promise as a therapeutic agent for the general population[19].

Multigenic disorders

It has long been clear that overweight and obesity cluster in families; obesity is 2–8 times higher in the families of obese individuals than in the population at large and estimates of heritability range from 50–85% in twin studies down to 10–30% in adoption studies[10,20]. Quantitative trait analysis has found associations between obesity and genes on every human chromosome, but the associations are frequently refuted by subsequent investigations in different populations[17]. Likewise, candidate gene analysis, in which defects are searched for among genes which might reasonably be expected to lead to obesity, has tended to be disappointing. There has been a large number of negative findings and a tendency towards false positives for many of the findings which do initially suggest associations with various aspects of the obesity phenotype (*e.g.* BMI, fat distribution, maximal life-time body weight, age of onset of obesity, *etc*)[21].

There are several possible interpretations of this generally disappointing picture. The first has already been alluded to with reference to Figure 2, namely that obesity is a distal phenotype and arises after many years in which a range of environmental and social influences can displace the natural linkage between genotype and phenotype. The environmental factors may act independently of the genetic background (creating an entire shift in the population distribution), or there may be gene–environment interactions in which a person's susceptibility to a given environment is modified by their genes[11]. In the present context of early programming of the thrifty phenotype, it is interesting to note that the gene–environment interactions could also operate in the reverse direction since genetic expression is sensitive to diet at critical stages of development.

Although it is self-evident that gene–environment interactions must be important in determining obesity and other aspects of the metabolic syndrome related to the thrifty phenotype, they are very difficult to study in humans. Unfortunately, statistical constraints require the use of extremely large sample sizes even if the interactions are quite strong, and this seems likely to inhibit our future understanding of this important topic[22]. However, the study of gene–diet interactions has been successfully used in animal models in which selective breeding has been used to

produce strains of mice that are highly susceptible or resistant to the obesity-inducing effects of a high-fat diet[23]. A similar genetic susceptibility to high-fat diets has been inferred in some human studies. For example, Heitman and colleagues demonstrated that only women with a family history of obesity appear to be susceptible to high-fat diets[24]. Another example in relation to the thrifty phenotype has recently emerged from the Isle of Ely study where Wareham and colleagues have demonstrated that a common mutation in the nuclear-receptor PPARγ alters fasting insulin levels, but that the effect is dependent on the P:S ratio of each subject's habitual diet (Wareham NJ, personal communication).

A further possible explanation for the disappointing progress in identifying common genetic causes of obesity is that their effects may be only significant when acting in concert with others – so-called gene–gene interactions[11]. Such interactions might simply be additive (where two genes acting in the same direction create a more noticeably distinct phenotype than either of them alone), or may be multiplicative (where one gene variant positively enhances the function of another). Recently, there have appeared several examples of claims of additive interactions emerging from candidate gene studies. For example, variants in the genes for uncoupling protein and the β_3-adrenoceptor have been reported to have an additive effect in causing morbid obesity[25]. However, caution must be exercised in interpreting such claims since the many possible combinations of gene x gene interactions are liable to throw up numerous false positive associations especially with the rather small sample sizes currently employed in such studies.

Insights into the mechanistic basis of obesity derived from genetic studies

The purpose of the above summary of genetic influences of obesity was to provide a perspective on the phenotypic influences described below and indicate how the two may interact. The genetic studies are currently driving progress into the understanding of the metabolic basis of obesity and in the course of just a few years have uncovered numerous new energy-regulatory pathways that lay hitherto unknown. A picture is emerging of bewildering complexity in which there is multiple overlap and redundancy between different neural networks with a wide range of feedback controls and tonic influences that have evolved to ensure, under most circumstances, an effective maintenance of energy balance. The complexity that is emerging humbles human efforts to summarise a mechanistic basis for obesity, and it is already proving necessary to develop '*in silico*' models of metabolism in order to cope with the problem[26].

However, there are some key messages that can be extracted from this complexity and which may inform our future understanding of the metabolic basis of obesity. The first is that despite the exquisitely-evolved design characteristics of a control system that has served the human race for millennia, it is quite unable to cope with the profound environmental shift driven by the technological revolution at the end of the 20th century. In terms of our understanding of the possible effects of early-life programming, this implies that there is considerable plasticity in the extent to which genotype models phenotype. A second interesting observation is that all of the monogenic forms of extreme obesity in animals and man are mediated through defects in the appetite control side of the energy balance equation, rather than through the energy expenditure side. This may be because there is much greater scope to alter energy balance by altering intake than there is by altering expenditure[27], and is an observation that may be useful in moderating the past and persisting tendency to focus heavily on mechanisms mediated through defects in the regulation of expenditure.

