THE SIGNIFICANCE OF PROTEINS IN NUTRITION THEIR PARTICULAR IMPORTANCE DURING CONVALESCENCE*

BY

D. P. CUTHBERTSON, M.D., D.Sc.

Director, Rowett Research Institute, Aberdeen

The protein component in nutrition is one of the most fascinating of all fields for study, for it deals with the essential fabric of growth, repair, and reproduction and with other dynamic expressions of vital activity involving continuous chemical change such as the maintenance of the osmotic relationships in the tissue fluids, immunity mechanisms, enzyme systems, and hormones.

Quality

There are some 23 different amino-acids in the body, and these are built up into the tissue proteins in the varying linkages and groupings which give to the tissue proteins their peculiar properties. These proteins thus subserve in some way or another the structural and functional requirements of the body, and variations in functional activity are coupled with greater or lesser difference in amino-acid make-up of the proteins concerned. Proteins subserving the same function in various species have differences in the proportion or arrangements or even in the numbers of these different amino-acids. Thus Williamson (1944) has shown that the proteins of human and cows' milk differ in the proportions of certain of the amino-acids, tryptophan in particular, and Mellander (1945) has shown that the caseins of human and cows' milk vary in their phosphorus content. The contradictory reports about the nutritive value of haemoglobin are apparently due to variations in the amino-acid composition of the haemoglobins of different species. Dog haemoglobin is deficient in methionine but not in isoleucine, while the reverse holds for human haemoglobin (Brand and Grantham, 1946). Prosthetic groups of carbohydrate origin—e.g., as in the pneumococcal antigens—or of lipin (see Cohn *et al.*, 1944) may give additional specificity to the proteins.

The proteins of our food are the exogenous source of the amino-acids or specific groups required by the body, and as a group they are relatively stable, though liable to suffer a slight change in molecular character on treatment—namely, the process of denaturation—which generally makes no appreciable difference in regard to utilization of the particular protein, although this physico-chemical change is of great assistance in cooking and baking. I need only instance the vast array of appetizing egg dishes, curds and cheese, and the texture of bread as examples of this.

Following ingestion, the proteins are digested by the hydrolytic proteases of the alimentary tract; the amino-acids so formed are then absorbed. There is some evidence that certain peptides or even larger fragments are absorbed

in small quantity as such. While the body has the faculty of synthesizing certain of these amino-acids or specific groups, others either cannot be synthesized at all or only at a very slow rate. Diets must therefore contain proteins which, when acting in supplementary fashion, will provide all the essential amino-acids required and sufficient nitrogen to provide for general purposes. It is very necessary that no key amino-acid be lacking, otherwise it will form a limiting factor in growth or even in maintenance. Dissociation in time of ingestion of the essential amino-acids, even though all the necessary ones are provided within the 24 hours (Henry and Kon, 1946), has been demonstrated to lead to inefficient functioning, as all are required at the same time. Further, dissociation in time of ingestion of protein and carbohydrate leads to an inefficient use of the protein (Cuthbertson and Munro, 1939; Cuthbertson, Munro, and McCutcheon, 1940). Better utilization is also obtained when the day's intake is spread over a number of meals than when it is divided over only two meals.

During the 1914-18 war, and in the years which followed, it became customary to divide dietary proteins into two groups, depending on the degree to which the proteins conformed to the then known requirements of man. It became the practice to regard the edible proteins of animal origin (gelatin as the main exception) as being in the first-class category and those of vegetable origin as second-class. These decisions were based on a few incomplete analyses and biological tests of the pure proteins rather than of the mixed proteins of the foodstuffs concerned. Nevertheless, this division was useful and served its purpose in drawing attention to the differences in amino-acid composition.

As the result of careful observation upon himself Corry Mann (1935) obtained evidence which suggested that there were pronounced differences in the biological value of such first-class proteins as those of meat and milk, and that the most likely explanation of his results was to be found in the superior quality of the milk proteins. Credit for pointing out the supplemental action of the proteins, not only in individual foodstuffs but in the diet as a whole, rests mainly with Mitchell (1924) and Terroine (1936). The natural selection of foodstuffs, even when entirely of vegetable origin, seems to permit adequate supplementations, but it is necessary to note that cereals tend to be low in lysine. The terms first- and second-class protein as applied to the mixed proteins in animal and vegetable proteins would appear in this sense to be meaningless provided there is sufficient protein in the diet and that the calorie requirements are fully met. Nevertheless the protein-rich animal foodstuffs are in part the vehicle of our intake of many vitamins, particularly the fat-soluble, and of many essential

*Read in opening a discussion in the Section of Nutrition at the Annual Meeting of the British Medical Association, Cambridge, 1948.

minerals. The full story of their contribution to the diet has not yet been completely unfolded, and the significance of natural selection in this sense must be explored.

In addition to the major differences in amino-acid composition which characterize the proteins, minor differences in the nutritive value of the proteins of a single foodstuff can be induced by certain natural and artificial means. The studies of Everson and Heckert (1944) have demonstrated that the growth-promoting qualities of legumes seem to vary with the source, the degree of inactivity of the seed, and the method of cooking used. These observers found that all the mature legumes, except peas, were improved by the heating procedures employed. Severe heat treatment of wheat and oat cereals during certain forms of processing confirm the detrimental effects noted by earlier workers (Murlin *et al.*, 1938; Stewart *et al.*, 1943). More recently Melnick *et al.* (1946) have shown that the biological value of soya and oat flours and of milk processed in different ways is related to the rate of release of amino-acids, particularly methionine, during digestion. Treatment of proteins during processing or cooking may thus alter the biological value of the product.

