



Obesity

Part three – failed solutions and new ideas

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‘The most beguiling aspect of diets is that, in the short term, they produce significant weight loss ... however, the only way to permanently lose weight on a diet is to stay permanently on the diet.’

In the first article in this three article series, I described the disturbing increase in the prevalence of obesity and the serious impact it has on the risk of developing grave illnesses. Obesity currently costs the UK economy around £2.5Bn every year and leads to the premature death of 30 000 people. In the second article, I separated two distinct facets of the obesity problem – the changes over time that reflect predominantly environmental factors, and the susceptibilities of different individuals, which probably mostly reflect their varying genetic constitutions. I then went on to describe the recent biological research on regulation of body weight and the spectacular advances in this field that followed the discovery of leptin in 1994.

Although this is not the only model available, many researchers, particularly molecular biologists, now believe that our body weight is controlled by a lipostatic regulation system. Fat in our bodies produces a compound called leptin, which signals how fat we are to the brain. In the brain, the actual fat level is compared to a target fat level in a complex and not yet fully resolved system of neuropeptides, bioamine transmitters and receptor systems. This ultimately leads to modulation of our food intake and energy expenditure and results in regulation of our body weight.

The lipostatic negative feedback model of body weight regulation has similarities with thermostatic regulation of temperature in our homes. In that system, a room temperature sensor compares the actual and desired room temperatures and an effector system (the radiators) can be modulated to bring actual and desired states into balance.

The beauty of this analogous system is that it allows us to understand why the traditional routes to achieve body weight control tend to be so unsuccessful. Lets take dieting for example. There is no doubt about it – dieting works. If you go on a low calorie intake diet that provides fewer calories than you expend, the result will be a reduction in energy storage – manifested as a loss of body tissue, some of which will be fat and some of which will be lean. Mostly, we burn off fat, but the proportions that are burned off depend on the magnitude of energy deficit. If you have a large deficit you tend to burn off an increased proportion of lean tissue relative to when the deficit is low. This is why sensible dieting regimes suggest you only lose about one to two kg (two to four lb) per week.

The perfect diet

Whatever is *claimed* to be the mechanism, all successful diets work on the same principle – caloric deficit. As far as we are currently aware, fad diets that include mystical ingredients in unusual combinations – papaya and egg, avocado and milk, prawns and beans, and diets dominated with particular macronutrient components, such as high carbohydrate, high fibre or high protein, all work by inducing caloric deficit. The major differences between these diets are the effects that they have on our short-term perceptions of hunger and their side effects on other systems.

A very popular diet in the 1980s was the high fibre diet (e.g., the F-plan diet). The basic argument underpinning

this diet was that the immediate sensations of hunger stem from the feeling of fullness in the alimentary tract. By bulking out the diet with large quantities of fibre, hunger could be satisfied with lower amounts of absorbed energy. The consequence is weight loss without feeling perpetually hungry. There are some side effects of taking in large amounts of fibre – such as elevated levels of flatulence – but generally the effects on bowel health are good. The major problem with high fibre foods is that they tend to be bland relative to foods that are high in fat or high in protein. Sustaining the high fibre intake over the long term is therefore difficult.

Current popular diets rely on large quantities of dietary protein – almost to the exclusion of carbohydrates. These diets have benefited greatly from the celebrity status of many of their adherents. Their scientific basis is that there appears to be a hierarchy of macronutrient effects on perceptions of hunger: fat is least satisfying, carbohydrates next and finally the most satiating macronutrient is protein. A diet providing a caloric deficit, where most of the calories come from protein, will therefore leave a person feeling less hungry than if the same deficit comes from a fibre-dominated intake. But weight loss will be the same for the same caloric deficit. The difference is that, because perceptions of hunger are different, it may be easier to adhere to a high protein diet than a high fibre diet, and the longer you stay on a diet the more weight you lose.

There are, however, major problems with the high protein diets. The first is they are generally deficient in micronutrients and also, potentially, in carbohydrates that are important for optimal function of some of our systems – such as the central nervous system. The second problem is that high protein intake is generally coupled with high levels of cholesterol and saturated fat intakes, both of which have been implicated as causal factors in cardiovascular disease, cancer and stroke, independent of the obesity they engender. Urinary calcium excretion is increased on high protein intake. Moreover, bowel cancer is strongly negatively correlated with dietary fibre content, and so excluding fibre from the diet will enhance the risk of developing bowel cancer. Processing high protein loads may also increase the risk of kidney failure because of the high production rates of urea.

