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REVIEW ARTICLE

Hunger Disease*

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Abstract—This paper examines three aspects of hunger disease: the effect of initial fat stores on macronutrient fuel selection during total starvation (no energy) and how it influences survival; the effects of different rates of weight loss on tissue and body function; and the importance of appetite sensations, including hunger, during malnutrition and during enteral and parenteral nutritional support. Long-term starvation studies in humans reveal major differences in fat carbohydrate and protein metabolism between lean and obese subjects, including a 2–4-fold lower contribution of protein oxidation to energy expenditure in obese subjects, which ensures that more of the excess body fat is oxidized. The rate of weight loss, determined by recent dietary intake, can have major effects on tissue and body function, including wound healing, the acute phase protein response, muscle fatigue and psychological/behavioural function in both clinical and non-clinical settings. In depleted states uncomplicated by disease, changes in appetite sensations can result in energy intakes as high as 6000 to 10 000 kcal/day (25 – 42 MJ/day). Long-term enteral tube feeding and parenteral nutrition are associated with frequent disturbances in appetite sensations, and in those able to eat normally they tend to add rather than replace oral intake to an extent that appears to depend on the regimen. It is concluded that 1) differences between lean and obese subjects in macronutrient fuel selection during starvation are adaptive because they optimize survival in both groups of subjects; 2) the rate of weight loss in health and disease has a major effect on certain tissue and body functions, independently of the magnitude of weight loss; and 3) clinically relevant disturbances in appetite sensations are common subjects receiving long-term enteral and parenteral nutrition. The clinical modulation of all these variables would be aided by greater knowledge of the mechanisms involved. © 2000 Harcourt Publishers Ltd.

Key words: hunger; starvation; enteral; parenteral; appetite; fuel

Introduction: historical aspects

Hunger, pestilence and disease have plagued mankind throughout history. The presence of Harrison's lines in bones and Wilson's bands in teeth suggest the existence of these conditions in pre-historic man (1). The first record of famine, more than 5000 years ago, was the Stele famine in upper Egypt (First Cataract of the Nile) (2). The disaster was so great that the writer Ipuwer described it in the following way: 'Towns are destroyed and Upper Egypt has become an empty waste... He that layeth his brother to the ground is everywhere to be seen.' The inscription on the tomb of the Egyptian Ankhtifi, about 4000 years ago, makes an even greater impression because it describes the dramatic effect of hunger disease on the total disintegration of social and family bonds (2): 'All of upper Egypt was dying of hunger to such a degree that everyone had come to eating his children'. The pyramid of Unas at Sakkara (5^{th} Dynasty) has on the Causeway, drawings of famine victims with wasted bodies, protrudent ribs and narrow waists. Another inscription on a tomb on the island of Sihel (3^{rd} dynasty) provides a vivid description of the effects of famine (3, 4).

'Each man has become a thief to his neighbour. They desire to hasten but cannot walk. The child cries, the youth creeps along, and the heads of the old men are bowed down; their legs are bent together and drag along the ground, and their hands rest in their bosoms. The council of the great one in the Court is but emptiness. Torn open are the chests of provisions, but instead of contents there is air. Everything is exhausted.'

A number of famines are also described in the bible, including the seven year famine (about 1700 BC) , when Joseph averted disaster by storing grain when food was more plentiful, and distributing it when it was more plentiful.

Hunger disease has had a major influence of the history of towns, countries and empires. For example, the famines that developed with the disintegration of communication and transportation systems toward the end of the Roman empire, had an important influence on its downfall. Many disasters produced suffering, but some had dramatic and devastating effects. In 1347, it is estimated that two-thirds of the population of Italy perished, and in 1438, one-third of the population of Paris perished. China, which has been described as 'the land of famine', had 1829 famines recorded between 108 BC and 29 AD (5), and many more since then. It is estimated that there were 9 million

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deaths in the famine of 1874–1878, and 15–26 million deaths (1, 6) (about 30 million according to better demographic reconstructions (7)) in the famine of 1959–1962, which occurred when the country was thrown into disarray as result of new social reforms that were ironically called 'The Great Leap Forward'.

