Protein metabolism following injury

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An increased rate of breakdown of body protein following injury was described almost 40 years ago (Cuthbertson, 1930 and 1932). Patients with limb fractures were shown to have an increased rate of catabolism of tissue protein as demonstrated by nitrogen-containing products excreted in urine. More recently, further studies (reviewed

by Kinney, 1962) have elucidated some of the complex mechanisms of this catabolic response. It appears to be dependent on the severity of injury (Moore and Ball, 1952; Cuthbertson and Tilstone, 1968); on the environmental temperature at which the experimental animals or injured patients are treated after injury (Caldwell, 1967; Campbell and Cuthbertson, 1967; Cuthbertson, Smith, and Tilstone, 1968; Davies, Liljedahl, and Birke, 1969); and on the state of protein nutrition before injury (Munro and Chalmers, 1946; Abbott and Albertsen, 1963). It is probably independent of an intact nervous pathway between the site of injury and the brain (Davies, Liljedahl, and Reizenstein, 1970b).

In most patients with injuries other than burns there is a close correspondence between the increased rate of nitrogen excretion and the increase in the metabolic rate (Cairnie, Campbell, Pullar, and Cuthbertson, 1957; Kinney, 1962). A similar close correspondence has been observed in patients with extensive burns (Cope, Nargi, Quijano, Rovit, Stanbury, and Wight, 1957; Rabelo, Clark, and Kinney, 1961) and also between plasma albumin catabolism and nitrogen excretion in patients with burns and other injuries (Davies, Ricketts, and Bull, 1959). A less satisfactory correspondence (Fig. 1) has been found between plasma albumin and γ G globulin catabolism and basal metabolic rate in patients with burns treated in different environmental temperatures (Davies *et al.*, 1969).

Studies of the catabolic response to injury have been considerably assisted by the development of methods for the isolation of single plasma proteins and their trace labelling with radioactive iodine (McFarlane, 1964). These methods of isolation and labelling do not alter the biological functions or survival of the proteins if they are carried out with considerable care (Cohn, Freeman, and McFarlane, 1961; McFarlane,

Fig. 1 Comparisons in two burned patients between the rate of catabolism of plasma albumin and γ G globulin (as g/kg body weight) and the basal metabolic rate (BMR) as percentages above the expected normal value. The patient treated in the cool environment had a burned area covering 30% of the body surface, 10% being full-thickness skin loss; the patient treated in the warm environment had a burned area covering 50% of the body surface, 25% being full-thickness skin loss. The expected normal range of catabolism of albumin lies between 0.15 and 0.20 g per kg, and that for γ G globulin between 0.035 and 0.055 g per kg per day.

1963a). The usefulness of almost pure labelled plasma proteins in studies of the catabolic process has been enhanced by the observations mentioned above, that the rate of catabolism of plasma albumin closely corresponds to the rate of excretion of nitrogen in the urine from patients with a variety of injuries. Further examples of this correspondence are shown in Fig. 2 from patients with burns or other forms of injury of

minor or major severity. Comparison of the quantities of albumin catabolized and the total quantity of protein catabolized to give the amount of nitrogen excreted in the urine indicates that albumin contributes between 10 and 15% of the urinary nitrogen. As will be discussed in more detail below the remaining nitrogen is probably derived from the labile protein pool (Munro, 1964).

Fig. 2.

Fig. 2 The correspondence between the daily rate of catabolism of plasma albumin and the quantity of nitrogen excreted in the urine each day for two patients with burns and two patients with other forms of injury. The filled circles denote the patients with severe injury and extensive burns, the open circles the patients with the less severe injury and the smaller burned area.

Fig. 3 The rates of catabolism of albumin and γ G globulin (as g per kg body weight) in patients with minor, moderate, and severe injuries for two to three weeks after the accident. The open circles denote six patients with burned areas of different extent of the body surface. The filled circles denote six patients with other forms of injury of varying severity. The horizontal broken lines indicate the expected normal range of the catabolic rate of each protein.

Fig. 3.

