Clinical Nutrition: Metabolic and Nutritional Aspects of Severe Injury Uptodate

University of London Audio-Visual Centre, 1978

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Made for British Postgraduate Medical Federation.

Black-and-white
Duration: 00:20:06:20

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<**Opening titles**>

<**Smith to camera**>

The human body may be injured in many ways as for instance by road traffic accidents, by surgery, by assorted domestic catastrophes and by burns. Such injuries produce complex metabolic changes and knowledge of these changes is of physiological and therapeutic importance. Today we shall be discussing these changes.

<**Smith over tables listing main points of discussion relating to body injury**>

Our knowledge of them comes from work on human injury and on human starvation and relevant work on animals. However, before discussing injury, we need to look at the composition of the human body, its energy supply and utilisation and its hormonal

control. These are, of course, linked since the constant composition of the body is maintained by energy-requiring processes which are influenced by hormones.

First, the composition of the body.

<**Smith over diagram showing body composition**>

This diagram shows the composition of the ideal 70kg man. There are two points which I would like to emphasise. The first one of these is that more than half the body is water. The other point is that within the organic fraction of the body solids there are two very different proteins. One of these is the intracellular protein of muscle which is intimately involved in the metabolic response to injury. The other is collagen which is extracellular and found predominantly in the skeleton. This protein is not metabolically inert but it appears to be little altered by injury.

<**Smith, standing, refers to diagrams depicting supply and use of energy, uses indication stick**>

Second, we need to look at the supply and use of energy in the normal human body. This has been well investigated by Cahill and his colleagues using obese subjects subjected to therapeutic starvation, and this scheme shows some of their results.

The important organ in the middle is the liver which acts as a metabolic transformer between the suppliers of energy – muscle protein and adipose tissue fat, and the main utilisers – the central nervous system represented by the brain, the circulating cells and the heart, kidney and muscle.

Now, there are two points about this scheme which are of vital importance. The first one is that fat cannot be used as a readily available supply of glucose. Glucose is normally required by the brain as an energy source. The reason why fat cannot be used to supply glucose is shown in this diagram of intermediary metabolism, and without going into details, it is clear the arrows go in the wrong direction for a direct link between fat and glucose.

This inability to convert fat to glucose is a pity. Fat is virtually anhydrous and provides 9 kilocalories per gram, compared with 4 kilocalories per gram provided by muscle protein.

<**Smith over illustration showing overweight and underweight men**>

Thus, if we compare this overweight man, say 140kg, with a normal man of 70kg, the difference in weight, which is largely due to fat, provides an additional potential energy source of more than half a million calories.

<**Smith refers to diagrams depicting supply and use of energy, uses indication stick**>

If protein is the sole supply of glucose, it has been calculated that to provide sufficient glucose for the brain, 200g of muscle per day would be needed to be broken down; this loss of muscle would soon lead to death. However, it is now realised that the brain can utilise ketone bodies derived from adipose tissue fat and this alternative pathway clearly will spare the breakdown of protein.

These are the formulae of the ketone bodies with which we are concerned: acetoacetate and β-hydroxybutyrate. In order to properly understand some of the recent work on amino acid and protein metabolism, we need to look at another scheme.

This demonstrates the normal fate of amino acids absorbed through the gut. Amino acids go to the liver where they may have the amino group removed in the form of urea and this is the main constituent of the total urine nitrogen. They may be completely oxidised to CO_2 and water, or they may be converted to glucose by gluconeogenesis, in which case the glucose goes to muscle and may be reaminated again and come back as alanine; the so-called glucose-alanine cycle.

There are two main exceptions to this scheme. One has to do with the branched-chain amino acids which are initially metabolised in muscle, having bypassed the liver, and measurement of branched-chain amino acids in the blood indicates muscle events. The second has to do with 3-methylhistidine which is the component of the contractile proteins actin and myosin; when these proteins are broken down, the 3-methylhistidine is not incorporated and is excreted quantitatively in the urine and is a valid indicator of breakdown of these muscle proteins.

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<**Smith refers to diagram depicting branched-chain amino acid formula**>

Now, these diagrams show the formula of the branched-chain amino acids, so-called because of their branched-chain structure. Leucine, isoleucine and valine. The formula of 3-methylhistidine is shown in this next diagram with the 3-methyl shown on that five-membered ring. There is also a 1-methylhistidine but this is of less relevance to a present discussion.

<**Smith refers to diagrams depicting the role of hormones in metabolic processes**>

The metabolic processes which we have described are controlled by hormones. It is only possible in this talk to outline their effects. Classically they are divided into those which promote overall synthesis – anabolic hormones, and those which cause overall breakdown – the catabolic hormones. Insulin is the main anabolic hormone. Examples of catabolic hormones are catecholamines, glucagon and cortisol.

