The Enigma of Mass Regulation

WITH SPECIAL REFERENCE TO OBESITY

F. W. FOX

SUMMARY

The factors involved in the regulation of body mass, particularly those relating to the special case of obesity, are considered in the light of recent investigations which often make use of techniques not previously available.

Attention is first drawn to certain difficulties arising in the diagnosis and in the estimates of the prevalence of obesity. After a brief consideration of the components of body mass and the metabolism of fat, whether normal or abnormal, the numerous factors influencing the intake and expenditure of energy are examined in some detail, together with the way in which the body responds when the balance of energy is deliberately altered by dietary changes. This leads to an examination of the mechanisms known to exert a regulatory effect on our mass, especially the new role assigned to adipose tissue.

A good deal of the work described is new and may need revision, but evidently some cherished ideas must be modified if not abandoned, such as the widespread assumption that mass varies more or less automatically according to the amount of food eaten or the amount of exercise taken, or both. It is suggested that whether a person tends to gain, or maintains an almost constant mass over long periods, or is intractably thin, depends on the behaviour of mass-regulating mechanisms that are more numerous, complex, interrelated and powerful than was formerly suspected. Which of these patterns develops is primarily determined by heredity, but can be modified by the environment, particularly during the early stages of development. In other words, mass pattern is an expression of the constitution.

S. Afr. Med. J., **48**, 287 (1974).

Obesity is a continuing enigma for which there is only limited understanding of the pathophysiology and even less application of physiologic principles to weight reduction.

Editorial, *Journal of the American Medical Association*, vol. 211, p. 492, 1970.

Obesity an Enigma?

Many readers may be surprised that there can be anything enigmatic about the cause of so simple a condition as obesity. For body fat can only be derived from food; hence fat people must be eating too much and thin people too little. In any case are not thousands of people losing or gaining mass every day by means of reducing or fattening diets? So where is the mystery? Unfortunately, the view that the body responds more or less passively and automatically to an increase or decrease in the amount of food eaten—the 'kitchen scales' concept—does not accord with the facts. To dispose of obesity as being due to overeating 'is about as helpful as attributing alcoholism to the consumption of too much alcohol' (Mayer). This still holds good when due allowance is made for the amount of exercise taken.

South African Institute for Medical Research, Johannesburg
F. W. FOX, D.SC.

Date received: 14 May 1973.

How Ideas about Obesity have been Gradually Changing

Hippocrates taught that 'diseases which arise from repletion are cured by depletion'; since so many fat people were notorious gluttons, and since depletion, now as then, often gives such excellent results, the cause of obesity has long been regarded as settled, and so of little interest.

Van Noorden classified obesity into exogenous, or a simple type caused by manifest over-eating, and endogenous, a type produced by, or associated with, various metabolic abnormalities.

By the early 20th century a second stage became possible when the energy content of foods and the amount expended in various kinds of activity could be calculated. This led to the concept of a balance of energy which gained support when it was found that desirable changes in mass could be obtained not only by depletion, but by increasing the energy expended. By 1931 Newburgh was rejecting Van Noorden's second category declaring 'that all obesity is "simple" obesity. The increase in weight merely represents an inflow of energy greater than the outflow'. Although now known to be an oversimplification, this authoritative pronouncement, which confirmed earlier views, was widely accepted.

We are now at a third stage when remarkable advances in biochemistry and other relevant fields, as well as many entirely new techniques for the elucidation of the problem, have become available. We now know more about the number and complexity of the factors involved in the energy equation, as well as the way they can influence each other. That mass regulation is partly dependent on heredity has been established, together with some surprising insights into its mode of operation. Although obesity remains something of an enigma we are at least able to study it on a much broader front.

SOME ASPECTS OF OBESITY

Some of the reasons for the steady increase in obesity among Western populations are not hard to understand. Food has become freely available, more varied and more attractively presented, while the 'pressure to eat', whether we are hungry or not, is characteristic of our modern way of life. Unfortunately, this is combined with a marked reduction in energy expenditure owing to the rapid increase in all manner of labour-saving devices. Thus the 'pressure to eat' increases the intake of calories, while the 'pressure to be inactive' reduces the need for them.

The insidiousness of its onset, with increasingly serious effects emphasises the need for prevention and early treatment. At present the medical profession seems little interested in the preventive aspect, while the discouraging long-term results of treatment no doubt explain why overweight tends to be overlooked unless it is gross or help is asked for by the patient.

Diagnosis

Obesity is present, whether obvious or not, when the amount of fat in the body is greater than normal; the hypertrophy and hyperplasia need not occur only in the adipose tissues, but also in many other organs of the body. Formerly, obesity and overweight were regarded as synonymous, but body build, muscular development and changes in body composition must be taken into account. Not everybody who is overweight is obese, although many muscular men have been so classified. Similarly, if the lean body tissue has been partially replaced by fat, as happens not uncommonly with men in later life, obesity can be present although the mass lies within the accepted limits.

Diagnosis by determining mass. Obesity is usually diagnosed by determining mass, which is also useful for following progress during treatment. But difficulty arises when obesity is minimal or only suspected, for then the standard to be used becomes all-important. At one time such standards were based on what was typical for a given sex, height and age and although current standards have been much improved, they are still not very satisfactory. The tables of 'desirable' mass for men and women published in 1960 by the Metropolitan Life Assurance Co., USA, make an allowance for differences in body build but provide no criteria for making distinctions. A mass allowance for age was formerly accepted, but is now regarded as undesirable, so that mass at 25 years, is now the criterion. These standards have been criticised by Seltzer and Mayer[1a].

Diagnosis by means of indices. Many attempts have been made to allow for the influence of bodily proportions, but few of the indices obtained by combining different measurements have won general acceptance.[2a]

Diagnosis by skinfold measurements. Several ways of estimating the amount of fat in the body, although accurate, are too elaborate to be of practical value. But since from half to two-thirds of this fat is in the subcutaneous tissues, skin thickness provides a fairly accurate way of judging the degree of obesity. It is less reliable in extreme obesity and in middle age or in older individuals, since they gain more fat internally than subcutaneously. According to Seltzer and Mayer,[1a] only the triceps skinfold need be measured, but its limitations have been discussed by Shephard *et al.*[3]

Need for an early diagnosis. Since obesity in children is not easy to treat and many become obese adults, the need for an early diagnosis has become even more significant since the discoveries of Hirsch and others. Widdowson[4a] has pointed out that babies are reducing their need for calories by the third month of life and are already beginning to express their 'nutritional individuality'. Eid[5] notes the future effects of an unusually rapid gain in mass during the early weeks and months. Bryans,[6] found that even by 1 year babies whose birth mass and length were normal, were as much as 468 g heavier than their controls. Measurements of children from infancy onwards have been tabulated in great detail by several workers.[7-10] Skinfold measurements for children are given by Corbin[11] and Brook.[12a] According to Grant,[13] obesity can be diagnosed if a child's mass increases by more than 10% for a gain in height of 5,1 cm.

Prevalence

Estimates based on samples from private practice, insurance companies, hospitals, or other institutions rather than on a whole community are unsatisfactory. There is difficulty in assessing mild degrees of obesity; a great many people do not see themselves as obese, and either ignore the fact, or treat themselves. There is, however, the national survey made by the USA Public Health Service, which reports that 25 - 45% of adults over 30 years are more than 20% overweight;[14] the incidence in Britain is probably similar. At least 3% of British children are said to be overweight, while in the USA Bray[15a] believes that 2 - 15% of overweight children are as much as 40% too heavy!

Effects on health. These are well known and have been classified by Mayer[16] as causing changes in normal bodily functions; increasing the risk of developing certain diseases; having a detrimental effect on established diseases; and as having adverse psychological reactions. From a careful statistical study of over 11 000 men aged 40 - 59 years living in 7 different countries, Keys *et al.*[2b] concluded that when the age, blood pressure, cholesterol level and smoking factors are comparable, obesity, even if excessive, showed no significant correlation with the future development of coronary heart disease.

THE THREE MAIN COMPONENTS OF BODY MASS

The three main components of body mass are:

Water. At least 60% of the 65 kg mass of an average healthy adult male consists of water, or 50% for a woman. A day-to-day variation of a few kg either way can occur, while a change due to a temporary alteration in diet or

exercise may take as long as a week to register. In obesity the proportion of water may be considerably less, but it is substantial. In men, a reducing diet may at first give rise to a loss of water rather than fat, but obese women often have an unfortunate tendency to retain salt and water which can be decidedly discouraging. Since 100 g of triglyceride, when metabolised, yields about 112 g of 'metabolic water', there can be a gain in mass when fat is being lost. Gordon[17] remarks that this phenomenon has caused 'uncounted thousands' of obese women to give up in despair. Why this retention of water is confined mainly to women has not yet been explained, but he suggests it may be related to an increased production of aldosterone or vasopressin.

Lean body mass. This is the mass of the body devoid of all fat, or the mass of the skeleton, cells and extracellular fluid. Markedly muscular persons may have enough 'active tissue' to lead to a false diagnosis of overweight. When the obese are treated by complete starvation an undesirable loss of lean body mass can occur.

Adipose tissue. Durnin[18] gives the estimates for the amount of fat in the bodies of men and women of normal mass in Table I.