Numerous studies of the catabolism of plasma albumin, gamma G globulin, and fibrinogen labelled with radioactive iodine have been made in patients with a variety of injuries arising from accidents or major surgery. These changes in the catabolic rate of the various plasma proteins have been compared with changes in the concentration of the proteins in plasma. A summary of the results from many of these studies is included in the following sections.

Factors Modifying the Catabolic Response to Injury

SEVERITY OF INJURY

Studies with labelled plasma proteins have confirmed the observations made before the introduction of these materials (see review by Moore and Ball, 1952) that the catabolic response increases in proportion to the severity of injury. Examples of the results from studies with labelled plasma proteins in patients with minor, moderate, or severe injuries due either to burning or other forms of accidental injury are shown in Figure 3. The catabolic rate of both albumin and gamma G globulin (as g/kg/day) increases as the severity of injury increases.

The injury caused by a single simple mastectomy does not cause an increased catabolic rate of albumin (Mouridsen, 1967) and would not be expected to produce an increased rate of excretion of nitrogen in urine. The operative repair of a fractured tibia by compression plating is a more severe injury and causes a transient twofold increase in the rate of albumin catabolism (Davies *et al*, 1970b). Increased urinary nitrogen excretion also occurs in patients with injuries of similar severity (Flear and Clarke, 1955) and in patients with burns of up to one third of the body surface (Moore, Langohr, Ingebretsen, and Cope, 1950). Moderate injuries, such as an open compound fracture of the femur or burns involving more than one third of the body surface, and severe injuries arising from multiple fractures show a prolonged and greatly increased rate of catabolism of albumin and γ G globulin (Birke, Liljedahl, Plantin, and Wetterfors, 1959/60; Davies, Ricketts, and Bull, 1962 and 1963) and nitrogen excretion in urine (Moore *et al*, 1950; Moore and Ball, 1952). In these moderate and severe injuries prompt therapy of substantial haemorrhage by the transfusion of a volume of blood equal to that lost results in a less severe catabolic response than if the lost blood is only partly replaced (Flear and Clarke, 1955).

The proportional increase in catabolic response and severity of injury is reflected in changes of concentration of various plasma proteins. The characteristic pattern of these changes, reviewed by Owen (1967), consists of a decreasing albumin concentration and increasing concentrations of

alpha 2 globulin, gamma G globulin, and fibrinogen. The concentrations of alpha 2 globulin and fibrinogen usually increase soon after injury while that of gamma G globulin is usually delayed until the second or third week after injury. The effect of minor, moderate, or severe injury on the concentrations of albumin, alpha 2 globulin, and gamma G globulin are shown in Figure 4. The average concentration of albumin decreased in all patients; with minor and moderate injuries the concentrations only just became subnormal whereas in the patients with severe injuries the albumin concentrations were transiently 20% below the expected normal range. The concentrations of alpha 2 globulin did not increase above the expected normal range of values during the two-week period of study in any of the patients. The concentrations of gamma G globulin changed according to the characteristic pattern, the subnormal values observed during the first week after injury changing to normal or supranormal values during the subsequent weeks. These changes in injured patients have also been described by Baar and Topley (1956).

The patients with burns showed more marked depressions of the albumin concentration and more marked increases in the concentration of alpha 2 and gamma globulin than observed in the patients with other forms of injury. These more marked changes in patients with burns have been described by many authors (including Prendergast, Fenichel, and Daly, 1952; Birke, Liljedahl, and Troell, 1957; Davies *et al*, 1962 and 1963; Baar, 1965; Davies, Ricketts, and Bull, 1966; Davies *et al*, 1969).

The reductions in albumin concentration in some of these patients, particularly those with extensive injuries, may be due partly to haemodilution resulting from undertransfusion, as well as to the increased rate of catabolism of albumin. The accumulation of albumin in the tissues around the wound may also account for some of the albumin lost from the plasma (Birke *et al*, 1960; Liljedahl, Olhagen, Plantin, and Birke, 1963; Mouridsen, 1969).

