THE GEOMETRY OF HUMAN NUTRITION

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I. The Modern Human Nutritional Dilemma

In the previous article, we outlined an approach that we have developed to study the ways that nutrients interact in their influence on the nutritional biology of animals. The illustrations were drawn from research on insects, the group of animals that has featured most extensively in our research to date. In this article, we apply the approach to an analysis of some key aspects of human nutrition.

It is conservatively estimated that more than 1 billion people worldwide are overweight or obese. Rates of incidence are increasing, notably among the young, and the associated disease burden is immense (Must, et al. 1999; Björntorp 2001; Hill, et al. 2003). Fig. 1 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 meters. The curve is U-shaped – bringing to mind the final figure for locust mortality in the previous article. To the left, the risk of dying increases at low values of BMI. Clinicians categorise adults as underweight if they have a BMI of less than 18.5. To the right, risk of death rises as BMI exceeds 25. Adults with values between 25 and 30 are classed as overweight and those over 30 as obese. The target zone for health and longevity lies in between. If we humans were locusts, we would move inexorably to this target zone given adequate nutrition. Regrettably, in this case at least, we are not locusts.

Take as an example the USA, where currently 60% of adults are overweight or obese, while 25% are clinically obese. And the USA 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.

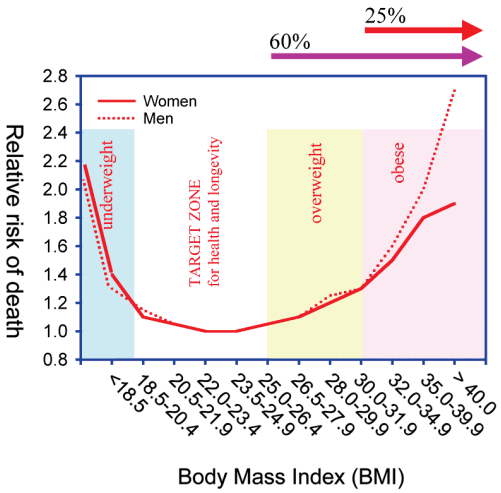


Fig. 1. The relative risk of dying prematurely as an adult against Body Mass Index (BMI) (based on Calle, et al. 1999).

As summarised in Fig. 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 (Eaton, et al. 1996). 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.

The first major transition in human nutrition occurred 10,000 years ago with the agricultural revolution, when there was a large increase in the amount of starch in the diet. This lifted the energy limitation but may have been associated with protein limitation and also micronutrient imbalances. As a result, people were, on average, small, 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 sugar. Around that time, most people were small and lean, with the wealthy few being corpulent.

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 un-

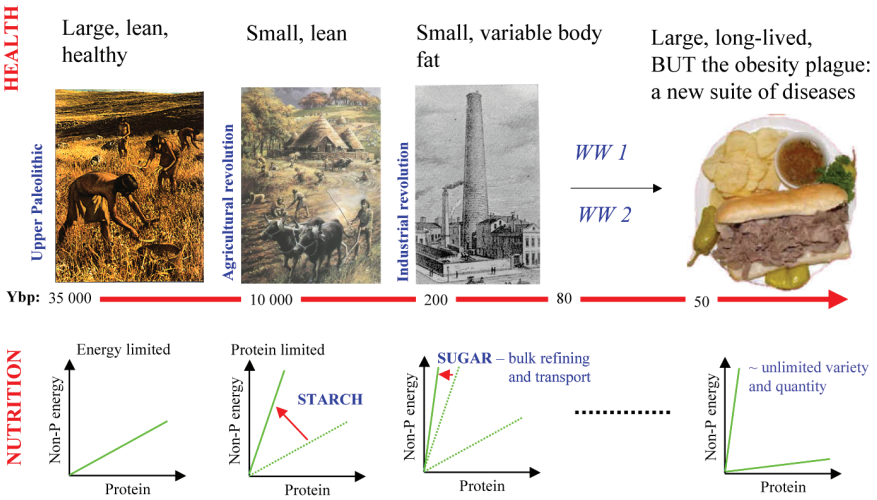


Fig. 2. A summary timeline for the changing human nutritional environment since the Palaeolithic.

precedented general access to all manner of foods and nutrients. We are large and long-lived, but are also suffering the obesity epidemic and an upsurge in a new set of non-transmissible 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 (e.g. Neel's (1962) "thrifty gene" hypothesis and the evolution of lactose tolerance among human populations with the advent of dairy herding), but the pace of evolutionary change in our metabolic physiology is considerably slower than the rate at which the human nutritional environment has altered (Diamond 2003).