TABLE I. ESTIMATES FOR AMOUNT OF FAT IN BODIES OF MEN AND WOMEN OF NORMAL MASS

	Men	Women
	%	%
Thin	<10	<20
Intermediate	10 - 20	20 - 30
Obese	20 - 30	30 - 40
Very obese	30+	40+

These estimates, derived from many countries, were obtained by measuring body fat by densitometry or 40 K techniques.

Cahill *et al.*[19] have published figures indicating the amount of energy available in the form of stored fuels in normal and obese people.

METABOLISM OF FAT

Normal

Since highly detailed accounts of the intricate chemistry involved in the normal metabolism of fat are available, it will be sufficient to note that glucose, derived from either the diet or the liver, if it is not required as an immediate source of energy, is converted into triglyceride which is then stored in the adipose tissues (lipogenesis). In the reverse process, lipolysis, these triglycerides are released from the adipose tissues and converted into free fatty acids and glycerol, the fatty acids are used by the muscles for the production of energy, or by the liver cells where they are either oxidised or re-esterified with glycerol to form triglycerides again. Even under normal conditions the body is largely dependent on fatty acids as a source of energy, but particularly during prolonged starvation, when the available glucose is conserved for the use of the nervous tissue and the brain. However, as Owen *et al.* showed in 1967,[19] if need be, even the brain can make use of ketones as a substitute for glucose.

The processes of lipogenesis and lipolysis take place concurrently; whether fat is being stored or removed from the adipose tissues depends on the balance between the two, and this, in turn, depends on such environmental factors as food, exercise, exposure to cold; and internally to the combined influence of various metabolic activities.

Lipogenesis. This is particularly sensitive to insulin which has been called the 'hormone of storage'; also, it is the main antagonist to the release of triglycerides from adipose tissue. Insulin stimulates the synthesis of fatty acids from blood glucose, and regulates the incorporation of fat into adipose tissue. A lack of this hormone is the signal for the mobilisation of the lipid stores into the blood stream; 'thus insulin serves as the body's "thermostat" for lipid accumulation or mobilisation'.

Lipolysis. Numerous hormones are involved in the stimulation of lipolysis, some acting rapidly, others more slowly. Variation in the sensitivity to insulin is believed to provide a 'fine control' for the release of free fatty acids under different physiological conditions.

Abnormal Fat Metabolism

That a metabolic abnormality can cause obesity in some animals is indisputable; and likewise that certain human diseases are accompanied by extreme obesity or leanness. But whether the metabolic abnormalities found in the common forms of obesity cause or are themselves caused by the obesity, is not yet clear. Bray[15a] has tabulated no less than 15 such abnormalities; well-established examples include resistance to ketosis, adrenal and cortisol over-activity, a tendency to retain salt and water, higher plasma levels of insulin and free fatty acids and lower levels of free human growth hormone. Perhaps it is significant that not all the obese exhibit the same abnormalities, and at least one is far more common in women than in men. That so many of these abnormalities vanish if the excessive mass is adequately reduced, strongly supports the view that they are adaptations to the obesity, but much depends on the distinction between normal and abnormal. Most people only gain mass slowly, so that even a slight difference in metabolism, although within the normal range, if long continued, might eventually produce obesity.

METABOLISM OF ENERGY

Factors Influencing the Intake of Energy

Subtle factors combine to decide when, what, and how much we eat; the foods available, group or family traditions, social pressures, the way the food is prepared and presented, as well as the atmosphere attending the meal, all play a part. But hunger, appetite, palatability and the sensation of satiety are basic determinants requiring some consideration.

Hunger. Yudkin[20] has defined hunger as 'the demand for calories' and appetite 'the demand for a particular food'. The sensation of hunger is so powerful that almost anything will be eaten to assuage the need for calories.

Appetite. While hunger gradually diminishes, appetite can 'grow with eating' and may be renewed if a fresh and attractive dish arrives. Unlike hunger, appetite bears little or no relation to physiological needs and can be trained in both directions. Also it is notoriously capricious, being affected by exertion, fatigue, illness, moods, while only responding erratically to the demand for energy; some eat more when worried or unhappy, others less. The modern habit is to eat at regular intervals whether we are hungry or not.

Taste sensitivity. The detection and appreciation of taste differences are far more highly developed in some than in others; this sensitivity can also be cultivated and can influence the amount consumed. A partiality for a sweet taste is common, but not invariable, and has been exploited to an incredible extent by the fairly recent development of the sugar industry.

Palatability. This exerts a powerful influence on appetite; yet habit can be so strong that those long accustomed to a monotonous diet may ignore even far more palatable foods when these become available.

Satiety. Both hunger and appetite are halted eventually by the onset of satiety which is a far more complicated sensation than used to be supposed. To some extent satiety is linked with the cessation of gastric contractions, while the right amount of distension seems the sign to stop for those on a monotonous diet. Numerous studies have shown that adolescents and adults, men and women, and especially the obese, differ in regard to satiety. Monello and Mayer[21] concluded from their investigations that 'apparently, people who are obese are relatively insensitive to physiological cues, and extra-sensitive to environmental and food-related cues associated with eating behaviour'. Various aspects of satiety and obesity are discussed in a recent paper by Linton *et al.*[22] The influence of centres in the hypothalamus on hunger and satiety will be discussed later.

Average daily requirements of various nutrients required to maintain the health of men, women and children under different conditions have been much studied and have led to the formulation of 'recommended daily allowances' that are designed to exceed minimal requirements by a considerable margin. These allowances agree fairly well with the average intakes found when large groups of Western people are investigated.

Individual requirements. When healthy individuals are studied it is often found that they are thriving on diets which are astonishingly low in respect to some of these nutrients. This even applies to the intake of calories after due allowance has been made for age, sex, mass or their amount of physical activity. This somewhat disconcerting fact was first clearly established in 1935 by Widdowson from a study of 63 men and 63 women; in 1947 she confirmed it on 1 000 children;[4b] after eliminating all other likely explanations, she concluded that 'we must accept the general principle—whether for adults or children—that *people do not eat and do not require the same amount of food*' (author's emphasis).

Influence of different nutrients. In Western countries there has been a progressive and marked reduction in the consumption of cereals, especially bread, and a corresponding rise in the consumption of refined carbohydrates, especially sucrose. These changes have had effects that should not be ignored. Thus bread, particularly if made from high-extraction meals, contributed indigestible matter that stimulated bowel motility; sugar is so palatable that while it increases the intake of calories its 'energy/satiety ratio', is negligible.[23] Moreover, the glucose derived from the sucrose can stimulate the production of insulin by the pancreas, which stimulates lipogenesis and inhibits lipolysis.

Absorption of nutrients. Obese persons are often emphatic that they must assimilate their food more efficiently than others, especially their thin friends who eat so much without gaining mass. Evidence obtained from balance experiments does not support this plausible explanation; there is general agreement that abnormal absorption from the gut does not account for obesity, nor does malabsorption explain the usual case of abnormal leanness. But other subtle and closely-related aspects must be mentioned.

Influence of size and number of meals. When the calorie intake of rats is kept constant they gain different amounts of adipose tissue, depending on the speed of eating and the size and frequency of the meals. The gain is less with a number of small meals than with a few which are larger. Miller and Mumford[24a] confirmed some of these findings for humans, while in 1964 Fabry[25] noted that obese persons lost more mass when the same intake of calories was distributed over 5 instead of the more usual 3 meals a day. Thus stimulated, Fabry continued his investigations. In 1969 he published a fascinating book on *Feeding Patterns and Nutritional Adaptations*, which contains a wealth of evidence; he concluded that the composition, size and the number of meals, together with the amount of physical activity, may well have unsuspected nutritional implications, not only from birth onwards, but possibly even earlier. He asks whether the current increase in obesity may not be related to the way modern living favours a main meal in the evening, after which exercise is less likely; similarly, he deprecates the common practice of the obese of eating little during the day only to be overcome by hunger in the evening. Salans *et al.*[26a] also noted that their obese subjects had an aversion to breakfast and that they became hungry late in the day. Recently Bray[15b] probed this problem more deeply by studying what happens within the body.

Efficiency of food utilisation. Bray[15b] defining this as the mass gained per gram of food eaten in a rather drastic experiment, detected a number of metabolic differences when he fed 5 000 calories daily to 6 grossly overweight patients, by means of meals which were either spread over 4 hours ('gorging'), or over 20 hours ('nibbling'). He concluded that 'when food is ingested rapidly it is stored more efficiently than when the same food is eaten over a longer period of time'; he therefore suggests that 'the frequency of food intake may be inversely related to obesity.' He also

refers to some previous reports claiming that the serum cholesterol level is lower for 'nibblers', while their glucose tolerance is improved.

However, at present the effect of meal size and numbers has become controversial since Young[27a] in a very thorough study on obese young men failed to confirm some of the foregoing differences.

FACTORS INFLUENCING THE EXPENDITURE OF ENERGY

Overhead expenditure. When consideration is given to the energy expended by an individual, the tendency is to concentrate on the kind and amount of physical activity engaged in during the day, and to overlook the high cost of merely keeping the body in running order. A normal man who is moderately active will spend some 1 700 of his 3 000 calories, or over 50%, for this purpose.