Mellanby (1946) has made the very important discovery that wheat-flour "improved" by the agene process, involving treatment with nitrogen trichloride, produces canine hysteria or, as it is called in the U.S.A., running fits when given as food to dogs. More recently ferrets have been shown to be susceptible (Mellanby, 1947). Mellanby considers that a toxic factor is produced in association mainly with the gliadin and glutelin fractions, and that the clinical signs are not due to a deficiency disease. Moran (1947) has also provided evidence against the deficiency theory, and has shown that not only the gluten fraction of flour but also certain other, but not all, proteins are capable of giving rise to canine hysteria when similarly treated. Further observations by Moran and his colleagues (Bentley *et al.*, 1948) have indicated that methionine has a unique capacity to react with nitrogen trichloride, but that other amino-acids may also be implicated.

Protein Allowances for Health

The term "allowance" has come to be used in place of "requirement," as no satisfying data exist to provide us with a real knowledge of actual requirements.

Protein is man's chief source of nitrogen and sulphur, and the rate of supply obviously conditions growth, maintenance, repair, reproduction, and lactation. This is its primary function. It can also serve as a source of energy, but in this respect it would apparently be no more useful than carbohydrate and fat unless its simultaneous metabolism with these substances is advantageous, or unless in virtue of its specific dynamic action under certain conditions it is peculiarly suited for those exposed to cold.

It may well be that our intake of protein-rich foodstuffs is also bound up with a need for those other essential nutrients contained in these foodstuffs and with the improvement in palatability and attractiveness of the diet which results. It is therefore possible that for these reasons we take in more protein than is strictly necessary, and also to safeguard against any special requirements that may arise. Very few diets exist in which the proportion of the calories derived from protein falls below 10%, and the level for a particular population tends to remain constant at all ages (except infancy) and at all grades of muscular activity. On the whole, people eat more or less of a mixed diet according to energy requirement.

If those races which are by circumstance predominantly carnivorous are excluded, then the percentage of the total energy derived from protein before 1939 lay generally

between 10 and 14%, and, whenever economic circumstances permitted, the intake of protein of animal origin was raised to the region of 60% of the total protein. How far this qualitative change is bound up with a real need for animal protein of a high biological value without requiring too much variety in foodstuffs, as in the case of the vegetarian, or for other dietary essentials associated with protein in these animal foodstuffs, is impossible to state. There is no doubt that the more attractive flavour and culinary properties of animal protein and its more easy assimilation are contributory factors, but it is possible for people to live and reproduce on diets containing little if any protein of animal origin.

To approach the problem from the experimental side is also very unsatisfactory. There have been three different types of assessment:

1. This is based on the requirement to replace the specific endogenous nitrogen expenditure, together with the requirements for the laying down of any fresh tissues or the expansion of existing tissues or for milk production. A correction is then made for the biological value of the proteins used. Such work is of considerable interest, but involves experimenting under highly artificial conditions. Generalization on dietary requirements from such data cannot be viewed with equanimity.

2. Nitrogen-balance experiments in which nitrogen equilibrium is established at low intakes of protein. The values obtained are thus maintenance requirements but are again the result of a restricted regime. To convert the maintenance requirements into "standard" allowances an empirical 50% has been added by some workers. The scale of this empirical addition is undoubtedly influenced by that required to bring the values into line with customary feeding habits.

3. Tests to determine experimentally the point to which protein intake can be reduced without any impairment to health and physiological efficiency. Such experiments, being of long duration, become monotonous, and psychological difficulties complicate the issue. Further, children and pregnant and nursing women cannot be subjected to such tests.

In the present state of our knowledge I believe that it is much safer to view our allowances in terms of the dietary habits of the best-nourished section of the community and to pay particular regard to the proportion of the total calories derived from protein. This gives us a measure of protein allowance which is safe. It may be regarded as providing too much protein at higher levels of energy intake, but, as the protein intake naturally rises *pari passu* with the calorie intake, it would in any event be extremely difficult to alter natural selection.

There is evidence that the physique of children is improving—Tuxford (1942) has had to alter his index of nutrition in the course of a quarter of a century; therefore, by basing protein intake on energy expenditure for age rather than directly on age, changing levels of intake are safeguarded.

On the basis of their study of children from 1 to 17 years whose restriction in food selection was at a minimum, Holt and Fales (1921, 1922) found that protein averaged 15% of the calories. Gephart's (1917) investigation of adolescent boys in a private school in America indicated that 14% of the calories were derived from protein. Wait and Roberts (1933) obtained a value of 12.4% for adolescent girls living in institutions in the same country. Polteva *et al.* (1935) found that in Russia the corresponding level was 13%.

Widdowson (1947), from her study of the individual diets of children—largely "middle-class"—found that one of the most constant features of the diets was the constancy of the percentage of the total calories derived from protein by children of various ages. The average levels for each age group fell within the range of 11 to 14%.

With regard to infancy, little can be said with confidence except that during the suckling period, when growth is most active and when presumably a perfect mixture of proteins is being consumed, the percentage of the total calories derived from protein ranges from 6 to 9%, according to the analyses quoted by the different authorities concerned. Adding 50% to the 9% gives 13.5%, which might safely cover the requirements of the weaning period and the next 12 months. Cows' milk has some 20% of the calories present as protein.

It should be noted that during the current period of sugar and fat restriction the percentage of calories derived from protein occupies a slightly greater proportion of the calories than was the case in more normal times. It is in the region of 12 to 14%.

