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The geometry of human nutrition[1]

Stephen J Simpson[2] and David Raubenheimer[3]

This chapter is an excerpt from a forthcoming book, titled 'The nature of nutrition: a unifying framework from animal adaptation to human obesity' by Stephen J Simpson and David Raubenheimer (Princeton University Press, 2012). In the book we present a graphical approach, the 'geometric framework', which we believe can help to integrate nutrition into the broader biological sciences and introduce generality into the applied nutritional sciences. In the present chapter we use this approach to show that the epidemic of human obesity and metabolic disease is linked to changes in the nutritional balance of our diet, with a primary role for protein appetite driving excess energy intake on a modern Western diet.

The modern human nutritional dilemma

It is conservatively estimated that more than one billion people worldwide are overweight or obese. Rates of obesity are increasing, notably among the young, and the associated disease burden is immense [1–3]. Figure 1A plots the relative risk of dying prematurely as an adult against body mass index (BMI), which approximates to body fatness and is calculated as body mass in kilograms divided by the square of height in metres. Clinicians categorise adults as underweight if they have a BMI of less than 18.5, as overweight if they have BMI values between 25 and 30, and as obese if they exceed 30. The curve is U-shaped, with the risk of dying prematurely increasing at both low and high values of BMI, and the target zone for health and longevity lying in between.

The relationship between body fat content and risk of premature death in humans is very similar to what we have observed in the locust, Figure 1B. This is a species that defends a target intake of macronutrients [4], and Figure 1B suggests a reason why that target is defended: because doing so minimises the risk of dying early. We have encountered similar 'nutritional wisdom' in caterpillars, as well as fruit flies and field crickets [4].

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1 We are grateful to Princeton University Press for permission to include this chapter from the author's forthcoming book: Simpson SJ and Raubenheimer D (2012). *The nature of nutrition: a unifying framework from animal adaptation to human obesity*, Princeton: Princeton University Press.

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Regrettably, the same cannot be said for our own species. Take as an example the US, where approximately 65% of adults are overweight or obese, while 30% are clinically obese. And the US is not atypical – the same trend is seen in all developed countries and increasingly in developing countries, too. Why have we gone so badly wrong? The answer lies in the interplay between the nutritional environment and regulatory physiology.

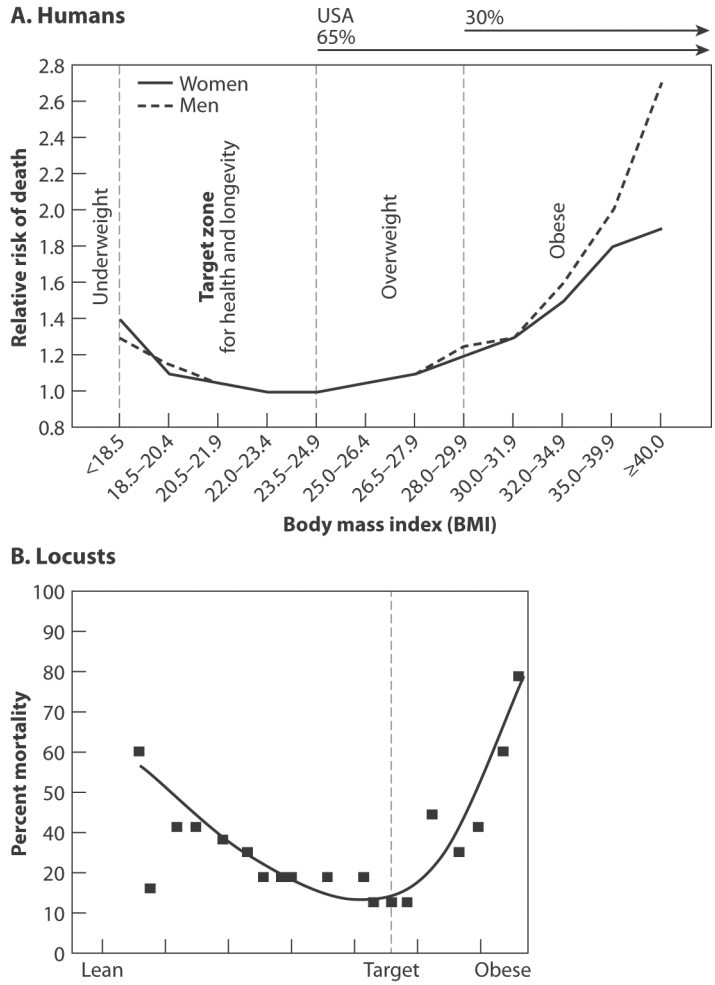

Figure 1A. The relative risk of dying prematurely as an adult against body mass index (BMI) in US adults (based on Calle et al. [72]); and B. an equivalent plot for locusts [73].

As summarised in Figure 2, the human nutritional environment has changed considerably over the past 35,000 years since the Upper Palaeolithic. Anthropologists and archaeologists have reconstructed the nutritional ecology of our forebears during this period [5]. The main conclusion is that people then were probably energy-limited, because sources of simple sugar, fat and starch were rare. In contrast, protein was relatively abundant in the form of

lean game animals. Skeletal analyses indicate that people were large, lean and healthy under such an environment [5].

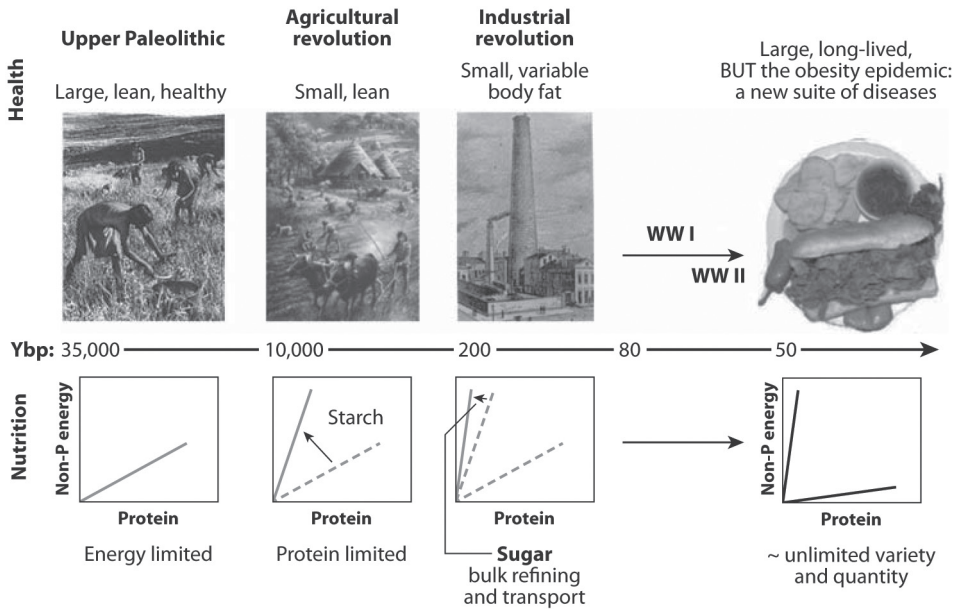

Figure 2. A summary timeline for the changing human nutritional environment since the Paleolithic.

A major transition in human nutrition occurred with the shift from hunter-gatherer lifestyle to agriculture. This took place at different times in different parts of the world, but the results were similar: there was an increase in the amount of readily available carbohydrate, particularly starch from grains, in the diet. This may have been associated with protein limitation and also micronutrient imbalances, and probably led to increased problems of famine as well as a greater disease burden as populations became more concentrated and sedentary [6–8]. As a result, people were, on average, smaller than in the Upper Palaeolithic, lean and less healthy.

The incorporation of carbohydrate into the diet increased further during the Industrial Revolution, due to the bulk refining and efficient transport of grains and sugar. Around that time, most people were small and lean, with corpulence being largely restricted to the wealthy few.

Since the Industrial Revolution, there has been a further major nutritional transition, between and following the two world wars. Today in the developed world, we have an unprecedented general access to all manner of foods and nutrients. We in the Western world are large and live long, but are also suffering the obesity epidemic and an upsurge in a new set of chronic diseases associated with our modern lifestyle.