Basal metabolic rate. That obese persons in the basal state produce less heat than normal per kg of body mass was once believed to be highly significant. But when the basal metabolism is calculated per unit of body surface, i.e. the basal metabolic rate, it is found to lie within the limits of normal, even for the grossly obese. Actually the oxygen and fuel consumption is high so that such people must be regarded as being hypermetabolic.[26] Nor is there any reduction in the specific dynamic action of the foodstuffs.

Physical activity. This is the main variable affecting the expenditure of energy and since the cost of a wide variety of ordinary activities expressed as calories/min has been determined, the amount spent over 24 hours can be calculated, provided the duration of each type of activity is also known; to allow for the cost of general restlessness, or nervous movements is less easy; for some people these can be quite costly.

Some obese persons manage to combine hearty eating with very active lives, but as the mass increases the more usual tendency is to become less and less active. Many young people who have been physically very active while at college, seem surprised that they gain mass at a sedentary office job, especially when they play games over the weekend. The effect of exercise on appetite is obviously relevant and not fully understood. According to Mayer the relationship varies with the intensity of the exercise; at low levels of intensity—the sedentary range—a decrease is *not* followed by a decreased food intake; over the normal range the appetite increases proportionately, and with excessive exertion—the exhaustion range—the appetite tends to decrease.

The contradictory evidence that obesity is associated with laziness has been reviewed by Lincoln.[29] Some investigations, including the ingenious study made by Bullen *et al.*[30] found that obese teenagers were less active at games or swimming than the non-obese, and they also spent more time sleeping; but other studies, including one recently made by Bradfield[31] indicate that this is not always the case; perhaps the findings depend on the type of obesity.

Obese persons should always be urged to take regular, but suitable, exercise. Arguments that to be effective the amount taken must be prodigious, or that it will only increase the appetite, are exaggerated; also overlooked is the stimulus to the metabolism that occurs besides the improvement of muscular tone.

Body mass. In some types of activity the energy expended is directly proportional to the mass of the body. Thus Passmore and Durnin[32a] found that when walking at 2 miles per hour the calories/min rose from 1,9 to 3,8 for gross body masses of 36,3 kg and 90,7 kg.

Mechanical efficiency. For the human engine this averages about 20%, varying from as low as 10% to the high figure of 33% under exceptional conditions; much depends on the type of work, the speed and the conditions under which it is performed, as well as on the training of the individual. There are categorical statements that the mechanical efficiency of obese persons remains unchanged, but Bloom and Eidex[33] disagree; indeed, one might expect that the obese undergo a degree of compulsory training as their mass increases. If this is true, it introduces a source of error into calculations of energy expenditure that would be hard to estimate.

Pregnancy. An unfortunate combination of factors is seen in pregnancy when women who are already eating as much or more than they require, are given rich diets, or even believe they must eat for two. They rest more than usual, and reduce their activities partly because they feel clumsy.

Many aspects of the relationship between activity and mass are discussed in a valuable chapter by Mayer.[16]

External temperature. Energy must also be expended on maintaining the normal body temperature, the amount depending partly on the environment as modified by the clothing worn, partly on the degree to which the body is insulated by the layer of subcutaneous fat; thus fat and thin people adjust more easily to cold and hot weather.

Thermogenesis. When work is performed the body, like other machines, dissipates much energy as heat. But unlike a machine, it can increase or decrease the amount of heat required by circumstances with such a high degree of precision that, for instance, the blood temperature varies only within narrow limits. Heat can also be generated quickly to meet exposure to cold or to combat infection.

As long ago as 1902 Rubner established that a meal is followed by an increase in heat production, the energy thus dissipated depending on the balance of nutrients in the diet. According to Miller and Mumford,[34a] when these are adjusted to cause a low loss of heat, healthy young men, if overfed, gain more mass than they do on a diet adjusted to cause a higher loss of heat. Even more significant is their evidence that at least under the conditions of their experiments, the body can control the gain in mass during overfeeding by stepping up the heat loss during exercise. Gordon,[35] commenting, writes 'this amounts to a regulation of energy balance by dietary induction of thermogenesis'.

Another significant observation has been reported by Quaade,[34] who measured the increase in oxygen consumption when obese or lean subjects were exposed to a standard cold stress. The individual responses obtained were so unexpected that he concluded that 'in certain

individuals obesity and leanness are not due to abnormal caloric intake, but are evidence of a disturbed thermoregulation'.

Gordon[17] discusses at considerable length the biochemical mechanisms believed to be concerned with thermogenesis. He stresses their importance in relation to the regulation of mass and thinks the major site is the adipose tissue and that this is one of its normal functions.

Stirling and Stock[35] go so far as to conclude that the regulation of the energy balance by dietary induction of thermogenesis is probably of greater importance in man than the control of intake, so that obesity is more likely due to a thermogenic defect than to aberrations of appetite.

Metabolic efficiency. Once food has been absorbed the general assumption is that it undergoes complete oxidation to carbon dioxide and water, i.e. a metabolic efficiency of 100%. This is not quite true, since the calorific value of protein is taken to be 4 calories/g to allow for the excretion of unoxidised urea. That these calories are wholly 'accepted' and then metabolised by the body, is regarded as axiomatic; yet investigations on animals have demonstrated 'an astonishing capacity to ingest diets of widely diverse calorie content with no change in body mass under conditions involving no significant variation in physical activity'. That this is also true for humans was noted by Widdowson.[4b] Evidently the human body can exercise a measure of control over the amount of incoming energy it 'accepts', or alternatively in the way such energy is metabolised.

Gordon[17] faced this problem in 1970 and suggested that the control of thermogenesis may provide a likely explanation. He speculates, for example, that the 'glycerophosphate shuttle' may possibly be one of several control points in normal energy metabolism through which an animal is able *'to modify the efficiency of his engine toward greater economy or greater extravagance, according to physiological needs'* (author's emphasis).

Differing metabolic pathways. Kekwick and Pawan,[36] writing in 1969, challenged the usual assumption that the pathways taken during metabolism are always identical, and they calculated what alternative pathways could mean to the energy balance. They found that obese women on a diet rich in fats can lose as much as 16% of their energy intake by excreting incompletely oxidised substances in their urine. A few years ago it was discovered that many animals, if they were fasted, or if their intake of carbohydrate was drastically restricted, excrete a substance in the urine which seems to be part of the physiological mechanism controlling fat metabolism. This substance has been shown to resemble, but is not identical with corticotrophin; no such excretion occurs in pituitary insufficiency nor after ablation of the gland. When this substance, termed the fat mobilising substance (FMS) is injected, a marked loss of mass occurs, although the appetite is not diminished, nor is there a rise in the uptake of oxygen; the amount of energy available to the animal decreases owing to the excretion of ketones, lactates, pyruvates, etc. In 1968 Kekwick and Pawan[36] extended experiments on mice to a small series of human volunteers, using normal saline as their control; following the injection of FMS the daily loss of mass rose from 81 to 231 g.

Kekwick and Pawan conclude that *'there is no firm relationship between the energy value of food and the energy available to the organism'*, (author's emphasis) or, in the words of Gordon, 'the effective caloric intake rarely, if ever, corresponds to the gross caloric content of the diet'.

These disturbing uncertainties about matters that most nutritionists have assumed to be beyond question, were already suggested in 1958 by Tepperman. Commenting on the complexity of the internal processes and the obvious variability of the individual, he remarked that *'it would be nothing short of astonishing if every person derived practically the same amount of utilisable energy from a mole of glucose'* (author's emphasis).

Comment on the energy balance: Because man must obey the law of the conservation of energy, the amount available to him must depend on 'calories in less calories out'. But it should be clear from the foregoing paragraphs that 'this simple statement is a superficial description of a very complex situation'.[34c] Experience has proved that the determinants used to estimate the energy balance give reliable results over short periods. But even a slight but continuing decrease or increase in the efficiency of one or more of the factors mentioned could slowly result in obesity or leanness.

HOW INDIVIDUALS RESPOND TO CHANGES IN THE ENERGY BALANCE

Decreasing the Intake of Calories

A great deal of information has been collected about the effects of decreasing the intake of calories on human health and behaviour; this includes the study of whole communities during war-time restrictions; professional fasters and, more recently, the obese when treated by starvation. Much of this information was reviewed in 1950 by Keys and his colleagues in their classical volume on underfeeding; this review prefaced their meticulous study of 32 young men who volunteered to live on a daily intake of 1 600 calories; after 6 months on this regimen they lost about 25% of their mass.

Response by the Obese

There is an obvious difference between reducing the intake of calories with persons of normal mass and with those who are obese. During starvation the reserves of energy in those of normal mass are strictly limited, so that eventually they must reduce their physical activity as well as break down their tissues; but the obese can utilise energy stored as fat and much will depend on the amount stored; the initial ketosis does not usually upset them for long, in fact, their health is improved. Fairly lengthy, or intermittent periods of complete fasting have become popular in recent years. Because of the inherent dangers involved—including death—such treatment must be undertaken in a hospital; however, in the opinion of Gastineau,[38] 'the risks of fasting are surprisingly small and yet not to be ignored'. A prodigious number of diets have been devised

based on reducing the intake of calories; trying the latest of these is a fashionable occupation for many of the obese. Careful comparison of the results obtained when the amount of the main nutrients is reduced, favours those low in carbohydrate, partly because of their greater acceptability; but numerous studies have shown that *in the long run* the mass lost depends on the calorie content rather than the precise composition.[27b,37] Unless the chosen diet is palatable and makes use of the customary foods, adherence for an adequate period is unlikely; hence the aim should be one of dietary re-education, the reduction in calories being obtained with as little alteration of the dietary habits as is practicable. On such a regimen the loss of mass may be slower than with the so-called 'crash diets' but it is likely to be more lasting. Mature people usually accept this form of treatment, but more drastic methods must be tried with the 'refractory' type of obesity.