It is suggested that an investigation is necessary to determine the level of calorie requirements by ages from 0 to 21 years based on the smoothed-out curves of the best data available for the best-nourished section of the child and adolescent population (Widdowson's might well serve as a basis unless some better data are available), and then to calculate the corresponding allowances for protein as described in the foregoing paragraphs. Similarly the various categories of adults can be treated, probably placing pregnant women during the latter half of pregnancy and nursing mothers at the upper end of the range.

Protein Deficiency

If the diet is insufficient in energy value, and if energy expenditure is not reduced, proteins which would have been available for growth, maintenance, or reproductive functions may be deflected to meet the energy demands. After the first day or two of starvation some 13% of the calories expended by the body are derived from protein, the rest from fat. The addition of carbohydrate or fat spares this wastage of body nitrogen which occurs on diets that are inadequate in energy. When carbohydrate or fat in excess of energy requirement is added to a normal diet a considerable storing of nitrogen and sulphur takes place (Cuthbertson and Munro, 1937). How long this goes on is uncertain and may depend on the body's facility to raise its metabolic rate. This may well be a highly individual characteristic and account for differences in energy intake by persons of apparently similar build.

At one time it was thought that the proteins could wax and wane in molecular structure without serious alteration in property, but it is now known that the large number of different proteins found in the body remain true to type, and that while alterations in the quantity and quality of protein in the diet or fluctuations in its energy value do not apparently induce the body to form imperfect or unusual proteins they may influence the total or relative amounts of the different proteins in the tissues or tissue fluids. But this does not mean that the proteins, even of the fabric of the body, are in a stable state. The work of Schoenheimer (1942) and his collaborators (Heidelberger *et al.*, 1942) has demonstrated that this apparent stability is in reality a dynamic equilibrium in which the proteins are participants in a constantly changing metabolic mixture and in which carbohydrates, fats, and other compounds take part.

For a long time it was thought that there was a store of protein in the body like that of fat in adipose tissue, but the search revealed only some waxing and waning in liver cytoplasm. The easily lost fraction of liver cytoplasm has been called "labile liver cytoplasm" in contrast to the "remaining liver cytoplasm" (Kosterlitz and Campbell, 1945-6). The view is now held that the body has the capacity to lose and replenish again its protein content by the increase or decrease of the existing and characteristic protein components of these tissues. The observations of

Upadhyay (1944) have shown that an intake of protein sufficient to prevent anaemia in the non-pregnant woman may be insufficient when she is pregnant. Due account must be taken of the haemodilution of pregnancy.

In general it may be said that from the dietetic standpoint deficiency of protein intake is generally coupled with a deficiency in calories. Evidence of these combined deficiencies were found only too often in the prisoners of war and political prisoners in the hands of our enemies in Europe and the Far East. The investigations of Keys and his collaborators (1946) on normal men subjected to a profound restriction in calorie intake has added considerably to our knowledge.

Vaughan, Dent, and Pitt-Rivers (1945) found that the best vehicle for administering protein to starving subjects was skim-milk rather than a hydrolysate of casein, but that occasionally it might be necessary to give intact protein by vein as plasma or serum.

Jorpes, Magnusson, and Wretling (1946) seem satisfied that an enzymic hydrolysate of casein fed as a supplement to breast milk produces an accelerated weight gain over breast milk alone. Loehle (1946) advocates the value of human plasma by mouth as the sole nutrient for the first day of life for premature infants and of plasma in addition to other foods thereafter.

Four types of diet for babies have been tested out by Albanese *et al.* (1947)—namely, an evaporated milk mixture, a mixture based on an enzymic digest of casein, a similar digest of lactalbumin, and an acid digest of casein supplemented with tryptophan and cystine. The retention of nitrogen and the weight gain of the infants while on the acid digest of casein mixture were respectively about 30 and 50% lower than those obtained when the same subjects were given synthetic diets based on enzymic digests of casein or lactalbumin. The biological value of the enzymic digests was about the same as the evaporated-milk mixture. It is thought that the acid digest of the casein lacks certain peptide-like substances ("strepogenin").

Plasma Proteins

Oedema is a frequent concomitant of a diet low in calories which thus causes a relative or absolute deficiency of protein. Keys *et al.* (1946) produced it experimentally in 34 normal men who lost a quarter of their body weight while subsisting for six months on a European type of semi-starvation diet consisting of whole cereals, potatoes, turnips, etc., providing an average of 49 g. of protein daily. Pitting oedema appeared within two months in some of the men and eventually in all but a few. The ratio of extracellular water to cellular water was doubled. It is of interest to note that this development of oedema was accompanied by only a slight decline in plasma protein concentration, averaging 0.73 g. per 100 ml. Meanwhile the venous pressure had fallen to some 50% below normal. The evidence seems to indicate that it is not simply a result of hypoproteinaemia or of renal or cardiac abnormality. It should be noted that the hypoproteinaemia only predisposes to oedema, and that where dehydration is superimposed it may not be seen until treatment with fluid begins.

Anorexia is a potential and sometimes direct cause of insufficient food intake. It is well known that when there is a deficiency of an essential amino-acid in the diet of experimental animals anorexia often ensues. Diarrhoea or undue intestinal hurry may be a cause of impaired absorption of amino-acids. Experience at Belsen concentration camp indicated that hydrolysed protein passed largely unabsorbed through the guts of many of the inmates.

The work of Whipple (1942) has emphasized the part played by the plasma proteins in relation to protein

metabolism, and recent experiments have shown that in experimental dietary deficiency some 30 g. of albumin are retained for each 1 g. of albumin in the circulation. This dynamic equilibrium between plasma protein and tissue protein means that a fall in plasma albumin concentration of 1 g. per 100 ml. implies a loss of protein of over 1 kg. In terms of actual muscle this is equivalent to 4 kg. In pregnancy, but more particularly in lactation, there is an increased demand for protein which must be met by an increased intake of food. The development of the mammary gland and its ability to secrete milk is determined by the food intake during the period of mammary development. This my colleagues have shown to occur in sheep. The effects of deficient intake of food during the latter half of pregnancy increased the number of neonatal deaths, and deficient lactation caused many deaths within the first 72 hours after parturition, especially in the case of twin lambs.