Hunger disease continues to plague us today. For example, the WHO global database on child growth (8) suggests that 28% of children less than 5 years of age are underweight, 35% are stunted and 8% are wasted. The prevalence is highest in South-East Asia. There may be as many malnourished individuals in the world today as at any time in history. The problem is not restricted to developing countries. In the developed countries it is common in elderly patients and those with a variety of chronic diseases. It is particularly common in institutionalized patients, such as those in nursing homes and hospitals. A survey of adult patients admitted to Irish and British hospitals suggest that 10–40% have a body mass index of $< 20\,kg/m^2$ (9), compared to 4–5% in the population. Furthermore, undernutrition is often unrecognized and untreated in hospital in-patients and outpatients, nursing homes and in the community (10). This has adverse effects on physical and psychological function, and on the clinical course of many diseases. The consequences of weight loss are not only important to those that lose weight unintentionally, but also those that lose it intentionally because of obesity, or for political reasons (hunger strikes).

Despite the world-wide presence of all these problems, it is surprising that there is still a poor understanding about the fundamental processes that control the components of weight loss, such as fat, fat free mass, and organ size. There is also a poor understanding about how different rates of weight loss affect physical and psychological function, and how these are modified by gender, age and adiposity. This brief article will discuss three aspects related to hunger disease: the effects of adiposity on fuel selection, and how it influences survival; the effects of different rates of weight loss on body function; and the importance of hunger sensations (and ad lib food intake) during malnutrition and during artificial nutritional support, when part or all of the gut is deprived of oral nutrients.

Metabolic regulation during starvation and the limits of human survival

Although some invertebrates may lose as much as 95% of body weight before they die from starvation (11), mammals generally lose much less (often less than 50%). Various workers in the 19th and early 20th centuries believed that there was a critical level of weight loss beyond which death was inevitable. This concept of lethal weight loss may have originated from Chossat (1843) (12) who noted that a variety of mammals and birds died of starvation when they lost 40–50% of body of their initial body weight. Krieger (1921) (13) suggested that the lethal level of weight loss in humans was about 40% during acute starvation and 50% during semi-starvation. However, Krieger's data showed substantial variability in the lethal limit of weight loss, in keeping with the modern view that obese individuals may lose well in excess of 50% of their body weight during therapeutic fasting. In some cases of gross weight reduction over a period of 7–24 months has successfully resulted in the loss of as much as 65–80% of body weight (14).

In order to obtain insights into the regulation of metabolic regulatory processes that optimize survival, it is first necessary to briefly consider some autopsy findings of humans and animals dying of starvation. A variety of studies in humans have reported that there is loss of 25–50% of lean tissues and organs (14). The brain and skeleton are preferentially preserved. Storage fat may be almost completely lost both subcutaneously and internally. It is sometimes replaced by translucent gelatinous material. Myers, who reported the autopsy findings of a man who died of voluntary starvation, noted that in the few areas where fat persisted (e.g. pericardial fat), the cells had become small and often filled with granular protoplasm rather than fat (15). Animals dying of starvation also have virtually no storage fat. However, some fat may persist in genetically obese Zucker rats undergoing starvation, but they survive after losing more than 82% of their fat (16). From these general observations it is reasonable to suggest that the initial amount of fat predicts survival time during starvation. A key issue is how the oxidation of macronutrients (essentially fat and protein) is regulated, so that they are lost in the most appropriate proportions to ensure prolonged survival. To consider this issue further, different models of weight loss in lean and obese individuals undergoing starvation have been established (17). A 70 kg man with 9 kg of fat and 12.2 kg protein (13% fat, 87% fat free mass) loses most of his fat (8 kg) and less than half of his protein (4.6 kg). Protein oxidation accounts for 21% of total energy expenditure. This model describes adequately the situation of the American tailor (15) (initial weight 61.4 kg and body mass index, $20.75\,kg/m^2$) who died after 63 days of starvation having lost 25 kg body weight (estimated 8 kg fat (75 200 kcal)) and 17 kg fat free mass ($\sim$15 000 kcal) and 90 200 kcal (1430 kcal/day), of which about 17% was derived from protein oxidation (14). In the model for an obese individual (140 kg body weight, 61.5 kg fat, 15.7 kg protein and 0.4kg protein) virtually all the fat but a little less than half of the protein (8.1 kg) are available for oxidation during starvation.