Can the Loss of Mass be Predicted?

Naturally, the obese would like to be assured as to the amount of mass they will lose on a given regimen and how long this will take. Authorities who accept that a calorie deficit of 3 500 *must* cause a loss of 454 g of fat, speak of 'the mathematics of weight reduction'. That a certain type of obese individual will lose mass at a regular rate is well known, though how much of this is fat, water, or even protein, is often overlooked. But there are several reasons why the losses predicted may fail to occur. Adipose tissue is not only fat, so that the figure of 3 500 may be on the high side. Moreover, the loss will continue only until the energy needed by the lighter body is being adequately met, when further reductions will be needed to achieve further losses. Again, during a reducing regimen there is often a decrease in the basal expenditure of calories, thus Bray[15a] found that the energy expenditure of 6 grossly overweight women, living on a diet of only 450 calories, fell by no less than 15%; in addition he showed that their bodies had become metabolically more efficient. Not the least objection to predicting what 'must' happen is the rather natural conclusion that failure is due to cheating.

Response to Overfeeding — Experimental Obesity

The initial response to overfeeding is usually a gain in mass which continues until the mass pattern of the individual begins to assert itself; however, with women the outcome may be complicated by their tendency to retain water.

Here are some examples of the way healthy individuals have responded to overfeeding. In 1902 Neumann reported that although he raised his calorie intake from 1 800 to 2 200 daily over a year, and to 2 400 during a second year, he failed to increase his mass. Particularly intriguing is the detailed story told by Gulick.[38] Although 'well below the average for my stature . . . a person of the difficult-to-fatten type derived from non-fattening strains', Gulick said he was 'inclined to eat a very copious diet of a predominantly starchy nature'. Over a period of 370 days he increased his calorie intake from 2 733 to 4 113 only gaining 11 kg, or 30 g *per diem*. He concluded 'that there is some factor at work which caused fuel food to be burned more freely than in the average individual'; also that 'he owed his resistance against fattening to an extravagant calorie requirement which persisted at all times despite a moderate daily round of activities'. Strong *et al.*,[22b] investigating the effect of grossly overfeeding 2 fat young women and 3 thin young men, found that after 9 days the women had gained mass faster and more economically in terms of calories/g increase, than the men, but they also gained considerable amounts of water.

The most recent study of what happens in experimental obesity—a study which Rabinowitz[39] considers to have 'contributed heavily to our understanding of obesity'—was carried out by Sims and his colleagues and has become known as the Vermont study.[40a] In their first experiment on 4 university students, it took from 3 to 5 months to obtain a 10 - 12% increase in mass, although their usual calorie intake had been doubled or trebled. They then persuaded 9 lean young male prisoners to consume 9 000 - 10 000 calories daily while taking vigorous exercise. With varying degrees of difficulty the men achieved a mean gain in mass of 24%; of the 4 men who gained more easily, 2 had a family history of diabetes and 2 of these found it hard to lose the mass they had gained; similarly, those who had most difficulty in gaining lost their additional mass with ease. The authors discuss the similarities and differences between their findings in this unique investigation of pure exogenous obesity with those occurring in ordinary obesity. In a later paper Sims *et al.*[40b] tabulate 28 of these differences; for example, the marked difference in the calories required to maintain the obese state, which was 2 700 calories/m^2 for the experimental, and only 1 300/m^2 for spontaneous obesity.

CLOSER LOOK AT THE 3 PATTERNS OF MASS REGULATION

Only 3 patterns are possible since the regulating mechanisms are efficient in maintaining the mass at a fairly constant figure, or are under- or over-efficient. Let us take a closer look at these 3 situations.

Mass Remains Almost Constant

Many people find that their mass remains more or less constant for years; this obtains although they pay no conscious attention to what, or how much, they eat, nor to their activity. They are subject to the same 'pressure to eat' and 'pressure to be inactive' already discussed, to variations in appetite, the amount of exercise taken, occasional illness, etc., yet only minor variations in their mass occur.

The number of mass-stable persons in a typical Western community does not seem to have been ascertained, but

personal inquiries suggest it may well be fairly high. The accuracy with which this control is maintained is remarkable. Thus Halpern[42] has shown that it can be within 0,1%; Hollifield,[41] who thinks it applies to the majority of normal adult humans as well as animals, remarks that 'the active man who maintains the same weight over a period of 20 years must have balanced his food intake against energy expenditure *to the nearest crumb*' (author's emphasis).

Since this phenomenon is poorly documented and still doubted in some quarters, a chart of the author's mass taken under standard conditions on the same Avery scales over the last 19 years is shown in Fig. 1.

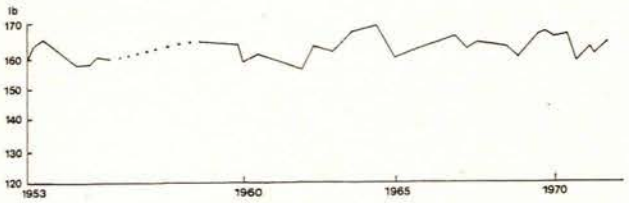

Fig. 1. Author's mass over 19 years taken under standard conditions. Mean mass 163 lb (73,9 kg); range 156 - 170 lb (70,7 - 77,1 kg). No conscious attention was given to amount of food eaten, or amount of exercise taken.

Although with advancing years some gain in mass may occur, the amount can be surprisingly small. According to tables published in 1959 by the Society of Actuaries the mean mass of insured males of 183 cm height increased from 75,3 kg at age 20 to 83 kg at age 60, or less than 200 g per annum. When the huge annual turnover of food and water is remembered, it seems clear that a measure of regulation must have occurred; for even the 30 calories in half an orange, if taken daily in excess of the calories required, should theoretically cause an annual gain of some 1,4 kg.

Of course the fact that the mass remains almost constant does not mean that the actual composition of the body remains unchanged, since an increase in fat and a decrease in muscle mass is usual with advancing age.

Mass Tends to Increase

There are people whose mass-regulating mechanisms are not as accurately adjusted, but it is not necessary to assume that these mechanisms are entirely inoperative. Those who gain mass usually do so slowly, although their propensity to overeat does not stop at half an orange! The rate of gain probably depends less on the daily surplus of calories than on the degree of inefficiency of their mass-regulating mechanisms; if, for example, the appetite is no longer under control, a rapid and big gain, which is only limited by the individual's ability to walk, or the effect on his health, can occur. Usually, after a more or less moderate gain, a new equilibrium is reached, although overeating may continue; then the obesity can be said to have passed from the 'active' to the 'passive' state. That the obesity then seems to decrease or even increase only with difficulty in some individuals, is seen by the tendency to return to about the same mass after reduction. How stubbornly an occasional case of obesity can cling to an excess of mass even under carefully supervised regimens in hospital, is well known; some examples of 'refractory' obesity are described by Bray.[15c]

Mass Remains Undesirably Low

Most communities also include a few otherwise healthy persons who are noticeably, or even occasionally painfully, thin. If those in whom the cause may be obvious, and who can be helped by suitable treatment are excluded, there remain a minority who fail to respond even to heroic measures; or, if they make some response, only too easily lose the few kg gained. Like the 'poor doers' well known to farmers, their leanness seems to be as refractory as the opposite condition just mentioned. Most clinicians would agree that in general it is harder to help such patients to gain, than to help the obese to lose mass. Evidently their controlling mechanism—whatever it may be—is set too high.

The striking differences between these 3 patterns as well as their high degree of stability offers strong support for the view that they are determined by the interaction of powerful mechanisms not under conscious control. When functioning efficiently the body mass remains approximately constant; if they are slightly or definitely inefficient obesity gradually develops; while if they are overefficient the individual remains lean.

MECHANISMS INVOLVED IN MASS REGULATION

The mechanisms, processes or substances known or suspected to be involved in the regulation of body mass, although of necessity considered separately, will be understood to influence one another and to be affected by the environment. For example, the genetic potential may be modified or not fully expressed, owing to environmental limitations, or modified by hormonal changes. Genetic and nutritional factors may interact even during prenatal development, with enduring results. Similarly, the nature and amount of enzyme activity can be changed profoundly by alterations in diet or physical activity.

Heredity

Animal husbandry has long established that a tendency to obesity can be inherited, and this has long been suspected in humans. Bauer[42] was probably one of the first to support these suspicions with evidence. Others, while readily accepting that obesity 'runs in families', have felt unable to exclude the role of such environmental factors as family food traditions. Some of the best evidence has emerged from the study of identical twins reared separately, or from adopted children.

