PROCEEDINGS OF THE
NUTRITION SOCIETY

TWENTY-EIGHTH SCIENTIFIC MEETING—FIFTEENTH ENGLISH MEETING

LONDON SCHOOL OF HYGIENE AND TROPICAL MEDICINE,
MAY 26TH, 1945

NUTRITIONAL FACTORS AFFECTING WOUND HEALING

Chairman, Professor J. R. LEARMONTH

Dietary Protein in Relation to Convalescence from Injury

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As protein forms the bulk of the organic constituents of the tissues and body fluids it is only natural that the process of protein metabolism involved in the repair of the injured zone should be the object of much study, particularly in war time. Histological study has taken us far in our appreciation of the repair process and it should not be forgotten that nearly all the staining reactions of the histologist are dependent on reactions with the proteins of the tissues.

At the close of the last war very little information existed concerning the biochemical changes involved in the healing process. I have discussed elsewhere these earlier observations (Cuthbertson, 1934, 1942, 1944). I wish now to deal with developments which have taken place during the last fifteen years and concerning which I have had a peculiar interest. That our Canadian and American colleagues are sharing in this is indicated by the number of conferences on this subject which have been held in America under the auspices of the Macy Foundation and of the American Physiological Society (1944).

Convalescence is the recovery of health and strength after illness. The act of applying external measures to speed up the return of the patient to normal, particularly by physiotherapy, occupational therapy and psychosomatic means, has been termed rehabilitation. Rehabilitation measures should be applied from the time a disability is sustained to the point when the individual resumes a normal existence or one as near to it as any irreversible change will permit.

Loss of Body Protein Due to Injury

The protein depletion which follows moderate to severe injury is due essentially to one or more of five main causes: (1) loss of actual tissue; (2) loss of blood or exudate from the damaged area; (3) loss due to

the excessive protein catabolism which normally follows injury; (4) loss due to infection if that be superimposed; (5) disuse or reflex atrophy. If, for example, a rough assessment is made of the protein losses during the first 10 days or so, in a case with a 60 per cent. burn involving the whole thickness of skin, the following quantitative data may be obtained (Cuthbertson, 1945):

(1) Protein lost in the mass of skin and other underlying tissues destroyed, together with the leucocytic response involved in the separation of the sloughs, 700 g.

(2) Protein lost in the exudate from the "weeping" surface, especially in superficial burns, but present also during sloughing and the granulation period, when the exudation may be copious, 600 g.

(3) Protein lost through the catabolic reaction to trauma which involves considerable urinary loss of nitrogen as urea, equivalent to some 700 to 800 g. protein.   This reaction to trauma is accompanied by slight fever ("traumatic fever").

(4) Protein lost through the coccal infections of the first week and the abundant, mixed coccal and bacillary infections of the second to fourth weeks when the necrotic tissues are separating.   It is, however, impossible to give a value to this fraction of the total loss. The continued fever and chronic suppuration lead to a continued loss of tissue protein.

(5) Protein lost through atrophy due to disuse and to reflex action may possibly be in the neighbourhood of 100 g.

(6) Protein lost through skin grafting operations which, though probably not inducing further catabolic loss of protein, nevertheless contribute in some measure to the state of depletion as further loss of blood and plasma occurs.

In injuries, such as fractures, dislocations and even meniscectomies, the protein loss is due to two factors, atrophy and excessive catabolism of body protein (Cuthbertson, 1929, 1932, 1936; Howard, Winternitz, Parson, Bigham, Eisenberg, Stein and Reidt, 1944, 1, 2).   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.   Its nature has recently been reviewed (Cuthbertson, 1942, 1944, 1945; J. P. Peters, 1944; Armstrong, 1944; Howard, 1945, 1).   In passing it is of interest to note that nearly 80 years ago Bauer (1872) reported an increased loss of nitrogen after haemorrhage, a finding confirmed later by Hawk and Gies (1904).   The latter demonstrated that even the operation of venesection without "blood letting" is sufficient to cause a slight rise in nitrogen and sulphur output in the dog.