If we are to understand how our "outdated" physiology interacts with our changed nutritional environment, we must answer three fundamental questions that were defined in the preceding paper:

1. Do humans regulate to an intake target?
2. What is the rule of compromise for humans?
3. How do humans deal with nutrient excesses – are we as effective as locusts at removing surplus ingested nutrients?

We will deal with these questions in turn, restricting our discussion to the three macronutrients – protein, carbohydrate and fat. We will then derive a new hypothesis to explain the obesity epidemic – the protein leverage hypothesis.

II. Do Humans Regulate to an Intake Target?

As yet, no properly controlled "defence" experiment, along the lines described in the preceding article for insects, has been done for humans. Partly for this reason, it remains contentious whether humans are able to regulate their intake of different macronutrients (Stubbs 1998; Friedman 2000; Berthoud and Seeley 2000). There are, nonetheless, three sources of information that suggest that we can regulate the intake of specific nutrients.

A. Comparative Data from the Rat

The rat is widely used as a model for human nutritional physiology. Reinterpreting published data on rats shows convincingly that these mammals have the capacity to regulate their intake of protein and carbohydrate (Simpson and Raubenheimer 1997). An example is shown in Fig. 3, in which we have replotted data collected by Theall, et al. (1984). 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.

B. Studies on Human Macronutrient Appetite

There are data that indicate that we have some capacity to regulate our intake of macronutrients, notably protein, despite the extreme complexity of our social and nutritional environments (see Simpson, et al. 2003). It appears that macronutrient-specific feedbacks operate over a period of 1–2 days, and that, at least for protein, we subliminally learn to associate foods with the nutritional consequences of eating them.

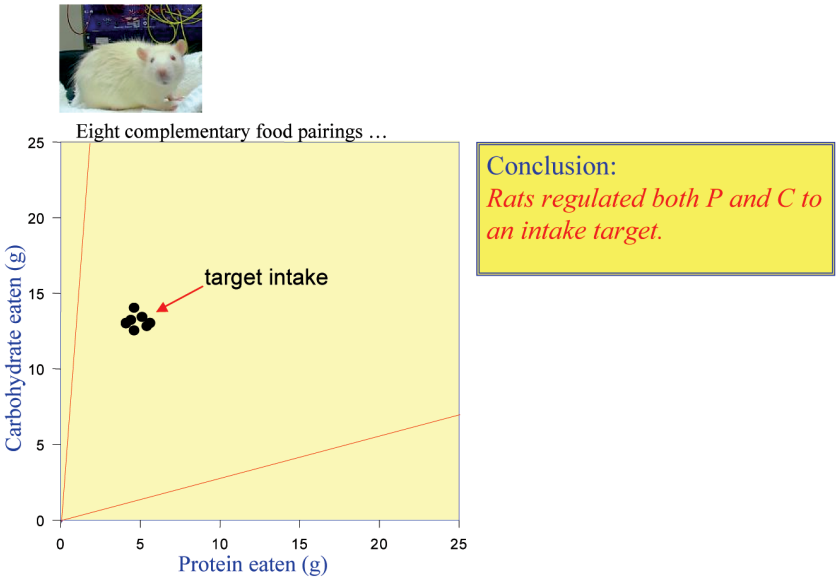


Fig. 3. Data for rats provided with one of eight different complementary food pairings (food rails not marked except for the two most extreme ratios). Rats converged on a point of protein-carbohydrate intake, indicating tight regulation of both macronutrients to an intake target (data from Theall, et al. 1984 reanalysed in Simpson and Raubenheimer 1997).

C. 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 10–15% of total energy, whereas fat and carbohydrate vary (Westerterp-Platenga 1994, Fig. 4). And not only the *proportion* of protein, but also the *amount* is consistent, at least in some populations. Fig. 5 plots estimates for per capita intake for the UK population taken from the FAOSTAT database (http://apps.fao.org/default.htm). 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

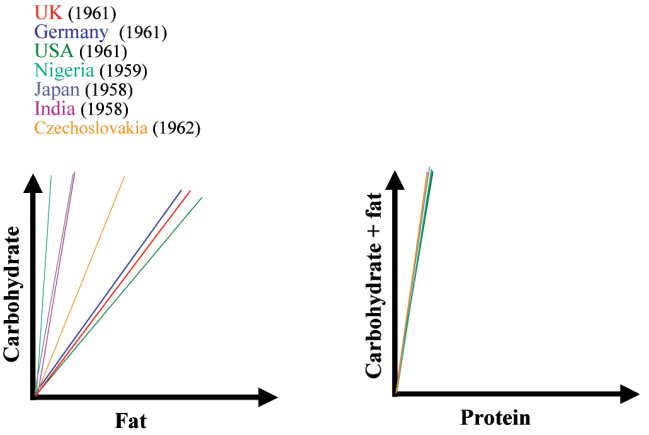


Fig. 4. Ratios of average macronutrient intake (scaled in units of energy) in various human societies during the late 1950s and early 1960s (from Westerterp-Platenga 1994 and FAOSTAT data).

