ORIGINAL PAPERS

METABOLISM AFTER INJURY. I: EFFECTS OF SEVERITY, NUTRITION, AND ENVIRONMENTAL TEMPERATURE ON PROTEIN POTASSIUM, ZINC, AND CREATINE

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SUMMARY

The effect of an environmental temperature of 28–30°C and a relative humidity of 35–45 per cent on the protein metabolic response to injury of one or more major long bones of the lower limbs has been studied in 29 male patients and 28 similar controls housed at 20–22°C. The metabolic response was reduced at the higher temperature compared with the controls, the more severely injured showed a greater metabolic response than the less severely injured, and the ameliorating influence of environmental temperature was more noticeable in the former.

The metabolic response seems to be principally one of catabolism of muscle, with increased urinary excretions of potassium, creatine, and zinc in the urine correlating well with those of nitrogen at 20°C but not at 30°C. The response (i.e., catabolism of muscle) was not affected by post-injury diet at 20°C ambient temperature. There was a reduction in the disturbance of the plasma proteins.

In general, the patients tolerated the warm drier conditions. Owing to the intrinsic difficulty in assessing minor changes in bone healing it was not possible to assess what, if any, beneficial change occurred in the fracture site. From our experimental observations on the rat and the work of others on burned patients the reduction in heat production at the higher ambient temperature is accompanied by an enhanced rate of healing of surface wounds.

THE metabolic response to injury is both local and general. It is with the latter in its post-shock manifestations following moderate to severe physical injury to the limbs of man that this report is concerned, and, in particular, with the effect on this response of raising the environmental temperature to the zone of thermoneutrality for clothed man (28–30°C). This topic has been of considerable interest to those working in the field of metabolic response to trauma (Campbell and Cuthbertson, 1967; Miksche and Caldwell, 1967; Barr, Birke, Liljedahl, and Plantin, 1968; Cuthbertson, Smith, and Tilstone, 1968; Caldwell, 1970; Davies and Liljedahl, 1970; Tilstone and Cuthbertson, 1970; Spivey and Johnston, 1972).

The essential elements in the generalized response to injury were described by one of us (Cuthbertson, 1930, 1932, 1936, 1942) and extended by Wilkinson, Billin, Nagy, and Stewart (1949, 1950) and Moore and Ball (1952) among others. The complex series of reactions to various forms of injury has as its main components over the first 10–14 days after injury increased net protein catabolism and parallel increases in heat loss and oxygen consumption. There are also characteristic changes in plasma-protein levels (Owen, 1967; Cuthbertson and Tilstone, 1969).

The extent of the metabolic response seems to depend on the nature and severity of the injury, being slight for uncomplicated surgery, greater for major skeletal injuries, and considerable in sepsis and major burns (Kinney, Long, and Duke, 1970).

The present report is concerned with our observations on the effect of severity of injury and environmental temperature on the magnitude of the metabolic response and with observations on the major source of the nitrogen which is lost in urine.

MATERIALS AND METHODS

Patients.—Patients were all males ranging in age from adolescence to 70 years. They were either victims of accidentally sustained injuries of moderate to severe extent involving one or more long bones of the lower limbs or were patients undergoing elective surgery.
arthroplasties of the hip or arthrodeses of the knee or ankle-joint.

Environmental Control.—The patients were housed in single-bed cubicles which had partition walls of double-sheet aluminum and double glazing. A two-way cupboard allowed urine collections and food residues to be removed without opening the door of the room. Each cubicle had a Rootes Tempair 1½ h.p. water-cooled air-conditioning unit (W. Kemp, Glasgow) with a cooling capacity of 15,000 B.Th.U. per hour, and a 3-kV.A. heating unit with an air flow of 400 c.f. per minute. Air passing through the unit was filtered in a washable polyurethane filter. Normally the dehumidification unit was not used since this cooled the air and produced rapid temperature drops if the humidistat was 'off' while the humidistat was 'on'. A 1-kV.A. convector heater was also used in winter. This apparatus could maintain a temperature of 29–30°C and relative humidity of 35–45 per cent in all normal external environmental conditions. Opening the door for access did not cause a major temperature fall (Fig. 1).