These high protein diets are consequently only appropriate in the short term. Even then, the benefits of weight loss need to be balanced against the other negative side effects. During 2001, the American Heart Association (AHA) and the World Cancer Research Fund both came down very heavily against these diets as aids in the fight against obesity. Proponents of the diets have, however, tended to ignore or belittle these warnings as scare mongering and point out that the links between the diets and risks have not been unequivocally proven. A very balanced report on high protein diets was published in July 2002. It concluded that high protein diets do result in greater weight loss than conventional diets but that probably one of the largest problems they pose is through greater calcium excretion in urine, which may ultimately contribute to excess bone loss. Caution should be taken in particular by people with kidney problems or diabetes mellitus (Eisenstein *et al.*, 2002).

The most beguiling aspect of all calorie-controlled diets is that, in the short term, they do result in significant weight loss. If you are in caloric deficit, then your system responds by trying to minimise the magnitude of the difference between what you are eating and what your body requires. You become lethargic, reduce your activity and your resting metabolic rate. Consequently, the rate of weight loss slows as time moves on and eventually the body

reaches a steady state where the reduced intake is matched by reduced energy expenditure. To sustain further weight loss requires an even more stringent reduction in calorie intake. You will maintain the weight that has been lost only if you sustain the dietary control.

The bottom line is that the only way to permanently lose weight on a diet is to stay permanently on the diet – or replace it with some alternative form of caloric intervention, like exercise. This is because once you stop the diet, your body fat content will be considerably lower than your target fatness. You will be producing low levels of leptin and the major impetus of your lipostatic regulation system will be to redress this balance by impelling you to eat more food. To emphasise this, it is noteworthy that an almost 100% successful permanent treatment for obesity is surgical intervention such as gastric banding. This works because it forces people to comply with caloric restriction forever.

Why diets don't work

We can understand why diets don't work by considering the analogy of the thermostat in a house. Imagine your thermostat is set really high and your house is hot. You aren't happy with this situation but, because you don't know how the thermostat works, you call in 'Dr Fad', a home temperature expert who opens up your sitting room window. There is an immediate improvement in the house temperature, which starts to plummet. Over the next few days the house cools down to a more comfortable level, but it is still a bit too warm, so you need to open up another window to keep it falling. Eventually you reach your target home temperature. It is great. Somebody comes by saying that they think you might have exposed yourself to some risks by opening your windows like that – your kids might get colds in the drafts and you might get burgled, but Dr Fad says that they are just scare mongering and there is no proven link between open windows and burglary. Eventually, however, when one of your children gets a cold. You decide that having the windows open is not a great idea and you close them. Immediately the temperature starts to rise again, and soon you are back to square one with your boiling hot house.

Diets are like miracle home temperature cures that aim to fix your house temperature by opening up a few windows. They are effective, but they only work as long as you stay on them, and they sometimes have undesirable side effects. Discontinuing the diet usually results in people regaining their original weight. In fact, the dieting industry is a multi-billion pound enterprise *because* diets work in the short term, but the population of potential customers is never seriously diminished by the diets themselves.

Re-setting your lipostat

So what are the alternatives? To consider these it is worth thinking about why some people get fat in the first place. Do they have a broken or wrongly set lipostatic control system that leads them to fail to regulate their weight when immersed in the western society? We can understand this interplay between genes and the environment by again resorting to the analogy of the thermostatically heated house. Imagine houses have a whole range of thermostatic temperature set points from cold to hot. If the houses were all in northern Alaska and poorly insulated then all the house temperatures might be on the cold side because even those with high set-points (or broken thermostats) couldn't get as hot as their thermostats want them to be because the capacity of their heating systems

wouldn't be able to match the heat loss through their roofs. This is equivalent to the genetic system being environmentally constrained. However, if the houses were all in central Africa, where the environmental temperature is much warmer, then those with high target temperatures (or broken systems) would reach their high temperatures (equivalent to the genetic system being released from environmental constraint).

The actual house temperatures depend on both the thermostat characteristics and the environment in which the houses are located. Obese people might have high target body fatness settings in their lipostats, or broken lipostats, which result in actual high body fatness in western societies where there is ready access to high calorie content foods. In rural primitive farming communities, a person might have a high target setting in, or breakage in their regulation system, but if they work 12 hours a day digging fields and pounding ground-nuts to extract a high fibre, not particularly nutritious, food source, they would be unlikely to get fat.