If the obese individual derived about 20% of total energy expenditure from protein oxidation, as in the lean subject, he/she would die with most of the fat stores in situ. This type of fuel partitioning is obviously not optimal for prolonged survival. Therefore, the following hypothesis can be established. Obese subjects can

survive considerably longer than lean individuals, not only because they have more energy stores, but also because the *p* ratio (the proportion of energy expenditure derived from protein oxidation) becomes lower than lean subjects undergoing prolonged starvation. Furthermore, although obese individuals have more protein (fat free mass) than lean individuals, the absolute rate of protein loss during starvation may be slower in the obese.

Evidence that obesity prolongs survival during starvation (no energy intake) is available for both animals (e.g. mice (18)) and humans (14–23). Nine out of the 10 Irish hunger strikers died between 57 and 73 days of starvation, after losing about 40% of their body weight. The other one, who had a prior gunshot wound, died after 45 day (14). The American tailor, who lost 41% of his body weight, died after 63 days of starvation. In contrast, there are several reports of successful fasts (no energy) in obese individuals who starved for more than 100 days (20–22), a few who starved for more than 200 days (20, 21, 23) and one starved for almost 400 days (19).

To test the hypothesis that obese individuals have a lower *p* ratio during starvation than lean individuals, it is necessary to examine the results of several starvation studies involving lean and obese subjects. So much emphasis has been placed on the single lean subject studied by Benedict (24) that it is important to assess whether this subject is typical of other lean subjects undergoing total starvation. This is indeed the case, both with respect to percentage loss of body weight, cumulative and daily N excretion, and *p* ratio (14, 17).

Although obese individuals have more body protein (lean body mass) than lean individuals, the cumulative N loss (14, 17), as well as the daily N excretion, tend to be lower than in lean individuals. These differences become apparent only after the first week of starvation. During the early phase of starvation, net protein oxidation and urinary N excretion are often similar or even greater in the obese than in the lean.

The cumulative N loss expressed as a ratio to weight loss (a surrogate measure of the *p* ratio) is also greater in lean individuals than obese individuals especially after the first week of starvation. Obvious differences between lean and obese subjects develop between 2 and 5 weeks of starvation (14). Figure 1, shows two major differences with respect to the proportion of resting energy expenditure derived from protein. First, the values for obese individuals are lower than those of lean subjects by as much as 3–4 times after the first 3 weeks of starvation. Second, the values in lean subjects do not appear to decline with time, but they do so in obese subjects. Therefore, differences between the two groups are not obvious during the first week of starvation, but they become progressively more obvious thereafter. Another demonstration of the effect of initial adiposity on fuel selection after two weeks of starvation is shown in Figure 2. Those with the lowest BMI ($\sim 20\,kg/m^2$) and smallest amount of initial body fat may derive five times