In contrast to the changing nutritional environment, our physiology seems to have remained much more constant over the same timescale. There is evidence of genetic adaptation in

human populations to changed patterns of food availability since the Upper Palaeolithic [8] – for example, the evolution of lactose tolerance among human populations with the advent of dairy herding and, possibly also the selection of genes that confer resistance to diabetes [9]. However, the pace at which our nutritional environment has changed is considerably faster than the rate at which our metabolism can evolve: we are caught in a time lag, in which our physiology is poorly adapted to our lifestyle.

If we are to understand how our 'outdated' physiology interacts with our changed nutritional environment, we must answer three fundamental questions:

1. Do humans regulate intake of multiple nutrients to an intake target (*sensu* Simpson and Raubenheimer [4])?
2. How do humans balance eating too much of some nutrients against too little of others when faced with an imbalanced diet – ie what is the rule of compromise for humans (*sensu* Simpson and Raubenheimer [4])?
3. How do humans deal with nutrient excesses?

We will deal with these questions in turn, restricting our discussion to the three macronutrients – protein, carbohydrate and fat. Of these nutrients, we argue that protein has played a pivotal role in the development of the obesity epidemic.

Do humans regulate to an intake target?

As yet, no properly controlled geometric experiment, along the lines described in [4] for numerous other animals, has been published for humans. Partly for this reason, it remains contentious whether humans are able to regulate their intake of different macronutrients [10–12]. There are, nonetheless, three sources of information that suggest that we can regulate the intake of specific nutrients.

1. Comparative data from rodents and other omnivores

Rodents are widely used as models for human nutritional physiology. From a nutritional perspective, there is some rationale to this because, like humans, rodents are broad-scale food generalists. Reinterpreting published data on rats showed convincingly that these mammals have the capacity to regulate their intake of protein and carbohydrate [13]. An example is shown in Figure 3A, in which we replotted data collected by Theall et al. [14]. Rats were provided with one of eight different complementary food pairings, and in every case converged on the same intake of protein and carbohydrate, indicating that these animals regulated their intake of both macronutrients. Subsequently, Sørensen and colleagues [15] conducted a full geometric analysis of protein and carbohydrate regulation in another model rodent, the mouse, and showed unequivocally that mice, too, regulate protein and carbohydrate to an intake target (Figure 3B).

2. Studies on human macronutrient appetite

There are data which indicate that we have some capacity to regulate our intake of macronutrients, notably protein, despite the extreme complexity of our social and

nutritional environments [12, see 16]. It appears that macronutrient-specific feedbacks operate over a period of one to two days, and that, at least for protein, we subliminally learn to associate foods with the nutritional consequences of eating them [17, 18].

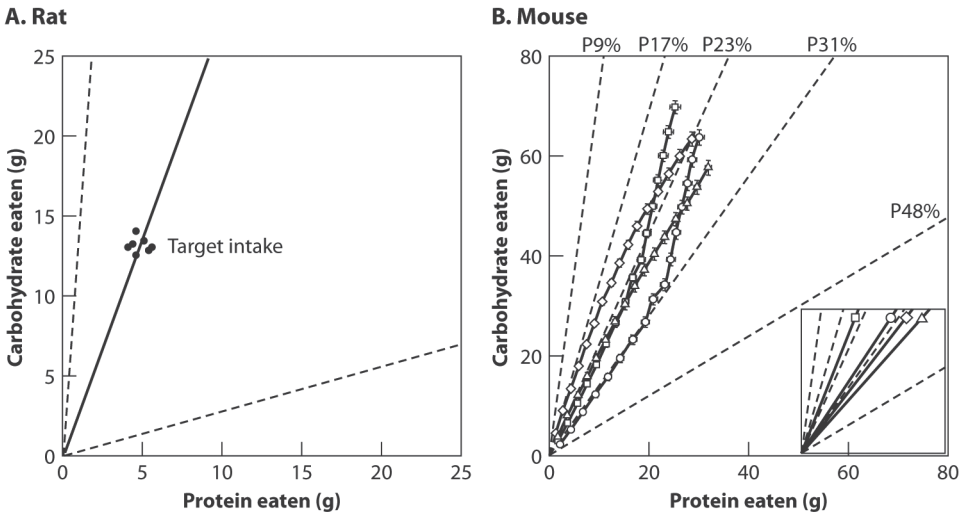

Figure 3. Rats and mice possess separate appetites for protein and carbohydrate. A. Data for rats provided with one of eight different complementary food pairings (food rails not marked except for the two most extreme ratios). Rats converged on a point of protein–carbohydrate intake, indicating tight regulation of both macronutrients to an intake target. (Data from Theall et al. [14], reanalysed in Simpson and Raubenheimer [13]). B. Cumulative protein–carbohydrate intake trajectories for mice offered one of five food pairings. Mice converged significantly relative to a common (target) intake trajectory. Had they fed indiscriminately between foods in each pairing, trajectories would have diverged markedly, as shown in the lower insert. (From Sørensen et al. [15], with permission).

3. Population-level data

A striking feature of the human diet is that the proportion of protein in the diet is highly consistent across populations and across time, comprising around 15% of total energy, whereas fat and carbohydrate vary [19] (Figure 4). And not only the proportion of protein, but also the amount is consistent, at least in some populations. Figure 5 plots estimates for per capita intake for the UK population from 1961 until 2000, taken from the Food and Agriculture Organization of the United Nations (FAOSTAT) database [20]. According to these data (which are based on nutrient supply rather than measures of actual intake), intake of protein and also fat and carbohydrate have remained remarkably stable since 1961. Not only that, they appear to have been 'defended'. If we first take the case of dietary fat supply and break down the total into fats derived from animal and vegetable sources, it is apparent that during the mid 1980s intake of animal fats fell precipitously, presumably in response to the public health campaign urging people to eat less of these fats. Thus, at this time there was a perturbation in the nutritional environment – was there a compensatory

change to counterbalance this? Yes – as can be seen in Figure 5, the intake of vegetable fats rose in direct proportion to falling intake of animal fats, leading to maintenance of total fat intake at a constant level. Similar substitutions between food groups were also seen over the same period for protein and carbohydrate. Sugar intake fell and was compensated for by increasing consumption of complex carbohydrates (starches, fruit and vegetables). Declining consumption of beef, pork and lamb was compensated by increased poultry consumption, reflecting increasing availability and cheapness of the latter with increased industrialisation of poultry production.

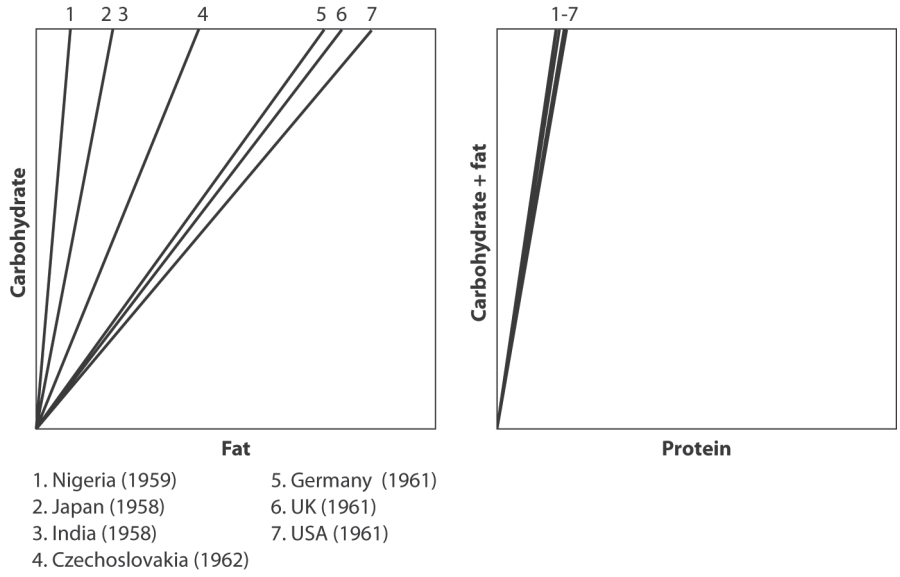

Figure 4. Ratios of average macronutrient intake (scaled in units of energy) in various human societies during the late 1950s and early 1960s. (Based on data from Westerterp-Plantenga [19] and the FAOSTAT database [20]).