A natural response to this explanation is to ask what sort of evolutionary process might result in a system with such high target lipostats. Our knowledge about the evolution of body weight regulation mechanisms in humans is very poor. Generally, arguments have tended to be very simplistic and emphasised that storing large amounts of fat might, at some point, have been selectively advantageous because it would provide increased resistance to starvation. However animal studies suggest that stored body fat may reflect a dynamic trade-off between the risks of starvation – promoting fat storage – and the risks of predation – promoting leanness. Julian Mercer and myself have suggested that early humans probably also faced these contrasting selective pressures, and they evolved a system that promoted fat storage to avoid starvation but also prevented excessive fat storage to avoid predation. Several key events in human evolution are likely to have dramatically reduced the risks of predation – the evolution of social behaviour to drive away predators (as currently observed in groups of chimpanzees), the harnessing of fire and construction of tools to actively aid defence. This would remove the strong selection imposing an upper limit on fat storage and target set-points might drift upwards although actual body weights might be constrained by food supply. Several hundred generations later, when faced with the western lifestyle, the continued absence of strong selection on the lipostat target would result in a diversity of targets and the consequent diversity of body fatness phenotypes that we currently observe.

Leptin to re-set the lipostat?

Once leptin had been discovered in 1994, there was immediate interest in whether obesity was a result of deficient leptin production. Obese people might have abnormalities in their ability to produce leptin in much the same way as the leptin deficient (ob)/ (ob) mouse. Imagine, for example, if my leptin production was only half the normal rate. My brain would think that I was only half as fat as I actually am and encourage me to eat more food and expend less energy until my fat content was high enough to redress the production deficiency. If this was the case, the potential to cure obesity was therefore in sight – one could treat people with leptin (or drugs to mimic its action or stimulate natural leptin production) to trick the brain into thinking that one was fatter than was true. The regulatory system would then downregulate food intake and increase energy expenditure to redress the balance. This would obviously

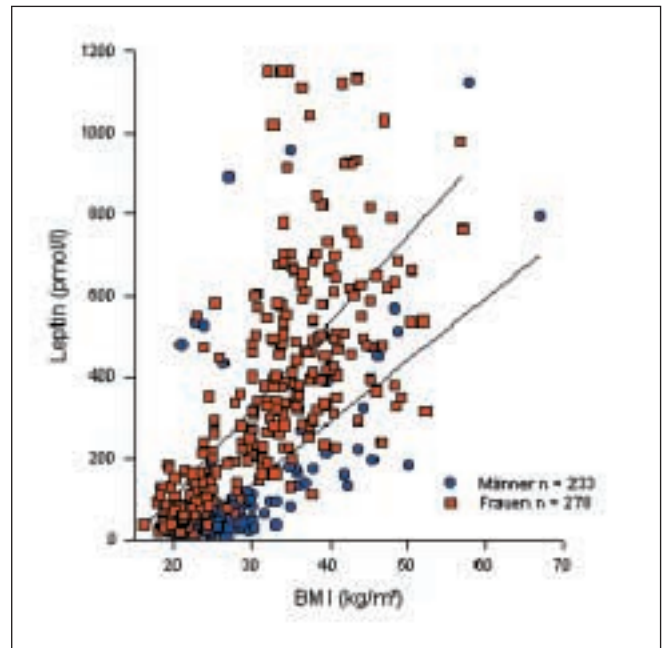


Figure 1. The relationship between body fatness and circulating leptin concentration in males and females. Following the discovery of leptin, hopes were that people might be obese because they have deficient leptin production. However, all cross-sectional surveys of circulating leptin have indicated that (with very rare exceptions, see text) leptin production is positively related to body fatness, as would be anticipated for a functioning lipostatic system (redrawn from Geldszus et al., 1996).

need to be a lifelong treatment since discontinuation would lead to leptin levels falling and weight gain. However, at least with this method, one would be *using* the system to one's advantage rather than fighting against it. In fact euphoria over the potential of leptin was short lived, because it was found that fat people in general have very high leptin concentrations (Figure 1) as might be expected from their high body fatness if their leptin production systems were working correctly. The vast majority of obese people do not have leptin production deficiencies.