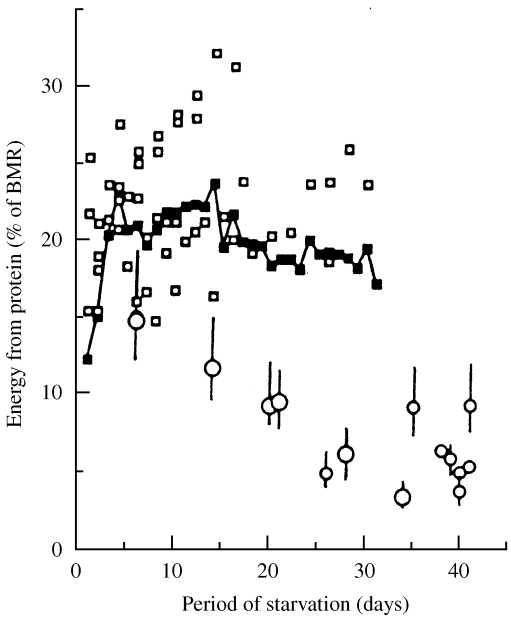

Fig. 1 The contribution of protein oxidation to basal metabolic rate (BMR) after various periods of starvation (no energy) in lean and obese subjects. Squares represent lean subjects (solid squares, from starvation study of Benedict (24); open squares, from other studies) and circles represent obese subjects (large circles from groups of subjects, and small squares from individual subjects. Based on Elia (14) and Elia et al. (17).

greater proportion of their energy expenditure from protein oxidation than obese subjects with a body mass index of 40 kg/m^2 or more. The dotted curve in the figure which represents the results of theoretical models (briefly discussed above with respect to a 70 kg and 140 kg subject), agree closely with the observed values (14, 17).

These observations suggest that during human starvation important metabolic processes operate to ensure prolonged survival. They also operate in other species and in disease as well as health. For example, obese animals such as pigs, and obese birds such as fattened geese, have low *p* ratios during starvation, whilst lean animals and lean birds have higher *p* ratios (14). Furthermore, the composition of weight loss during dietary restriction in humans (from less than 440 kcal/day to more than 1500 kcal day) varies according to initial adiposity. Gilbert Forbes has demonstrated that the ratio of lean tissue loss to total body weight loss is inversely related to the initial fat mass (25, 26). Thus, obese individuals lose a much smaller proportion of lean tissue during weight reduction than lean individuals. Mulligan et al. (27) have reported similar findings in HIV +ve men. Those who had more than 15% body fat (measured by dual energy X-ray absorptiometry) lost 16% of their body weight as lean tissue, whereas those who had less than 15% body fat lost 70% of their body weight as lean tissue. However, the total weight loss in these individuals was only a few kilograms, and therefore small errors in the assessment of body composition could affect the results substantially.