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 Fig. 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.

But regulation of macronutrient intake is not always perfect, as strikingly illustrated by the USA, where carbohydrate and fat intake (as again estimated from FAOSTAT data) have risen substantially over the period 1961–2000 (Fig. 6). However, protein intake has risen to a lesser degree over the same period. As a result, in the USA 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. Understanding the effect of such a change requires knowledge of the rule of compromise.

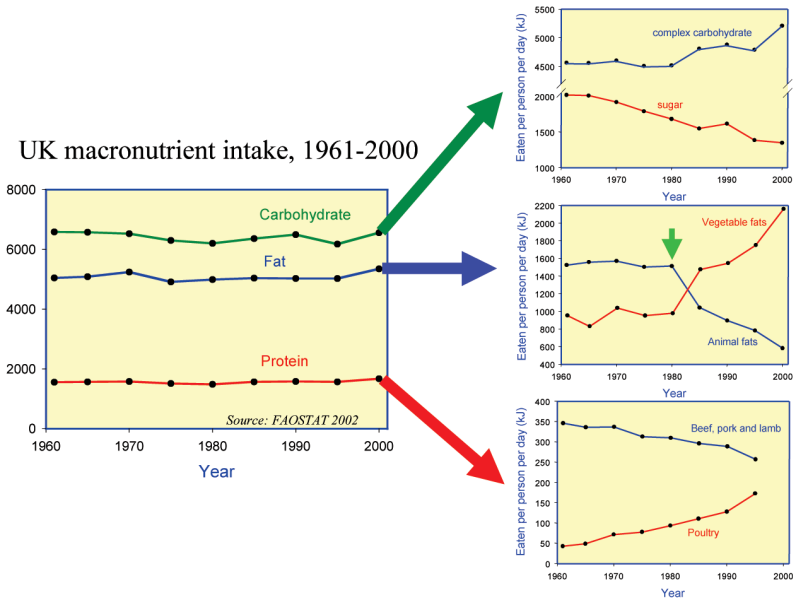


Fig. 5. Changing patterns of macronutrient supply (from which intake can be approximated) in the UK from 1961 to 2000, based on FAOSTAT data. See text for interpretation.

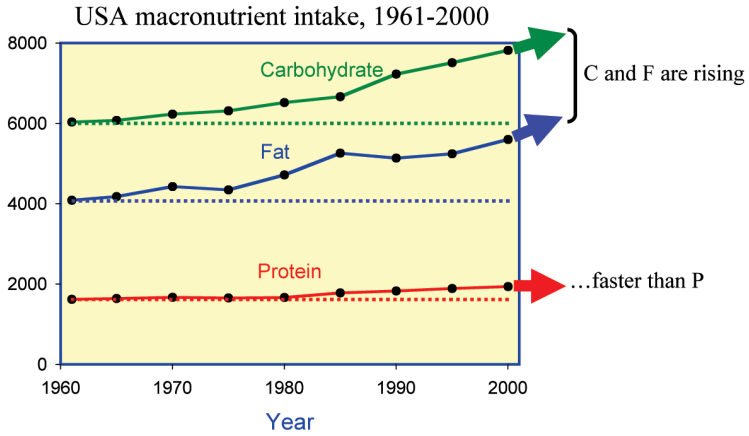
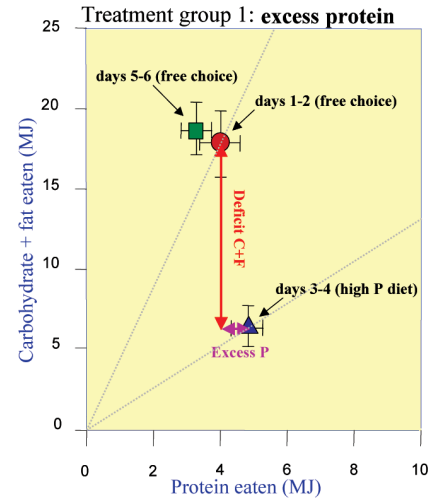


Fig. 6. Data as in Fig. 5, but for the USA.