An interesting exception to this general rule concerned two children discovered in Cambridge UK, by Stephen O'Rahilly and colleagues at Addenbrookes Hospital. These children were under 10 years old but already had ravenous, insatiable appetites. This had resulted in enormous obesity that had forced their parents to seek hospital treatment for them. Importantly, these children were not just slightly overweight, they were massively obese. The older child, for example, aged 10, already weighed 110 kg. These children had no detectable levels of circulating leptin in their blood. Further investigations showed they had a recessive mutation in their leptin gene preventing leptin production. These children were the human equivalents of the ob/ob mouse.

Happily, once this defect had been diagnosed, Amgen (the company that had the intellectual property rights for leptin) provided recombinant leptin to treat the children. With daily injections, their dramatic weight gain trajectories and compulsive eating behaviour have been reversed (Figure 2). Since this time, other families have also been described with leptin production deficiencies, including a family of three people from Turkey whose body weights almost halved when they received daily leptin injections for 10 months, and individuals also have been identified who harbour mutations of the leptin 'Ob-Rb' receptor (human equivalents of the Db/Db mouse). These single-gene-defect causes of obesity are, however, extremely rare,

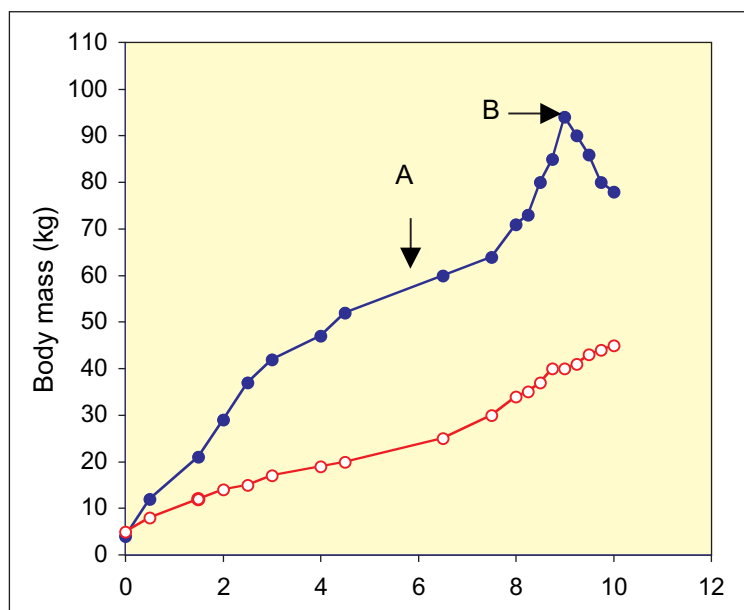


Figure 2. Body mass of a female child with leptin deficiency throughout the first 10 years of life (closed symbols) relative to the 98th percentile for the UK population (open symbols). The child was born at normal body weight and then grew enormously. The growth rate slowed at point A because of an enforced dietary intervention, following which the mass accelerated rapidly again. The child was treated with recombinant leptin at point B and from then onwards the gain in body weight was reversed (redrawn from Farooqi et al., 1999).

and can account for, at most, only a very small fraction of the obesity problem. The most important single gene defects, in terms of prevalence in the obese population, occur within the melanocortin system (notably the MC4 receptor). Polymorphic variation in this gene accounts for about 3% of all morbid obesity in populations that have been screened to date.

If leptin works in leptin-deficient subjects, then could it be used in other obese people to trick the brain into thinking they are even fatter than they are? After all, leptin administration to mice without genetic problems in producing leptin, caused weight loss (see article number 2 in this series). Clinical trials with leptin started in the late 1990s. The largest trial included around 75 obese patients who were given daily leptin injections as different doses. The subjects were also prescribed a diet that, over the six month study period, was expected to result in weight loss of around 12 kg. The study revealed that subjects on

placebo treatment lost on average only 1.4 kg, while those on the highest doses of leptin (0.3 mg/kg) lost five times as much (7.1 kg). Although this modest weight loss is lower than anticipated (12 kg) given the prescribed diet, it is clear that the people on leptin treatment found it easier to adhere to the dietary prescription. The major problem, however, is the dose of leptin required to obtain this result involved an injection of around 30 mg of leptin each day. The current price of leptin is around 100\$ per mg. At a cost of 3000 \$ per day, this is unlikely to be the sort of treatment that could be envisaged for large numbers of patients in general therapy. In addition, about 15% of the patients on the trial receiving leptin exhibited moderate to severe allergic reactions at the injection sites.