In 1966 Seltzer and Mayer[1b] undertook a critical review of the evidence then available and concluded that 'in a society where food is abundant and hard physical labour unnecessary, genetic factors do predispose to the development of human obesities and, to some extent, their occurrence . . . The data reviewed would tend to suggest that there are multiple genetic factors involved. It is possible they may be different for obese persons with early age of onset, than for those with late onset.'

In his book on overweight Mayer[16] devotes a chapter to genes and obesity, saying that 'the indications are that in man, as in experimental animals, genetic traits largely determine, if not obesity, at least potentialities for overeating (or underexercising) and obesity. In a society such as ours . . . we have the ideal conditions for genetic potentialities to express themselves.'

He marvels at the way people readily accept the similarity of genetics in man and animals in so many other respects, yet refuse to admit that heredity, rather than mere overeating, can ever be responsible. Animal breeders, he says, have long known the ease with which Aberdeen-Angus cattle, the Berkshire hog, chows and bulldogs can be fattened, in contrast to Jerseys, razor-backs, greyhounds or terriers; also that some animals even of the same breed, are 'poor doers', while there are breeds of mice in which obesity is unquestionably inherited.

How heredity is expressed. This was well described by G. W. Gray in his book, *The Advancing Front of Medicine*. 'The hereditary pattern is a scroll inscribed at the moment of our conception, but with its writing in invisible ink and requiring the chemistry of a specific environment, the impact of a given experience, or sequence of experiences to render it visible.'

Body Build

Hippocrates distinguished between persons who were long and thin and those who were short and thick. Galton in 1889 was the first to demonstrate that inheritance plays a major role in determining bodily habitus, although the inherited potential may not be fully realised if the environment is unfavourable. Numerous ways of classifying and assessing body types have been devised, and for practical purposes 3 types are usually accepted. The ectomorphic, linear or asthenic individual is longitudinal, slender, though not necessarily tall, with a relative preponderance of surface area over mass. The endomorphic, lateral or pyknic type is broad and stocky, though not necessarily short, with a preponderance of mass over surface area. The mesomorphic, or athletic type, has a preponderance of bone and muscle development. Of course, most people fall into intermediate groups.

What is surprising is the relation of these types to the regulation of body mass. This was clearly brought out by Robinson and Brucer,[43] whose findings on over 3 000 men and women have been condensed in Table II. They concluded that 'obesity is an attribute of the lateral or broad build. Conversely, underweight is an attribute of the linear or slender build . . . persons with the lateral build type can be regarded as carrying a genotypic affinity for obesity, although the obesity may not be manifest until the last half of the life span . . . the germ plasm which transmits the build type also transmits the characteristic weight tendency for that build type.'

TABLE II. RELATION BETWEEN MASS AND BODY BUILD

	Body build			
Mass	Linear	Linear intermediate	Lateral intermediate	Lateral
Men				
Light	49	23	11	2
Medium	48	71	75	61
Heavy	3	6	14	37
Women				
Light	40	21	8	9
Medium	55	63	54	83
Heavy	5	16	38	67

(Adapted from Robinson and Brucer (1940): Amer. J. Med. Sci., **199**, 819). 3 436 men and 2 184 women were studied. The percentage of light, medium and heavy individuals, whose build was of linear, lateral or intermediate type, are compared.

In his classical work on somatotypes Sheldon called attention to the same phenomenon, while when studying adolescent girls, Bullen *et al.*[39] concluded that 'nature seems to be intolerant of obesity in ectomorphic types, which are rarely subject to obesity; *these people may apparently follow the dictates of their appetite without fear of growing fat* . . . While these results in no way detract from the concept that calorie intake in excess of calorie expenditure is the *immediate* cause of obesity, a recognition of the constitutional individuality of the person may well give a greater understanding of the fact that some of us become obese and others do not under *similar environmental circumstances*' (author's emphasis).

Enzymes

In his presidential address to the Endocrine Society of America in 1962, Astwood[44] declared his belief that 'obesity is an inherited disorder due to a genetically-determined defect in an enzyme (or enzymes)'. Gordon,[17] commenting in 1970, suggested that what is transmitted is an enzymatic mechanism which provides 'a greater degree of thermodynamic efficiency to the biological engine in the obese than in the non-obese individual', and that even an increase of 1 - 2% would be effective if continued for any length of time.

Metabolic processes depend on highly complex enzymatic sequences, which, though usually similar, are not necessarily identical; and since each biochemical reaction is under the ultimate control of a separate single gene, the possibilities for minor or even quite abnormal variations are very great. Moreover 'the formation of these enzymes is determined by the genes characteristic of the species,

while other genes may determine the existence of "repressors" which mask the action of genes in certain diseases.' In addition 'there may be complete failure to synthesise the special enzyme protein, or a severe reduction in the rate of synthesis, so that very little is actually present at any one time'. Enzyme systems can atrophy or become hypertrophic; this led Gordon to suggest that the increase in fat content without gain in mass so characteristic of the ageing process in man, may be due, as it is with a similar condition in rats, to a hypertrophic enzyme system controlling lipogenesis.

Presumably the degree of activity of these enzyme systems must be considerably affected by the diet consumed, for instance, whether this is composed mainly of cereals, meat, or vegetables. Their versatility, which enables them to adjust quickly to sudden, even extreme, dietary changes, is astonishing. Bjorntorp[45a] has studied the changes in metabolism of the obese after physical training, and Johnson *et al.*[46] have demonstrated changes in the metabolism of fat and carbohydrate of athletes in training.

As would be expected, attempts are now being made to determine the nature of the enzymatic changes associated with obesity. Writing in 1968 Mayer concluded that 'the genetic abnormality prior to all others' may be the presence of glycerokinase activity in the adipose tissue due to the absence of the repressor to the synthesis of the enzyme normally present. Galton[47] has offered evidence that extreme obesity of early onset may be associated with an enzyme defect in the metabolism of alpha-glycerophosphate 'which would be expected to increase its availability for the synthesis of triglyceride'. Of particular interest is a study by Bray,[15b] who placed grossly overweight women on a diet of only 550 calories and then, studying samples of their subcutaneous fat by biopsy, he detected a fall in activity of 2 enzymes in the glycerophosphate cycle; this, he concluded, provided further support for the conclusion reached by Stirling and Stock:[35] 'that this cycle may serve as the biochemical mechanism for modifying the amount of useful energy obtained from oxidative processes.'

This new approach to the enigma of mass regulation obviously opens up exciting possibilities. For if a specific enzymatic defect can be established, some way of treating it may be forthcoming. Phenformin and fenfluramine are examples of this approach.[48,49a]

Hormones

Metabolic processes are profoundly influenced by the many hormones secreted into the blood stream by the endocrine glands. Over 60 substances considered to be hormones, or possessing hormone-like activity, have already been identified, and no doubt others await discovery. No less than 12 of these are involved in stimulating lipogenesis, and 9 stimulate lipolysis. That their influence on mass regulation is highly significant is clear, even if this merely depends on the precise balance existing between those promoting, and those antagonistic to, lipogenesis. Even a very slight change, if long continued, could have significant results. For example, growth hormone is a potent fat-mobilising substance, and an intrinsic defect in its production, which has been detected by Hammar *et al.*[50] in a few cases, might have this effect.

Some hormones act quickly, mobilising free fatty acids for flight or fight; others more slowly, to meet the needs arising during growth, fasting, etc. They also vary in their sensitivity to each other. The fundamental role played by insulin in relation to obesity has already been mentioned and the sensitivity of some of the other hormones to it 'may well provide the fine control over the release of free fatty acids required to meet different physiological conditions', thus serving, in the words of Cahill,[39] as the body's 'thermostat' for lipid accumulation or mobilisation. The endocrine system is affected by the plane of nutrition; as the food intake increases the beta cells of the pancreas produce more and more insulin, which not only promotes the deposition of fat, but, by increasing the output of glucosteroids, stimulates the production of insulin antagonists.

Now that the plasma hormone levels can be assayed, much effort is being directed to detecting departures from normal in various conditions, including obesity. Here the insulin level is usually reported to be increased, but Sims *et al.*[40b] warn that there are pitfalls in interpretation, since a value should not be labelled abnormal 'if it is appropriate to the particular stimulus or situation.'

When the endocrine glands and their hormones were being discovered a confident belief arose that the cause of obesity had at last been found. This was understandable since obesity is often associated with conditions such as Cushing's syndrome, adrenal feminism, eunuchoidism, and spontaneous hyperinsulinism. However, these conditions are so rare as to be of little practical importance. While the possibility that some hormonal disturbance may be present must be considered, the consensus is that obesity seldom results from endocrinopathies, nor has hormone therapy usually proved of value. Many obese persons are confident 'that it must be my glands'—and of course on occasion this may be true.

Because a loss of mass is so usual in hyperthyroidism, obesity is often attributed to hypothyroidism and this is treated accordingly. Yet, as long ago as 1940, Plummer showed that even cretins or myxoedematous individuals do not accumulate more adipose tissue than those with normal thyroid activity. Today, treatment with thyroxine is only advocated after hypothyroidism has been established, for there is no point in substituting mild thyrotoxicosis for obesity. However Bray[15a] reports encouraging results when a certain type of obesity is treated with tri-iodothyronine.

The value of chorionic gonadotrophin in the treatment of obesity remains controversial, and is reviewed by Schwartz.[51] Rabinowitz[52] has recently reviewed the hormonal changes occurring in obesity.