Metabolic factors underlying susceptibility to obesity

In any given individual, the combination of their genetic background and their life-time exposures to diet and activity will create a metabolic setting which may be more or less susceptible to the obesogenic influences of the modern life-style. The possible routes through which this susceptibility might be mediated have commonly been clustered into a small group of possible explanatory theories. A very brief summary of some of the leading theories is provided below.

Slow metabolism

The theory that obesity resulted from an energy-sparing metabolic defect dominated research in this area for several decades. It had its origins in the misplaced belief that obese people do not overeat, and was given cogency by the unjustified extrapolation to man of the known defects in brown adipose tissue metabolism of the *ob/ob* mouse. Subsequent research has shown that obese people are characterised by a high energy expenditure and are hyperphagic[28–30]. In spite of many years' research throughout the world using techniques such as whole-body calorimetry and doubly-labelled water for measuring total energy expenditure, the mythical obese subject with a low metabolic rate has proved entirely elusive. Furthermore, many groups have now demonstrated that the apparently low energy intakes of obese people, which

underpinned the search for putative metabolic defects, can be explained by profound under-reporting of energy intake by the obese[28,31,32].

Few people now subscribe to the low-metabolic-rate theory of obesity as a major aetiological route. However, Ravussin and colleagues demonstrated that a relatively low metabolic rate was a risk factor for weight gain in the Pima Indians[33], and in a recent review have concluded that it explains 12% of their susceptibility[34]. The discovery of the new uncoupling proteins (UCP2 and UCP3), which might be a source of energy-dissipating mechanisms in muscle and other tissues[35], has also renewed interest in this area despite the physiological evidence that obesity cannot be readily traced to a low energy expenditure[36]. Current evidence from genetic mapping suggests that neither UCP2 nor UCP3 are involved in the genetic transmission of obesity, though there is some evidence that polymorphisms in UCP1 may play a role[37]. The β_3-adrenergic receptor has also been the target of much interest because of its role as a specific receptor involved in stimulating thermogenesis in brown adipose tissue. Over 100 studies have explored associations between a β_3-adrenoceptor coding mutation (Trp64Arg) and obesity, but with very mixed results. About half claim an association and the other half fail to find any linkage[17,37].

Much of the current interest in the metabolic regulators of thermogenesis and energy expenditure is driven by the pharmaceutical industry which views the up-regulation of the β_3-adrenoceptor or of the UCPs as potential drug targets. The high level of research activity generated by this interest has a tendency to mislead the uninitiated into attributing to them a central role in the aetiology of obesity which probably would not be justified by a more objective assessment of the evidence. In the context of the early programming of a thrifty phenotype, it is unlikely that the transmission of any such effect is mediated through more than a very subtle effect on metabolic rate. Perhaps the strongest evidence for this comes from observations on Indians who can be assumed to have suffered a life-time of energy restriction and yet who fail to show any evidence of a low metabolic rate compared to well-nourished controls once appropriately adjusted for differences in body composition[38]. Our own research in The Gambia also reveals only subtle differences in metabolism between rural villagers who have been subjected to a life-time of under-nutrition and well-nourished Swiss controls once adjusted for differences in body weight[39].

Altered fuel selection

The energy balance equation (energy in – energy out = change in energy stores) can usefully be re-expressed in terms of each of the four energy-giving macronutrients (fat, carbohydrate, protein and alcohol)[40]. It can

then be seen that the oxidation of fat must be equal to the sum of fat intake and any fat synthesis in order to avoid fat gain and ultimate obesity[41]. Any systematic displacement of the balance of fuel selection towards a low fat oxidation rate could gradually enhance fat deposition. The balance of fuel selection in an organism can be measured from the respiratory quotient (RQ) with a high RQ indicating high carbohydrate oxidation (and hence low fat oxidation).

The assessment of the characteristic RQ of an individual is difficult since it is highly variable over time as it responds to the short-term ebb and flow of energy balance and substrate availability between meals. The interpretation of data claiming to represent habitual RQ, therefore, requires caution. Nonetheless, a number of groups have shown a tendency towards an altered RQ in groups susceptible to obesity. A recent summary of the likely aetiological factors among the Pima Indians attributes 5% to the high RQ phenomenon[34]. Astrup and others have shown an altered fuel selection in post-obese patients, but the differences are small[42,43].