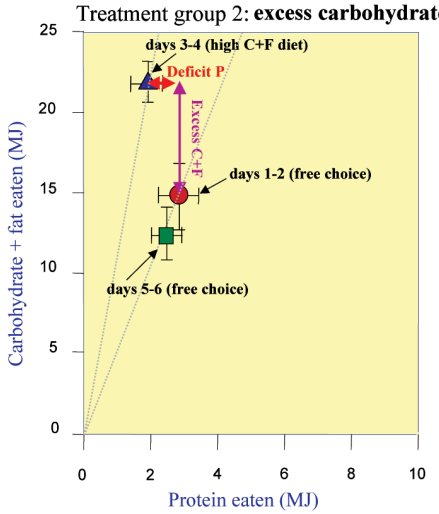
III. What is the Rule of Compromise for Humans?

Recently, with our colleague Rachel Batley, we used our geometric framework to explore the human rule of compromise (Simpson, et al. 2003). It was a short-term experiment involving 10 subjects and focusing on intake of protein vs. carbohydrate and fat, the latter two being combined into a single nutrient dimension scaled in energy units (carbohydrate + fat). We decided to treat fat and carbohydrate as a single dimension since the existing evidence from humans and rats suggested to us that the key interaction was between protein and non-protein energy in the diet. Our subjects were domiciled together for 6 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 + fat, while the remaining subjects in treatment group 2 were provided with only low-protein, high-fat + high-carbohydrate items. For the final two days of the experiment (days 5 and 6), all subjects were given the same free choice of foods as on days 1 and 2. The results are summarised in Fig. 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 + fat than they had self-selected during days 1 and 2, they maintained their intake of protein at the expense of the regulation of carbohydrate + fat intake. Thus, treatment group 1 underingested carbohydrate + fat rather than overeat protein, while treatment group 2 overate carbohydrate + fat to gain limiting protein.

From these data, we can derive an hypothesis for the form of the human rule of compromise for protein vs. carbohydrate + fat, which is that when forced to trade off intake of protein vs. carbohydrate + fat, humans prioritise protein intake (a rule of compromise similar to that shown in the previous article for salt regulation in the locust). Are there other data that support this hypothesis? In Fig. 8, we have plotted the results from our experiment along with data recast from several earlier publications. As we predict, in all these cases where subjects were restricted to a diet consisting of a fixed ratio of protein to carbohydrate + 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. Also consistent with the hypothesis are comparative data from the rat (Fig. 9). Rats forced to eat a diet containing a lower protein-to-carbohydrate ratio than at the intake target maintained protein intake



Conclusion:
•People under-ate C + F when the diet had too much protein: P intake maintained near constant



Conclusion:
•People over-ate C + F to maintain protein intake on high C+F diets

Fig. 7. Results from our Swiss study (Simpson, et al. 2003). See text for details.

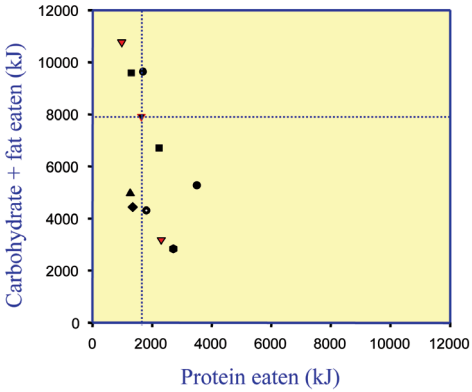


Fig. 8. Evidence of the rule of compromise in humans. ▼ Data from Simpson, et al. (2003) in which subjects were given a free choice of foods for 2 days before being restricted to either a low-P, high-C+F, or a high-P, low-C+F diet (see Fig. 7). The dotted lines intersect at the free-choice treatment. ■ Data from Skov, et al. (1999) in which subjects were restricted to a high-P or a low-P diet for 6 months; ● Data from Komoronski, et al. (2002), in which subjects were confined to a high-P diet for 14 days. Remaining points come from long-term studies [▲ Evans, et al. (1974) for a 20% P diet; ◆ Yudkin and Carey (1960), 23% P; ⬢ Rickman, et al. (1974), 48% P; ❍ Larosa, et al. (1980), 29% P] from Freedman, et al. (2001), Table 4. Taken together, the data strongly suggest that protein intake is prioritised when humans are restricted to nutritionally imbalanced diets.

constant, and in so doing overate carbohydrate. In contrast, rats provided with a high-protein diet did not substantially overeat protein to gain their intake target level of carbohydrate.