Now the three diagrams which follow indicate the main effects of insulin – epinephrine and glucagon on adipose tissue fat, liver and muscle. Firstly, insulin promotes storage of fat in adipose tissue and prevents ketosis. It encourages the liver and muscle to take up glucose and promotes protein synthesis. In contrast, epinephrine promotes mobilisation of fat from adipose tissue; it encourages the formation of glucose by the liver and the breakdown of protein by muscle. Glucagon,

shown in the next diagram, appears to have very little effect on muscle. It encourages mobilisation of fat, it increases ketosis and promotes glucose production by the liver.

There are, of course, many other hormones with metabolic effects and this is a reminder of them – they include the controlling hormones of the hypothalamus and the locally acting prostaglandins.

<**Smith to camera**>

It is against this background of the normal metabolic processes that we can now consider the effects of injury. In considering injury we should recall that this is a complex insult and that its effects tend to occur in phases.

<**Smith over tables and diagrams showing what happens to the body after injury**>

This table shows what happens after the average injury. In addition to the mechanical damage and the response of the body to it, there is a degree of starvation relative to energy demand, there is immobility and sometimes infection. It is customary to divide the time after injury into two phases. In the first of these, heat production falls and the body is trying to recover from the initial insult – this is called the ebb phase; if survival is not going to occur, heat production falls further and there is cell death, necrobiosis. In those who do survive, heat production and the metabolic processes increase through the flow phase towards eventual recovery.

00:10:04:00

<**Smith to camera**>

What then are the effects of injury on body composition, on energy exchange and on hormonal control?

<**Smith over histogram depicting body composition**>

Body composition may alter considerably after injury depending on such factors as the severity of injury, the degree of starvation and the type of treatment. In this histogram, the amount before injury is shown as 100%, after injury there are disproportionate changes in these body compartments. Thus, body weight, body solids, body potassium and body magnesium tend to fall whilst body sodium and magnesium change little. The result of this is that the ratio of the body solids to body water decreases and there is a fall in intracellular cations. These changes are very similar to those seen in starvation.

<**Smith to camera**>

If we now look at energy supply and utilisation, it has long been known that one of the main metabolic effects of injury is an increase in urinary nitrogen excretion reflecting a net loss of muscle protein.

<**Smith over diagrams depicting changes in protein metabolism after injury** >

These diagrams remind one that there is normally a balanced process of synthesis and breakdown of protein, plus a net loss of protein could be due to an increase in protein breakdown as represented here, or to a decrease in protein synthesis as shown in this next diagram, or to both. Although it has often been assumed that increased breakdown has been the cause, there is evidence that in elective surgery at least, there is a temporary decrease in protein synthesis. This conclusion is supported by measurements of urinary 3-methylhistidine after injury.

In this diagram, the black line shows the change in urinary 3-methylhistidine excretion in a group of three patients after elective orthopaedic surgery. Mean values are shown with one standard error, and there is clearly no increase. This implies that there is no increase in muscle protein breakdown after this form of surgery despite the increase in urinary nitrogen excretion. In contrast, this white line shows the widely

variable, but increased secretion, in severely injured subjects after road traffic accidents, which suggests an increase in muscle catabolism in such subjects.

Measurements of circulating branched-chain amino acids also give us clues about protein metabolism after injury. In this diagram, the black line shows that significant and progressive increase in branched-chain amino acids occur in a group of road traffic accident victims. The white lines show other amino acids for comparison.

<**Smith to camera**>

It is clear that there are significant changes in muscle protein metabolism after injury. These changes appear in some way to be related to ketone body metabolism and we should now consider these ketone bodies.

<**Smith over diagrams showing ketone involvement after injury**>

Measurements of circulating levels of ketone bodies in the first 24 hours after road traffic accidents show that they are either normal or considerably elevated. Thus we may define a normoketonaemic group shown by this black line, and a hyperketonaemic group shown by the white line. You should note that the scale on the vertical axis is a logarithmic one and the differences between these groups are therefore considerable and significant. We do not know the causes of these differences but we do have some interesting clues.

The next figure shows an apparent relation between the ketone body levels and protein metabolism. The black squares show the values for the mean daily nitrogen excretion for seven days after injury, and the branched-chain amino acid concentration on the seventh day, in a group of accident victims without an initial increase in ketone body levels. The point of interest is that these are higher than in the hyperketonaemic group or after elective surgery, shown by the white symbols.