Differences in the muscle fibre-type profile have been postulated as a plausible physiological mechanism through which an altered fuel selection might be mediated. There is some evidence from exercise tests and muscle biopsies to support this suggestion[44], but others have failed to replicate this work[45]. On balance, the theory is attractive and could readily accommodate a long-term programming element if early-life nutrition caused a permanent anatomical resetting of fibre-type pattern. Phillips and colleagues have observed a number of metabolic differences in muscle according to size at birth confirming the possibility that this could be a route for programming and adjustment in fuel selection[46,47].

Adipose tissue hypercellularity

There is an extent to which adipose tissue depots regulate their own size. This accounts for the wide range of body shapes and the fact that fat distribution is more strongly inherited than absolute fat mass[48]. At the extreme end of the spectrum, the profoundly asymmetric fat distribution of patients suffering lipodystrophy underscores the importance of this level of autonomy of the fat stores.

Again this could provide a route for the long-term programming of a tendency towards obesity. Such a proposal was made several decades ago when the 'fat-cell number' theory postulated that early infant feeding (especially high-solute formula feeds) stimulated the creation of new adipocytes during a critical developmental window in infancy and that these were then permanently carried throughout life[49]. However, subsequent work has shown that fat cell numbers can increase beyond

infancy, that adipocyte apoptosis can lead to a remodelling of fat cell numbers[50], and that there are very poor correlations between adipocity in infancy and in later life[49]. The constant fat-cell number theory is, therefore, no longer widely supported.

The refutation of the fat-cell number theory with respect to early-life programming does not invalidate the possibility that metabolic alterations which lead to an expansion of fat stores may be important in driving the positive energy balance which results in obesity. The reciprocal of this is also true; namely that any individual with very small numbers of adipocytes which show little tendency to hypertrophy will have nowhere to store excess lipid and may, therefore, have more powerful satiety signals and thus be resistant to weight gain. There is currently considerable interest in the factors regulating adipocyte hyperplasia and hence the control of fat depot size[50]. For instance, the terminal differentiation step in the conversion of pre-adipocytes into adipocytes is regulated by the nuclear-receptor PPARγ[51]. There are several natural ligands for this receptor which could induce fat cell division including some of the long-chain n-6 polyunsaturated fatty acids and their prostaglandin end products[52]. These could provide a link between diet composition and adipocity.

The possibility that glucocorticoids and stress may stimulate an excess deposition of intra-abdominal adipose tissue has been mooted for some years[53]. This may be of particular interest with respect to early programming of the thrifty phenotype in view of the evidence that maternal undernutrition may increase the exposure of the fetus to excess glucocorticoids[54] which in turn lead to a reduction in glucocorticoid receptors in the hippocampus and hence elevated levels of glucocorticoids in adult life[55]. There is some evidence that small size at birth is associated with a higher waist-hip ratio in adulthood[56].

Adipocytes also release a number of active peptides which may play a role in attempting to self-limit the expansion of the adipose tissue; including leptin, TNF-α, IL-6 and resistin[57,58]. It is conceivable that early programming effects might influence the tonic setting for the release of these compounds and hence alter the tendency towards adipocity. Evidence for the long-term programming of leptin has been published[59,60].

Altered 'set point'

Over the years, there has been much speculation and debate concerning the possibility that body weight is regulated according to a natural set point acting as a ponderostat or an adipostat by controlling the setting of regulatory feed-back loops linking appetite and energy expenditure. Experiments using hypothalamic lesions in rats strongly support such a

concept by demonstrating that ventro-medial or lateral lesions will displace the natural growth trajectory and that the animals will then defend their growth along the new trajectory against both under- and over-feeding. There is strong evidence for some degree of set point control in humans, but it is clearly not an infallible system and an overly literal interpretation of the theory led it into disrepute for many years. During this period, Flatt developed the theory of a 'settling point' in which it was argued that body weight settled at a given level within any individual according to the balance of a number of metabolic factors; particularly the relationship between fat and carbohydrate oxidation[41].

The set point theory is making a strong come back (though in a more subtle guise) in view of the new molecular discoveries which have revealed the component elements necessary for the feedback control loops[14,16]. It would be easy to envisage ways in which early-life nutrition could adjust the position of the set-point and lead to a lifelong susceptibility or resistance to weight gain, but so far there is no concrete evidence.

Altered appetite control

As has been indicated, most of the monogenic examples of severe obesity are mediated through defects in appetite control, and simple calculations based on the natural variance of energy intake and energy expenditure confirm that there is much greater scope for displacing energy balance through changes in the energy intake side of the balance equation[27].