IV. What are the Implications of Having Protein Intake Prioritised Over Fat and Carbohydrate?

The implications of such a rule of compromise are enormous 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 m tall and stably weighing 76 kg (BMI 23.5). His total daily energy requirements to remain in energy balance are ca. 10,700 kJ. Achieving a diet comprising 14% protein requires him to eat 1,500 kJ per day of protein and 9,200 kJ of carbohydrate and fat combined (Fig. 10). This represents a daily intake of 88 g protein and a total mass of carbohydrate and fat eaten that will depend on the relative

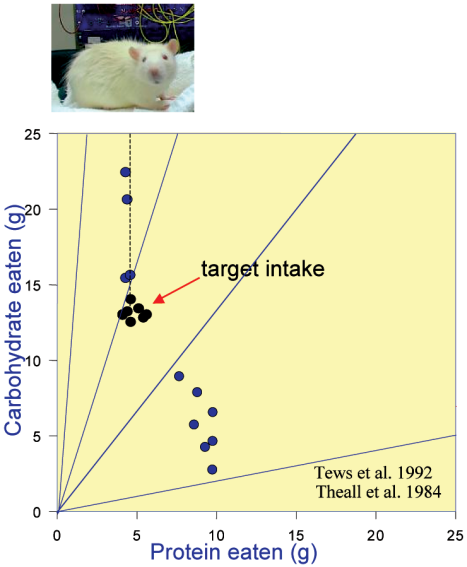


Fig. 9. The rule of compromise in rats: they prioritise protein intake (Theall, et al. 1984; Tews, et al. 1992).

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:

A. There is a Shift to the Diet Containing a Higher % Carbohydrate + Fat

This could occur where fat- and/or carbohydrate-rich foods are more accessible, more affordable, in greater variety, or more palatable than alternatives (Hill, et al. 2003), leading to people being effectively trapped on a sub-optimal diet. Under such circumstances, maintaining the amount of protein eaten requires over-consumption of carbohydrate + fat.

Since protein is a minor component of the total diet, only a small decrease in % protein results in a substantial excess of carbohydrate + fat eaten – what we could call the protein

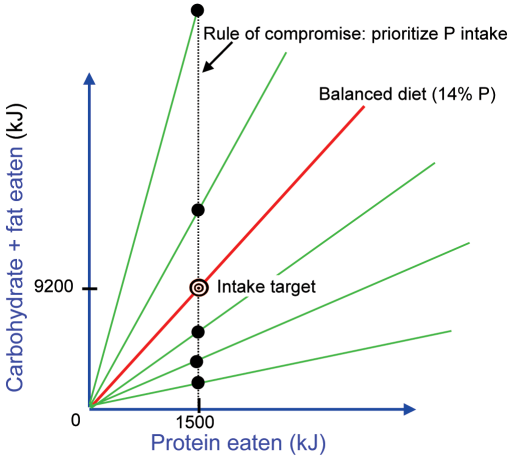


Fig. 10. A hypothetical case of the intake target for a 45-year-old man whose daily intake target is 1,500 kJ of protein (14% of total energy intake) and 9,200 kJ of carbohydrate and fat combined and whose rule of compromise is to prioritise protein intake.

leverage effect. Let us return to the above example of the USA, where the FAOSTAT data suggest that, since 1961, the average diet composition has changed from 14% protein:86% carbohydrate + fat to 12.5% protein:87.5% carbohydrate + fat. Maintaining protein intake under these circumstances requires a 14% increase in carbohydrate + fat eaten (Fig. 11 A). A further reduction to 11% protein in the diet would lead to a 32% increase in intake of carbohydrate + fat (Fig. 12).

The implications for body weight regulation are clear: unless the excess carbohydrate + fat ingested to maintain protein intake is removed, i.e. 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 + 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 + fat is lower than the intake target ratio, but nutrient density is low (e.g. in the diets of macrobiotic vegetarians), physical bulk may inhibit reaching the protein intake target (see Rolls, 2000), thus leading to cessation of intake before the protein target is reached. In contrast, the fact that modern processed 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 + fat.