Hypothalamic Mechanism

That obesity, or excessive thinness, can follow tumours in the region of the pituitary gland, has been known and investigated for over 70 years. These studies have shown

that mechanisms in the hypothalamic area are involved in the control of food intake, but their mode of operation and the way in which they respond to influences impinging on them, as well as to other parts of the brain, is very complicated and is only slowly being elucidated. In 1955 Brobeck interpreted the evidence then available as indicating that the hypothalamic centre 'was itself divisible into a lateral "feeding centre" and a medial "satiety centre", with the 2 reciprocally innervated, but with the medial centre being dominant since it could override feeding.' Although this concept is accepted, can be used for general purposes, and is indeed supported by much experimental evidence, it is now recognised to be an oversimplification which has had to be modified by later discoveries; these are discussed by Bell.[53]

A variety of stimuli impinge on these centres, some nervous, some chemical, and some even thermal. Chemical factors include the specific dynamic action of food, the availability of glucose, fat metabolites, or amino acids in the body fluids, but 'evidence to date does not suggest that any single metabolite controls the activity of the neural regulating process.' Gordon,[17] discussing the nervous factors that may be involved, remarks that 'because of the multitude of complex nervous pathways that connect the hypothalamus with all other portions of the brain it is easy to understand how emotional disturbances might have a profound effect upon eating habits'.

That these centres can be deranged by trauma, infection, as well as by certain diseases, is well established; these may lead to the 2 extremes of pathological fatness or thinness depending on which of the centres is affected. Brobeck has shown that even small lesions can cause striking changes in the feeding behaviour of animals. In 1955 Mayer concluded that a minimal amount of exercise is probably necessary for the accurate regulation of appetite; this may have a bearing on the tendency to gain mass in middle or later life, i.e. that the 'setting' of the mechanism controlling the appetite is being affected.

That the precise 'setting' of these 2 opposing centres may differ in different people, and that this is an inherited characteristic, seems a plausible hypothesis which gains support from the fact that satiety has been shown to be experienced less suddenly by some than by others, particularly those who are obese.

Opinions vary as to the extent to which this intricate mechanism controls our feeding patterns, but there is general agreement that it is of outstanding importance; however, Kekwick and Pawan[36] think this may have been overstressed.

Adipose Tissue

Adipose tissue constitutes a large organ amounting to some 20% of the body mass in well-nourished males and 30% in females. It consists of an extensive network of fat cells and a supporting structure of collagen and vessels. Formerly it was regarded as a more or less inert mass, which served as a compact store of energy, protected the body from injury, and insulated it from changes in the external temperature; the vital role that it plays was quite unsuspected. But, today, this tissue is recognised as being one of the most metabolically active in the body, with a continuous turnover of its lipid constituents and an oxygen uptake above that of resting muscle measured on a basis of nitrogen/g. The deposition of fat normally occurs in only certain parts of the body, which differs in males and females as well as in individuals of the same sex. The site and amount of the fat deposited is influenced by mechanisms operating at the level of the cells in the tissue itself, with oestrogens and the adrenal steroids being of particular importance. For example, hyperadrenocorticism tends to cause the accumulation of fat in the face, neck and trunk, while the extremities are spared. Abnormalities in the regulation of the location, or in the maximal size of the fat cells can also account for the unusual distribution and the amount of fat found in some unfortunate individuals.

The site both of lipogenesis and lipolysis, adipose tissue, is known both to contain and control alternative metabolic pathways; indeed, it seems that it is this tissue, supplemented by the centres for appetite and satiety in the hypothalamus, which maintains the homeostasis of body mass. Moreover, being mainly located under the skin, it can act as a heat-producer as well as an insulator, thus somewhat resembling an electric blanket.[19] Finally thermogenesis is believed to be one of the primary functions of this formerly underrated tissue.

To this radical reassessment of the roles played by adipose tissue must be added the recent and far-reaching discoveries of Hirsch and his colleagues[54a,54b] which Gordon[17] describes as 'not only valuable, but stunning'.. By using collagenase to separate them from their connective tissue, the workers were able to examine the adipocytes, determining their number, size and behaviour in persons of different ages and conditions.

Their main findings can be summarised as follows: the number of adipocytes increases from birth to early adulthood; once produced it is difficult, if not impossible, to alter their number. Moreover, the cell number of their obese subjects was almost 3 times greater than those not obese. This led them to the highly significant conclusion that at least in some obese persons *the primary abnormality may be in adipocyte (fat cell) numbers* (author's emphasis). In obese subjects they also found that the adipocytes were full to capacity with triglycerides, but became smaller, or even smaller than those measured in normal persons, when the excess mass had been reduced. However, the number of adipocytes did not decrease, so they could be regarded as dormant, ready to be filled once more with fat. Hence it would appear that once such a person becomes obese he is no longer 'normal', even should his excess mass be reduced to a normal level, because the number of his adipocytes remains excessive and thus the tendency to gain mass remains. This 'hypercellularity' also helps to explain the ease with which an obese person regains such mass as he manages to lose. Adipocyte size was also found to affect the sensitivity to the physiological action of insulin, decreasing as the size increased, and vice versa. These remarkable discoveries have been fully confirmed[26b,45a,54a] and reviewed by Bjorntorp and Ostman.[46b]

When is the Number of the Adipocytes Established?

Because of its theoretical and practical significance this question is being actively studied. Lipocytes have been identified in the human embryo and can be recognised early in foetal life; apparently the birth masses of children who later become obese may be normal, but there is evidence that nutritional experiences during the first year of life, and perhaps even *in utero*, can be of crucial importance by virtue of their effect on cellularity. In a detailed study Shukla *et al.*[55] found that 28% of 300 otherwise normal children were overweight, and 17% obese at 13 weeks. According to Taitz[56a,56b] artificially-fed infants were already appreciably heavier, even at 6 weeks, than those breast-fed, and he deplored the way they were being overfed. Brook[12b] considers that the period extending from approximately 30 weeks' gestation to the age of about 1 year is 'the finite sensitive period during which the basic complement of cells is determined . . . The earlier events occur during this sensitive period, the more serious their effects', but that cell size rather than number, alters with later nutritional changes. Brook *et al.*[12a,12b,12c] who studied 29 children who were obese at 1 year, found a mean cell size of 0,64 μg as against 0,30 μg for 64 controls. The above findings are of great interest, since they suggest a new approach to the prevention of at least this type of obesity. However, Sims *et al.*[49b] suspect that young adipocytes, too small and devoid of lipid to be measured by present methods, may gradually proliferate later in life, since some increase in cell number has been detected in obesity beginning after age 20. They also conclude that both experimental obesity and that following the destruction of the ventromedial nuclei of the hypothalamus come about exclusively by an increase in adipose cell size.

In the review already mentioned Bjorntorp and Ostman[45b] remark that 'the spectacular development of knowledge in the metabolism of obese tissue in the last decade puts adipose tissue in parity with liver and muscle as the 3 main tissues regulating energy homeostasis'. Kekwick and Pawan,[36a] writing before the latest discoveries, were so impressed with the known functions exhibited by this tissue that they concluded; 'if we had to design a system to cope with the variation in available energy and fluctuation in energy demand while at the same time maintaining the body-mass control, we could not improve on the model provided by adipose tissue'.

Psychological factors: Without accepting the view that obesity is merely a problem for the psychologists, we should not minimise the influence that psychological factors can have on the nature and amount of food eaten. Some of these have already been mentioned. Dietary habits can also be used to obtain psychological gains; thus, as Mayer says, 'there are thousands of children busily earning their parents' approval by eating "everything put before them", even when it is both more than they need and more than they want.' Alternatively, young persons who are fat for 'natural' reasons may diet themselves heroically to meet the current craze for slenderness; indeed, at this age serious disturbances of the 'body image' are not uncommon.[50,58] Anorexia nervosa, the 'compulsive eater', and the 'night nibbler' illustrate the influence of mental states on food consumption.'

Psychologists have carefully studied this aspect of obesity. When hyperphagia begins at an early age they have offered such explanations as oral fixation due to inadequate or excessive maternal care, family instability, or the effect of some early traumatic experience; or that it is a learned response found valuable because it reduces tension. Simple psychotherapy, psycho-analysis, learning theory techniques, hyphosis and aversion therapy are among the treatments used, either alone or combined with dieting and appetite-suppressant drugs. The results obtained as well as other aspects of this approach have been discussed by Mayer, Craddock, and more especially by Kiell.[16,57,58]

That those who are obese, particularly the young, suffer psychologically, is well known; unfortunately, a vicious circle may develop. Real or imaginary social unacceptability often leads to isolation, despondency, indolence and indulgence in cakes, sweets, etc. Older people may laugh off their fatness although they are secretly worried both by their appearance and the deterioration in their health; how deeply they are affected may only appear when their mass is normalised. As noted by Dr Hilda Bruch, some people have 'a compulsion to be thinner than their natural make-up allows—their real problem is that society will not let them be themselves.' At the other extreme are those who are best described as having a vested interest in their size!

The attitude adopted by the clinician can be most important. While this must, of course, be adjusted to the individual patient, it is well to remember that most have become discouraged by many previous failures to reduce. Much patience and encouragement must be shown, especially when setbacks occur; initially, fairly frequent visits are desirable until sufficient progress has proved that success is possible.