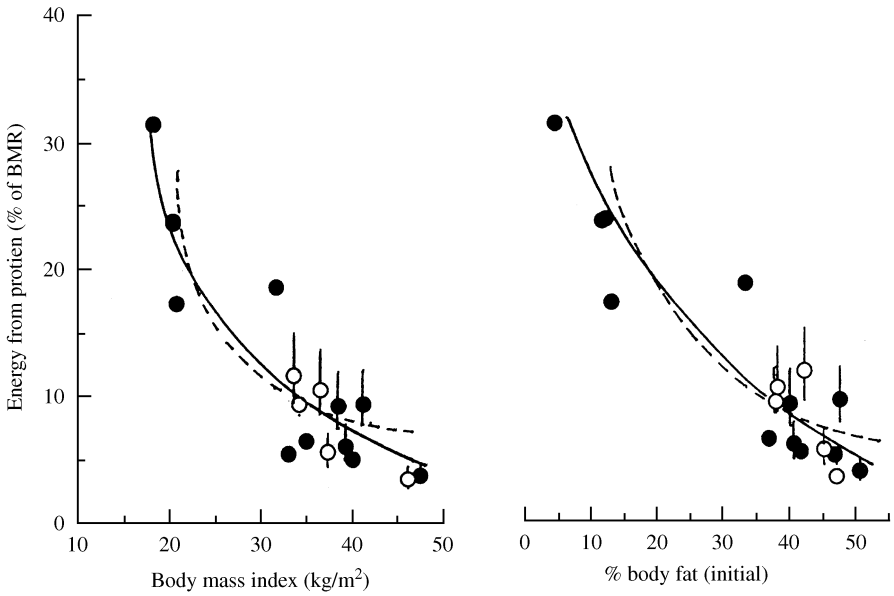

Fig. 2 The effect of initial body mass index (left) and percent body fat on the contribution of protein oxidation to basal metabolic rate (BMR). Solid circles are from individual subjects (9M 4F) and open circles from groups of subjects. The dashed curve is a theoretical curve based on similar calculations to those in text. Based on Elia (14) and Elia et al. (17).

These observations raise questions about the key biochemical processes that control fuel selection. What signals does the body respond to, to ensure that fuel selection (the *p* ratio) is optimal for survival? How do lean and fat tissues communicate, so that when there is excess fat, lean tissue is lost more slowly? These fundamental questions remain largely unanswered. However, since some of the differences between lean and obese individuals do not become apparent until at least after a few days of starvation (and in some cases more than a week; see Fig. 1), long-term regulatory processes are probably involved. Furthermore, it has also been suggested that there may be a 'memory effect' so that the composition of weight regain during refeeding follows a similar pattern as that which occurred during weight loss (28). If this is the case the processes involved have diverse implications in nutritional science and biochemistry.

Irrespective of the mechanisms involved, the differences in *p* ratio between lean and obese subjects have a variety of implications. One of these concerns the relative importance of the liver and kidney in gluconeogenesis from amino acids during prolonged starvation. This gluconeogenesis can occur in the liver, which converts amino acids to urea and glucose, and in the kidney, which converts amino acids to ammonia and glucose. The increase in urinary ammonia excretion during starvation, which occurs as a result of the mild metabolic acidosis (hyperketonaemia), is associated with utilization of 'extra' amino acids for the purpose of ammoniagenesis. The carbon skeletons of the 'extra' amino acids can also be used to form extra glucose. However, since in lean individuals there is considerably more urinary N in urea than ammonia ($\sim$71% of total urinary N is in the form of urea during prolonged starvation), the liver remains the dominant organ for gluconeogenesis from amino acids (17, 29). The much greater reduction in urine N excretion in obese than lean individuals undergoing prolonged starvation, occurs predominantly at the expense of urea (29), which account for as little as a third of total urine N excretion, compared to 85% under normal circumstances. This implies that during prolonged starvation the liver becomes much less important for gluconeogenesis from amino acids than after an overnight fast, whilst the kidney becomes more important. Indeed, arteriovenous catheterization studies in obese individuals undergoing prolonged starvation suggest that the kidney may become as important as the liver in producing glucose (29). A recent study involving obese individuals who starved for 3 weeks suggests that the kidney produces more glucose than the liver (29). There are a number of other differences between lean and obese subjects during starvation, including the following (30).

1. The circulating ketone body concentration rises more rapidly during the first 3–4 days of starvation (17, 30). The values in lean subjects are often twice as high as those as in obese subjects at the same time point.
2. The ratio of 3-hydroxybutyrate to acetoacetate, which is an index of mitochondrial redox state, increases more rapidly in lean subjects than obese subjects (up to two-fold difference) (17, 30).
3. The deterioration in glucose tolerance during starvation is greater in lean subjects than obese subjects (31).

4. After 60 h of starvation leucine oxidation (assessed by 14C-leucine) increased significantly in lean subjects (233% compared to an overnight fast) but hardly changed in obese subjects (only 17%) (32).

All these observations suggest that it is no longer acceptable to consider the metabolic response to starvation as stereotyped. Many textbook descriptions of the biochemistry of human starvation are based on observations made in obese individuals, which do not necessarily apply to lean individuals. Some of the differences between lean and obese subjects described above, particularly the *p* ratio, are not trivial. They are adaptive and of fundamental biological importance to prolonged survival.