ENVIRONMENTAL TEMPERATURE

Studies reported by Caldwell (1962) in burned rats indicate that a much smaller catabolic response is observed when the animals are kept before and after burning in an environmental temperature of 30°C. More recent studies in rats with a fractured femur (Campbell and Cuthbertson, 1967) and in patients with limb fractures (Cuthbertson *et al*, 1968), maintained at the same environmental temperature, have shown similar reductions in the severity of the catabolic response with less nitrogen excreted in the urine.

More detailed studies have been made in patients with burns, who were treated either in a very warm, dry environment (air temperature,

32°C, relative humidity 20-30%) or in a cooler, moister environment (air temperature 22°C, relative humidity 30-70%) (Barr, Birke, Liljedahl, and Plantin, 1968; Davies *et al*, 1969). Two groups of patients with comparable burned areas were studied, one group of patients being treated in the warmer environment and the other group in the cooler environment. Some of the results from two patients, one taken from each group, with comparable burns are shown in

Figure 5. The results are representative of those found in the two groups of patients and indicate that the patients treated in the warm, dry environment had lower basal metabolic rates, lower rates of catabolism of albumin and γ G globulin, and smaller losses of body weight than in the control group treated in the cooler, moister environment.

The plasma concentrations of albumin and gamma G globulin only reflect to a limited

Fig. 4 Average plasma concentrations of albumin, alpha 2 globulin, and γ G globulin from groups of four to six patients with minor, moderate, or severe injuries. The open circles (B) denote the results in patients with burns of differing extent of the body surface; the filled circles (I) denote the concentrations observed in the patients with other forms of injury of differing severities. The horizontal interrupted lines indicate the range of the expected normal concentrations of the three proteins.

Fig. 5 Values for the basal metabolic rate (BMR), body weight, and the catabolic rate (g/kg) of plasma albumin and γ G globulin in two patients with burns for five weeks following the accident. The filled circles indicate the results in a patient treated in a cool environment with a burn of 30% of the body surface, 10% of which was full-thickness skin loss. The open circles indicate the results from a patient treated in a warm, dry environment with a burn of 20% of the body surface, 15% of which was full-thickness skin loss. The single horizontal broken line indicates the body weight on admission to hospital (called 100%) and the other horizontal broken lines indicate the expected normal range of the catabolic rates of albumin and γ G globulin. The BMR values are expressed as percentages of the expected normal value. Op. denotes the time of the operations for excision of the burned area and the transplantation of skin.

Fig. 6 Average values for the changes in the concentration of plasma albumin, alpha 2 globulin, and γ G globulin in two groups of patients with burns for three to four weeks after the accident. The patients treated in the warm, dry environment are denoted by the open circles (W) and the patients treated in the cooler environment by the filled circles (C). The horizontal broken lines indicate the expected normal range of the concentrations of each protein.

Fig. 6.

extent the catabolic rates of these proteins. With albumin the catabolic rate is highest in the patients treated in the cool environment, who show the lowest albumin concentrations. In the warm environment the lower catabolic rate is associated with slightly higher albumin concentrations. Different results are found with gamma G globulin, since the highest catabolic rate is associated with high concentrations of the protein, and the lower catabolic rates found in the patients treated in the warm environment with lower plasma concentrations of the protein. These differing results with the two plasma proteins most probably reflect changes in the rates of synthesis of the proteins (see below). The concentration of the remaining serum globulins (alpha 1, alpha 2, and beta) does not appear to be modified by the treatment in a warm, dry environment (see the results for alpha 2 globulin in Fig. 6).

EFFECTS OF PROTEIN DEPLETION OR STARVATION

Part of the body stores of protein are in a form which is labile. When the diet contains adequate amounts of protein (about 2 g/kg body weight per day) the amount of labile protein in the body reaches a maximum of about 5% of the total body content of protein. A change to a low protein content or a protein-free diet results in a rapid depletion of the body content of labile protein (Munro, 1964). A chronic deficiency of dietary protein is associated with a very small labile protein pool.