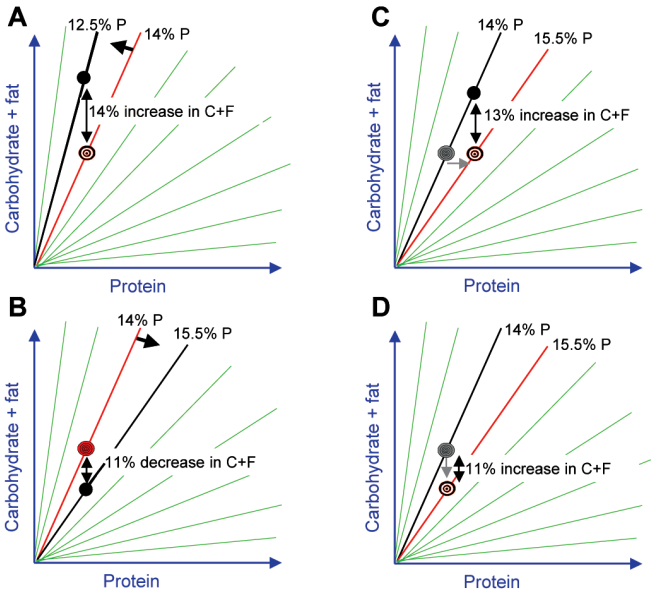


Fig. 11. The consequences of four nutritional scenarios, given a rule of compromise that is to maintain protein intake. See text for details.

B. There Is a Shift to a Diet Containing a Higher % Protein

If humans are restricted to a diet that contains a higher % protein, yet the absolute amount of protein eaten is regulated to the intake target, the result will be that carbohydrate + fat intake will fall, bringing the body into energy deficit and promoting weight loss. A 1.5% increase in dietary protein from 14% to 15.5% results in an 11% decrease in C+F eaten (Fig. 11 B). As seen in Fig. 8, available data suggest that some overconsumption of protein is tolerated, but not sufficient to maintain carbohydrate + fat intake. This explains why high-protein diet regimes promote weight loss (Freedman, et al. 2001; Elsenstein, et al. 2002).

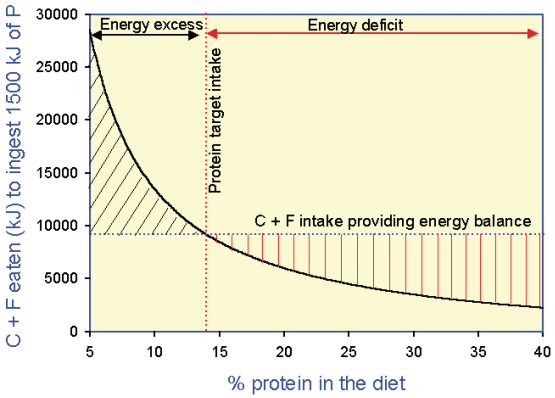


Fig. 12. The protein leverage effect. Minor changes in the % protein in the diet will translate into large perturbations in carbohydrate + fat intake if the human rule of compromise is to maintain protein intake.

C. There Is an Increase in the Requirement for Protein

If diet composition remains unchanged, yet protein requirements increase, then overconsumption of carbohydrate + fat will result (Fig. 11 C). Shifting the intake target ratio from 14% to 15.5% P in the diet leads to a 13% increase in carbohydrate + 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 (Saltiel and Kahn 2001; Boden 2002). The result is an increased requirement for protein. Unless either more high-protein, low-carbohydrate + fat items are included in the diet (i.e., scenario IV B) or rates of removing excess co-ingested carbohydrate + fat are increased, weight gain will occur. And the system becomes unstable – the increased fat deposits [especially abdominal fat (Saltiel and

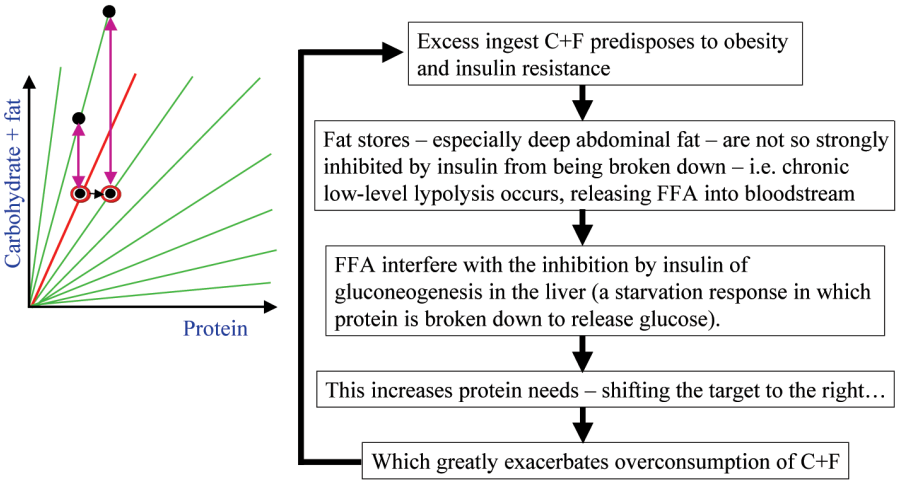


Fig. 13. The vicious cycle in which protein appetite may drive obesity.