The effect of different rates of weight loss on body function

The quality of life and the function of tissues during malnutrition, with and without associated disease, can be markedly affected by recent dietary intake. Part of our interest in this area arose from studies of the acute phase protein response in experimental models of injury. In a series of studies in rats we demonstrated that malnutrition not only delayed the healing of aseptic abscess (33), but also greatly attenuated the acute phase protein response (33–41). This observation has also been confirmed in humans (42). An attempt was then made to assess whether the acute phase protein response was altered by recent dietary intake (recent weight loss) independently of the extent of weight loss. Thus, the dietary intake of different groups of rats was restricted so that they lost weights at various rates. When they reached their target weight (20–25% lower than initial body weight), subcutaneous injections of turpentine were administered to induce formation of aseptic abscesses. After this injection, the weight of the animals was 'clamped' by administering a weight maintenance diet (40). If under these circumstances there were a difference in the acute phase protein response, they would reflect the effect of dietary intake before the formation of the abscesses, and not to dietary intake after the injection or the magnitude of weight loss, which were similar in all groups. This is exactly what was noted. There was a four-fold difference in the peak concentration and the area under the a_2 macroglobulin-time curve, which was inversely related to both the rate of prior weight loss and the dietary intake prior to the insult (turpentine injection). Animals that had lost this weight over a shorter period of time had an acute phase protein response that was four-fold lower than those that had lost just the same amount of weight over a more prolonged period of time.

A series of human studies were also initiated to examine the effects of different rates of weight loss on body structure, metabolism, and both physical and psychological function. Preliminary analysis suggest that a number of biochemical as well as a functional tests are affected by the rate of weight loss, independently of the extent of weight loss. For example, liveliness, vigour, efficiency and activity levels deteriorated considerably whilst weight was being lost (starvation period), but the scores improved almost to pre-fasting levels when the reduced weight was clamped using a weight maintenance diet. Other physical function tests, such as muscle fatigue, also followed this pattern (Gibney E, et al. unpublished). These observations are consistent with data from other studies, which suggest that functional tests, such as those involving electrical stimulation of muscle and wound healing in humans (43, 44), can be strongly affected by recent dietary intake. Therefore, both chronic nutritional state and recent nutrient intake independently affect body function. Furthermore, a number of peri-operative studies (45) suggest clinical benefits (e.g. lower rates of infection and other complications, and shorter length of hospital stay) occur as a result of short-term oral supplements containing as little as 200 kcal/day and 2 g N/day. It is difficult to explain these benefits on the basis of gross changes in body composition, which are estimated to account for only about 1–2% 'increase' in total body N compared to the control groups. However, it is possible that the function of particular tissues or cells may respond to extra dietary nutrients given at a critical time in the course of an illness. Temporary mild post-operative hypothermia may also affect the function of such cells. For example, a mean drop of about 1°C for only 4–6 h after elective colorectal surgery has been reported to produce a three-fold higher incidence of sepsis, a decrease in wound collagen deposition, and slower clinical recovery compared to the normothermic group (46).

Ad libitum food intake and hunger sensations during malnutrition and artificial nutritional support

Despite the large number of short-term starvation studies in humans, few have recorded hunger sensations during the fasts and ad lib food intake after the fasts. In a recent preliminary report of 10 lean men (47), we reported that hunger sensations assessed on visual analogue scales every hour during the day (0 = no hunger at all; 100 = as hungry as I have ever felt) rose from a mean values of about 40 in the control period to about 80 during the fast, and rapidly returned to normal values on the day after the fast, when ad lib food intake was allowed to occur. The energy intake on the day after the fast was only 13% greater than in the control period. Therefore, in this group of men an acute fast did not induce a strong and rapid compensatory elevation in energy intake on the day after the fast, although it is possible that compensatory