Not all proteins appear to be equally useful in the maintenance of a normal level of protein in the plasma (Madden and Whipple, 1940; Whipple, 1942). Per unit of protein fed, beef serum will favour the production of three times as much plasma protein as beef heart, and more than five times as much as beef stomach; there is thus a qualitative as well as a quantitative aspect to the influence of animal proteins. Casein and lactalbumin have also high potencies. Animal protein is twice as effective as vegetable protein in combating oedema and hypoproteinaemia. Under certain conditions sulphur-containing amino-acids occupy a key position in the synthetic process (Whipple, 1942; Himsworth, 1946).

The evidence points to the liver as being of primary importance in the production of plasma proteins, although some globulins may be produced elsewhere. The association of hyperglobulinaemia with proliferation of the reticulo-endothelial system suggests that certain of the globulins of the plasma may possibly arise in that tissue.

Factors adversely affecting protein nutrition, such as direct or indirect starvation, haemorrhage, etc., lead to a fall in the plasma albumin while the plasma globulin is but little affected. These changes may affect the plasma proteins of the foetus, as my colleagues have found in the case of the sheep. The relatively small size of the albumin molecule permits leakage in conditions of increased permeability—e.g., inflammation. Albumin is apparently synthesized more slowly than globulin, and mild damage to the liver seems to affect its formation. Where the protein intake is satisfactory and yet there is a fall of albumin due to deficient formation or loss from the circulation there may occur a slow, apparently compensatory rise in the globulin, probably to offset the lowered osmotic pressure due to the plasma protein.

Haemoglobin

Hahn and Whipple (1939) have clearly demonstrated that by limiting the protein intake in anaemia haemoglobin production can be reduced. When the erythrocytes disintegrate, much of the globin is saved and is probably used again to form a new haemoglobin or to supply some other protein needs of the body. Infection and to some extent nephritis in its later stages (Whipple, 1942) modify haemoglobin production. Robschey-Robbins, Madden, Rowe, Turner, and Whipple (1940) have found that in dogs given an abundant supply of iron, but fed to maintain a blood level of about one-third normal, two to three times as much haemoglobin was produced as plasma protein even when the stimulus was apparently maximal.

Protein Regeneration following Partial Starvation

The pattern of recovery of the blood proteins following extreme protein insufficiency has been described by

Rossiter (1946). In his study of Indian prisoners of war who had a normochromic macrocytic anaemia at the time of their liberation he found a reduced serum protein concentration coupled with their reduced body weight, the former being almost entirely confined to the albumin fraction of the plasma proteins. There was also a reduction in the total circulating haemoglobin as well as in the total circulating plasma protein. When these ex-prisoners of war were given a diet rich in calories, protein, and vitamins the above factors returned to normal according to a definite pattern. The first stage, lasting up to four weeks, was characterized by a rapid rise in plasma volume to normal and the disappearance of oedema. The improvement in the haemoglobin and haematocrit reading was not so rapid, but the red cells quickly became less macrocytic. The total circulating plasma protein increased, but because of the rapid rise in plasma volume the plasma protein concentration changed but little. More albumin was formed than globulin.

The second stage (2 to 12 weeks) was characterized by a rise in plasma volume to well above normal. There was also a rapid increase in body weight and in total circulating haemoglobin and plasma proteins. The total circulating albumin increased more rapidly than the globulin, but the latter did eventually reach figures in excess of normal. The third phase (8 to 16 weeks) was marked by a return to normal values.

Immunity

The evidence is fairly conclusive that antibody properties are associated with specific modifications of the globulin molecule, but the definition of the relation between plane of protein nutrition and antibody response is by no means as clear as some workers would make out. Antibody production during active immunization appears to be a continuous process of production and shares in "labelled" N^{15} which has been added to the diet. On the other hand, passive antibody formation during passive immunity seems to have little relation to dietary nitrogen (Heidelberger *et al.*, 1942). How far antibody formation is affected by competition for available amino-acids in conditions of protein under-nutrition is not quite clear. It would appear that in animal experiments severe hypoproteinaemia is coupled with a loss of ability to produce antibodies of several kinds (for review see Cannon, 1944), but in man conditions seldom develop which cause a pronounced reduction in the level of globulin in the blood.

My colleagues, Dr. J. W. Howie and Dr. E. I. McDougall, have confirmed in the sheep that there is a direct correlation between the rapid decrease in globulin level and antibody titre in ewes' colostrum in the first few days after lambing, and that there is a correlation between the absorption of globulin and antibody ingestion of colostrum by the newborn lamb—a specialized phenomenon which has no parallel in later life. They have further found that the proteinuria of the newborn lamb after ingestion of colostrum is essentially globulin, and it retains the specific antibody properties of that developed in the mother in response to the particular antibody used.

Convalescence

Convalescence is the recovery of health and strength after illness. The illness may have been of sudden or insidious onset; it may have been the result of infection, abnormal metabolism or growth, or trauma; it may afflict the healthy, or it may supervene when the individual is poorly nourished.