Kahn 2001)] will further increase protein needs, which will in turn drive even greater weight gain (Fig. 13).

D. Diet Remains Unchanged But Exercise Levels Decline

The intake target level of non-protein energy is that required to maintain energy stasis. As such, it includes a component for energy expenditure through exercise and thermogenesis – both of which can change with lifestyle and temperature. It seems that while humans respond by increasing intake following very high levels of high energetic expenditure, we are less responsive to lowered needs (IARC 2002). But why should the mechanisms controlling our feeding behaviour be "hard wired" to "assume" that a certain level of energy intake will be required to fuel metabolism? Studies of modern day hunter-gatherers, such as the Aché of Paraguay and the Kung of southern Africa, suggest that our ancestors expended 1.8 times their resting metabolic energy expenditure, whereas a modern couch potato is considerably less active (Fig. 14). It seems that our intake target has evolved to "assume" a certain level of energy expenditure, and we may therefore be "hard wired" to eat that amount, even if we do not use it.

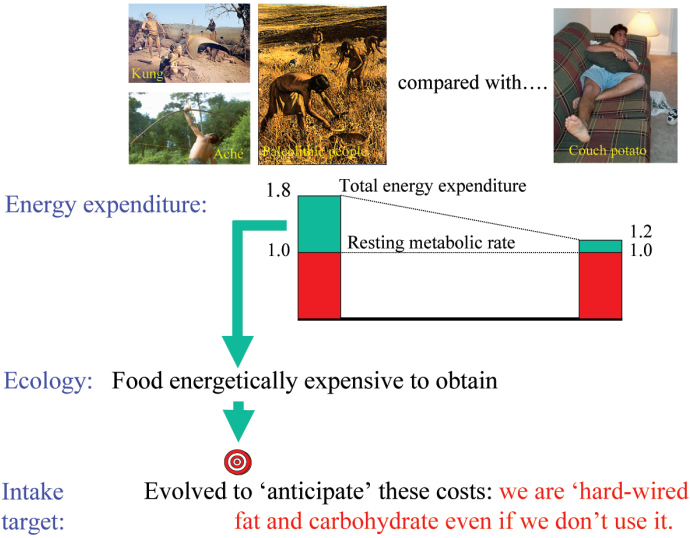


Fig. 14. The modern lifestyle involves less energy expenditure, but we are programmed to assume a higher energy expenditure.

For example, as we discussed above, in the UK macronutrient and energy intake has remained relatively stable over the past 40 years, yet obesity has risen rapidly, in direct correlation with causes of declining activity levels, such as the use of cars and television viewing (Prentice and Jebb 1995) (Fig. 15). As well as lowering the demand for fuel, decreasing levels of exercise has a direct influence on metabolic physiology, being associated with increased resistance to insulin and thus enhanced gluconeogenesis (IARC 2002).

Therefore, the result of lowered levels of exercise is, in effect, to lower the position of the intake target on the carbohydrate + fat axis (Fig. 11 D), while causing protein requirements to increase (scenario IV C). Unless the diet changes towards a higher % protein, the result will be weight gain.

E. Interacting Consequences

The scenarios introduced above are not independent. Either shifting the diet composition to a lower % protein (scenario IV A), or effectively doing the same by having low levels of

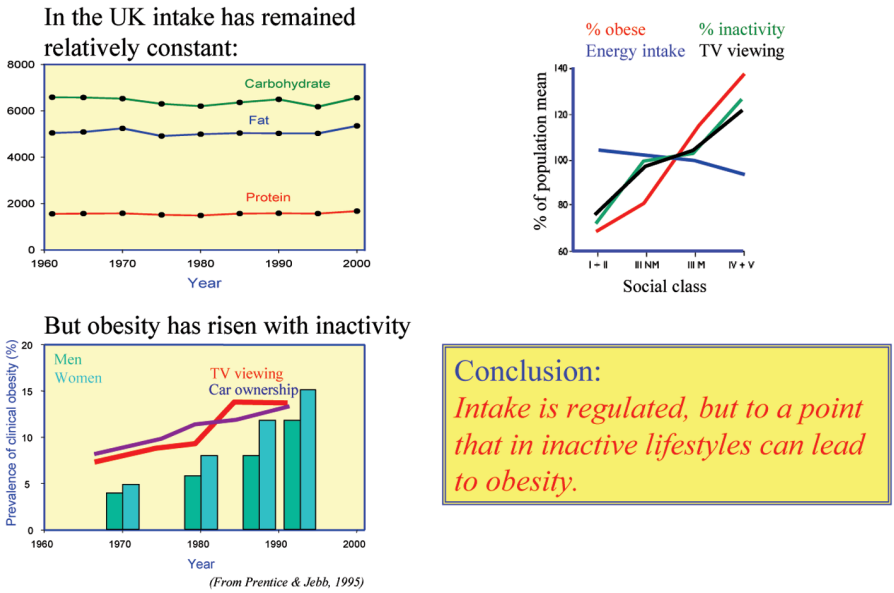


Fig. 15. The relationship between lowered exercise levels and obesity.