That the obese can help each other is amply proved by the success of such self-help organisations as TOPS (Take Off Pounds Sensibly) and the Weight Watchers. A short-term study of the former has been published by Stunkard *et al.*[49b]

MASS REGULATION AN EXPRESSION OF THE CONSTITUTION

Sometimes it is as important to know what kind of man has the disease as to know what kind of disease the man has.

Dr C. H. Parry of Bath (1755 - 1822)

We have seen how differently people react to the many factors involved in the regulation of body mass; also, that these differences are due partly to heredity and partly to environmental circumstances. Although now widely accepted, the realisation that, far from being a standard entity, individuals possess a high degree of variability, has had a chequered history.

To Hippocrates, a man was 'that infinitely variable organism without which disease is impossible', while Galen taught that 'no cause can be efficient without an

aptitude of the body'. That people differ from one another, some being more predisposed to certain diseases than others, seems to have been generally accepted until early in the 20th century.

But the spectacular rise of scientific medicine, leading to the discovery of specific causes for so many diseases, together with the brilliant successes following the use of specific remedies, led many to reject such vague concepts as predisposition, constitution, or diathesis, as being entirely unnecessary; indeed, precisely the opposite concept was adopted, namely, that disease was the variable, and that, with some exceptions, man was a standard entity. Although plenty of evidence accumulated to show the inadequacy of this view, it continued to dominate the outlook even after 1902 when Garrod described certain 'inborn errors of metabolism, and dared to suggest that 'no 2 individuals of a species are absolutely identical in bodily structure, neither are their chemical processes carried out on exactly the same lines.'

The evidence confirming Garrod's views, particularly that derived from the study of genetics, gradually led to an almost complete reversal of ideas; but how gradually this took place can be gauged by the cool reception accorded to such outstanding books as Julius Bauer's *Constitution and Disease*,[42] or R. S. Williams' *Biochemical Individuality*,[50] published as recently as 1942 and 1956; yet by 1968 Professor H. Harris, the Galton Professor of Genetics, caused no sensation when he wrote 'one may plausibly expect that in the last analysis every individual will be found to have a unique constitution . . . People who are otherwise normal or healthy may often be classified into distinct types according to the manner in which they synthesise some particular enzyme or protein.'[60]

Nobody doubts that hair colour, our characteristic fingerprints, or alkaptonuria are inherited; or that scurvy and malaria are caused by environmental factors, but there are often instances when it is hard to disentangle the influences acting prior to fertilisation of the ovum (those due to nature), from those occurring subsequently (those due to nurture); indeed both can be involved, and yet the outcome may long remain masked.

This quiet, but surely fundamental change in outlook, has now won fairly general acceptance in most biological fields, but seems to be insufficiently recognised by nutritionists, especially those interested in the enigma of mass regulation; otherwise how could the 'kitchen scales' explanation for obesity survive as it still does?[61]

How different and how stimulating is the thinking of Gordon[17] who, after noting that 'endless variation and individuality are the hallmarks of biological systems', suggests that 'every person probably has a "natural" body build and a "natural" adult body weight; accordingly, only certain individuals are destined at the time of birth *to possess the potentiality for obesity*, while certain others with metabolic machinery operating with lower efficiency may be *predestined to combat the problem of extreme thinness for most of their lives*' (author's emphasis). The fact of biological variability, though so fascinating, is going to be the cause of endless difficulty; but Keys says, 'variability is not merely a confounding nuisance; it is a challenge for explanation; careful attitudes to it can provide unexpected and valuable clues. Unexplained variability means that one or more influential variable is being overlooked.'[12c]

TYPES OF OBESITY AND THEIR CLASSIFICATION

Sims *et al.*[40b] remark than anyone dealing with the clinical aspects of obesity must be impressed with the different types that occur, and several attempts to classify them have been published. Thus, from the clinical angle Halpern[62] accepts 3 main types including a juvenile form, which he says 'differs as radically from that occurring in adult life as does juvenile and maturity-onset diabetes.'

Some of the efforts to explain the nature of these types have already been mentioned. Mayer,[16] discussing a classification first made in 1953, tabulates 5 types for man, his main distinction being between the regulatory and the metabolic obesities. Recent discoveries have enabled Bjorntorp[45] to propose that a clear distinction should be made between the hyperplastic type, due to an increase in cell number, which is apt to be severe, of lifelong duration and with a poor prognosis for treatment; and the hypertrophic type, due to fat cell enlargement, which is of more moderate degree, is more amenable to treatment, but is associated with aberrations both of lipid and carbohydrate metabolism, suggesting that the hypertrophy may not be the primary change. Subjects whose mass is stable are characterised by a normal number of small fat cells; here he thinks the degree of physical activity may be of significance.

Type Determination

Although numerous reports show that the obese respond differently to various tests—mostly biochemical—this possible method of differentiation does not seem to have been sufficiently explored. But, as pointed out by Jacobson *et al.*[63] and Sims,[40a] unnecessary confusion could be avoided if the groups being studied were not merely characterised as obese. In addition to information about age, sex and the degree of obesity, mention could at least be made as to the age of onset; whether the individuals are in the dynamic, or static phase; whether of the refractory type; whether obesity or diabetes occurs in the family, and whether a psychological factor is obvious or suspected. Informative correlations might then emerge.

PHILOSOPHICAL ASPECTS

Wild animals do not apparently become obese, although some, e.g. bears, some insects and migratory birds, can anticipate future needs by storing energy as fat before hibernating or migrating. Several writers have suggested that man once needed to be prepared for times when food was scarce and only obtainable at erratic intervals; perhaps the interval has been too short for most of us to readapt to the surplus of food now usually available, and also

to the even more recent decline in the need for physical activity.

Whatever the explanation, man's control system seems better adjusted to secure enough calories rather than to avoid an excess. Indeed, Bortz[64] thinks that 'the metabolic characteristics of the obese are primed for starvation, or exposure to cold'; since these emergencies are now so seldom encountered he regards this as a 'vestigial adaptation which has become a liability to health'.

Miller[34c] has drawn attention to an interesting question when he asks how does the body 'know' that an upward or downward adjustment is required to maintain mass homeostasis so accurately over such long periods, despite wide variations in the day-to-day intake or expenditure of energy?

CONCLUDING HYPOTHESIS

In conclusion we submit the following hypothesis for consideration and criticism:

Every individual follows one of 3 patterns of mass regulation: either the mass remains stable, tends to gain, or is undesirably low. The particular pattern is established at an early age by the interaction of heredity and environment. Since the mechanisms involved in maintaining this pattern vary in their stability, they are affected to a greater or lesser extent by internal changes, by changes in the environment that subsequently occur, or by both.

An obvious objection to such a constitution-orientated hypothesis is that it would not explain the remarkable increase in the prevalence of obesity taking place in Western communities. Two explanations are suggested:

Many people who tend to gain mass do so very easily, and can effect temporary losses of mass with similar ease. The regulating mechanisms of such persons may well have been sufficiently stable to cope with the former environment, when refined cereals, sugar and other foods with a high energy/satiety ratio were luxuries; their successors may not be sufficiently stable to adjust to an environment where such foods are ubiquitous and where the 'pressure to eat' is reinforced by the 'pressure to be less active'.

Alternatively, breast-feeding has declined markedly during the same period, to be replaced by diets for infants now believed to cause over-nutrition; by increasing the number of adipocytes such diets could induce a life-long obesity.

CONCLUSION

Body fat can only be derived from food, so that obesity can only develop when there is an excessive assimilation of calories.

The widespread assumption that mass automatically increases or decreases according to the amount of food eaten or the amount of exercise taken or by both means, is not invariably true.

Whether a person tends to gain, maintain an almost constant mass over long periods or is intractably thin, depends primarily on the behaviour of his mass-regulating mechanisms which are more numerous, complex, interrelated and powerful than were formerly suspected. The 3 patterns are a visible expression of the degree of efficiency with which they are operating.

How these mechanisms function depends on hereditary and environmental factors which are an expression of his individuality and hence of his constitution.[65]

Heredity is of primary importance. Genes, acting through enzymes, hormones, etc. determine, for example, the type of body build, the 'setting' of the opposing centres for hunger and satiety in the hypothalamus, and the balance predominating between the processes of lipogenesis and lipolysis.

The expression of the genetic potential can be modified by environmental factors; for example, overfeeding during infancy may increase the number of adipocytes, which then promote the development of obesity.

People with a tendency to gain mass seem to respond more readily to environmental or other changes than those who follow the other 2 patterns.

Except in a few rare diseases, the numerous well-marked metabolic abnormalities that can accompany obesity have been found to be the result rather than the cause of this condition. To be effective, differences between the metabolism of persons who do or do not gain mass need only be very slight because they are long continued; this makes them difficult to detect.

Obesity is not a single disease, in fact it is not a disease, but rather the common end-point of various disturbances—genetic, enzymatic, hormonal, neurological and enviromental—which either singly or in combination determine or modify the pattern of mass regulation.

Excess mass can be reduced with varying degrees of ease, success, and permanence, by using current therapeutic measures; but the tendency to gain remains unchanged.