mechanisms persisted after this time. Another study by our group (E Gibney et al. unpublished) studied ad lib food after 5% weight loss in lean men (starvation induced weight loss, weight maintenance followed by ad lib food intake). The energy intake rose to a mean value of about 3600 kcal/day (~18% increase over the control period of ad lib food intake) and persisted at this level for at least 2 weeks. In another group of lean men who had lost 8% of their body weight through ingestion of a low calorie diet, energy intake during the first week after the fast was 4100 kcal (~25% increase over the control period). With more severe degrees of undernutrition (15–30%) energy intake increases even further. Keys et al. (3) reported an energy intake of 7000–10 000 kcals/day during the first 2 weeks of rehabilitation in 12 undernourished men who had lost 25% of their body weight during experimental semi-starvation. Murray (48) reported that the victims of the Sandbostel concentration camp (mean weight 54 kg) had an energy intake of 8 000 kcal/day, which was maintained for 3 weeks. Prisoners of war from Russia were reported to ingest 7000 kcal/day (49). A separate group of 20 men who had lost 17% of their body weight in Wuppertal, Germany (oedema noted in some subjects), ate a mean of 6000 kcal/day. One subject was eating more than 8 800 kcal/day (49). The mean intake of the group (6000 kcal/day) persisted for at least 6 weeks. These remarkably high intakes are not well tolerated by normal subjects, who may develop nausea, vomiting, and short-term aversions to such large quantities of food. The observations in malnourished subjects (Fig. 3) provide strong support for the existence of physiological feedback signals that control appetite so that ad lib food intake increases as the degree of nutritional depletion becomes more severe.

The signals responsible for this extraordinarily high food intake are probably multiple. Some of the satiety signals are considered to arise peripherally from the gastrointestinal tract. Since part or all of the gastrointestinal tract is bypassed during enteral tube feeding and parenteral nutrition, it is reasonable to expect disturbances in appetite sensations in patients receiving artificial nutritional support. In a small study undertaken by our group (50), 87% of patients on home parenteral nutrition reported a desire to eat, 67% admitted to hunger, and 33% to clinically distress from hunger. Similar results were obtained in a group of patients receiving home enteral tube feeding. In addition, the following observations were made in patients whose appetite sensations were assessed with visual analogue scales every hour during waking hours.

1. The variability in the mean daily appetite sensations were much greater in patients than in normal subjects. Some patients had no hunger and others were distressed by it.
2. The disturbances in hunger sensations occurred even in patients who did not have a low body mass index and were receiving adequate or even excess nutrient intake.