But regulation of macronutrient intake is not always perfect, as strikingly illustrated by the US, where carbohydrate and fat intake (as again estimated from FAOSTAT data) have risen substantially over the period 1961 to 2000 (Figure 6). However, protein intake has risen to a lesser degree over the same period. As a result, in the US there has been a shift in diet composition towards a lower ratio of protein to carbohydrate and fat, with protein comprising 12.5% as compared with 14% of total energy intake. Almost certainly this shift has been away from the intake target ratio. Data from the National Health and Nutrition Examination Survey (NHANES) in America indicate a similar pattern: a small decline in percent dietary protein, caused largely by increasing fat and especially, carbohydrate intake [21, see also 22, 23]. Understanding the effect of such a change requires knowledge of the rule of compromise.

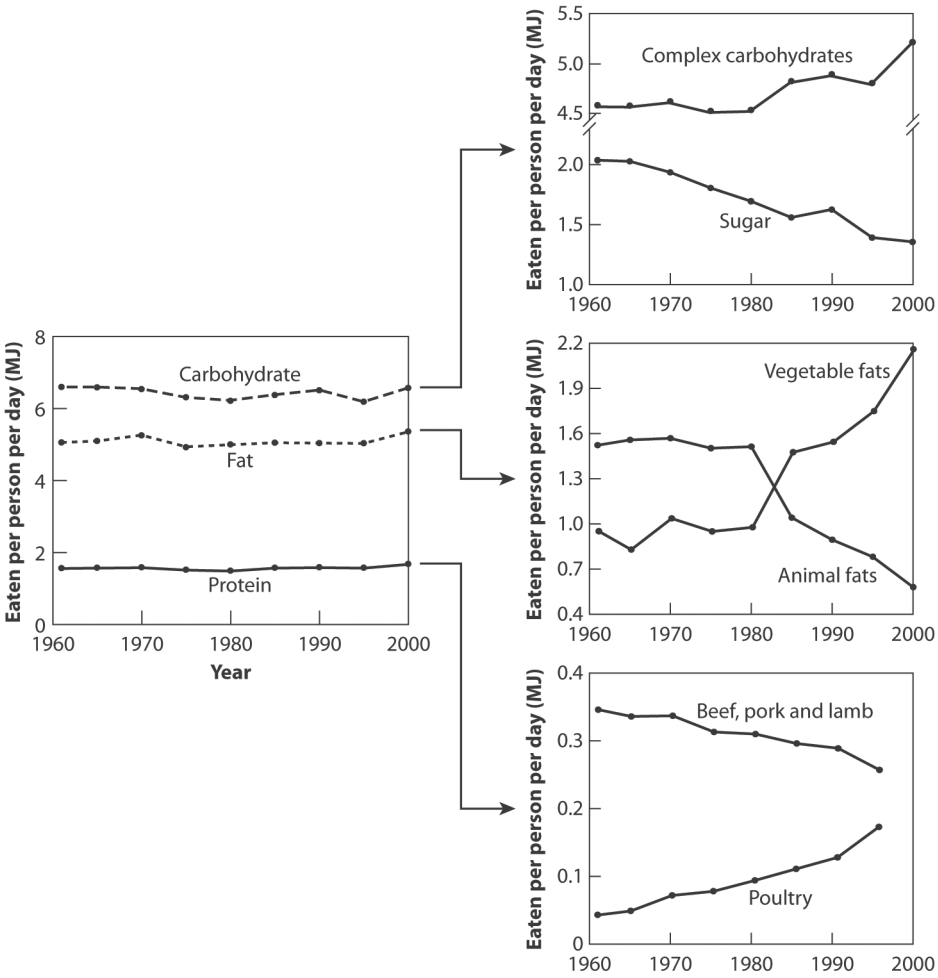

Figure 5. Changing patterns of macronutrient supply (from which intake can be approximated) in the UK from 1961 to 2000, based on FAOSTAT data. Macronutrient intake remained stable and seemingly regulated. See text for interpretation.

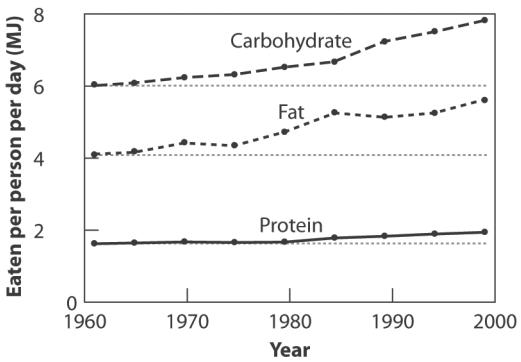

Figure 6. Data as in Figure 5, for the US. Intake of carbohydrate and fat rose faster than that for protein and as a result the percentage of protein in the daily diet fell.

What is the human rule of compromise?

To address this question, we used the geometric framework to explore the human rule of compromise [16]. Our initial study was a short-term experiment, involving ten subjects incarcerated in a chalet in the Swiss Alps, focusing on intake of protein vs carbohydrate and fat combined. We decided to treat fat and carbohydrate as a single dimension (carbohydrate and fat) scaled in energy units since the existing evidence from humans, rodents and other omnivorous animals suggested that the key interaction was between protein and non-protein energy in the diet.

Subjects were housed together for six days. For the first two days, they were provided with the opportunity to select their breakfast, lunch, afternoon snack and dinner from a buffet of items comprising a wide range of macronutrient compositions. Everything they ate was weighed and their macronutrient intake was estimated from food composition tables. For the next two days, one group of subjects (treatment 1) was restricted to foods that were high in protein and low in carbohydrate and fat, while the remaining subjects in treatment group two were provided with only low-protein, high-fat + carbohydrate items. For the final two days of the experiment (days five and six), all subjects were given the same free choice of foods as on days one and two. The results are summarised in Figure 7. The overriding message of the experiment was that when subjects were restricted to a diet that contained either a higher (treatment 1) or lower (treatment 2) ratio of protein to carbohydrate and fat than they had self-selected during days one and two, they maintained their intake of protein at the expense of the regulation of carbohydrate and fat intake. Thus, treatment group one underingested carbohydrate and fat rather than overate protein, while treatment group 2 overate carbohydrate and fat to gain limiting protein.

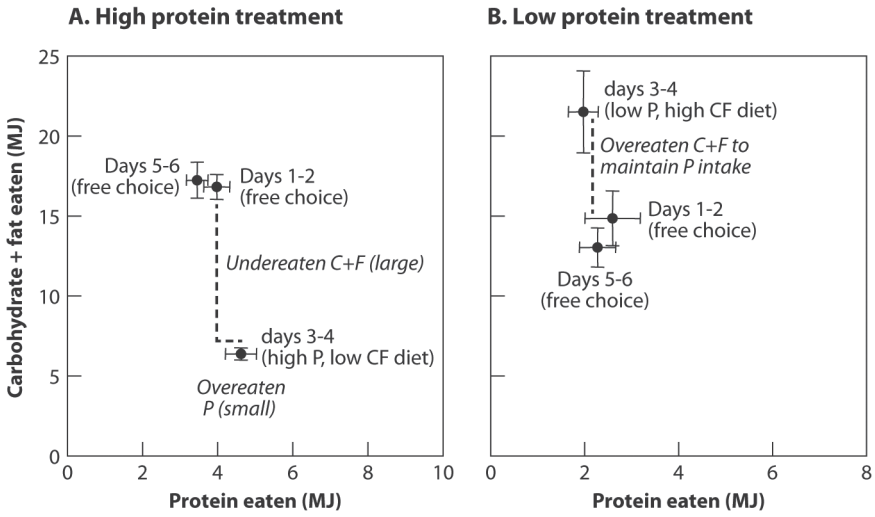

Figure 7. Results from our Swiss study [16]. See text for details. (After Simpson et al. [16], with permission).