On the surgical side protein depletion may also result from conditions affecting the ability to ingest, digest, and absorb sufficient food, and it may also occur as the result

of disuse atrophy, infection, and as a consequence of trauma, which includes surgical operations, fractures, dislocations, and burns. One, if not the main, problem of convalescence is the restitution of tissue loss. On the medical side protein deficiency may result from impaired digestion and absorption, excessive catabolism in fever, impaired synthesis in liver disease, and loss in certain types of nephritis, ascites, and haemorrhage. Reference will now be made to a few out of many clinical states. No reference will be made to liver diseases in relation to protein intake, as Dr. Glynn will deal with this aspect.

Trauma

The protein depletion which follows moderate to severe injury is due essentially to two or more of five main causes: (a) loss of actual tissue; (b) loss of blood or exudate from the damaged area; (c) loss due to excessive protein catabolism which normally follows injury and subsequent surgical manipulations; (d) loss due to infection if that is superimposed; and (e) disuse or reflex atrophy (Cuthbertson, 1947).

During the period of traumatic shock there is a pronounced reduction in anabolism and catabolism. This then gives way to what seems to be a generalized catabolic phase coupled with local anabolic activity at the zone of healing. In injuries such as fractures, dislocations, and even meniscectomies the protein loss is generally due to two factors: atrophy, and excessive catabolism of body protein (Cuthbertson, 1932; Beattie, 1947). Of these two factors the excessive catabolism of protein, which reaches a maximum usually between the fourth and eighth day in injuries due to direct violence, constitutes the major cause of protein depletion. Following the peak of nitrogen loss there is a gradual decline, though subsequent surgical procedures may cause further disturbance. Even after a month there may still be a slight negative nitrogen balance, but normally there is a slow merging into a general anabolic phase (Schenker, Stevenson, and Browne, 1946). In burns all five causes generally operate to produce a considerable loss of body nitrogen. In man the negative nitrogen balance in the first ten days after a fracture of the leg may amount to a loss of as much as some 856 g. of protein, or 8% of the total body protein (Cuthbertson, 1932). This is some three to four times the total protein content of the liver. Although it would appear that this organ cannot be the source of the material catabolized, nevertheless it may play a vital part in the catabolic path of material supplied to it from other tissues. Occasionally this catabolic phase is not seen or occurs only to a small extent.

Disuse atrophy, though a contributory factor, does not provide an adequate explanation (Cuthbertson, 1929; Keys, 1944). The increased catabolic processes are more general than local, and seem to be conditioned by a reflex mechanism which leads either to the raiding of the body protein reserves in order to supply endogenously the necessary substrate of amino-acids or peptide groups for the reparative process or to a mobilization of oxidizable material for the enhanced metabolism of the healing process. The fact that there is a parallel rise in the excretion of nitrogen and sulphur, at least in fracture cases, suggests that there is not a preferential retention of the sulphur-containing amino-acids. It has been suggested that the reflex exists in order to render the healing process independent of food supply (Cuthbertson, 1932). The so-called "toxic destruction of protein" in fever may be explained in this teleological fashion. Wild animals when ill or wounded seek security in hiding until they recover or die. The innate reparative processes must operate irrespective of an exogenous supply of energy or repair material.

When an animal has been depleted of its protein reserves no increase in the rate of loss of body protein occurs on fracture (Munro and Cuthbertson, 1943). Madden and Clay (1945) have shown somewhat the same effect in acute sterile inflammation. The greater the proportion of protein in the diet before and after injury, the greater the nitrogen loss (Munro and Chalmers, 1945). Browne *et al.* (1945) have also noted the apparent absence of a catabolic response after operation or injury in persons in a poor nutritional state at the time of injury.

Attempts have been made to stem the catabolic loss of protein by (a) substantial increases in the energy and/or protein value of the diet, or (b) by administration of amino-acids singly (e.g., methionine), as mixtures, or as hydrolysates given intravenously. The evidence is now weighted against methionine having an effect in diminishing the negative nitrogen balance in burns where the previous diet is not deficient in methionine but yet the loss of cystine is quite considerable (Gribble, Peters, and Wakelin, 1947; Sellers and Best, 1947; Meyer, Hirshfeld, and Abbot, 1947). Emerson and Binkley (1946) have reported a retention of nitrogen in a few cases in which the ten amino-acids which are essential for the growth of the rat were given intravenously. An increase in the protein content of the diet did not apparently have a similar effect. But much more evidence is needed, and I am doubtful if there is any real merit in such lines of parenteral therapy when the patient's ability to ingest and absorb normal dietary proteins is not impaired.

Pre-operative Treatment

Despite substantial increases in the intake of abundant protein-rich food by patients with moderate or serious injuries it was found that a negative nitrogen balance generally, but not always, exists at the height of the catabolic period (Cuthbertson, 1936). A similar situation has been reported in acute infections (Peters, 1944). I consider that there is no special need to worry unduly about the loss of nitrogen following injury in the previously well-nourished patient; its measure is rather a measure of the nutritive state of the organism in respect of protein. Where, however, the patient is debilitated before operation it is considered that the ingestion of a diet adequate in protein should be instituted before the operation, for this realimentation is as effective or more effective pre-operatively than corresponding increments made available in the post-traumatic phase, because a condition of nutritional imbalance is usually present in the latter state.

Satisfactory nutritional preparation will undoubtedly extend the benefits of surgery to a group of patients who in the past have often been denied surgery on the basis that they were too poor a risk. Wherever possible the pre-operative steps should involve not only restoration of the water and electrolyte equilibrium but so far as is possible a high-protein high-carbohydrate diet fed, where necessary, by tubal methods. Skim-milk powder has been shown to have many advantages as the principal source of protein in the pre-operative diet of cases in which there is difficulty in management. Varco (1946) has described a regime for the pre-operative treatment of patients classified as "poor risks." Diet 1 consisted of 160 g. of protein, 407 g. of carbohydrate, 18 g. of fat (2,426 calories, 1.6 calories per ml. of fluid diet); diet 2 consisted of 120 g. of protein, 409 g. of carbohydrate, 37 g. of fat (2,446 calories, 1.6 calories per ml.). This was a less tasty diet rendered suitable for feeding by a nasal tube.

