Metabolic Disturbances in Clinical Medicine

Edited by

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With 35 illustrations

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PREFACE

THERE are several excellent textbooks concerned with metabolism, but they tend either to deal with metabolic diseases (using the term "disease" in the sense developed in the medicine of the nineteenth century) or to deal with metabolic abnormalities and disturbances from the point of view of the biochemist. The present book attempts to steer a course between these two and to describe for the practising clinician some of the more important of those disturbances of metabolism which he may encounter in the course of his work. It is, of course, impossible and undesirable to be confined by any hard and fast barriers and therefore it has at times been necessary to enter into certain biochemical details and at others to describe so-called metabolic diseases. Nevertheless, it is hoped that the physician who has not specialized in this aspect of medicine will be able to gain some insight into its more recent developments and to obtain definite practical help in diagnosis and in therapy.

The metabolism of disease is one of the most rapid growing-points of internal medicine and a complete presentation is beyond the scope of any textbook. A book suitable for the purposes outlined above should be neither too large nor too expensive and thus, inevitably, there must be many omissions. In selecting suitable subjects duplication has, so far as possible, been kept to a minimum. Thus there is no section devoted specifically to the alimentary tract, for many of the results of, for example, malabsorption are dealt with in other connections. Nutrition, being the study of those substances forming the necessary raw materials for metabolism, and endocrinology, the study of the system devoted to the chemical regulation of metabolic processes, are vast subjects in themselves and no attempt has been made to consider them in isolation; instead they are woven where appropriate into the general theme. Selection of material has also been made as a result of experience in both undergraduate and postgraduate teaching, so far as possible those subjects of common importance which are least understood being included.

It is difficult with a very rapidly advancing subject to include all of the most recent knowledge in a book of this kind. There are inevitable delays which are more annoying and frustrating to the contributors than to anyone else, since they mean constant revision if the writing is still to be topical at the time of publication. Every effort has been made to ensure that this is so and the opportunity is taken here of thanking

the contributors for all the efforts which they have made to this end. I would also like to thank those authors, editors and publishers who have kindly allowed illustrations from their works to be reproduced.

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CHAPTER 1

PROBLEMS OF GENERAL NUTRITION IN CLINICAL MEDICINE

G. A. SMART

The Calorie Balance

SINCE energy is derived from chemical processes it is inevitable that the body should maintain a calorie balance with its environment. This fundamental concept can be represented as follows:

Calorie value of food intake = heat output (cal.)
+ calorie value of urinary organic chemicals
+ calorie value of faecal organic constituents
+ change in calorie value of body tissue.

In normal health the body weight remains substantially constant over long periods of time and under these conditions the proportions of various tissues do not significantly change. It follows, therefore, either that the calorie value of food intake is accurately correlated with energy expenditure or that if the calorie intake varies there must be a corresponding variation in one or more of the three other terms of the equation. It can easily be shown experimentally that substantial changes in calorie intake are not associated with any corresponding change in the calorie value of faeces and urine. It is technically a good deal more difficult, however, to measure the total heat output of the body over long periods of time, and the question has often been posed whether changes in calorie input are followed by compensatory changes in heat output. The chemical processes involved in the metabolism of nutrients require in themselves a certain amount of energy, particularly in the case of protein materials (the specific dynamic action), so that to some extent there may be an increase in heat production and loss with an increase in calorie intake. This, however, is small and is in no way sufficient to maintain the equilibrium of the equation. The possibility of any additional change in heat loss in association with an alteration in calorie intake has been carefully investigated by many workers, in particular by Wiley and Newburg (1931) and more recently by Pass-

more, Meiklejohn, Dewar and Thon (1955). There has in fact been no evidence of substantial change, either in basal metabolic rate or in the metabolism resulting from activity, which would compensate for changes in calorie intake.