From these data, we derived an indication of the form of the human rule of compromise for protein vs carbohydrate and fat, which is that, when forced to trade off intake of protein vs carbohydrate and fat, humans prioritise protein intake. We termed this the 'protein leverage hypothesis' [24].

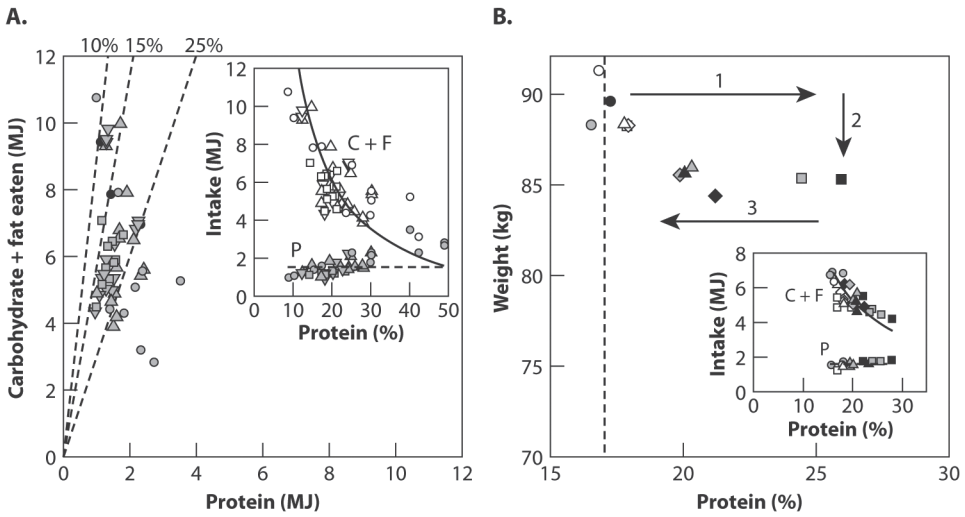

Figure 8A. Protein intake is more tightly regulated than non-protein intake in humans. Protein versus non-protein intakes from a meta-analysis of 23 studies measuring *ad libitum* daily intake on diets of different macronutrient compositions for time periods ranging from less than two months (circle), two to four months (upwards triangle), six to eight months (downwards triangle) and 12 months (square). The rails represent 10%, 15% and 25% protein diets. The inset shows that as the percentage of protein in the diet increases, non-protein (carbohydrate and fat) intake decreases but protein intake remains relatively constant. The dashed line is the mean protein intake for all studies (1.52 MJ). The solid line is calculated as the non-protein (carbohydrate and fat) intake given the percent protein intake in each study but assuming protein intake was equal to the mean (1.52 MJ); in other words, the case where protein leverage is complete and regulation of absolute protein intake dominates total energy consumption. B. Three published weight-loss studies, each showing changes in weight between baseline (circle), two months (square), six months (diamond) and 12 months (triangle). In each study participants were prescribed one of the following weight-loss regimes: the Atkins (black); Zone (grey); and Ornish (white) diets. Percent of dietary protein vs weight (kg) was plotted for each time point in each study. As percent of protein of the diet increases as a result of the Atkins and Zone regimes during the first two months (1) body weight decreases (2). Between six and 12 months the weight loss that occurred on the Atkins and Zone diets is maintained but no further weight loss occurs (3). The inset shows percent dietary protein vs (i) protein intake (dashed line: mean of protein intakes) or (ii) carbohydrate and fat (non-protein; solid line calculated as above) intake information for the three studies. From Gosby et al., unpublished.

To examine whether other experimental data supported this result, we plotted the data from our experiment along with data recast from several earlier experiments. The signature pattern of protein leverage emerged [24]. A more recent update including 23 separate studies measuring *ad libitum* intake on diets of different macronutrient compositions for time periods ranging from several days to 12 months, shows the pattern very strongly indeed (Figure 8). As predicted by the protein leverage hypothesis, in cases where subjects were restricted to a diet comprising a fixed ratio of protein to carbohydrate and fat, either in the short or long term, they maintained daily protein intake at a more constant level than that of the other two macronutrients.

Two other notable features appeared from the compilation of data in Figure 8. First, stable patterns of energy intake in response to altered dietary protein develop within one to two days and persist over at least 70 days thereafter (eg the study by Weigle et al. [18]). Second, there is evidence of an asymmetry in protein leveraging in humans. Hence, humans appear to be more willing to overeat low-protein diets to gain limiting protein than to limit intake to avoid ingesting excess protein [25]. This asymmetry may reflect the fact that the evolutionary costs of eating too little protein exceed those of eating too much. Hence, underconsumption is costly because protein is the only macronutrient to contain nitrogen, which is essential for growth and reproduction. On the other hand, excess protein consumption has been shown to have associated performance costs in some animals [eg 26, 27] – and perhaps also in humans, and suggested risks include increased insulin resistance, kidney damage, bone decalcification, ketoacidosis, cardiovascular disease and some cancers [28–31].

Also consistent with the protein leverage hypothesis are comparative data from rodents and other omnivores such as chickens and pigs [13, 15, 32–34] – and even from herbivorous and omnivorous insects such as locusts and cockroaches. Hence, rats and mice confined to a diet containing a lower protein–to–carbohydrate ratio than at the intake target, maintained protein intake near constant and in so doing overeat carbohydrate. In contrast, rodents provided with a high-protein diet did not substantially overeat protein to gain their intake target level of carbohydrate (although the asymmetry in protein leverage, alluded to above for humans, is apparent) (Figure 9). More strikingly still, data for another primate, the spider monkey, show the signature of extreme protein leverage in which protein intake is maintained near constant and non-protein energy intake allowed to vary freely to attain the protein target [35].

An acid test of protein leverage: disguising the macronutrient composition of the diet

All of the studies summarised in Figure 8 involved offering subjects diets composed of varying numbers of types of familiar foods. There was therefore the possibility that changes in the proportion of protein in the diets were confounded by other factors, such as differences in the palatability of the treatment foods, the variety of options available within each treatment, and prior experience. An acid test of the protein leverage hypothesis requires that these potentially confounding effects are controlled for. Recently, Gosby and colleagues [36, 37] set out to do just that.