Although leptin has not provided the solution it once promised, it does provide some reassurance that the system in humans is not radically different to that in rodents. Using animal models, therefore, is the best hope we have of coming up with general solutions to the obesity problem. If leptin production is not the problem, then other possibilities are that leptin fails to cross the blood brain barrier, or the signal is not read properly by the receptor system (so called leptin resistance) or obese people may have wrongly-set, or broken lipostats, in their brains. At present, we do not know the genes that control the lipostatic target. However the promise of their discovery has tremendous potential. Progress is

currently being made in this field using what, at first sight might appear an unlikely source of information – the Siberian hamster. However, Siberian hamsters, like several other species of small mammal, exhibit profound cycles of body weight over the annual cycle (Figure 3). Several groups around the world, among them a component of the Aberdeen Centre for Energy Regulation and Obesity (ACERO), based at the Rowett Research Institute, are using this model to study the manner in which the brain encodes the target body weight. The seasonal weight changes in hamsters are triggered by an alteration in the photoperiod. When a hamster is exposed to a long photoperiod (16 hours of light) and then switched to a short photoperiod (eight hours of light) its body weight starts to fall precipitously until it reaches a new stable point, about 30% lighter than it started out (Figure 3). It is as if the hamsters target body weight slowly slides downwards to the new level.

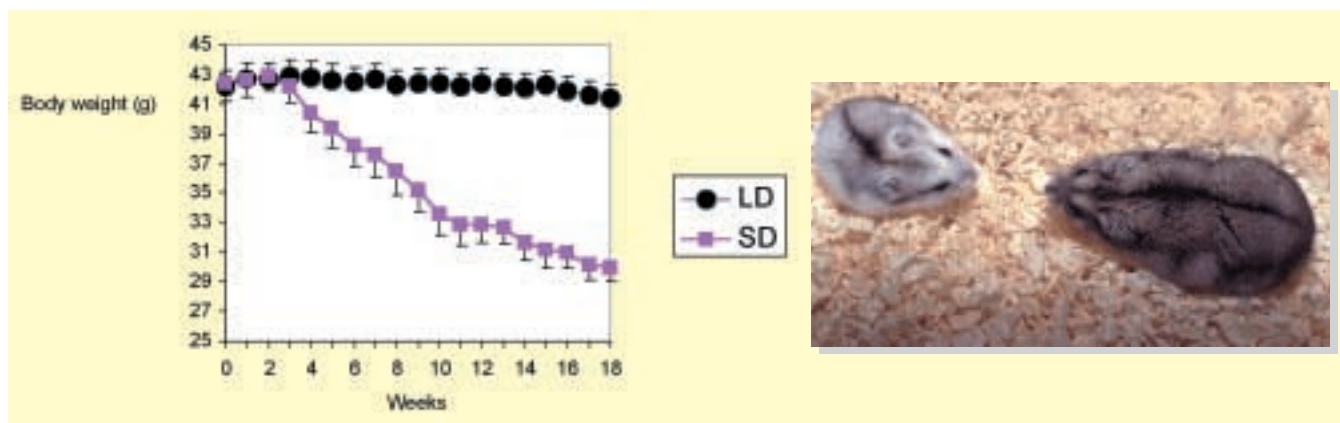


Figure 3. Pattern of body mass change in Siberian Hamsters exposed to long (LD) and to short (LD) photoperiod at constant ambient temperature. Animals switched to a short photoperiod start to lose weight about 2 weeks after the switch and continue to do so until their body masses are about 30% lower than the control group maintained on long photoperiods (from original data provided by J. Mercer). The photograph shows Hamsters maintained on a short day (left) and long day (right) regime.

The postulated re-setting of the lipostat is confirmed by the following experiments. If you put a long-day hamster onto a diet for a few weeks it loses body weight for a period of time. Then, when it is returned to ad libitum food, it comes back up to the same starting weight. If a hamster is switched onto short days first and has started to lose body weight before being put on a diet, it also loses weight. Then, after the period of weight loss, its weight also rebounds back, but not to the point at which it was placed on the diet. In this case the hamster's weight returns to the short-day place it would have been at had it not been placed on the diet (Figure 4). This suggests that the target weight has changed.