Experimental Protocol.—Twenty-nine patients were studied with the cubicles maintained at 28–30°C and 28 with the cubicles maintained at 20–22°C—the normal range of ward temperature. Subsequently only the figures 30 and 20°C will be used as most of the cases fell into these temperature levels. The metabolic investigations began as soon as the initial shock phase was over and usually was within 24 hours of injury. Informed consent was obtained from all the patients. A few cases could not tolerate the warmer conditions and were removed from further study. The pattern of the diets presented was based on the patients' normal home intake which had been elicited by questioning, except that a protein intake (76 per cent of animal origin) which contributed not less than 13 per cent of the total calorie intake was always attempted.

Observations were made daily on various parameters of protein and tissue catabolism. Results for all of these are not available for all the patients. In general, results have been averaged for the following four periods: the first 4 days after injury (and we usually did not have results for the first day) and the three subsequent 3-day periods (but some patients were discharged before the end of the last of these 3-day periods).

Excess urine nitrogen was calculated by subtracting each day's food nitrogen intake from the total urinary nitrogen excretion from 08.00 on that day to 07.55 on the next morning. Faecal nitrogen was not measured since it is not indicative of endogenous protein metabolism and Cuthbertson (1936) has shown it to be a fairly constant 6 per cent of intake at all stages after injury in man, and Campbell and Cuthbertson (1967) also found it to be unaffected by trauma in the rat.

Food Intake.—Net food intake was obtained by weighing food presented to the patient and subtracting all the residues. Intake of nitrogen and energy was calculated from the tables of McCance and Widdowson (1960), with occasional checks of nitrogen by analysing one-quarter of total homogenized diets.

Chemical Methods.—Nitrogen was estimated by a semi-mechanized Kjeldahl technique based on that described by Fleck (1967). Zinc was estimated by atomic absorption spectrophotometry using a Pye Unicam SP90, potassium by flame photometry, and creatine by a fluorescent technique using the Auto Analyzer (Tilstone and Fell, 1971). The urine was preserved by providing 5 ml. of 10 per cent thymol in isopropanol.

Statistical Analysis.—Statistical analysis of results was performed on an IBM 1130 computer using standard programmes for analysis of variance, Student's t-test, correlation coefficients, and linear regressions with one or more independent variables.

RESULTS

1. Patients.—Retrospective analysis shows that the two groups of patients, that is those at 20°C and those at 30°C, were not significantly different in age (t-test, \( P > 0.05 \)), extent of traumatic fever (t-test, \( P > 0.05 \)), and perhaps also degree of trauma. The extent of traumatic fever was measured by scoring the number of days within the 13-day period on which oral temperature was over 38.3°C, 37.7–38.2°C, or over 38.3°C. At least once a day, the scoring being 1, 2, and 3 points respectively for these zones. The severity of trauma was assessed in two ways: the first was dependent upon the amount of blood replacement which was necessary and the other on the extent of the trauma as defined on an arbitrary scale ranging from 1 to 7, for example, fracture of both femora and both tibiae and fibulae, 7; fracture of one femur and the tibia and fibula of the other leg with deep lacerations including severed tendons of the arm, 5; fracture of both tibiae and fibulae with lacerations and contusions, 4; comminuted fracture of the femur, 3; fracture of the neck of the femur, 2; fracture of the tibia and fibula, 2; Pott's fracture, 1; Charnley arthroplasty of one hip-joint, 5; triple arthrodesis of the ankle-joint, 2. On these two bases of assessment the two groups did not appear to be significantly different (t-test, \( P > 0.05 \)). The results are shown in Table I. A subsequent division in each group into moderate to severe injury on the one hand (+), and
3. Excess Urine Nitrogen Excretion.—Trauma has been shown not to affect appreciably the digestibility of protein and thus the extent of catabolism of endogenous protein can be measured by following excess nitrogen excreted in urine, that is, the difference between urine nitrogen and food nitrogen. As well as by analysis in temperature groups as described above, the results for excess nitrogen were also subdivided according to the severity of trauma, as scored on the arbitrary scale. Within this subdivision the excess urine nitrogen excretion for the patients at each temperature was compared in each period, that is, those more severely injured and housed at 20°C were compared with those less severely injured and kept at the same temperature, the comparison being made separately for periods 1, 2, 3, and 4; and similarly for the patients housed at 30°C. Comparisons were also made on the basis of equivalent injury but different temperature, that is, more severely injured at 20°C against more severely injured at 30°C, and similarly for the less severely injured. These comparisons were made both for the means of the individual periods and for all the periods taken together.