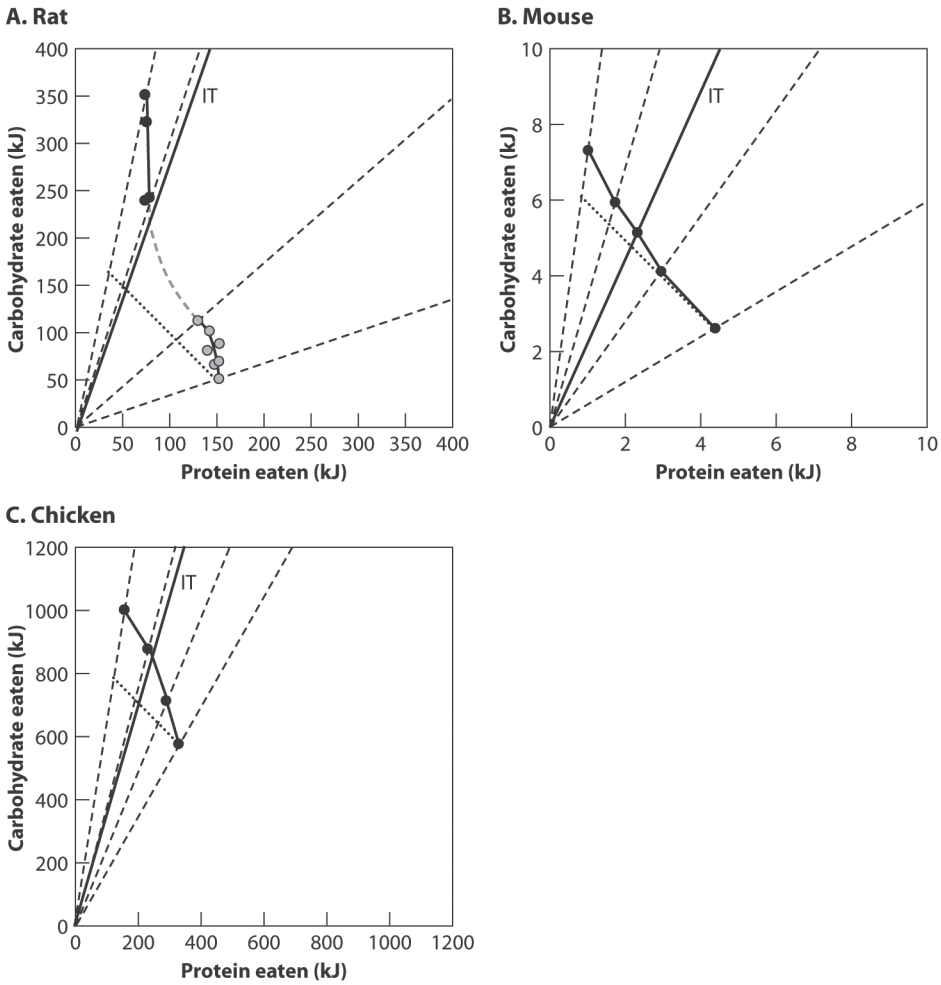

Figure 9. The rule of compromise in rats, mice and chicken. These omnivores prioritise protein intake when confined to diets (dashed rails) requiring them to tradeoff protein versus non-protein energy intake. IT indicates the position of the intake target ratio, as derived from experiments in which animals were offered one of eight (A), five (B) or four (C) complementary food pairings and demonstrated tight convergence to a nutrient intake point. The dotted line indicates isocaloric intakes, to emphasise the point that as percent of dietary protein fell, total daily energy intake rose (ie the intake arrays have slopes steeper than –1). A. After Simpson and Raubenheimer [13], derived from data by Theall et al. [14], with extra data (grey points) added from a study by Tews et al. [74]. The grey dashed curve is an interpolation between the two experiments. B. From Sørensen et al. [15]. C. From Raubenheimer and Simpson [34], based on data from Shariatmadari and Forbes [75].

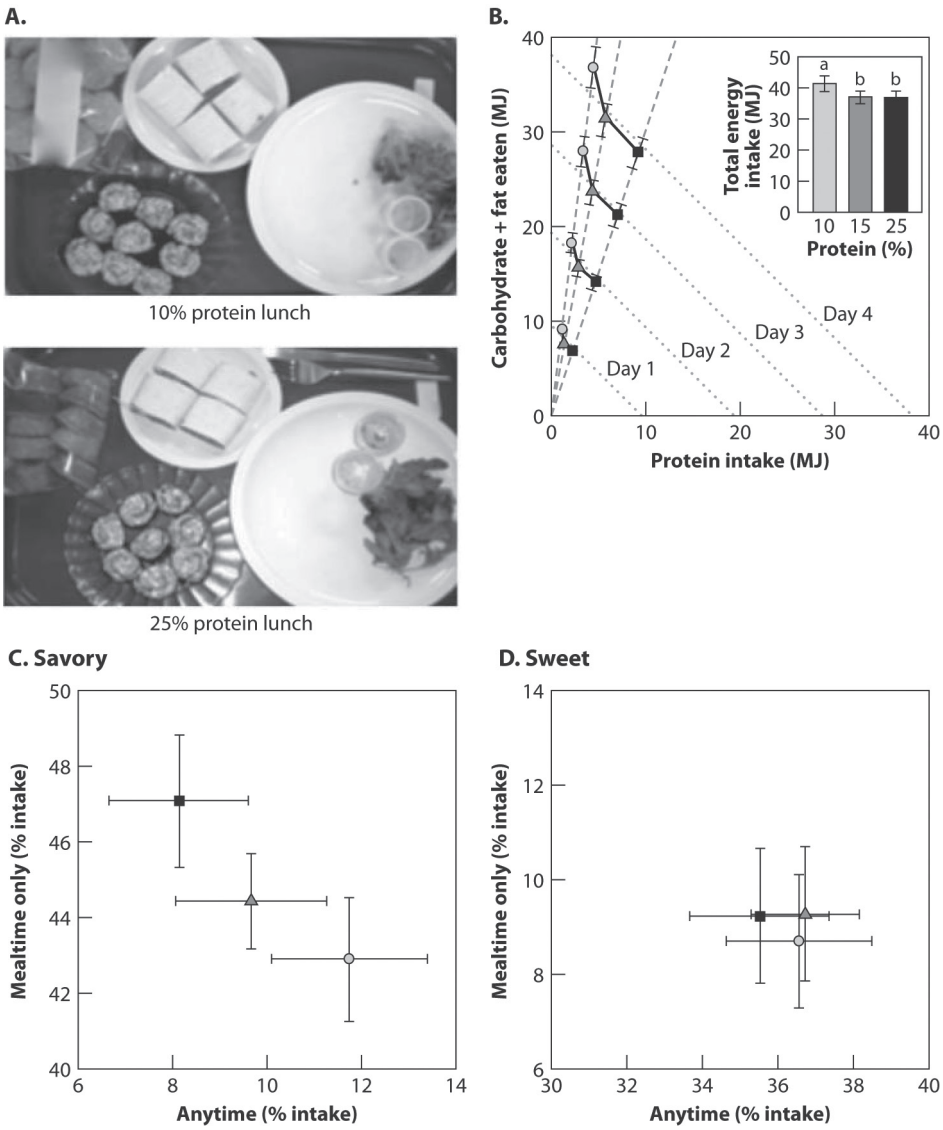

Figure 10. The Sydney protein leverage trial in which subjects were confined to four-day menus in which protein content of all foods was the same but disguised. Each participant spent three four-day periods in the trial. In one, all foods for the period contained 10% protein, in another all foods were 15% protein and in the third they were all 25% protein. Foods were matched for pleasantness and variety. A. An example of a lunch from the 10% protein week and its equivalent in the 25% protein week. Participants were provided with a selection of sweet (apple crumble muffins) and savory (Teriyaki sushi rolls and Mexican wraps) foods to choose from as well as a serving of salad leaves and dressing. Participants were asked to eat until they felt comfortably full. B. Cumulative daily bi-coordinate means for protein and non-protein (carbohydrate and fat) intake (MJ) for participants during the four-day 10% (light-grey circles), 15% (grey triangles) and 25% (black squares) protein study

periods. The dashed lines represent the nutrient rails participants were restricted to during the 10%, 15% and 25% study periods. The dotted lines represent intakes that may occur on the 10%, 15% and 25% foods if intake was regulated to energy requirements. The inset shows total energy intake (MJ) for participants over the four-day 10% (white), 15% (grey) and 25% (black) periods. Bi-coordinate means for 'anytime' and 'meal time' savory (C) and sweet (D) foods as a percent of total intake for participants over the four-day 10% (white circles), 15% (grey triangles) and 25% (black squares) *ad-libitum* study periods. As the percent of protein in the diet fell, not only did total energy intake rise, also the proportion of intake from savory snack foods rose, indicating protein-seeking behaviour (From Gosby et al. [37], with permission).

We began by designing a series of experimental foods that were disguised in their macronutrient composition. The recipes were manipulated to produce three versions of each food, containing 10%, 15% or 25% protein. Dietary fat was kept constant at 30%, and carbohydrate was adjusted to be 60%, 55% or 45% of total energy. Some of these foods were designed to be sweet, others savoury; some were to be presented as part of a main meal (breakfast, lunch or dinner) and others available between meals. Volunteers were recruited to taste-test the foods to make sure that the 10%, 15% and 25% protein versions of each food were equally palatable. As a result, we ended up with three versions of a four-day menu comprising 28 foods. For one version, all foods contained 10% protein, another 15% protein and the third 25% protein. An example of a 10% and the equivalent 25% protein lunch is shown in Figure 10A.