The available evidence indicates that the excessive amounts of nitrogen mainly as urea, sulphur mainly as inorganic sulphate, and phosphorus as inorganic phosphate, which appear in the urine are derived from protein, and the magnitude of the $S:N$ ratio suggests that they are derived from muscle protein.   In addition there is a loss of creatine and potassium (Cuthbertson, 1931, 1932, 1936; Cuthbertson, McGirr and Robertson, 1939; Howard, 1945, 1).   In the writer's experience the

negative nitrogen balance in the first 10 days after a fracture of the leg may amount to as much as 137 g. nitrogen, equivalent to some 856 g. protein or 8 per cent. of the total body protein. This is some 3 to 4 times the total protein content of the liver and this organ cannot, therefore, be the source of the material catabolized. Disuse atrophy, though a contributory factor, does not provide an adequate explanation (Cuthbertson, 1929, 1942). The increased catabolic processes are more general than local and appear to be conditioned by a reflex mechanism which leads to a raiding of the body protein reserves in order to supply endogenously the necessary substrate of amino-acids for the reparative process and, perhaps, also to a mobilization of oxidizable material for the enhanced metabolism of the healing process and for the "alarm reaction" of Selye (1940). It has been suggested that this reflex exists in order to render the healing process independent of food supply (Cuthbertson, 1932). The so called "toxic destruction of protein" in fever also may be explained in this teleological fashion.

When an animal has been depleted of its protein reserves no increase in the loss of body protein occurs on fracture (Munro and Cuthbertson, 1943) and, more recently, Munro (1945) has found that, in animals with fractures, the greater the proportion of protein in the diet before and after injury, the greater the nitrogen loss. Howard (1945, 2), in some as yet unpublished observations, has noted that the marked nitrogen loss which takes place after contraction of chills in patients with malaria induced for the treatment of neurosyphilis, decreases in quantity with succeeding chills. J. P. Peters (1944) has pointed out that, in the malnourished subject, injury produces little or no rise in nitrogen excretion. That an increase in the protein and energy content of the diet plays some part in diminishing this loss of protein in fracture cases has been shown by the writer and his colleagues (Cuthbertson, 1936; Cuthbertson *et al.* 1939), but even diets of high calorie value, up to 5000 Calories, and of very high protein content, still fail to prevent a negative nitrogen balance at the height of the catabolism, a finding comparable to that noted by Shaffer and Coleman (1909) and by Lauter and Jenke (1925) in typhoid fever at the height of the infective process. Howard *et al.* (1944, 1, 2) have confirmed the writer's finding that the negative nitrogen balances at the height of the catabolic process still remain negative even when the calories and protein of the diet are raised to a considerable extent. A number of observations (Taylor, Levenson, Davidson and Adams, 1943; Taylor, Levenson, Davidson, Browder and Lund, 1943; Browne, Schenker and Stevenson, 1944; Hirshfeld, Williams, Abbott, Heller and Pilling, 1944; Hirshfeld, Abbott, Pilling, Heller and Meyer, 1944; Co Tui, Wright, Mulholland, Barcham and Breed, 1944) seem to show that it is possible to diminish this nitrogen loss by giving a diet of high carbohydrate and protein content, and the experimental work of Croft and R. A. Peters (1945) demonstrated that in burned rats the negative nitrogen balance can in a large measure be suppressed by doubling the protein intake or by including 1 per cent. of *dl*-methionine in the diet. This last and very important observation fits in with the conception that whole protein molecules are raided for one key amino-acid. It is very essential that this effect of methionine should be examined in man, in whom the protein loss is probably relatively greater than in the rat where there is little loss

by exudation.   Not only cystine and methionine are lost but a large number of other essential amino-acids as well.

After the catabolic phase where protein depletion is the most marked feature, the patient enters into a period when, through lack of appetite, the loss of protein is not rapidly made good. From the fourth to the eighth day onwards, after moderate and serious injuries, active steps should be taken to replace that which is lost.   Transfusions of blood, plasma or serum should already have been administered to correct their loss if this has been serious.   In previously depleted subjects this phase of excessive catabolism of protein apparently does not take place and active steps may be instituted at an earlier date.

Before discussing the effects of the quality and quantity of the diet, a brief account must be given of the post-traumatic anaemia and depletion of plasma proteins which accompany moderate and severe injury, and are related to protein depletion.