The evidence fully summarized by Newburg (1942) would thus seem to point to the likelihood that calorie balance is ultimately maintained to the largest extent by regulation of the intake. This would appear superficially to be a somewhat surprising conclusion at variance with everyday experience. During discussions of this kind one is always reminded of people who remain lean despite a large appetite, and of others who tend to become fat although their food intake is only moderate. The work already quoted, however, by Passmore and his co-workers was carried out on lean individuals who were able to increase their calorie intake from 2100 to 4000 per day. There was no evidence of a significant increase in metabolism nor decrease in absorption resulting from the increased intake of calories, and the subjects did in fact gain weight, although not as much as would have been expected from a consideration of their calorie balance. Moreover, it has been shown by McCance and his associates (Edholm, Fletcher, Widdowson and McCance, 1955; and Booyens and McCance, 1957) not only that the basal metabolic rate of normal individuals may depart from the average of normals much more than was at one time anticipated, but that the amount of energy expended when lying, sitting, standing or at other forms of exercise might also be very different from individual to individual. Thus different people, outwardly similar, might expend very different quantities of energy although their activities might not appear to be so very different. Those who carry out their daily activities efficiently in the physical sense require a smaller calorie intake to maintain weight than their more thermodynamically inefficient counterparts. This does not mean that persons who tend easily to get fat necessarily use less energy in standing, sitting or lying, etc., than thin people; such people evidently have an appetite which tends to cause them to ingest more calories than in fact they require.

It is important, therefore, to inquire into the mechanism of appetite regulation and of satiety and into any other factors which control the amount of food which is eaten. It is obvious that the capacity of the organism itself will set crude outer limits to the intake of food, and it may be that this partly determines the frequency with which patients who have had a partial gastrectomy are found to be underweight. However, that the crude mechanical limitation of stomach distension is not crucial in the normal animal has been suggested by Adolph (1947). He showed that in young rats the calorie content of the diet seemed to be the overriding factor which governed the amount of food ingested.

Nor would it appear that hunger contractions which have been

shown to exist both in animals and in man (Quigley, 1955), and which greatly increase the drive to obtain and eat food, are more than a crude but urgent mechanism which tends to set a lower limit to the food intake. They would certainly seem to be of minor importance in communities where food is easy to come by.

In 1940 Hetherington and Ranson discovered that animals with certain lesions confined to the hypothalamus would become obese, and this obesity was shown by Brobeck, Tepperman and Long (1943) to result from hyperphagia. Subsequent work suggested that another centre existed in the hypothalamus, destruction of which caused aphagia (Anand and Brobeck, 1951). On the basis of these findings it has been suggested by Brobeck (1955) that two centres exist, one a satiety centre, situated medially, destruction of which causes hyperphagia by increasing the level of satiety, and the other an appetite centre, situated laterally, destruction of which will cause aphagia because of a complete lack of appetite. Thus increased food intake may result from overactivity of the appetite centre (more frequent eating) or from underactivity of the satiety centre (bigger meals); by contrast the intake of food will be decreased if the appetite centre is underactive or if the satiety centre is overactive so that smaller meals are eaten. How the particular activity of each of these centres is controlled so that the normal precise calorie balance is maintained has not yet been shown. Brobeck (1948) has suggested that it is the specific dynamic action of the ingested food which is mainly responsible, that a centre is sensitive to temperature changes. Although it is possible that this may be one factor, Kennedy (1952) has produced evidence which would suggest that it probably plays only a minor part, if any, and seems to be of little importance when causes of experimental obesity are considered. The work of Gasnier and André Mayer (1939) would suggest that there is a short-term day-to-day regulation of food intake, dependent in some way upon energy requirements, and that there is in addition a long-term mechanism which can correct errors in the day-to-day regulation and which is related in some way to body weight.

Jean Mayer (1955) has put forward evidence suggesting that appetite is dependent upon the rate of utilization of glucose. Thus there will be no desire to eat when glucose is being rapidly utilized—when there is a large difference between concentrations of glucose in arterial and venous blood; by contrast, an increase in appetite will occur when there is little difference between these concentrations (Van Itallie, Beaudoin and Mayer, 1953; and Mayer, 1953). It should be noted, however, that several investigators have failed to suppress food intake in animals or subjective desire for food in humans (Bornstein and Grossman, 1956); by means of intravenous infusions of glucose. It was also noted by Bruce and Kennedy (1951) that, apart from changes in palatability or

gross adulteration, the calorie intake of hyperphagic or lactating rats remained much the same regardless of the composition of the diet. This would suggest that metabolites other than glucose might be involved in the regulation of food intake.