Lean adult subjects were next recruited who spent three four-day periods confined in an apartment at the Woolcock Institute Sleep Study Centre at the University of Sydney. Subjects were given breakfast, lunch and dinner each day and also offered free access to snack foods throughout the day. For one of the four-day periods every food eaten contained 10% protein; during another all foods contained 15% protein; and for the third period all foods were 25% protein. Subjects could eat as much as they liked and their food intake was measured. Because macronutrient composition was disguised and palatability, availability, variety and sensory aspects of foods were matched between treatment periods, the experiment provided a strong test of the effect of protein leverage on energy intake.

As predicted by the protein leverage hypothesis, reducing the protein content of the diet from 15% to 10% resulted in subjects increasing total energy intake. The extent of the increase was 12% over the four-day trial (Figure 10B); which if continued, would be expected to promote an increase in body fat of one kilogram per month. The increased energy intake was already evident within the first day and was mainly due to eating more of foods available between meals (Figure 10 C, D), with a predilection for savoury over sweet-tasting foods (although remember that all foods were actually the same in their macronutrient composition within the four-day trial). This preference for savoury-flavoured foods is strongly suggestive of protein-seeking behaviour.

In contrast to previous studies using undisguised foods (Figure 8), increasing the percent protein from 15% to 25% did not result in a lowering of energy intake (Figure 10B). This

result suggested that continual access to a variety of energy-dense foods may counteract the inhibition of energy intake due to elevated dietary protein [37]. We return to this important point below.

What are the implications of protein leverage?

The implications of such a rule of compromise are considerable when considering the modern nutritional dilemma. To illustrate this, we will consider four scenarios for the case of a 45-year-old, moderately active adult male 1.8 ms tall and stably weighing 76 kg (BMI 23.5). His total daily energy requirements to remain in energy balance are 10 700 kJ. Achieving a diet comprising 14% protein requires him to eat 1500 kJ per day of protein and 9200 kJ of carbohydrate and fat combined. This represents a daily intake of 88 g protein and a total mass of carbohydrate and fat eaten that will depend on the relative proportions between the two in the diet, given that fat has twice the energy density of carbohydrate. As before, we will combine fat and carbohydrate into a single value for energy, since their relative contributions are not germane to the logic of our argument.

The four scenarios are:

1. There is a shift to a diet containing a higher percentage of carbohydrate and fat

This could occur where fat- and/or carbohydrate-rich foods are more accessible, more affordable, in greater variety, or more palatable than alternatives [3, 38], leading to people being effectively trapped on a suboptimal diet. Under such circumstances, maintaining the amount of protein eaten requires overconsumption of carbohydrate and fat.

Since protein is a minor component of the total diet, only a small decrease in the percentage of protein results in a substantial excess of carbohydrate and fat eaten: the protein leverage effect. Let us return to the above example of the US (Figure 6), where the FAOSTAT data suggest that, since 1961, the average diet composition has changed from 14% protein: 86% carbohydrate and fat to 12.5% protein: 87.5% carbohydrate and fat [20]. Maintaining protein intake under these circumstances required a 14% increase in the carbohydrate and fat eaten (Figure 11A). The implications for body weight regulation are clear: unless the excess carbohydrate and fat ingested to maintain protein intake is removed through increased physical or metabolic activity, body weight will rise, predisposing to obesity.

One important caveat that must be considered here is that the opportunity to overeat carbohydrate and fat to an extent sufficient to reach the protein intake target will depend on the energy density of the foods available. Where the ratio of protein to carbohydrate and fat is lower than the intake target ratio, but nutrient density is low (eg in the diets of macrobiotic vegetarians), physical bulk may inhibit reaching the protein intake target [see 39], thus leading to cessation of intake before the protein target is reached. In contrast, the fact that modern packaged and convenience foods are often energy-dense makes it easy to achieve the protein target on a diet with a lower than optimal ratio of protein to carbohydrate and fat.

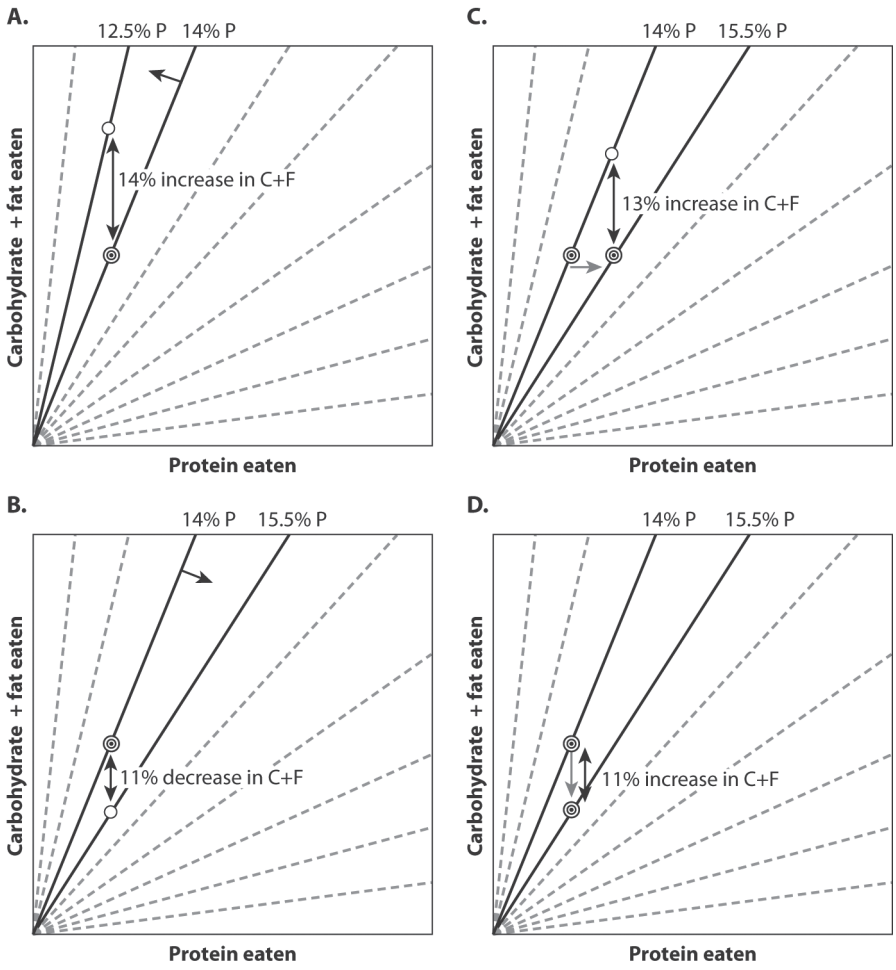

Figure 11. The consequences of four nutritional scenarios, given a rule of compromise that is to maintain protein intake. See text for details.

Additionally, having 24-hour access to food in the modern world, rather than restricting food to meal times, allows people the opportunity to 'snack' and 'graze', ie to increase the number of eating episodes in a day [40]. Hence, in the study by Alison Gosby et al. [37], subjects achieved greater consumption of the 10% protein diet not by eating more during main meals, but by increasing intake between meals (Figures 10C, D). In free-living individuals in the US the number of eating episodes per day is on the increase [41]. To make matters worse, increased food variety may also play a role in helping reach the protein target by stimulating increased intake on low-protein diets [37]. Variety can increase total energy intake independently of macronutrient composition [42], which may be an evolved response to ensure that we eat enough different foods to achieve our requirements for various micronutrients [43] and to overcome boredom effects and 'sensory specific satiety' [44–46].

2. There is a shift to a diet containing a higher percentage of protein

If humans are restricted to a diet that contains a higher percentage of protein, yet the absolute amount of protein eaten were regulated to the intake target, the result will be that carbohydrate and fat intake would fall, bringing the body into energy deficit and promoting weight loss. For example, a 1.5% increase in dietary protein from 14% to 15.5% would result in an 11% decrease in the carbohydrate and fat eaten (Figure 11B). As seen in Figure 8, available data suggest that some overconsumption of protein is tolerated, but not sufficient to maintain carbohydrate and fat intake. This explains why high-protein diet regimes promote weight loss and improve weight-loss maintenance [29, 30, 47–49]. It also explains why the most successful fad diets in terms of proponents and product sales over recent years have been those containing an elevated percentage of protein. Irrespective of the supposedly scientific claims made, and whether these diets promote omitting carbohydrates, reducing fat intake, or both, the primary reason why they encourage weight loss is simply because people eat less.