energy expenditure (scenario IV D), will result in overconsumption of carbohydrate and/or fat to maintain protein intake. This in turn will predispose towards weight gain and lead to disinhibition of gluconeogenesis, which will increase protein demand (scenario IV C). Unless this increased demand is met by selecting high-protein foods, protein appetite will drive increased intake of carbohydrate + fat, resulting in further weight gain, and so on in a vicious cycle leading to obesity and its associated diseases.

This cycle is broken when protein intake is increased independently of carbohydrate + fat (scenario IV B), which requires access to high-quality protein-rich foods that are low in carbohydrate + fat. Very high protein diets (> 35% of energy from protein) are currently promulgated in the popular diet literature, but are associated with potential health risks such as bone decalcification and kidney stones (Freedman, et al. 2001; Elsenstein, et al. 2002). However, it can be seen from Fig. 11 B that only relatively small increases in dietary % protein are predicted to lower intake of carbohydrate + fat. The result would be to pro-

mote weight loss and the likely rectification of associated metabolic disturbances (Parker, et al. 2002).

There are obvious socio-economic implications of the protein leverage effect. Obesity is most prevalent among the less affluent sectors within societies with established market economies (Prentice and Jebb 1995; Björntorp 2001) (Fig. 15). Levels of exercise are lower, intake of inexpensive, processed foods – which tend to be high in % carbohydrate + fat – is greater, and high-protein foods such as lean fish and meat are relatively more expensive to those on lower incomes than to the more affluent.

The key assumption upon which our hypothesis resides is that when humans are forced to trade off protein intake against that of carbohydrate and fat on nutritionally imbalanced diets, they prioritise protein. If this is true, then all else that we say must follow – it is a mathematical inevitability. We have provided evidence which suggests that this is the case. Given the implications that follow from our hypothesis, we would suggest that quantifying what we term the "rule of compromise" for protein versus fat and carbohydrate is a vital subject for future research in human nutrition.

V. How Do Humans Deal with Nutrient Excesses?

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 (Stubbs 1998) (Fig. 16). 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.

VI. Conclusions and Perspectives

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

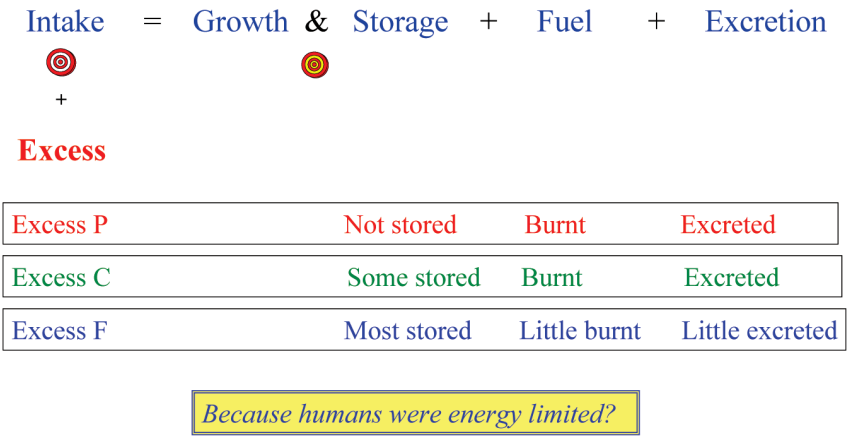


Fig. 16. The metabolic hierarchy in humans. We store excess ingested fat and retain it until other fuels are depleted.

A. 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, i.e. for activity and thermoregulation, and also periods of food shortage. Failure to use this stored fat, e.g. through insufficient exercise, promotes obesity.

B. Rule of Compromise

When faced with imbalanced diets, protein intake is prioritised. Therefore, on low-protein/high-carbohydrate + fat diets, carbohydrate and/or fat are overeaten; and on high-protein/low-carbohydrate + 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 to overeat carbohydrate + fat – the higher the energy density of foods. High energy density is a key feature of the modern western diet. 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 a) it typically comprises only 10–15% of dietary energy and b) 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 to assuage it.

C. 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 Fig. 1.

VII. References

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