In non-obstructive cases there is presumably adequate enzymic activity without having recourse to predigestion measures. The diets of Varco have applications to the treatment of cases with neoplasms of the colon,

sigmoid, and rectum and of patients with burns. Varco has suggested that when the loss in body weight is at least 5 to 10%, three to five days of proper treatment are sufficient. When the loss approaches 20%, 10 to 12 days of proper feeding are necessary, and three weeks are necessary when the loss approximates 25 to 30%.

A more recent prescription by Varco (1947) for a high-protein, high-calorie diet is made up of six whole eggs, two egg whites, 4 oz. of skim-milk powder, 300 g. of lactose or cane sugar, 1,000 g. of skim-milk, and 5 gr. (0.32 g.) of salt, and is estimated to provide 2,446 calories and 120 g. of protein in 1,500 ml. When this is the sole diet Varco recommends about 3 litres, equivalent to 4,900 calories. This recent line of treatment is very suggestive, although it does not yet provide concrete proof that such measures of nutritional readjustment can yield a margin of safety for the patient requiring surgery in spite of previous and co-existing deleterious influences on metabolic processes. The clinical evidence in support of this thesis is certainly worthy of consideration and confirmatory trial.

There is no doubt that too much stress has been placed on forced feeding of surgical cases. Those who have had clinical experience of burns know that it is almost impossible to force-feed patients during the first few days after injury, when fluid and electrolyte balances are becoming adjusted and the illness is at its height.

I have on many occasions stressed the limitations in the use of protein hydrolysate and would deplore much unsound physiology shown by many workers in this field of therapeutics who give the hydrolysate by mouth even when the patient can adequately hydrolyse intact protein. Although Cox and Mueller (1939), Elman and Weiner (1939), and many other later observers have recorded a measure of success with intravenous alimentation by protein hydrolysates and glucose, some using it as a means of total feeding, these preparations nevertheless possess some very distinct limitations owing to the large volumes which have to be given and the time taken—90 g. of protein takes eight to nine hours and a volume of 2,500 ml. (Elman, 1943)—the febrile reactions, nausea, and vomiting which may occur, and the thrombophlebitis which often results through prolonged intravenous treatment. Plasma and glucose are safer fluids. An extensive study of a mixture of the ten essential amino-acids and glycine as an 8% solution has been made by Spence, Evans, and Forbes (1946), but the end-result is somewhat equivocal. Six-molar sodium lactate was given separately to provide a base when the amino-acids were given intravenously.

Subsequent operative procedures may accentuate the degree of negative balance, as the metabolizable material required for the processes of repair may necessitate a further breakdown of protein. This latter response is known to be conditioned by the nutritive state of the organism.

I consider that the immediate phase of protein catabolism is related to the healing process and should not be interfered with. There is little point in trying to supply the patient with food in excess of that which appetite dictates. In severe injuries involving prolonged convalescence every reasonable step should be taken to maintain, if not to extend, the patient's intake so as to make good the tissue losses. A diet of high energy and high protein content is required. An intake of 150 g. of protein a day is often desirable. The amount of protein which is lost in extensive burning can be very great indeed (Cuthbertson, 1945).

Fever

Leaving out of account external causes and certain peculiar forms of hyperthermia, fever generally arises from an infection or in a milder form as a result of trauma—

traumatic fever. In both forms the basal metabolism is increased. For every degree Fahrenheit rise in temperature there is a 7% increase in the basal metabolism. At the height of the fever appetite fails and the energy required comes from a utilization of the tissues. In addition to a loss of fat, an increased excretion of nitrogen, sulphur, and potassium occurs, indicating an actual breakdown of tissue material. The situation is rather analogous to starvation, where some 13% of the energy expended comes from protein and the remainder from fat. The destruction of protein is apparently due neither to the raised metabolism nor to the fever, for the protein breakdown in fever is greater than in normal subjects whose metabolism has been elevated to the same degree by exercise (Kocher, 1914) and is not induced by external sources of hyperthermia (Graham and Poulton, 1912–13). The hyperthermia in traumatic fever is generally very slight unless there is infection.

In *acute febrile illnesses*—e.g., pneumonia—the outcome is generally a matter of a few days, and the diet should be such as to save the patient from undue exertion. There is usually no need to worry about the actual amount of food eaten. It is sufficient to provide small and frequent feeds of milk or milk plus egg, sweetened fruit juice, and, later, light cereal dishes. Nevertheless, in the acute phase of certain infectious conditions, even although there is evidence of a catabolic phase, unless it can be shown that generous diets are injurious, efforts to feed such patients should not be abandoned.

In *long-continued fever*—e.g., typhoid fever—it is necessary to prevent undue loss of body tissue, and for this purpose the diet should have as high an energy and protein value as possible without causing ill effects. The aim is to try to secure an intake about 50% above the normal maintenance intake. A high-carbohydrate diet has a protein-sparing effect, and it should be given in a readily digestible form—large meals being avoided. The protein intake should be such as to offset the catabolic loss of tissue protein which takes place particularly during the height of the fever. It should be noted that it is generally impossible to establish nitrogen equilibrium at this stage. Small semi-solid or fluid meals every two to three hours is a good regime. The protein required is readily obtained if two pints (1.14 litres) of milk are used daily. As the patient improves, the diet is modified by the addition of toast or bread with butter or margarine, milk puddings, custards, stewed or fresh fruit, chicken, rabbit, and fish. During convalescence it is wise not to push the patient to take quantities of food beyond his normal capacity.