Perhaps then, augmenting the proportion of protein in the daily diet offers a means of ameliorating obesity by taking advantage of the inhibition of intake once the protein target is reached? Three things take some of the gloss from this optimistic suggestion. First, as we mentioned above, Gosby et al. [37] (Figure 10) did not find a decrease in intake when the diet contained 25% rather than 15% protein and concluded that

> it appears that the benefits of protein leverage – reduced intake on high percent protein diets – may be circumvented in [W]esternised countries in which the variety and availability of foods, especially snack foods, is greater than it has ever been in our evolutionary history [37]

Consistent with this conclusion, it is commonly reported that when subjects begin on a high-protein dietary regime they initially lose weight as a result of eating less, but over time the temptations of the modern nutritional environment lead to a gradual reduction in the percentage of protein in the diet, with associated cessation of weight loss (Figure 8B).

A second difficulty with increasing dietary protein is that, as well as the benefits in terms of weight loss, eating too much protein (even though this is resisted by protein regulatory feedbacks) may come at a cost to health (see above). A third problem is that increasing the proportion of protein in the diet has economic and potentially also environmental costs.

Brooks et al. [38] conducted an analysis of the economic costs of macronutrients in relation to the biology of protein leverage. We partitioned the energy content of supermarket foods and demonstrated that increasing overall energy content only modestly raises the cost of foods, largely because carbohydrate and fat are cheap. In fact, *lower* food prices were associated with *higher* carbohydrate content; whereas higher food prices were associated with increased protein content. It follows that the different costs of protein and carbohydrates may bias consumers – especially those on limited incomes [2, 50] – towards diets higher in carbohydrate and lower in protein energy content, which will then cause them to eat excessive energy to meet their dietary protein needs via the protein leverage effect. It also follows that there is economic pressure on processed food manufacturers to

substitute protein in their products with cheaper energy sources, thereby driving increased energy intake in consumers via protein leverage. Such an economic pressure acts not only upon the manufacturers of human foods, but also upon those producing feeds for domestic animals [4]. In the case of food animal production, the result is to further increase the lipid content of the human diet through production of fatty meat.

Brooks et al. [38] used estimates of the strength of protein leverage from a compilation of published studies (an earlier version of Figure 8, from Simpson and Raubenheimer [24] and analysed further by Cheng et al. [25]) to estimate the extent to which dietary protein would need to be augmented to achieve a reduction in levels of obesity in a population, and the cost of this to the economy. Under the assumptions used (which in light of the results of Gosby et al. [37] may have overstated the inhibitory effect of protein on long-term intake), the cost of providing the extra protein needed to reduce intake was substantially less than the health costs of obesity.

There are, of course, important environmental implications for raising protein supply, especially when that comes from animal sources. However, an increase in dietary percentage of protein may be more effectively achieved by reducing consumption, and therefore production, of non-protein energy, rather than by increasing intake and production of protein. For example, taxation of foods rich in sugar (or starch or fat) but poor in protein could simultaneously reduce the need for large increases in protein production and reduce the land used for sugar (or starch or oil) crops, therefore helping to offset the environmental costs of increasing protein supply [38].

3. There is an increase in the requirement for protein

If diet composition remains unchanged, yet protein requirements increase, then overconsumption of carbohydrate and fat will result (Fig 11C). For example, shifting the intake target ratio from 14% to 15.5% protein in the diet leads to a 13% increase in the carbohydrate and fat eaten – with attendant risks of weight gain. But under what circumstances might this occur?

One source of protein loss is hepatic gluconeogenesis, whereby amino acids are used in the liver to produce glucose. This is inhibited by insulin, as is the breakdown of muscle proteins to release amino acids, and therefore usually occurs mainly during periods of fasting. However, inhibition of gluconeogenesis and protein catabolism is impaired when insulin release is abnormal, insulin resistance occurs, or free fatty acids circulate in the blood at high levels. These are interdependent conditions that are associated with overweight and obesity and are especially pronounced in type 2 diabetes [51, 52]. The result is an increased requirement for ingested protein. Unless either more high-protein, low-carbohydrate and fat items are included in the diet (ie scenario 2 above) or rates of removing excess co-ingested carbohydrate and fat are increased, weight gain will occur. And the system becomes unstable – the increased fat deposits (especially abdominal fat [51]) will further increase protein needs, which will in turn drive even greater weight gain [24, 27] (Figure 12). Data from rodents also support such a scenario – a vicious cycle to morbid obesity

[53, 54]. Further evidence in support of our 'vicious cycle' come from Newgard et al. [55], who discovered that obese humans are distinguished from lean subjects by a metabolic signature indicating elevated protein catabolism.

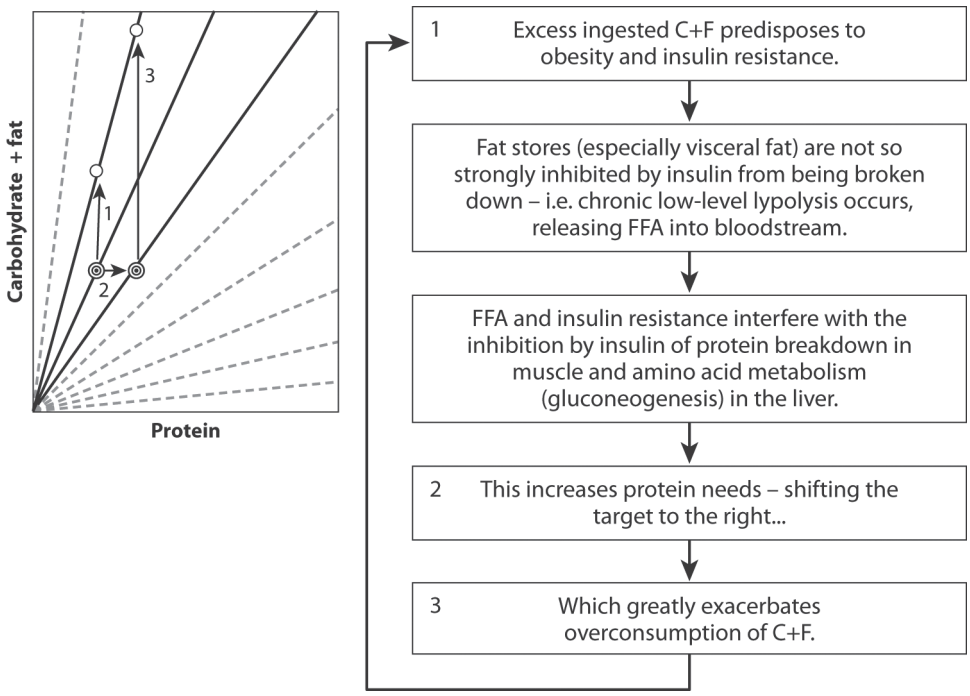

Figure 12. The vicious cycle by which protein appetite may drive obesity.

Another reason why protein needs may increase is during periods of lean muscle growth, for example during adolescence, accompanying weight training, or after a period of starvation. The effect of an increased protein requirement will depend on the extent to which requirements for non-protein energy change as well, but if the net movement of the target is to the right on a carbohydrate + fat vs protein intake plot (as in Figure 11 C), placing such a person onto a low-protein diet would predispose to excessive energy consumption and weight gain. This might help explain the 'yo-yo' diet effect, whereby subjects regain weight rapidly following a period on a crash diet [56]; and perhaps also why some athletes are prone to weight gain once they cease training.

A corollary is that we might predict that individuals and populations with an elevated intake target for protein should be more prone to developing obesity on a low-protein diet than those with a lower protein target [24]. Organisms evolve such that their intake target reflects the composition of their natural diet [4]. Humans too adapt to their current diet, genetically, developmentally and culturally [7, 57–59]. Perhaps populations that have traditionally eaten a high-protein diet have an elevated protein target, and therefore suffer increased susceptibility to obesity and metabolic disease when making the transition to a modern Western diet in which carbohydrate-rich foods are cheap and abundant [24]? The

prevalence of obesity and type 2 diabetes among Oceanic populations is particularly telling, since such populations have until recently remained on a protein-rich marine-based diet, rather than having shifted like many others to terrestrial agriculture in the Neolithic with a consequent increase in dietary carbohydrate [60–62].