Kennedy showed that his hypothalamic rats ate ravenously whilst they were gaining weight, i.e. during the 'dynamic' phase of their obesity. Eventually, however, having reached a state of considerable obesity, the static phase, the food intake dropped so that it was not very different from that of a normal rat. When such rats were underfed they lost weight, only to regain their excessive appetite so that when again fed *ad libitum* they would eat large quantities until they had again regained their former excessive weight. Adulteration of the food by means of kaolin during the dynamic phase resulted in greatly increased intake, so that the total calorie intake remained much the same; when the static stage had been reached, however, adulteration resulted in a decreased calorie intake and weight loss. These findings would indicate that even these animals with a damaged hypothalamus have some form of regulation of body weight, that they have a 'preferred' weight at which they tend to remain as a result of changes in food intake.

It has also been found (Kennedy, 1952) that intact rats, nursing litters of ten to twelve, in order to produce maximum lactation, ate even larger quantities than rats rendered hyperphagic from hypothalamic damage. Furthermore, if the medial hypothalamic nuclei of such rats were damaged there was no marked tendency for them to become obese until lactation had ceased. Rat milk has a high fat content, and it seems possible that the maximum rate of disposal of fat might be a factor which limits food intake.

Adipose tissue, thought at one time merely to be a relatively inert storehouse of excessive calories, has been shown in fact to be an active tissue in dynamic equilibrium with the rest of the body. Wertheimer and Shapiro (1948) and Bates, Mayer and Nauss (1955) have produced evidence which suggests that, under conditions where food is freely offered, the amount of fat mobilized daily is proportional to the total size of the fat depots, and the findings of the latter group of workers also suggest that there are probably metabolic differences in different types of experimental obesity. It is suggested that the accumulation of excessive fat in hypothalamic rats and gold thioglucose mice is largely secondary to the hyperphagia, whereas in mice of the hereditary obese type there is an inherent metabolic defect with increased synthesis and decreased mobilization of fat. As pointed out by Mayer, these findings are complementary to those of Alsonso and Maran (1954), who found that hereditary obese hyperglycaemic mice, after prolonged periods on restricted diets so that they weighed 30% less than their control littermates, nevertheless had several times more fat than these controls.

Clinical Considerations

The experimental and chemical considerations discussed above are likely to have, in due course, some importance in the clinical field. In man, however, other factors, such as food habits and emotional changes, assume a greater importance than would appear to be the case in animals. It is not proposed to discuss weight change arising from hypothalamic lesions or endocrine abnormalities; attention will be confined to a consideration of so-called simple obesity and to the effects of marked loss of weight.

It is important, however, that consideration should first be given to the criteria by which a subject may be said to be underweight or overweight. Figures for the mortality rates and the incidence of various disorders in relation to body weight are largely derived from insurance statistics, and are thus mainly concerned with deviations in body weight for height from the average. There is no justification for accepting the average as the ideal; indeed, there is much to suggest that the average weight is higher than the ideal weight (the ideal weight being that associated with the minimum amount of physical disability and the greater longevity) in most countries where the food supply is relatively plentiful (Marks, 1956). Ideally one would like to obtain some knowledge of the amount of adipose tissue present, of the amount of extracellular fluid and of the amount of bone. The rest of the body weight would be made up of more or less metabolically active tissue. These estimations might be of particular importance if the results produced by Kurlander, Abraham and Rion (1956), which suggest that in *men* components in body-build other than adipose tissue are the factors which produce the association between a heavy body weight and a high incidence of cardiovascular disease, are shown to be correct.