Diseases of the Kidney

Apart from rest in bed and protection from cold, dietetic measures constitute the most important part of treatment in acute nephritis. In subacute and chronic nephritis with oedema, massive proteinuria, and hypoproteinaemia, a properly constructed diet is of both symptomatic and general value. In chronic nephritis without oedema but with failure in renal concentrating power there is much less satisfactory evidence that dietetic treatment will delay to any considerable degree the final onset of uraemia. For this reason, and because of the chronicity of the disease, it is unwise to insist on premature or too rigid dietetic restrictions which may depress the patient and impair his strength without appreciably improving his primary lesion (Davidson and Anderson, 1947).

The aims in treating nephritis by dietary means are: (1) to spare the diseased kidneys—particularly in acute nephritis; (2) to prevent uraemia—i.e., the accumulation of waste products; (3) to prevent oedema, which is caused by retention of water and salts; and (4) to maintain nutrition.

Apart from acute or subacute nephritis, or in states of renal insufficiency with marked nitrogen retention, the protein intake should be maintained at normal levels.

REFERENCES

- Albanese, A. A., Holt, L. E., Irby, V., Snyderman, S. E., and Lein, M. (1947). *Bull. Johns Hopk. Hosp.*, **80**, 149, 158.
- Beattie, J. (1947). *British Medical Journal*, **2**, 813.
- Bentley, H. R., Booth, R. G., Greer, E. N., Heathcote, J. G., Hutchinson, J. B., and Moran, T. (1948). *Nature*, **161**, 126.
- Brand, E., and Grantham, J. (1946). *J. Amer. chem. Soc.*, **68**, 724.
- Browne, J. S. L., Hoffman, M. M., Schenker, V., Venning, E. H., and Weil, P. (1945). *Conference on Bone and Wound Healing*, Josiah Macy Jr. Foundation, **9**, 15.
- Cannon, P. R. (1944). *J. Amer. diet. Ass.*, **20**, 77.
- Cohn, E. J., Oncley, J. L., Strong, L. E., Hughes, W. L., and Armstrong, S. H. (1944). *J. clin. Invest.*, **23**, 417.
- Cox, W. M., and Mueller, A. J. (1939). *Proc. Soc. exp. Biol., N.Y.*, **42**, 658.
- Cuthbertson, D. P. (1929). *Biochem. J.*, **23**, 1328.
- (1932). *Quart. J. Med.*, n.s., **1**, 233.
- (1936). *Brit. J. Surg.*, **23**, 505.
- (1945). *Brit. med. Bull.*, **3**, 96.
- (1947). *Ann. Rev. Biochem.*, **16**, 153.
- and Munro, H. N. (1937). *Biochem. J.*, **31**, 694.
- (1939). *Ibid.*, **33**, 128.
- and McCutcheon, A. (1940). *Ibid.*, **34**, 1002.
- Davidson, L. S. P., and Anderson, I. A. (1947). *A Textbook of Dietetics*. Hamilton, London.
- Elman, R. (1943). *Med. Clin. N. Amer.*, **27**, 303.
- and Weiner, D. O. (1939). *J. Amer. med. Ass.*, **112**, 716.
- Emerson, K., and Binkley, O. F. (1946). *J. clin. Invest.*, **25**, 184.
- Everson, G., and Heckert, A. (1944). *J. Amer. diet. Ass.*, **20**, 81.
- Gephart, F. C. (1917). *Boston med. surg. J.*, **176**, 17.
- Graham, G., and Poulton, E. P. (1912-13). *Quart. J. Med.*, **6**, 82.
- Gribble, M. de G., Peters, R. A., and Wakelin, R. W. (1947). *J. Physiol.*, **106**, 36P.
- Hahn, P. F., and Whipple, G. H. (1939). *J. exp. Med.*, **69**, 315.
- Heidelberger, M., Treffers, H. P., Schoenheimer, R., Ratner, S., and Rittenberg, D. (1942). *J. biol. Chem.*, **144**, 555.
- Henry, K. M., and Kon, S. K. (1946). *J. Dairy Research*, **14**, 330.
- Himsworth, H. P. (1946). *Proc. R. Soc. Med.*, **40**, 27.
- Holt, L. E., and Fales, H. L. (1921). *Amer. J. Dis. Child.*, **22**, 371.
- (1922). *Ibid.*, **24**, 311.
- Jorpes, J. E., Magnusson, J. H., and Wretling, A. (1946). *Lancet*, **2**, 228.
- Keys, A. (1944). *Conference on Bone and Wound Healing*, Josiah Macy Jr. Foundation, **7**, 90.
- Taylor, H. L., Mickelsen, O., and Henschel, A. (1946). *Science*, **103**, 669.
- Kocher, R. A. (1914). *Dtsch. Arch. klin. Med.*, **115**, 82.
- Kosterlitz, H. W., and Campbell, R. M. (1945-6). *Nutr. Abstr. Rev.*, **15**, 1.
- Loehle, J. F. (1946). *J. Pediatr.*, **28**, 145.
- Madden, S. C., and Clay, W. A. (1945). *J. exp. Med.*, **82**, 65.
- and Whipple, G. H. (1940). *Physiol. Rev.*, **20**, 194.
- Mann, H. C. C. (1935). *Lancet*, **1**, 145.
- Mellanby, E. (1946). *British Medical Journal*, **2**, 885.
- (1947). *Ibid.*, **2**, 288.
- Mellander, E. (1945). *Acta paediatr.*, **32**, 668.
- Melnick, D., Oser, B. L., and Weiss, S. (1946). *Science*, **103**, 326.
- Meyer, F. L., Hirshfeld, J. W., and Abbot, W. E. (1947). *J. clin. Invest.*, **26**, 796.
- Mitchell, H. H. (1924). *Physiol. Rev.*, **4**, 424.
- Moran, T. (1947). *Lancet*, **2**, 289.
- Munro, H. N., and Chalmers, M. I. (1945). *Brit. J. exp. Path.*, **26**, 396.
- and Cuthbertson, D. P. (1943). *Biochem. J.*, **37**, 12P, 396.
- Murlin, J. R., Nasset, E. S., and Marsh, M. E. (1938). *J. Nutr.*, **16**, 249.
- Peters, J. P. (1944). *Fed. Proc.*, **3**, 197.
- Polteva, J. K., Gube, A. M., Popov, K. F., and Smirnova, A. M. (1935). *Probl. Nutr., Moscow*, **4**, No. 3, 13.
- Robschey-Robbins, F. S., Madden, S. C., Rowe, A. P., Turner, A. P., and Whipple, G. H. (1940). *J. exp. Med.*, **72**, 479.
- Rossiter, R. J. (1946). *Nature*, **158**, 304.
- Schenker, V., Stevenson, J. A. F., and Browne, J. S. L. (1946). *Fed. Proc.*, **5**, 91.
- Schoenheimer, R. (1942). *The Dynamic State of Body Constituents*. Cambridge, Mass.
- Sellers, E. A., and Best, C. H. (1947). *British Medical Journal*, **1**, 522.
- Spence, H. Y., Evans, E. I., and Forbes, J. C. (1946). *Ann. Surg.*, **124**, 131.
- Stewart, R. A., Hensley, G. W., and Peters, F. N. (1943). *J. Nutr.*, **26**, 519.
- Terroine, E. F. (1936). *Quart. Bull. Hlth Org. L.O.N.*, **5**, 427.
- Tuxford, A. W. (1942). *J. Hyg., Camb.*, **42**, 549-51.
- Upadhyay, S. N. (1944). *Indian med. Gaz.*, **79**, 193.
- Varco, R. L. (1946). *Surgery*, **19**, 303.
- (1947). *Surg. Gynec. Obstet.*, **84**, 611.
- Vaughan, J., Dent, C., and Pitt-Rivers, R. (1945). *Proc. R. Soc. Med.*, **38**, 395.
- Wait, B., and Roberts, L. J. (1935). *J. Amer. diet. Ass.*, **9**, 403.
- Whipple, G. H. (1942). *Amer. J. med. Sci.*, **203**, 477.
- Widdowson, E. M. (1947). *Spec. Rep. Ser. med. Res. Coun., Lond.*, No. 257. London.
- Williamson, M. B. (1944). *J. biol. Chem.*, **156**, 47.