Post-traumatic Anaemia

The anaemia which develops after all serious forms of trauma has recently been the subject of much intensive study.   Grant (1944) found that loss of 20 per cent. of the total blood volume, about a litre in the average man, may be expected to reduce the haemoglobin level from 100 per cent. to about 85 per cent., usually within 48 hours after wounding, when the compensatory increase of plasma is complete or nearly so.   Loss of about 40 to 60 per cent. of the blood volume may be expected to reduce the percentage haemoglobin to about 70 and 50, respectively; the actual fall is often greater.   Blood volume studies show that, after injury, and although bleeding is arrested and obvious infection remains in abeyance, the red cell volume continues to decrease for several days at a rate that varies in different cases.   The meaning of this is not yet understood, but it is essential to take all possible steps to maintain the haemoglobin at a level of at least between 60 and 70 per cent.   It is still not known to what level the haemoglobin may fall without interfering with recovery from potentially infected wounds.

After the initial period of haemoconcentration in severe burns there is a reduction in the red cell level, a feature common to burns of almost all degrees, and Brown (1944) considers that this anaemia is haemolytic in origin, damage to a portion of the red cells occurring at the time of burning.   The anaemia tends to worsen in severe burns, reaching a maximum in 10 to 14 days.   How far it is due to sepsis and how far to depletion of body protein through injury is not easy to determine. Brown believes that failure of red cell production cannot explain the rapid development of a reticulocyte response which occurs in those who recover, and it would appear that, at this stage, marrow dysfunction is not a significant factor but, in the later stages, with failure to recover after one or more months, and without evidence of progressive blood destruction, defective marrow function may well be responsible for the chronic anaemia which persists until the body temperature has settled and the healing is well advanced.   This anaemia corresponds in many of its features with that seen in other chronic infections (Vaughan and Saifi, 1939).   Ryland (1942) has produced some evidence that depletion of body protein may be a contributory factor, but it is not conclusive.

Sepsis and the requirements for the repair of large areas of denuded tissue are the factors apparently responsible for the anaemia. When sepsis can be eliminated, the drain on body protein is reduced, healing is hastened, and anaemia generally disappears. The wasting or cachexia of the body consequent on wound sepsis has been termed by Rosakov (1943) "wound phthisis". It is obviously very important to determine how far there is an actual inhibition of haemopoiesis in response to a toxin, or how far the haemopoietic system suffers in competing for available protein with the area of healing.

A protracted period of protein deficiency leads eventually to marked atrophy of the liver, spleen, bone marrow and lymphoid tissues, and from these tissues most of the phagocytic cells originate. The absence of protein stores necessary for further construction of leucocytic reserves also may reduce the continued production of phagocytes. Further, the capacity of the antibody mechanism to respond effectively will determine both the extent and outcome of many types of infection, especially those which are otherwise imperfectly opposed by the forces of natural resistance. The problem of antibody production is only a part of the larger problem of protein synthesis, since antibody is but a specifically modified globulin. The γ globulin fraction consists of these modified globulins and constitutes about one-third of the globulin.

Depletion of Serum Proteins

The adverse effect of protein deficiency upon protein reserves and their capacity to generate serum proteins has recently been demonstrated by immunological and chemical methods in the white rat (Cannon, Wissler, Woolridge and Benditt, 1944). The fall in serum proteins which occurs particularly in severe burns is an indication that serious depletion of the plasma reserves has taken place. This fall mainly affects the albumin fraction.

It has been recommended that, if the total serum protein concentration in surgical cases is found to be less than 5 g. per 100 ml. serum, pre-operative protein repletion should, if possible, be attempted by the oral or intravenous administration of high quality proteins.

Replacement by Dietary Means of Protein Lost through Injury

The calorie requirements of an uninjured healthy person lying in bed are probably in the neighbourhood of 2100 Calories. The energy expenditure rises as the result of an injury, an infective process, or a condition which causes restlessness, but it is difficult to envisage for a person convalescing in bed a requirement greater than 3500 Calories.