A particularly striking example is the Kosrae district of Micronesia, where nearly 90% of adults are overweight and 53% are obese. Here, the recent development of a wage-based economy has led to altered eating habits from a traditional diet high in fish, fruit and vegetables to a diet based on imported packaged food [39, 62].

4. Diet remains unchanged but energy expenditure declines

We must take account of changes to the demand side of the energy budget when considering the implication of protein leverage. Because much of our metabolic fuel comes from carbohydrate and fat, the result of lowered levels of exercise and other forms of energy expenditure is, in effect, to lower the position of the intake target on the carbohydrate and fat axis (Figure 11D). Unless the diet changes towards a higher percentage of protein, the result will be weight gain.

As we discussed above, unlike the US where intake has risen (Figure 6), in the UK macronutrient and energy intake appear to have remained relatively stable over the period from 1960 to 2000 (Figure 5); yet obesity rose rapidly, in direct correlation with causes of declining activity levels, such as the use of cars and television viewing [50]). As well as spending more time inactive, many of us now live (and drive around) within temperature controlled environments – cooled during summer and warmed during winter – with consequent metabolic savings for thermoregulation, especially in higher latitudes [8].

To make matters worse, as well as lowering the demand for fuel, decreasing the level of exercise has a direct influence on metabolic physiology, associated with increased resistance to insulin and thus enhanced gluconeogenesis [63]. As we saw above (scenario 3), insulin resistance and its consequences will cause an increased need for protein, shifting the intake target towards an even higher percentage of protein that results from the lowered need for carbohydrate and fat to fuel metabolism under a low-exercise regime.

And to compound matters, while humans respond by increasing intake following high levels of energetic expenditure, we tend not to compensate fully by eating less when our energy needs fall [63]. Possibly our intake target has evolved to 'assume' a certain level of energy expenditure based on our ancestral lifestyle, and we may therefore be 'hard wired' to eat that amount, even if we do not use it [24].

Interacting consequences

The scenarios introduced above interact with one another. Either shifting the diet composition to a lower percentage of protein (scenario one), or effectively doing the same by having low levels of energy expenditure (scenario four), will result in overconsumption of energy to maintain protein intake. This in turn will predispose towards weight gain and insulin resistance, leading to disinhibition of protein breakdown and gluconeogenesis,

which will increase protein demand (scenario three). Unless this increased demand is met by shifting to a higher percentage protein diet, protein appetite will drive increased energy intake, resulting in further weight gain, and so on in a vicious cycle leading to obesity, metabolic disease and associated pathologies (Figure 12).

One nagging question remains. If humans do regulate protein intake, why do we not simply select protein-rich foods to rebalance our diet, as a locust would? It seems that we are led astray by our sweet tooth. For most of our evolutionary history the human diet consisted of a high proportion of animal foods [64–66]. Simple sugars were rare, and wild animals typically have much lower fat content than modern commercial meat (4 g compared with 20 g fat per 100 g meat) [67, 68]. Hence, hunter-gatherer peoples around the world go to considerable risks to collect honey from tall trees and cliff faces, and fat is highly prized. A history of short supply of simple sugars and fat has been proposed as an explanation for their high palatability, which may predispose towards the overconsumption of fat and carbohydrate-rich foods even when these are not required [69]. Similar arguments have been put to explain aspects of human metabolic physiology, most notably the ease with which we store rather than eliminate excess ingested energy [70] (see below). Because it appears that we have limited evolutionary experience of excess carbohydrates (especially simple sugars) or fats, it seems reasonable to infer that natural selection against their overconsumption would not have been strong.

These evolutionary predispositions interact with the modern nutritional environment to misdirect our regulatory physiology. As we have seen, highly energy-dense, fat- and carbohydrate-rich foods are constantly available and affordable, and levels of energy expenditure are lower than it is anticipated by our ancestral physiology. It is also telling that taste stimuli naturally associated with protein-rich foods, such as sodium and umami stimulants, are extensively used in low-protein processed foods, and may as a result subvert protein regulatory systems and lead to overconsumption of fat and carbohydrates [24]. For example, Americans increased intake of salty snack foods between 1977 and 1996 [71] – perhaps as part of a subliminal effort to gain protein, but in fact exacerbating the problem.

How do humans deal with nutrient excesses?

We return finally, and briefly, to the third of our initial questions: having eaten excess energy, what happens to it? The extent to which weight gain occurs following ingestion of excess nutrients depends on what happens to such excesses once they enter the body. There is a clear relationship between the priority with which surplus nutrients are voided from the body through being metabolised and excreted, and the extent to which they are stored [10]. Excess carbohydrates are readily metabolised and excreted, and stores are minimal (in the form of glycogen in the liver and muscles). Surplus protein is also metabolised and excreted with high efficiency and little if any is stored. In marked contrast, ingested fat is the last fuel to be burned, and excesses are mostly stored in adipose tissue – a store with virtually unlimited capacity. These metabolic patterns are consistent with our having evolved in an environment where energy was limited and periods of food scarcity were not uncommon, especially since the post-agricultural era [7].

Conclusions

An analysis of the modern human nutritional dilemma using the geometric framework leads to the following conclusions.

1. The intake target

The available evidence suggests that humans can regulate macronutrient intake, but that the intake target contains a built-in component for fat storage. This has probably evolved to 'anticipate' energetic demands for activity and thermoregulation, and also periods of food shortage. Failure to use this stored fat promotes obesity.

2. Rule of compromise

When faced with imbalanced diets, protein intake is prioritised. Therefore, on low-protein/high-carbohydrate and fat diets, carbohydrate and/or fat are overeaten; and on high-protein/low-carbohydrate and fat diets, carbohydrate and/or fat are undereaten. When the ratio of protein to carbohydrate in the diet is lower than optimal, it is easier to gain the required amount of protein – and hence overconsume fat and carbohydrate – when foods are high in energy density, present in great variety, and easily available throughout the day. These are defining features of the modern Western nutritional environment. Regarding dietary causes of obesity, most emphasis in research over the past 40 years or more has been on changing patterns of fat and carbohydrate consumption. In contrast, the role of protein has largely been ignored because it typically comprises only 15% of dietary energy and protein intake has remained near constant within and across populations throughout the development of the obesity epidemic. We have shown that, paradoxically, these are precisely the two conditions that provide protein with the leverage both to drive the obesity epidemic through its effects on food intake and potentially (with caveats) to assuage it.

3. Post-ingestive regulation

Regulation of nutrient intake has evolved 'assuming' a higher level of energetic expenditure than is usual today. Energy limitation in our ancestral nutritional environment may well explain our predisposition to store fat and poor ability to void excesses. The combined consequences of the interactions between our regulatory physiology and our changing nutritional environment can be seen in Figure 1.

Whereas it is not our intention here to give detailed dietary recommendations, our hope is that we have provided an awareness of the unconscious appetites that shape our feeding behaviour. Managing diet and health, whether at the level of individuals, societies or nations, requires such an understanding if we are to work with, rather than against, biology; otherwise, biology will always win. The evidence indicates that efforts to fight our powerful protein appetite will be bound to fail. As can be seen in Figure 11, small changes in the percentage of protein in the diet can potentially yield big effects on intake, with consequences – both good and bad – for weight management. Diluting protein with fat and sugar will drive excess energy intake and promote weight gain, because more must be eaten to reach the protein target. In the extreme, sugary beverages (carbonated drinks

or fruit juice) and many high-fat and carbohydrate snack foods take the consumer up the Y-axis in Figure 11 to infinity and no closer to the protein intake target, leaving the protein appetite unsatisfied. In contrast, a modest reduction in fat, sugar and other readily digested carbohydrates in the diet will make it far easier to limit energy intake and lose weight, by effectively concentrating protein in the diet and allowing the protein target to be achieved at lower total energy intake.

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