Estimates of the total amount of adipose tissue in the body have been made by measurements of body specific gravity—either by weighing the patient under water or by estimating his total body volume. This latter estimation is carried out by placing the patient in an enclosed space of known volume and measuring the pressure of air in the enclosure; a tap is then opened which joins this space with another of known volume containing air at a known and different pressure from the vessel enclosing the patient. The final equilibrium pressure in the whole system is read and from the figures obtained the volume of the patient can be determined. The temperature of the system must of course be carefully controlled. Estimates of the proportion of total body weight contributed by adipose tissue then depend upon the assumption that the specific gravity of the 'lean-body mass' is 1·103, whereas that of adipose tissue is 0·93 (Behnke, Osserman and Welham, 1953). It is obvious that these are only approximate assumptions and are likely to be more or less correct only if there is no abnormality of water and electrolyte

metabolism involving an increase in extracellular fluid on the one hand or dehydration on the other.

Since it has also been found that the proportion of water in the lean-body mass is 72%, and since, apart from a small amount of extracellular fluid, adipose tissue is almost anhydrous, the proportion of adipose tissue in the body has been estimated from measurements of total body weight and total body water—the latter being measured by the dilution of substances such as heavy water, urea or antipyrine, which are evenly distributed throughout all the water phases of the body. Again this method of estimation suffers from grave errors in the presence of abnormalities in water metabolism and consequently it has been refined by estimating total body water *and* extracellular water (inulin or thiocyanate space) and thus intracellular water—which is much more constant, constituting about 67% of the lean-body mass, and being virtually absent in adipose tissue (McCance and Widdowson, 1951).

Probably the most useful means of estimating adipose tissue for clinical use is by measuring skin-fold thicknesses. This method has been investigated in particular detail by Edwards (1950), who has designed a special caliper which exerts a constant pressure (10 g. per mm.^{2}) between its jaws (Edwards, Hammond, Healy, Tanner and Whitehouse, 1955), by Brožek (1955), by Brožek and Keys (1951), by Garn (1954) and by others. The skin-fold is some measure of the thickness of two layers of skin plus two layers of the underlying subcutaneous tissue, and of course it varies greatly from one part of the body to another. From these measurements some estimate can be made of body density and thus of total body fat (Pascale, Grossman, Sloane and Frankel, 1956), certainly for young men. A serious disadvantage, however, consists in the fact that no allowance can be made for relatively greater deposits of internal fat which occur with increasing age; nor is the method suitable in cases of endocrine abnormality in which fat distribution might be quite abnormal.

Edwards (1956) considers that when a change in body fat occurs as a result of a change in calorie balance, all the cells of adipose tissue are equally affected and that there is thus a proportionate change in skin-fold thicknesses at all sites. This view is supported by the work of Garn (1954), who found that the pattern of fat deposition changed little during a weight drop of as much as 11%.

Suggestions have also been put forward whereby a clinical estimate of skeletal size and of musculature can be made. Body height and the greatest distance between the lateral margins of the iliac crests are probably the best indicators of the size of the skeleton, and the diameter of the upper arm, corrected for skin-fold thickness, can give a good estimate of musculature ("Recommendations", 1956).

Simple Obesity

Whether from emotion, from habit or from some underlying, as yet undetected, metabolic abnormality resulting in a wrong control of body weight, simple obesity is one of the commonest nutritional problems in those countries where food is easy to obtain. The ill effects on general health, on morbidity and mortality are well known and will not be considered in detail. Very little work has been done on the long-term effects of weight reduction in obese people, for only a small proportion of obese people do in fact reduce their body weight to normal and keep it there. It has been shown by Fellows (1931), however, that those who maintain a reduced weight suffer less from those conditions known to be associated with obesity than similar subjects who remained obese. It would also appear that a small but significant fall in blood pressure may occur with weight reduction (Adlersberg, Coler and Laval, 1946; Ley, 1939). There has been some criticism of this view, partly because change in the arm diameter will affect the blood-pressure reading as obtained by the usual indirect method, but Danowski and Winkler (1944) do not consider this factor to be of much significance. It is, of course, also well known that the diabetes of obese diabetics may show a very considerable improvement with weight reduction. Dublin (1953), in a careful statistical appraisal of the mortality rates of obese subjects who reduced their weight, concludes that the resultant mortality rate was considerably less than that of those subjects who did not reduce.