Even normal subjects can be made to store nitrogen and sulphur if they ingest more energy-giving foods than are normally required by their energy expenditure and anabolic processes. The writer and his colleagues (Cuthbertson, McCutcheon and Munro, 1937; Cuthbertson and Munro, 1937) found that it was possible, by giving some 25 per cent. more calories than were required for maintenance, to induce a reduction in the urinary excretion of nitrogen and sulphur of some 3·72 g. and 0·28 g. per day, respectively, and this was accompanied by an increase in body-weight. Carbohydrate was superior to fat in this respect. When excess food is given the body appears to burn what it can, and store what it cannot burn. The capacity for storing carbohydrate being strictly

limited, storage of protein and fat takes place. This laying down of protein appears in the normal uninjured subject to be only temporary and, on resumption of a normal level of energy intake, the stored nitrogen tends to be excreted. In the anabolic phase of convalescence additional storage of protein may take place if the patient can be persuaded to take food in excess of his caloric requirement, for again the organism, confronted with more food than it needs, replenishes what has been depleted and stores what it cannot burn. It is not known whether the effect of this storage is to fill more quickly the void caused by the injury, or whether the protein is laid down as some purely temporary store which is readily catabolized when the intake of energy yielding foods again corresponds with the actual requirement. On the whole this would seem unlikely, but further investigation is necessary.

Protein generally forms some 10 to 12 per cent. of the total calories of the diet of adults in this country at all levels of energy expenditure (Cuthbertson, 1940). Even for the growing infant subsisting on its mother's milk, protein forms only some 8 per cent. of the calories, and this at a period when the energy requirements in relation to the anabolic requirements are low. When a variety of natural foodstuffs is used the body's normal requirements for the essential amino-acids or specific groupings will almost certainly be covered and the distinction between first and second class protein tends to disappear.

If attempts are made to establish nitrogen equilibrium in injured cases during the early catabolic period when the organism appears to have geared the non-injured parts to an anti-anabolic phase, it is found that with a rise in the protein intake more nitrogen appears in the urine. It is highly probable that in a previously well nourished subject the dictates of appetite will, in general, determine the optimum amount of food that is needed during this period, particularly in terms of the energy requirement and that there is no real indication to attempt forced feeding; indeed, this might even cause harm.

When the catabolic phase is diminishing about the fifth to ninth day, the patient, particularly if the injuries are burns, should be encouraged to eat as much as he conveniently can and, since the requirement of protein for repair and recovery of depleted reserves may be very considerable, enough of it should be present in the diet to meet the patient's needs during the recovery period. For this purpose it is essential that there should be sufficient carbohydrate and fat to cover the energy requirements and thus permit the maximum anabolism of tissue protein.

In convalescence a protein intake of 150 to 200 g. a day would appear to be indicated in, for example, the process of replacing gradually the 2 kg. of protein which may be lost during the first 10 days after infliction of a third degree burn extending over 60 per cent. of the body surface.

Milk, particularly separated milk, cheese, eggs, meat, poultry and fish should form the basis of the supply of animal protein, cereals that of vegetable protein.

In facio-maxillary injuries and other conditions where the administration of normal forms of food by mouth is precluded, it is most convenient to give the diet by tube. New preparations of dehydrated, high-protein, high-calorie food blocks are suitable for making such half-liquid foods. Ground meat with its extractives is appetizing. Ordinary milk

reinforced with dried skim milk, egg flips, cereal preparations, cream, and so forth have long been used for maintaining an adequate protein and calorie intake. It is always necessary to review such diets to ensure that there is no prolonged deprivation of any vitamin or mineral.

If it is required to increase the intake of protein when the energy requirement is already covered, this can most conveniently be done by reducing the amount of fat, which can be replaced by rather more than twice its weight of protein. Similarly, if it is desired to increase the total intake of food and the satiety value is being approached, non-fatty, protein-containing foods such as skim milk can generally be added to the diet between meals, particularly if suitably flavoured and made up as milk shakes (Stevenson, 1945). It is very necessary, however, to watch carefully for any tendency to reduce the intake of protein by too frequent feeding.

If an operation has to be performed on a patient depleted of protein, steps should be taken beforehand to replenish his tissues. It is not only unnatural but often distressing, and at any rate unpleasant, to be fed by tube or parenterally, and any departure from the normal way of feeding should be undertaken only if the patient's condition would otherwise be adversely affected. Where there is any state present likely to impair seriously the process of ingestion, digestion or absorption of food over a period of time, protein may be given in a predigested form with glucose.