The results (Table III) show that at 20°C the more severely injured patients had a significantly higher excretion of excess nitrogen in the third and fourth periods ($P < 0.01$) than did the less severely injured, but at 30°C the more severely injured did not have such a significantly increased nitrogen excretion.

2. Intake of Energy and Nitrogen in Food.—Taking all the patients at 20°C as one group and all those at 30°C as the other, their food energy and food nitrogen were compared on the basis of the means for each successive period of study, that is, over the first 4 days, then the subsequent three 3-day periods. A comparison was also made on the basis of the means of all periods taken together. As can be seen from Table II there was no significant difference between the two groups at any time in respect of energy or protein intake. It is of interest that intake was not reduced by the warmer atmosphere.
excretion at any time. The less severely injured at 20° C. did not have a significantly greater excess nitrogen excretion than those at 30° C., the average being 1.04 g. per day higher at 20° C. but with \( t = 0.62 \). Taking the more severely injured there was a marginally significant difference in period 2 \( (P = 0.05) \) and overall the average difference was 3.01 g. per day. When all the degrees of injury are taken together then the difference between the two temperatures is more statistically significant, probably due to the greater number of degrees of freedom. Analysis shows that, taking all the periods together, the patients at 30° C. have a very significant reduction in their nitrogen excretion \( (P < 0.01) \), which is probably mainly in the early stages of the response, with the first period being significantly reduced at \( P < 0.05 \).

In the present paper we further report highly significant correlations between urinary nitrogen and potassium both at 20 and 30° C. \( (P < 0.001) \) and also a significant correlation between creatine and potassium at 20° C. but not at 30° C. These correlations

<table>
<thead>
<tr>
<th>AMBIENT TEMPERATURE (°C)</th>
<th>METABOLITE</th>
<th>OVERALL</th>
<th>PERIOD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>20</td>
<td>Nitrogen (g. per day)</td>
<td>Mean (N) S.E.M.</td>
<td>16.5 (98)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.4</td>
</tr>
<tr>
<td>30</td>
<td>Nitrogen (g. per day)</td>
<td>Mean (N) S.E.M.</td>
<td>15.1 (109)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.5</td>
</tr>
<tr>
<td>20</td>
<td>Zinc (mg. per day)</td>
<td>Mean (N) S.E.M.</td>
<td>11.32 (24)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>104</td>
</tr>
<tr>
<td>30</td>
<td>Zinc (mg. per day)</td>
<td>Mean (N) S.E.M.</td>
<td>11.13 (34)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>93</td>
</tr>
<tr>
<td>20</td>
<td>Creatine (mg. per day)</td>
<td>Mean (N) S.E.M.</td>
<td>241 (57)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>47</td>
</tr>
<tr>
<td>30</td>
<td>Creatine (mg. per day)</td>
<td>Mean (N) S.E.M.</td>
<td>391 (54)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>542</td>
</tr>
</tbody>
</table>

* Significantly different from 20° C. result, \( P < 0.005 \).

### 4. Excretion of Products of Tissue Protein Catabolism.

Excretion of total urinary nitrogen was never significantly different between the two groups no matter how the comparison was made (Table IV). It may be felt that if the excess nitrogen is significantly different between the two groups, then food nitrogen and/or urine nitrogen should differ significantly also. Food nitrogen did not differ (see above), and the large variance of urine nitrogen excretion, being the sum of the variance due to intake-associated factors and the variance due to endogenous protein catabolism, placed the average difference found in urine nitrogen excretion well below the level required for a statistically significant difference.

We wished to test the extent to which tissue catabolism, particularly muscle, might be responsible for the response of increased net nitrogen as had been shown in the rat (Cuthbertson, McGirr, and Robertson, 1939). To this end the urinary excretions of potassium, creatine, and zinc were examined.

Potassium is primarily an intracellular ion and it is well established that total-body potassium correlates well with the lean body mass.