Progress in differentiating and in understanding the nature of the different types of obesity may well provide more effective methods of prevention, treatment and, hopefully, cure.

REFERENCES

1a. Seltzer, C. C. and Mayer, J. (1965): Postgrad. Med., **38**, A101.
1b. *Idem* (1969): Ann. N.Y. Acad. Sci., **134**, 688.
1c. *Idem* (1964): J. Amer. Med. Assoc., **189**, 677.
2a. Keys, A., Fidanza, F., Karnoven, M. J., Kimura, N. and Taylor, H. L. (1972): J. Chron. Dis., **25**, 329.
2b. Keys, A., Aravanis, C. and Blackburn, H. (1972): Ann. Intern. Med., **77**, 15.
2c. Keys, A. (1966): Ann. N.Y. Acad. Sci., **134**, 505.
3. Shephard, R. J., Jones, G. and Ishii, K. (1969): Amer. J. Clin. Nutr., **22**, 1175.
4a. Widdowson, E. M. (1971): Proc. Nutr. Soc., **30**, 127.
4b. *Idem* (1966): Spec. Rep. Ser Med. Res. Coun. (Lond.) No. 257.
5. Eid, E. E. (1970): Brit. Med. J., **2**, 74.
6. Bryans, A. M. (1967): Canad. J. Publ. Hlth, **58**, 486.
7. Nelson, W. E. (1964): *Textbook of Pediatrics*, 8th ed. Philadelphia: W. B. Saunders.
8. Tanner, J. M. and Whitehouse, R. H. (1962): Brit. Med. J., **1**, 446.
9. Vickers, R. S. and Stuart, H. C. (1963): J. Pediat., **22**, 155.
10. Jackson, R. L. and Kelly, H. (1945): *Ibid.*, **27**, 215.
11. Corbin, C. B. (1969): Amer. J. Clin. Nutr., **22**, 836.
12a. Brook, C. G. D. (1971): Arch. Dis. Childh., **46**, 182.
12b. *Idem* (1972): Lancet, **2**, 624.
12c. Brook, C. G. D., Lloyd, J. K. and Wolf, O. H. (1972): Brit. Med. J., **2**, 25.
13. Grant, M. W. (1966): Med. Offr., **115**, 331.
14. US Public Health Service (1966): Publication No. 1485.
15a. Bray, G. A. (1970): Amer. J. Clin. Nutr., **23**, 1141.
15b. *Idem* (1972): J. Clin. Invest., **51**, 537.
15c. *Idem* (1970): Ann. Intern. Med., **73**, 565.
16. Mayer, J. (1968): *Overweight: Causes, Cost, and Control*. Englewood Cliffs, N. J.: Prentice-Hall.

17. Gordon, E. S. (1970): Adv. Metab. Disord., **4**, 229.
18. Durnin, J. V. G. A. (1971): S. Afr. Med. J., **45**, suppl. 19 June.
19. Cahill, G. F., Owen, V. E. and Morgan, A. P. (1968): Adv. Enzyme Regul., **6**, 143.
20. Yudkin, J. (1963): Lancet, **1**, 1335.
21. Monello, L. and Mayer, J. (1967): Amer. J. Clin. Nutr., **20**, 253.
22. Linton, P. H., Conley, M., Kuechenmeister, C. and McClusky, H. (1972): *Ibid.*, **25**, 368.
23. Heaton, K. W. (1972): In the press.
24a. Miller, D. S. and Mumford, P. (1966): Proc. Nutr. Soc., **25**, 100.
24b. Miller, D. S., Mumford, P. and Stock, M. J. (1967): Amer. J. Clin. Nutr., **20**, pp. 1212 and 1223.
24c. Miller, D. S. *in* Baird, D. S. and Howard, A. N., eds (1969): *Obesity: Medical and Scientific Aspects*. Edinburgh: Livingstone.
25. Fabry, P. (1969): *Feeding Patterns and Nutritional Adaptations*. London: Butterworths.
26a. Salans, L. B., Knittle, J. L. and Hirsch, J. (1968): J. Clin. Invest., **47**, 153.
26b. Salans, L. B., Horton, E. S. and Sims, E. A. H. (1971): *Ibid.*, **50**, 1005.
27a. Young, C. M. (1971): J. Amer. Diet. Assoc., **59**, pp. 466 and 473.
27b. Young, C. M., Scanlan, S. S., Im, H. S. and Lutwak, L. (1971): Amer. J. Clin. Nutr., **24**, 290.
28. Gastineau, C. F. (1972): Med. Clin. N. Amer., **56**, 1021.
29. Lincoln, J. E. (1972): Amer. J. Clin. Nutr., **25**, 390.
30. Bullen, B. A., Reed, R. B. and Mayer, J. (1964): *Ibid.*, **14**, 211.
31. Bradfield, A. B., Paulos, J. and Grossman, L. (1971): *Ibid.*, **24**, 1482.
32a. Passmore, R. and Durnin, J. V. G. A. (1955): Physiol. Rev., **35**, 801.
32b. Strong, J. A., Shirling, D. and Passmore, R. (1967): Brit. J. Nutr., **21**, 909.
33. Bloom, W. L. and Eidex, M. F. (1967): Metabolism, **16**, 685.
34. Quaade, F. J. (1964): J. Obesity, **1**, 1.
35. Stirling, J. L. and Stock. M. J. (1968): Nature, **220**, 801.
36a. Kekwick, A. and Pawan, G. L. S. (1969): Lancet, **1**, 822.
36b. *Idem* (1968): *Ibid.*, **2**, 198.
37. Hood, C. E. A., Goodheart, J. M., Fletcher, R. F., Gloster, J., Bertrand, F. V. and Crook, A. C. (1970): Brit. J. Nutr., **24**, 39.
38. Gulick, A. (1922): Amer. J. Physiol., **60**, 371.
39. Rabinowitz, D. (1970): Ann. Rev. Med., **21**, 241.
40a. Sims, E. A. H. and Horton, E. S. (1968): Amer. J. Clin. Nutr., **21**, 1455.
40b. Sims, E. A. H., Horton, E. S. and Salans, L. B. (1971): Ann. Rev. Med., **22**, 235.
41. Hollifield, G. (1968): Amer. J. Clin. Nutr., **21**, 1471.
42. Bauer, J. (1942): *Constitution and Disease*. New York: Grune & Stratton.
43. Robinson, S. C. and Brucer, M. (1940): Amer. J. Med. Sci., **199**, 819.
44. Astwood, E. B. (1962): Endocrinology, **71**, 337.
45a. Bjorntorp, P. and Sjostrom, L. (1971): Metabolism, **20**, 703.
45b. Bjorntorp, P. and Ostman, J. (1971): Adv. Metab. Dis., **5**, 277.
45c. Sjostrom, L. (1972): Acta med. scand., suppl. 544.
46. Johnson, R. H., Walton, J. L., Krebs, H. A. and Williamson, D. H. (1969): Lancet, **2**, 1383.
47. Galton, D. J. (1966): Brit. Med., J., **2**, 1498.
48. Sedgewick, J. P. (1970): Brit. J. Clin. Pract., **24**, 251.
49a. Stunkard, A., Rickels, K. and Hesbacher, P. (1973): Lancet, **1**, 503.
49b. Stunkard, A., Levine, H. and Fox, S. *in* Masek, J., Osancova, K. and Cuthbertson, D. P., eds (1970): *Nutrition*, p. 223. Amsterdam: Excerpta Medica.
50. Hammar, S. L., Campbell, M. M., Campbell, V. A., Moores, N. L., Sareen, C., Gareis, F. J. and Lucas, B. (1972): J. Pediat., **80**, 373.
51. Schwartz, J. B. (1970): Year Book Endocr., p. 377.
52. Rabinowitz, D. (1970): Ann. Rev. Med. **21**, 241.
53. Bell, F. R. (1971): Proc. Nutr. Soc., **30**, 103.
54a. Hirsch, J., Knittle, J. L. and Salans, L. B. (1964): J. Clin. Invest., **43**, 1776.
54b. *Idem* (1966): *Ibid.*, **45**, 1023.
55. Shukla, A., Forsyth, H. A., Anderson, C. M. and Marwah, S. M. (1972): Brit. Med. J., **4**, 507.
56a. Taitz, L. S. (1971): *Ibid.*, **1**, 315.
56b. *Idem* (1973): Clin. Sci., **45**, 10.
57. Craddock, D. (1969): *Obesity and Its Management*. Edinburgh: Livingstone.
58. Kiell, N. (1973): *Psychology of Obesity: Dynamics and Treatment*. Springfield Ill.: C. C. Thomas.
59. Williams, R. S. (1956): *Biochemical Individuality*. New York: J. Wiley.
60. Harris, H. (1968): *New Scientist*, Feb. 15, p. 370.
61. Nordin, B. E. C. (1972): Brit. Med. J., **2**, 287.
62. Halpern, S. L. (1964): Med. Clin. N. Amer., **48**, 1283.
63. Jacobson, G., Seltzer, C. C., Bondy, P. K. and Mayer, J. (1964): New Engl. J. Med., **271**, 651.
64. Bortz, W. M. (1969): Ann. Intern. Med., **71**, 833.
65. Brock, J. F. (1972): Lancet, **1**, 701.