In injured animals or man having an adequate protein diet before injury, this labile protein pool is the probable source of the increased amount of nitrogen which is excreted in the urine. Experiments in rats (Munro and Chalmers, 1945) maintained on a diet very low in protein and then injured resulted in very little increase in the amount of nitrogen excreted in the urine, i.e. the catabolic response was substantially reduced, presumably because of the very small labile protein pool. Similar conclusions have been

described by Moore and Ball (1952) and Abbott and Albertsen (1963) in patients undergoing operations of varying severity, and could be expected in injured patients suffering from protein deficiency diseases such as kwashiorkor. As the survival of labelled albumin in patients suffering from kwashiorkor has been shown to be abnormally long, ie, the catabolic rate is reduced (Picou and Waterlow, 1962; Cohen and Hansen, 1962), the interpretation of results from studies on the effects of injury in these patients will require considerable care. Neither an increased rate of catabolism of albumin nor an increased rate of urinary excretion of nitrogen may be observed.

Specific Effects of Injury Shown by Protein Metabolism Studies

STUDIES OF CATABOLISM WITH LABELLED FIBRINOGEN

The specific function of fibrinogen which results in its conversion to fibrin complicates the interpretation of metabolic studies with labelled fibrinogen (Davies *et al*, 1966). Following skeletal injury the plasma concentration of fibrinogen increases (Owen, 1967; Davies, Liljedahl, and Reizenstein, 1970a). When such patients receive intravenously fibrinogen tagged with radioiodine the body content of fibrinogen becomes labelled and then any fibrin that is formed contains labelled protein molecules. Elderly injured patients in particular show considerable fibrin formation which accumulates mainly as deep vein thrombi or microthrombi in lung tissue (Sevitt and Gallagher, 1959; Eeles and Sevitt, 1967). Patients with burns also show extensive accumulations of fibrin, mainly in the tissues around the burned area (Sevitt, 1957). The radioactive label excreted in urine arises from both labelled fibrinogen and labelled fibrin, so the apparent catabolic rate depends on the proportion of the injected labelled protein which is converted into fibrin. Published data (Davies *et al*, 1970a) indicate that when the quantity of extravascular radioactivity is about five times greater than the intravascular content the whole body content of radioactivity decreases at a rate which has a biological half life of 6.0 days. When the extravascular:intravascular ratio is about 1.0, as found in many patients, or less than 1.0, as found in normal individuals, the biological half life of the whole body content of radioactivity is shorter, with a value of three to four days.

Although anticoagulants have been shown to reduce the incidence of deep vein thrombus formation following injury (Sevitt and Gallagher, 1959), there appear to be no detailed studies of the effects of various anticoagulants generally used for this purpose. The limited evidence from three patients given dicoumarol for four to six

weeks following myocardial infarction (Adelson Rheingold, Parker, Buenaventura, and Crosby, 1961) and from a few dogs (Lewis, Ferguson, and Schoenfeld, 1961) indicates that with the dosages used the dicoumarol did not alter the catabolic rate of fibrinogen from its normal value.

STUDIES WITH ALBUMIN IN PARALYSED PATIENTS

Studies have been carried out to investigate whether an intact nervous pathway is essential for the production of the increased catabolic rate of tissue and plasma proteins which follows injury in many patients (Davies *et al*, 1962). Labelled albumin was injected intravenously into eight patients with mainly limb injuries, four of whom were also paralysed from spinal cord injury at the level of C7, Th 11 and 12, or L 1 (Davies *et al*, 1970b). Operative repair of the limb injuries was followed by very similar increased rates of catabolism of albumin in both the paralysed and non-paralysed patients (Fig. 7). Not only was the rate of catabolism increased following the operation in both groups of patients but also certain synthetic mechanisms were stimulated. The alpha 2 globulin levels rose similarly and there were corresponding rises in the erythrocyte sedimentation rates to which increased fibrinogen formation may have also contributed. The concentration of this latter protein has been observed to increase in other patients with similar injuries (Davies *et al*, 1970a). These results suggest that an intact nervous system proximal to the site of injury is not required for the initiation of an increased rate of catabolism of albumin.