A perusal of the literature reveals how difficult it is to induce obese patients to lose weight and to maintain the lower weight which they may attain. In general it is probable that the long-term failure rate is in the order of 70–80% (Rony, 1940). Although various substances are now available which appear to depress appetite, it has been the experience of the author that one is doomed to failure unless the patients can be completely and utterly convinced that they must lose weight and are consequently prepared to make the necessary effort of will to restrict food intake. As a rule, the first three to five weeks are the most difficult, and patients should be informed of this. During this time they feel hungry, sometimes light-headed and weak, and they become very sensitive to cold. Subsequently, after weight reduction has taken place, these patients must control their food intake by measurements of body weight. If appetite is relied upon they will revert to their previously obese state.

From the considerations given above it would appear that a diet involving a simple and adequate reduction in calorie intake would be sufficient to cause a reduction in body weight. Provided such a diet contains enough protein, the weight loss accrues solely from a loss of fat; cellular tissue is not broken down (Newburg, 1944). Exact and

elaborate diets have been constructed which will do this, and naturally, where the psychology of the situation is so important, some will be more suitable than others for any individual patient. However, in general the author has found that patients tend not to confine themselves to diets which are too rigid, too elaborate or too far removed from an ordinary dietary régime. The most flexible and easily understood diet and one which invites a considerable degree of collaboration from the patient is that devised by Marriott (1949). This is in fact more a 'guide to eating' than a therapeutic diet, and in practice it has been found to work very well, producing a fall of some 2–4 lb. in body weight per week.

MARRIOTT'S REDUCING DIET

1. Eat or drink as much as you like (or can get) of:

   Lean meat, poultry, game, rabbit, hare, liver, kidney, heart, sweetbread—cooked in any way, but *without the addition of flour, breadcrumbs or thick sauces.*

   Fish (not tinned) boiled or steamed only; *no thick sauce.*

   Eggs, boiled or poached *only.*

   Potatoes, boiled, steamed, or baked in skins, but *not fried, roast, sauté or 'chips'; not potato powder.*

   Other vegetables of all kinds (fresh, tinned or dried), cooked in any way not involving the use of fat.

   Salad and tomatoes *without oil or mayonnaise.*

   Beetroot, radishes, watercress, parsley.

   Fresh fruit of any kind, including bananas. Also bottled fruit, if bottled without sugar. *Not tinned or dried fruits (including dates, figs and raisins).*

   Sour pickles, *not sweet pickles or chutneys.*

   Clear soup, broth, 'Bovril', 'Oxo', 'Marmite'.

   Salt, pepper, mustard, vinegar, Worcester sauce (*no other sauces*).

   Saccharin for sweetening.

   Water, soda-water and *non-sweetened* mineral waters.

   Tea and coffee (milk only as allowed below).

2. You may have milk (not condensed) up to half a pint daily.
   No cream.
3. You may have three very small pieces of bread per day, and take them either one at each main meal or all three at one meal as desired ('very small' means *not exceeding* 1 *oz.*).
4. You may have *nothing else whatever*: particularly note that this means:

   No butter, margarine, fat or oil (except for cooking meat, *not fish*).

   No sugar, jam, marmalade, honey, sweets, chocolate, cocoa.

   No puddings, ices, dried or tinned fruits, nuts.

   No bread (except as above) cake, biscuits, patent reducing breads, cereals, oatmeal, 'Albran', 'Ryvita', 'Vitawheat'.

No barley, rice, macaroni, spaghetti, semolina, sausages, cheese.
No cocktail savouries, alcohol (beer, cider, wines and spirits).

Weigh before you begin, and thereafter weekly, on the *same scales* in the *same clothes*, and at the *same time of day*.