Cell potassium may at times be quickly depleted following trauma (Moore and Ball, 1952). In the fractured rat an increased urinary excretion of potassium was found, reaching a peak some 3 days after injury, and the loss of potassium from muscle may be greater than for nitrogen over the first few days (Cuthbertson and others, 1939). Wilkinson and others (1950) and Le Quesne (1967) have described the increased excretion of potassium after abdominal injuries and the former showed that it is greater than that attributable to reduced food intake after partial gastrectomy. Moore and Ball (1952) have further delineated the situation, showing that in burns the potassium loss may last for only 2–4 days. They have also drawn attention to the normal early postoperative response whereby there is a greater potassium excretion than would be predicted from nitrogen loss.

Criatinuria is commonly observed in muscle diseases (Pennington, 1971). In diverse conditions involving acute wasting of muscle, such as when carbohydrate is absent from food, in diabetes, in hyperthyroidism, and during involution of the uterus following parturition, large increases in urine creatine are reported (Allison and Bird, 1964). After injury a marked rise in plasma creatine was observed in severely injured goats, treated or untreated with penicillin (Gillette, Oppenheimer, Mansberger, Johnson, and Kookootsedes, 1958). The rise in plasma creatine was much greater than that of the other nitrogenous constituents examined, suggesting a rapid release of creatine from muscle cells at a rate faster than the conversion process to creatinine can effect, or a failure of uptake by an effectively reduced muscle cell mass of the creatine synthesized in the
liver, leading to incomplete renal tubular reabsorption and creatinuria. The results of our studies are shown in Table IV, where they are analysed period by period. The most striking feature is the up to fivefold increase above the normal excretion which was observed, and also that the creatinine excretion was less in the first period for the 30° C. group (t-test, P<0.05). This finding has subsequently been repeated in a further series after injury (Cuthbertson, Fell, Fleck, and Queen, 1972), and confirms the diminution in the response at the higher ambient temperature.

Table V.—Results of Multiple Regression

\[ Y = a X_1 + b X_2 + c \]

where \( Y \) is Urine Nitrogen (g. per day), \( X_1 \) is Food Nitrogen (g. per day), \( X_2 \) is Food Energy (MJ. per day)

<table>
<thead>
<tr>
<th>AMBIENT TEMPERATURE (°C.)</th>
<th>PERIOD</th>
<th>( a )</th>
<th>( b )</th>
<th>( c )</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>1</td>
<td>0.67</td>
<td>0.67</td>
<td>15.3</td>
<td>N.S.</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.30</td>
<td>0.40</td>
<td>4.4</td>
<td>N.S.</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>0.37</td>
<td>0.95</td>
<td>1.25</td>
<td>N.S.</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>0.40</td>
<td>0.90</td>
<td>1.15</td>
<td>N.S.</td>
</tr>
<tr>
<td>30</td>
<td>1</td>
<td>0.45</td>
<td>2.44</td>
<td>3.7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.88</td>
<td>0.59</td>
<td>1.07</td>
<td>N.S.</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>0.48</td>
<td>0.40</td>
<td>1.38</td>
<td>N.S.</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>0.82</td>
<td>0.81</td>
<td>1.55</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Results are average values for each period, with all severities of injury taken together.

N.S., Not significant.

The urinary excretion of zinc is low. For 16 normal subjects we found a daily excretion of 496 ± 197 μg. (mean ± s.d.). It is not affected by urinary volume or dietary intake (Spencer, Osis, Kramer, and Samachson, 1971). More than 60 per cent of the total body zinc is in skeletal muscle and the urinary excretion is known to rise after injury (Henzel, De Weese, and Lichti, 1970). The results shown in Table IV demonstrate the two- to threefold increases found after injury, although there was no significant difference in the amount excreted by the two groups of patients.

The evidence of increased potassium, creatine, and zinc excretion in urine after injury clearly demonstrates the quantitative importance of muscle in the protein metabolic response to trauma.

5. Relation between Dietary Nitrogen and Energy and Urine Nitrogen Excretion after Trauma.—Normally one would expect urine nitrogen to be a variable dependent linearly on food nitrogen and food energy, the regression coefficient being positive for food nitrogen and negative for food energy. We tested this relationship in the injured subjects. The multiple linear regression of urine nitrogen on food nitrogen and food energy was computed for the mean intake and excretion values for each patient in each of the four time periods. The results from patients at 20° C. were analysed separately from those at 30° C. Statistically significant linearity was tested by analysis of variance. The results are shown in Table V. It is clear that there is never a significant linear relationship at 20° C. and indeed the regression coefficients do not even have the expected signs. At 30° C., however, the regression coefficients all have the expected sign and a statistically linear relationship is achieved in period 1 (P<0.005) and nearly so in period 4 (P<0.01).