These results have been compared with those from studies in injured dogs by Egdahl (1959) and Egdahl, Peck, and Mack (1968). These authors suggest that an intact nervous pathway

Fig. 7 Average catabolic rates of albumin in two groups of injured patients. Four of the patients had injuries which included paraplegia (filled circles); the remaining four patients were injured but not paralysed (open circles). Studies were made for two weeks before the operative repair of limb injuries as well as postoperatively in the paralysed patients and only postoperatively in the non-paralysed injured patients. The horizontal broken lines indicate the expected normal range of the rate of catabolism of albumin.

from the site of injury to the brain is required for the initiation of the adrenocortical response which is associated with accidental or surgical injury, and that there is no evidence for the production of a 'wound hormone' from damaged tissue since there was no adrenocortical response to injury by burning or long bone fracture when the nerves proximal to the site of injury were divided before injury.

It may be concluded from these studies that although afferent nerve impulses are required for an adrenocortical response, and an increase in adrenocortical activity is associated with an increased catabolic rate of plasma and tissue proteins, the role of the adrenal cortical hormones in this catabolic response is permissive rather than causative. Similar conclusions have been drawn from extensive studies in patients who were injured but not paralysed (Cuthbertson, 1964).

STUDIES OF THE RATE OF PROTEIN SYNTHESIS

In studies made more than 20 years ago it was rarely possible to determine whether the observed increases in the concentration of various proteins in the plasma of injured patients were due to increased rates of synthesis or to reduced rates of catabolism of the proteins. An exceptional situation concerns proteins such as the C-reactive proteins and specific immunoglobulins which appear in the plasma of injured patients though absent in the plasma of normal individuals. As studies with radioiodine-labelled albumin, γ G globulin, and fibrinogen have almost always shown increased rates of catabolism of these proteins following injury, any increase of concentrations must be due either to translocation of preformed proteins from the extravascular compartment into the plasma or to an increased rate of synthesis.

A number of different methods have been developed to investigate whether the rate of synthesis is increased. None of them are entirely satisfactory however, particularly when the patient is in an unsteady metabolic state since considerable assumptions are required for the mathematical interpretation of the data.

Albumin synthesis using the ^{14}C carbonate method

This method (McFarlane, 1963) depends on the relationship between the specific activities of a single labelled precursor (^{14}C carbonate) and those of all products derived from the precursor, eg, ^{14}C arginine, ^{14}C urea, and ^{14}C albumin. Measurements of the ^{14}C content of urea and albumin gives estimates of the rate of synthesis of albumin (Reeve, 1965; Tavill, Craigie, and Rosenoer, 1968). Studies in patients in a steady metabolic state confirmed the assumptions involved in the calculation of the rate of synthesis of albumin using ^{14}C carbonate since the calculated rate of synthesis was very similar to the rate of catabolism deduced from measurements

with ^{131}I -labelled albumin (Tavill *et al*, 1968). No studies appear to have been made in patients in the unsteady metabolic state which follows injury. As the rate of synthesis of albumin may be changing in these patients repeated estimates of the rate of synthesis may be required, but they are not without some hazard due to the persistence of some ^{14}C in the body.

Studies using ^{15}N labelled amino acids

An increased rate of incorporation of ^{15}N -labelled glycine into tissue and plasma proteins has been observed in burned rats compared with the findings in normal animals (Levenson and Watkin, 1959) even when the amino acid was given at the peak of the catabolic rate of protein a few days after burning. Carcase analysis for ^{15}N indicated that the labelled amino acid had been preferentially incorporated at a greater than normal rate into the essential organs and plasma proteins rather than into muscle tissue. When the labelled amino acid was given a few days before injury and had been incorporated into all body tissues the response to burning was an increased rate of loss of ^{15}N from the muscle compared with little loss from the essential organs (Levenson, Pulaski, and Guerico, 1966). These studies strongly suggest that muscle contains the labelled protein pool (Munro, 1964) which is the main source of the excess nitrogen excretion following injury.