<**Smith to camera**>

Thus, it does seem that after injury the breakdown of protein is least where the ketone body levels are increased – there could be many causes for this relationship. When we come to look at the effect of injury on hormones, there is agreement about the general patterns but there is controversy about the individual changes.

<**Smith over table showing hormone changes after injury**>

There is a decrease in insulin, the anabolic hormone, and increases in the catabolic hormones. The time sequence of these changes is variable. At some stage there is a change in the relation of glucagon to insulin and this is considered to be of considerable importance.

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<**Smith to camera**>

We have now dealt with the changes in body composition, energy supply and hormonal control which injury produces. However, as we have noted, injury is a complex insult which may be associated with immobility and sepsis. We ought to look at their effects in more detail and also briefly consider burns.

<**Table**>

The Dangers of Going to Bed
Richard Asher – BMJ 1947

Weightlessness: A Matter of Gravity
Nello Pace – NEJM 1977

<**Smith over table**>

Immobilisation produces very important metabolic effects and these articles, separated by 30 years, emphasise this.

Asher, in a classical article entitled ‘The Dangers of Going to Bed’, stressed the loss of muscle and bone in people kept immobilised. And Pace has recently reviewed the evidence for similar effects in astronauts.

<**Smith over table showing effects of immobility on metabolism following injury**>

Thus immobility and removal from the effects of gravity rapidly cause a loss of skeleton and loss of muscle, probably due to sudden failure of new synthesis of these tissues.

<**Smith over table showing effects of infection on metabolism following injury**>

Infection may follow injury and prolong recovery. Thus it is bound to accentuate the metabolic effects of the injury itself. Infection also appears to have specific effects of its own on protein breakdown and fuel consumption, and this is an area in which much recent work has been done.

<**Smith to camera**>

Of the forms of accidental injury inflicted on man, burns are the most severe.

<**Smith over table showing effects of burns on metabolism**>

A burn differs from other forms of injury in the extensive loss of skin surface, the increased fluid loss and the intensity of the biochemical changes. This diagram shows the initially high metabolic rate, the changes in hormones that we have discussed and the initially high negative nitrogen balance in a burned patient. And it is in patients of this sort that particularly useful work has been done on the therapeutic affect of insulin and glucose and insulin in correcting cellular and metabolic abnormalities.

<**Smith to camera**>

In the opening slide of this talk, I commented on the relevance of animal research. Whilst we do not have time to discuss this in detail today, I would briefly like to draw your attention to a natural physiological experiment which is relevant to injury.

<**Smith over illustration of American black bear**>

This is the American black bear which, in its winter sleep, switches over to burning its own fat as a sole source of fuel. Apart from the loss of fat, there is no other change in body composition and no loss of muscle protein. This is exactly what we would like our accident patients to do if we knew how.

<**Smith to camera**>

Before concluding, we should consider if there are any important nutritional or therapeutic messages and what the future problems are. The nutritional and therapeutic messages are closely related and are listed on the next two tables.

<**Smith over tables listing new ideas in the area of injury and nutrition**>

We now recognise the importance of ketone bodies as a potential source of fuel, the possibility of failure of protein synthesis as a cause of negative nitrogen balance after injury, and the existence of important changes in the branched-chain amino acids.

What are the therapeutic implications of this information? We can question whether it is therapeutically useful to have hyperketonaemia; if so, we should not attempt to reduce it and we should be infusing amino acids rather than glucose. Further, if the negative nitrogen balance is due to a protein synthetic failure, we all ought to be concentrating on the stimulation of protein synthesis. These are merely suggestions based on recent evidence and are now being actively studied.

<**Smith to camera**>

There are very many problems left in the study of the metabolic effects of injury and these are three important ones.

<**Smith over table showing three key problems in the study of metabolic effects of injury**>

How do ketone bodies influence gluconeogenesis – the production of glucose from protein? It is known, for instance, that infusion of ketone bodies into fasting man reduces nitrogen excretion. It also appears that after injury, gluconeogenesis and ketonaemia are related. Is this effect a direct one or is it merely by supplying an alternative source of fuel for those tissues which can metabolise ketone bodies?

What is the importance of branched-chain amino acids? There is increasing evidence that these distinctive amino acids have specific effects on protein synthesis. It is not only important to measure them after injury, but to see if they can be used therapeutically in the protein repletion of such subjects.

Finally, what are the biochemical effects of immobility? And more importantly, how are they produced? As we reach the age of space travel we may find an answer to this much more rapidly than to the other metabolic effects of injury.

<**Smith over table summarising main points of lecture**>

In summary, severe injury in man disturbs both energy supply and utilisation and produces complex nutritional problems which may require treatment.

<**End credits**