Parenteral feeding must be regarded always as a temporary substitute for normal eating and should be confined to conditions where the ability to ingest, digest or absorb protein is seriously impaired. Complete alimentation with an enzymic hydrolysate of casein and glucose over a period of forty days has been recorded by Albright (1944).

The use of protein hydrolysates has recently been reviewed (Elman, 1943; Martin and Thompson, 1943; Gaunt, 1944; J. P. Peters, 1944; Cuthbertson, 1944). The general consensus of opinion is that an enzymic hydrolysate of casein can be obtained almost, if not entirely, free of pyrogens, and that this material can be injected intravenously without inducing untoward reactions. From the nutritive standpoint it is apparently an effective substitute for intact dietary protein. Obviously a safe product has distinct uses in conditions where through injury or disease the patient is unable to ingest or absorb from the intestine sufficient amino-acids to meet his requirements.

Casein hydrolysates are usually prepared in 5 per cent. concentration dissolved in 5 per cent. glucose solution, or a 5 per cent. solution of the hydrolysate is given simultaneously with a 5 to 10 per cent. glucose solution, the latter being administered at the same rate as the hydrolysate or twice as fast. Local thrombosis sometimes results, particularly during long infusions with higher concentrations. Care should be taken to see that the needle extends well within the vein beyond the insertion of a tributary and that it does not occlude the lumen. One and a half litres a day of a 5 per cent. solution is required to meet the normal basic requirement of 1 g. protein per kg. bodyweight. Since the amount of protein available for anabolic purposes is conditioned by the caloric value of the diet, the energy requirement should be covered by intravenous or oral feeding.

It has been customary in America to recommend that, before use,

enzymic preparations should be neutralized with NaOH to a pH of 6·5. When this is done a concentration of 0·3 g. NaCl per cent. usually results (National Research Council. Committee on Convalescence and Rehabilitation, 1944).

The rate of infusion of glucose should not exceed 0·85 g. per kg. bodyweight per hour, which represents roughly 10 ml. per minute. The rate of infusion of a 5 per cent. hydrolysate should probably not exceed 3 to 5 ml. per minute. With the administration of large quantities of solution there is a liability for oedema to develop, particularly in those who are on the verge of oedema from undernutrition or from the traumatic anuria or oliguria which generally occurs during the period of shock and for the ensuing 24 hours.

The members of the vitamin B complex appear to be needed for the optimum utilization of carbohydrate. During short and moderate periods of illness it is probably not necessary to supplement hydrolysates with vitamins but, if this type of therapy has to be continued over a period of time, daily doses can be given of 2 mg. aneurin, 2 mg. riboflavin, 20 mg. nicotinic acid, and 50 mg. ascorbic acid.

Shohl and Blackfan (1940), Madden, Carter, Kattus, Miller and Whipple (1943), and Bassett, Woods, Shull and Madden (1944) have demonstrated that mixtures of pure amino-acids are suitable for injection in conditions where parenteral administration is necessary for protein nutrition. Preliminary accounts would indicate that they can be given in higher concentration and with greater rapidity than hydrolysates without causing untoward reactions. These pure amino-acids are at present so costly that only a very few clinical experiments are possible at a time. Casein digests may be given orally or by gavage. Unfortunately they are rather unpalatable. Hydrolysates of meat may prove better.

J. P. Peters (1944) has stated that neither blood nor plasma appears to be as efficient a source of protein for general nutritive purposes as hydrolysates of high class protein, although they specifically correct anaemias and plasma protein deficits. Further investigation is, however, necessary, particularly in view of the observations of Fink, Enns, Kimball, Silberstein, Bale, Madden and Whipple (1944) that dog plasma given by vein can satisfy all the nitrogen requirements of the dog.

In this paper an endeavour has been made to outline the nature of the protein depletion which follows serious injuries, and the nutritional problem which confronts the clinician. Fortunately the resilience of the organism is such that it can survive and heal most serious injuries, provided the zone to be healed is not too extensive and provided infection is prevented or kept in abeyance. It is the patient with very extensive burns who presents the greatest problem. His need for protein is greatest and yet the very nature of his injury leads to anorexia.

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