Studies with iodine-labelled plasma proteins

Although these proteins labelled *in vitro* have been extensively used in catabolism studies, few reports include calculations of the rate of synthesis of the proteins. With patients in a steady metabolic state it has been justifiably assumed that the rates of synthesis and catabolism are equal. In the unsteady state, however, the rate of synthesis can only be deduced from frequent specific radioactivity measurements (counts per milligram protein) made by isolation of measurable amounts of the labelled protein followed by assay of the radioactive content and protein concentration of each sample. The specific radioactivity values are only altered by the dilution effect of new unlabelled protein entering the plasma; they are unaffected by catabolism since this process equally affects labelled and unlabelled molecules. In the absence of synthesis the specific radioactivity values remain constant; in patients in a steady metabolic state the specific radioactivity values change at the same rate as that of the plasma content of radioactivity.

In the unsteady metabolic state following injury, rates of synthesis calculated from changes in the specific radioactivity values have been reported using labelled albumin, γ G globulin, and fibrinogen (Davies *et al*, 1966 and 1969). Examples of the results are shown in Figure 8. In patients with burns treated in a cool environment and given labelled albumin intravenously

Fig. 8 Average values for the maximum and minimum rates of synthesis (as mg/kg body weight) of albumin, γ G globulin, and fibrinogen in groups of patients with burns or other forms of injury for the two to three weeks after the accident. The horizontal broken lines indicate the expected normal range of the rate of synthesis of each protein.

the rate of synthesis of albumin was approximately normal during the first week after burning and then subnormal during the following two weeks. When labelled γ G globulin was given to the same burned patients the rate of synthesis of γ G globulin was always substantially above normal. An even higher rate of synthesis of fibrinogen was observed in the burned patients studied with labelled fibrinogen. Patients with burns treated in a warm environment show similar subnormal rates of albumin synthesis and rates of γ G globulin synthesis which are considerably less (although still supranormal) than those observed in the patients treated in the cool environment (Davies *et al.*, 1969).

These rates of synthesis of the various plasma proteins are reflected by corresponding changes in the plasma concentrations of the proteins. As discussed in detail above, the albumin concentra-

tion is almost always subnormal following burning while the concentrations of γ G globulin and fibrinogen rapidly become supranormal.

In patients with injuries other than burns a similar, although less marked, pattern of plasma protein synthesis is observed. Albumin synthesis is depressed to below the normal range during the second and third weeks after injury, at which time the rate of synthesis of γ G globulin is approximately twice normal, and that of fibrinogen is just above the expected normal range.

Conclusions

A review of protein metabolism following burning and other forms of injury indicates that the rate of catabolism of plasma albumin and γ G globulin increases as the severity of injury increases. In patients with burns the catabolic rate of the two plasma proteins is reduced by nursing the patients in a very warm environment. In this environment less albumin is catabolized and less γ G globulin is synthesized.

The plasma concentrations of albumin, alpha 2 globulin, and γ G globulin remain nearer the expected normal values in the patients with skeletal injuries compared with the low albumin concentrations and the high alpha 2 and γ G globulin concentrations observed in the burned patients. The changes in concentration appear to be unaffected by the severity of injury or burning.

Studies of the catabolic response to injury using labelled fibrinogen are complicated by the formation of insoluble fibrin from the body content of soluble fibrinogen. Fibrinogen and fibrin formation are increased after both burning and other forms of injury.

Studies in patients with paraplegia and other injuries indicate that an intact nervous pathway between the site of injury and the brain is not required for the initiation of the catabolic response to injury shown by an increased rate of catabolism of plasma albumin.

The methods for estimating the rate of synthesis of various plasma proteins *in vivo* are discussed. The methods using ^{14}C and ^{15}N are difficult to perform and require considerable assumptions for the interpretation of the results. The alternative method using iodine-labelled proteins is much simpler and has been used to show the rate of synthesis of albumin, γ G globulin, and fibrinogen in patients with burns and other forms of injury. In these patients the rate of synthesis of albumin is usually subnormal and that of γ G globulin and fibrinogen usually supranormal.

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