Some authors have suggested that better results can be obtained by restricting carbohydrate and giving a lot of fat. In particular, Pennington (1953) summarized evidence which suggests that there may be some metabolic abnormality in obesity. He further postulates that in obese subjects there is a lowered rate of mobilization of fat per unit of adipose tissue, and that this is compensated for by an increased total of fatty tissue. Obesity, he suggests, might be considered as a compensatory hypertrophy of adipose tissue allowing for an increased use of fat by a subject who suffers from an impairment in the ability to oxidize carbohydrate. Acting upon this theory he prescribes a diet in which only carbohydrate is restricted. Protein and fat are allowed *ad libitum*. He finds that patients on such a régime derive roughly 80% of their energy from fat and 20% from protein. The total calorie intake varies from 2000 to 3100 calories per day. Each of the three meals of the day contains 6–9 oz. of lean meat and 2–3 oz. of fat (cooked weight). In addition, not more than 60 g. of carbohydrate may be taken in the day. On such a régime he claims that patients lose weight satisfactorily at a rate of about 2 lb. per week; moreover, they do not show the usual tendency to relapse which is so common on diets based on a simple reduction in calories. Recently, Kekwick and Pawan (1956) have published some curious findings with regard to the rate of weight reduction of obese individuals on isocaloric diets of varying fat, protein and carbohydrate content. They kept the water and salt intake constant and measured total body water by the urea-dilution method of McCance and Widdowson (1951). They found that patients lost weight more rapidly when they were on a high-fat diet than when they were on a high-protein or high-carbohydrate diet of the same total calorie value. Moreover, whereas five obese patients maintained or slightly gained weight over a seven-day period on a 2000-calorie diet containing similar proportions of protein, fat and carbohydrate to that found in an average diet, four of them actually lost weight when the calorie value was increased to 2600 per day, there being increased proportions of fat and protein in the diet. Measurements of body water by the urea method revealed that its proportion to body weight remained unchanged. There was no difference in the proportion of nutrients absorbed, and measurements of BMR revealed no significant difference when the patient was on the different diets. The insensible loss of water was estimated in some patients, and it was found to increase when the diet was high in carbohydrate and fat. Calculation shows that the difference in the latent heat

of evaporation is insufficient to account for the discrepancy in apparent calorie balance, but the authors feel that the difference in insensible water loss is some evidence of a change in metabolism.

In summary, it may be said that although in the last resort gain or loss of weight is a question of calorie balance, to regard this as the whole problem is grossly to oversimplify the situation. As a practical measure, however, restriction of calorie intake will produce a fall in body weight, and although a high fat intake may in some way also result in loss of weight in obese persons, a good deal more investigation is needed before this method of slimming should be generally applied; in particular, the effect of such diets on the production of arterial disease needs careful elucidation.

Loss of Weight

Just as simple obesity results from an intake of calories greater than metabolic requirements, so loss of weight may result from the opposite, from the ingestion of fewer calories than are required. Loss of weight can also occur, however, if the metabolism becomes deranged or if there is a deficient intake of some essential nutrient, so that either the full utilization of the calorie value of ingested nutrients becomes impossible or certain tissues are unable to maintain themselves in the normal fashion. The appetite is, of course, nearly always depressed in these situations.

The effects of undernutrition have been very fully described by Burger, Drummond and Sandstead (1948), Keys, Brožek, Herschel, Mickelsen and Taylor (1950) and by McCance (1953) among others. The observations were made on subjects who were living under famine conditions or who were experimentally subjected to an over-all deficiency in food intake. The syndrome described, therefore, was that which arose in previously healthy subjects, and thus hunger and mental changes associated with an intense 'drive for food' were very prominent. These naturally are not frequently found in clinical conditions associated with inanition, since other factors such as toxaemia, an initial anorexia or nausea and vomiting are usually present. Nevertheless, the physical changes resulting from the inanition are usually seen in malnourished patients whatever the cause.

If the patient is obese the first stage of inanition consists in a loss of body fat, for, even when the protein intake is quite low, there may be no net loss of nitrogen during loss of weight in obese subjects. Thereafter the patient begins to lose nitrogen in excess of intake, and since this is accompanied by a loss of potassium in protoplasmic proportions it would seem that a break-down of cellular material was occurring. Animal studies would indicate that the greatest loss occurs from voluntary muscles, the heart and the alimentary tract. On the other hand,