By comparing gene expression profiles in the brains of hamsters between the long-day animals and the short-day animals, we can find genes that have been switched on and off by photoperiod changes. To do this requires state of the art genomics methods involving gene expression microarrays. These arrays have on them thousands of cDNA strands that correspond to putative messenger RNAs. By extracting RNA from the hypothalami of short- and long-day hamsters one can discern changes in the levels of expression of large numbers of genes. These genes are then candidates that can be further pursued using more conventional molecular biology approaches to see if they are components of the target weight regulation system. This approach is sometimes disparagingly called a 'genetic fishing trip' – looking for genes with no *a priori* knowledge of their function. However, the fact is that going on fishing trips is generally a successful method of catching fish. With so many genes of unknown function still littering the genome, the approach is probably the fastest method we have to match together genes and function.

These studies are in their infancy but their potential is clear. Once we know which genes are involved in setting the lipostat target, we can start to think about manipulating the system. These manipulations could include production of agonists and antagonists to the gene products and their receptors. Alternatively, gene expression could be modulated to turn someone with a high target weight into someone with a low target weight. This might also be achieved by drugs, and considerable research effort is currently directed towards identifying pharmaceuticals that switch genes on and off by activating elements in their promoter regions. In addition, a really blossoming area of research is the study of nutrient-gene interactions where specific nutrients are identified that turn genes on and off – so called nutraceuticals.

A permanently re-set lipostat?

The attractiveness of this approach is that, once we start to change the target body weight, then the changes in actual body weight will occur as easily as the weight falling off after the overindulgence at Christmas or holidays. It will be slow and imperceptible with slight changes in appetite and weight loss until the new target is reached. There will be no need for diets that demand copious amounts of willpower, because you will no longer be perpetually fighting against the impetus of your genes. Rather, you will be using the system that controls your body weight to take it to a level that you want, instead of an arbitrary setting based on your genetic inheritance. An additional benefit is the reduced risk of developing severe degenerative disease such as type two diabetes and heart disease. The effect of treatment would be gradual, but, unlike conventional approaches that fight against your genes, you would be working with your genes. The ultimate 'Holy Grail' solu-

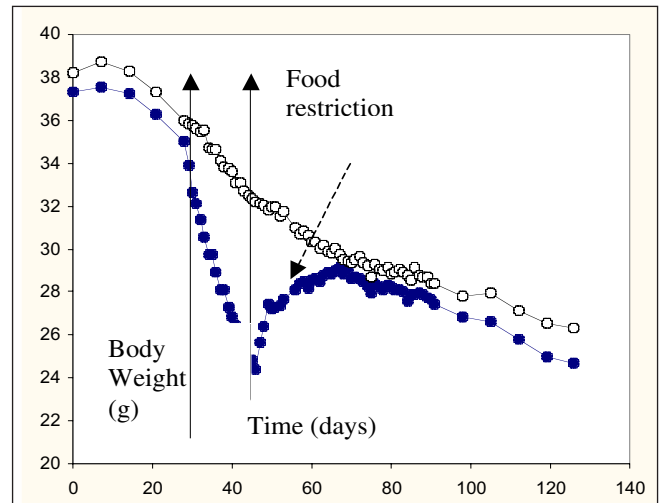


Figure 4. Body masses of hamsters exposed to short photoperiods (open circles). The filled circles represent the body masses of hamsters that were exposed to short photoperiods but then, between days 30 and 45, were also placed on a dietary restriction. During this period, the body mass fell more rapidly than that of the animals exposed to short photoperiods only. On returning the animals to ad lib feeding the body mass increased (dotted arrow) until it matched the expected mass for that duration of exposure to short days. This model suggests that the animals have a target body mass that continually slides downwards as a function of the time spent under short photoperiods (redrawn from Mercer and Speakman, 2001).

tion is that we could permanently switch the system, then the effects would also be permanent.

This work, aiming to modify the target system, is radically different from most current work on the prospective treatment of obesity. Most, aim to either modulate energy expenditure or decrease appetite to effect changes in body fatness. Although the lipostatic regulation system enjoys popular support among molecular biologists, it is not accepted by everyone. If there is no lipostatic regulation system for body fatness, is the search for pharmaceuticals for its intervention fundamentally flawed? Surprisingly not. The reason is that even if the lipostatic model is incorrect, almost all researchers agree that food intake and expenditure are under some form of regulatory control. Work on the upstream and downstream events from leptin are likely to be useful either within or outside the lipostatic framework of interpretation. Leptin could function as a key signalling component of a lipostatic system, or simply a starvation/ energy imbalance signal. Whatever the case modulation of this signal and its related downstream events might allow a means of controlling body fatness.