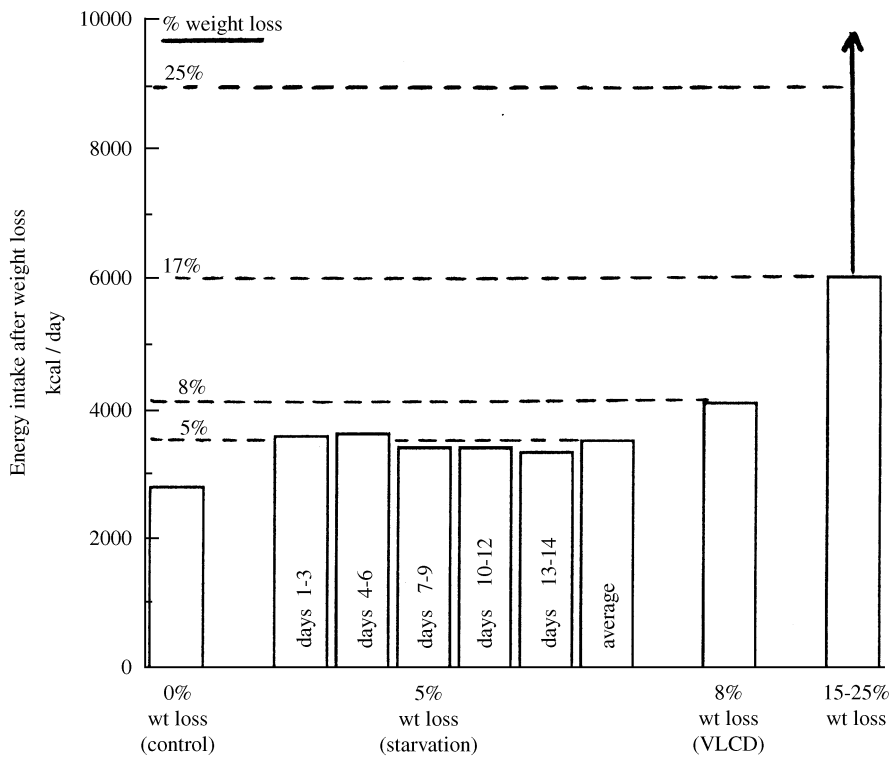

Fig. 3 Ad lib food intake during recovery from weight loss in lean individuals (uncomplicated by disease). The energy intake for 2 weeks after 5% weight loss is divided into periods. Data for energy intake after 0%, 5% (starvation) and 8% weight loss (very low calorie diet, VLDL) are from E. Gibney, M. Elia et al., unpublished). For energy intake after 15–25% weight loss, see text.

3. In some patients the distress associated with these sensations was so severe that they ingested food, which they knew was contraindicated. They were aware that they would suffer from abdominal pain or vomiting if they ate, but their appetite sensations were so strong that they were prepared to eat and suffer the consequences. Other subjects chewed and spat out food in an attempt to relieve some of the distressing appetite sensations.
4. The distressing appetite sensations may abate with time, but in some patients they persist even after years of receiving artificial nutritional support.
5. Some subjects exhibited a dissociation of appetite sensations. For example, some patients were distressed by the desire to eat even though they had no hunger.

Dissociation in appetite sensations has also been noted during recovery from malnutrition. Such subjects felt very full after eating large meals but they continued to experience hunger. Such dissociations are unusual in healthy subjects under normal circumstances.

In view of the above appetite disturbances it is important to assess the extent to which artificial nutritional support influences appetite sensation in health and disease, and the extent to which it adds or replaces oral food intake in those who are able to eat. Much of the human and animal literature in this area has been recently summarized by Stratton & Elia (51). Overall, it appears that much of the energy delivered either enterally by tube or parenterally by an intravenous catheter, is additive to oral energy intake (although temporal patterns remain poorly documented). The reasons for this remain unclear, but they may be related to the following: the absence of the full cephalic phase response; the liquid nature of the feed; the continuous infusion of nutrients; and the use of unusual feeding schedules, which sometimes operated nocturnally. The circulating concentration of a variety of metabolites (glucose, non-esterified fatty acids, triacylglycerol, 3-hydroxybutryrate, lactate) and other hormones/signals (leptin, insulin, glucagon, cholecystokinin) and the respiratory quotient, failed to predict the short-term (first hour after the measurements were made) or longer-term food intake during the day.

Recent studies in healthy lean subjects (52, 53) have confirmed that most of the energy delivered by a nasogastric tube adds to ad lib oral energy intake, and that diurnal feeding regimens tend to suppress oral intake more than nocturnal or 24 h feeding regimens (52). There is also preliminary evidence that bolus feeding reduces intake more than continuous feeding. Furthermore, daily oral intake after 6 days of nasogastric tube feeding was found to reduce voluntary oral intake more than after 3 days of tube feeding (54). Overall, these preliminary studies suggest that the longer the duration of tube feeding and the more physiological the feeding schedule (e.g. diurnal > nocturnal; bolus > continuous feeding), the more likely the suppression of voluntary food intake. These observations are of some clinical relevance since suppression of appetite is desirable when food intake is contraindicated, whereas stimulation of appetite (or attenuation of appetite suppression) is desirable in other situations, such as during weaning from artificial nutrition to oral food intake. However, it is clear that such studies need to be extended to different patient groups.

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