BRONCHIAL CARCINOMA*

BY

R. C. BROCK, M.S., F.R.C.S.

Thoracic Surgeon to Guy's Hospital; Surgeon to the Brompton Hospital

The surgical treatment of bronchial carcinoma is now fully established and is generally accepted as the most desirable treatment of this condition at our disposal. Indeed, the success of surgery has placed bronchial carcinoma among the curable diseases, in marked contrast to the position it held a few years ago, when its diagnosis was synonymous with a death sentence. At the same time it is still a terrible disease with a high mortality, and we must remember that operation is possible in only a minority of cases. Furthermore, the importance of the problem it presents can be realized when it is stated that it occurs nearly as often as carcinoma of the stomach and of the colon.

With the establishment of the successful surgical treatment of bronchial carcinoma it becomes more and more imperative that the disease should be recognized at an early date so that the patient can be referred to the surgeon while operation is still possible. The operative technique is now largely standard, and although there will doubtless be further improvements, notably in regard to a more radical operation, the surgeon's place in treatment is now largely defined. He is, however, powerless to effect a cure unless he receives patients suitable for operation; it is impossible for him to save the advanced case. It follows, therefore, that the most important task in the management of this terrible disease lies not so much with the surgeon as with the general practitioner and the consultant physician, who are usually the first to see these patients. Although the ultimate act of treatment is in the surgeon's hands, the greatest responsibility and the greatest chance of saving the patient's life unquestionably lie in the hands of the earlier medical attendants.

I have often thought, when contemplating a patient successfully operated upon, that his life has been saved not so much by surgery as by the doctor who first made the diagnosis and who directed him to a surgeon. For this reason I will give a simple presentation of the leading clinical features of the disease, and especially the early symptoms and signs; the part that surgery plays is described chiefly to emphasize the need for early diagnosis.

Clinical Features of Bronchial Carcinoma

Bronchial carcinoma varies considerably in its pathology, in its clinical manifestations, and in the duration of the illness it causes. Occasionally one sees patients who have lived several years with the disease, more particularly elderly patients with a slowly growing squamous-celled growth. These are the exception, and it must be remembered that the average expectation of life from the time the patient first consults his doctor is no more than six months; therefore it is useless to spend three to four months making a diagnosis and to expect the disease to be still in a curable phase. This is especially true in the case of patients below the age of 50. It is almost a truism to-day to plead for early diagnosis in cases of cancer, but the urgency justifies the emphasis.

The most important step in making a diagnosis of any disease is to think of it. So often the patient with a cancer of the lung has been observed or treated empirically

*Read in opening a discussion in the Section of Diseases of the Chest at the Annual Meeting of the British Medical Association, Cambridge, 1948.