I should clarify, however, that treatments are not being developed to assist in the loss of a few pounds prior to one's summer holidays. It is unlikely that you will be able, in the foreseeable future, to nip down to the local chemist for a five Kg target-weight resetting pill. The aim of these treatments is to alleviate chronic levels of obesity that are linked to negative health outcomes, thereby saving millions of people from premature death and alleviating the massive burden on the health service and economy. Inevitably, it seems likely that drugs (and nutraceuticals) developed for health reasons will find their way into body weight control at lower levels, since this has already happened with most other drug-related interventions aimed at alleviating obesity.

How far in the future is this dream of manipulating body weight by target re-setting? Inevitably, progress will depend on making key breakthroughs in gene identification

and control, and development of suitable pharmaceuticals. Since drug evaluation and testing generally takes about a decade this could become a reality in 15–20 years—by which time, if current trends continue, perhaps 30–40% of the UK population will be clinically obese. Meanwhile, the main alternative strategy is willpower. This does work, but for a permanent solution needs permanent lifetime commitment and struggle. The evidence suggests that few people are able to sustain this. Novel behavioural therapies that assist us in using our brains to overcome our genes may be another important avenue for future interventions. At present, however, the only solution that has almost guaranteed success is forced adherence to energy restriction by surgical intervention – such as gastric banding.

In conclusion, obesity is a serious condition currently affecting around 20% of western society with a further 45% of people overweight. Differences between individuals probably reflect, in large part, their genetic constitution. Attempts to fight against one's genetic legacy are difficult to sustain so most diets are successful in the short term, but unsuccessful in the long term. Current research effort is to identify and ultimately manipulate the control system for body weight, so that solutions can work in harmony with one's genes instead of against them. In the coming two decades, we are likely to see dramatic advances with drugs or nutraceutical therapies hitting the markets and, hopefully, having a significant impact on obesity shortly thereafter.

Further reading

- Barsh G S, Farooqi I S and O'Rahilly S (2000) Genetics of body-weight regulation. *Nature*, **404**, 644–651.
- Eisenstein J, Roberts S B, Dallal G and Saltzman E (2002) High-protein weight-loss diets: are they safe and do they work? A review of the experimental and epidemiologic data. *Nutrition Reviews*, **60**, 189–200.
- Farooqi I S, Jebb S A, Langmack G, et al. (1999) Effects of recombinant leptin therapy in a child with congenital leptin deficiency. *New England Journal of Medicine*, **341**, 879–884.
- Friedman J M (2000) Obesity in the new millennium. *Nature*, **404**, 632–634.
- Geldszus R, Mayr B, Horn R, Geithovell F, von zur Muhlen A and Brabant G (1996) Serum leptin and weight reduction in female obesity. *Eur J Endocrinol*, **135**, 659–62.
- Mercer J G and Speakman J R (2001) Hypothalamic neuropeptide mechanisms for regulating energy balance: from rodent models to human obesity. *Neuroscience and Biobehavioral Reviews*, **2**, 101–116.
- Mercer J G, Hoggard N and Morgan P J (2000) Leptin and obesity – the story so far and its therapeutic implications. *CNS Drugs*, **14**, 413–424.
- Morgan P J and Mercer J G (2001) The regulation of body weight: lessons from the seasonal animal. *Proceedings of the Nutrition Society*, **60**, 127–134.
- O'Rahilly S (1999) The role of leptin in human physiology: Lessons from human experiments of nature. *Atherosclerosis*, **144**, 149–150.
- Yeo G S H, Farooqi I S, Aminian S et al. (1998) A frameshift mutation in MC4R associated with dominantly inherited human obesity. *Nature Genetics*, **20**, 111–112.
- Yeo G S H, Farooqi I S, Challis B G, Jackson R S and O'Rahilly S (2000) The role of melanocortin signalling in the control of body weight: evidence from human and murine genetic models. *QJM-Monthly Journal of the Association of Physicians*, **93**, 7–14.

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