Our understanding of the factors regulating appetite and satiety is currently at an exciting cross-roads between the evidence gleaned from classic physiological experiments on appetite and the emerging insights based on newly discovered neural network pathways[61] and novel methods for imaging the activity of the brain[62]. The older evidence points to a range of physiological differences in satiety mechanisms between lean and obese people[63] especially in response to dietary fat[64], and to a variety of psychological syndromes associated with compulsive eating and addictive behaviours in relation to food in the obese[65]. New discoveries will ultimately explain these physiological and behavioural phenomena at a molecular level.

The question as to whether any of these 'satiety defects' could be programmed by early-life events remains wide-open and has received little attention. In the short-term, there is evidence of a mixture of physiologically and cognitively driven over-consumption following food deprivation[66] and this is probably responsible in part for weight rebound after restrictive dieting, but there is little evidence in support of longer-term influences. A single study reports the development of adult hyperphagia in rats subjected to fetal undernutrition[67], but such evidence

would be very difficult to replicate in humans given the multiplicity of confounding events that occur between infancy and adulthood.

Behavioural and environmental factors

There is overwhelming evidence that the modern epidemic of obesity is caused by life-style changes over the past few decades that can be paraphrased[5,68] as 'gluttony and sloth'. Our analysis of the relative impact of gluttony and sloth on obesity rates in the UK suggests that it is the high levels of inactivity created by the technological revolution (and especially excess television viewing) which have been the dominant factor[68]. This is somewhat surprising conclusion in the light of comments made above about the greater scope of manipulating energy balance through changes in energy intake. Nonetheless, the evidence does suggest that at the **population** level it is inactivity which is creating the underlying susceptibility and at the **individual** level it is a failure to match appetite to these low levels of energy usage which is the key determinant of susceptibility.

Any putative effects of the early programming of a thrifty phenotype will be operating within these new environmental conditions and may show complex phenotype/environment interactions. The role of inactivity may emerge to be particularly important and will need to be factored into future research designs. For instance, it has been shown that adults who were small babies have alterations in muscle composition and metabolism[46,47]. It has also been shown that physical activity is a very powerful modulator of the cardiovascular metabolic syndrome[69]. This leaves plenty of scope for differences in activity patterns to have a major confounding effect on the emergence of the thrifty phenotype.

Excess adipose tissue as a cause of chronic disease

It may be useful to conclude with a reminder of the link between excess adipose tissue and the metabolic derangements associated with the thrifty phenotype, especially insulin resistance. It has been repeatedly shown that the development of obesity is the most important permissive factor which exposes the latent defects inherent in the thrifty phenotype. For many years, it was assumed that this was mediated through the release of high levels of fatty acids from adipose tissue, and that these caused insulin resistance through Randle Cycle competition with the utilisation of glucose, though this theory is now contested[70].

More recently, it has become apparent that adipose tissue is a highly active tissue releasing a broad range of bio-active signalling molecules

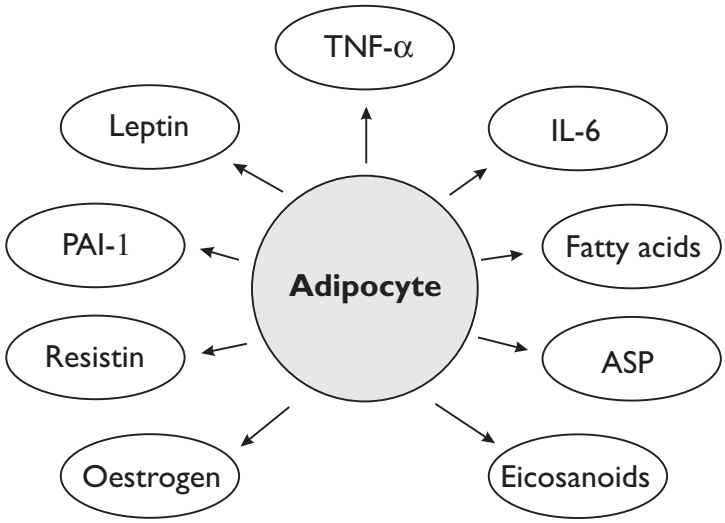

Fig 3 Adipose tissue as a source of bio-active signalling molecules.

which may influence insulin sensitivity (see Fig. 3)[57]. There has been great interest in the possibility that TNF-α may be the key link between adipocity and insulin resistance and there is much supporting evidence[71,72]. However, the very recent discovery of another new hormone, resistin, provides another candidate mediator for which there is provisional evidence of a very specific role in diabetes[58].

It is clear that future studies of the thrifty phenotype phenomenon and its link with obesity will need to explore modes of transmission involving these new molecular modulators of insulin action.

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