6. Correlation between Urine Nitrogen and other Excretory Products of Tissue Catabolism.—Single correlation coefficients were computed for urine nitrogen on urine zinc, urine nitrogen on urine creatine, and urine nitrogen on urine potassium. Urine nitrogen always correlated significantly with urine zinc (P<0.005), with urine creatine (P<0.001), and with urine potassium (P<0.001). Creatine correlated significantly with zinc (P<0.001) and with potassium (P<0.01) at 20° C. but not at 30° C. This further suggests that muscle catabolism is a major factor in the metabolic response and that this is somewhat reduced at ambient temperatures of about 30° C. The results are shown in Table VI.

Table VI.—Correlations between Urine Nitrogen and Products of Muscle-tissue Catabolism (Creatine, Zinc, and Potassium) and between Urine Creatine and Other Products of Muscle-tissue Catabolism (Zinc and Potassium) for Patients with All Severities of Trauma at All Intervals after Injury

<table>
<thead>
<tr>
<th>AMBIENT TEMPERATURE (°C.)</th>
<th>CORRELATION</th>
<th>( r )</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>Nitrogen and zinc</td>
<td>0.5233</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td></td>
<td>Nitrogen and creatine</td>
<td>0.5337</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Nitrogen and potassium</td>
<td>0.6992</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>30</td>
<td>Nitrogen and zinc</td>
<td>0.5967</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Nitrogen and creatine</td>
<td>0.5955</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Nitrogen and potassium</td>
<td>0.5964</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>20</td>
<td>Creatine and zinc</td>
<td>0.5910</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Creatine and potassium</td>
<td>0.3200</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>30</td>
<td>Creatine and zinc</td>
<td>0.2970</td>
<td>N.S.</td>
</tr>
<tr>
<td></td>
<td>Creatine and potassium</td>
<td>0.2219</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

DISCUSSION

The results reported in the present paper allow two important conclusions to be drawn. First, the metabolic response to bony injury (mainly fractures) involves net catabolism of muscle tissue to a quantitatively important extent, and secondly, this response is significantly reduced in the severely injured patient if he is housed at 30° C. ambient temperature.

It has long been inferred that muscle breakdown is involved in the metabolic response to injury. Indeed, the early observations of Cuthbertson (1930) arose from an investigation of the calcium and phosphorus balance in patients with fracture of the long bones of the lower limbs, where there was found to be an unexpected considerable negative phosphorus balance but not a corresponding calcium deficit. Soft tissue seemed to be implicated and further investigations showed a marked loss of nitrogen and sulphur as well as of phosphorus in the first 10-12 days following fracture of a major long bone. These three elements were excreted in proportions which suggested that muscle might be the source of the loss. A few years later Cuthbertson and others (1939) observed similar responses in the rat given experimentally a fracture of femur, and they also reported a creatinuria which paralleled the increased urine-nitrogen loss. This work was not taken much further at the time owing
to war-time conditions, but the importance of a dietary-dependent endogenous protein pool was demonstrated by Munro and Cuthbertson (1943) and Munro and Chalmers (1945), who found no increased urine nitrogen following fracture of the femur in the rat if the animals had been fed a protein-free, but calorie-sufficient, diet for some time before injury. They also showed that the proportion of protein in the pre-injury, but not post-injury, diet quantitatively affected the response to trauma. However, in spite of the well-accepted clinical observation of muscle wasting in severe injury and the above observations of Munro and his colleagues, some workers claim that the observed metabolic response to injury is simply that of the reduced voluntary food intake which usually follows major trauma (Abbott and Albertsen, 1963).

The results which we report quite clearly demonstrate the involvement of muscle catabolism in the presence of undiminished food intake, and that this response, entirely separate from dietary conditions, is diminished at the higher ambient temperature. The results of the regression analysis both confirm the effect of the 30°C environment in reducing the metabolic response and also cast doubt on the value of intensive nutrition, in which high-calorie, high-nitrogen diets are given by intubation or intravenously in the early stages post trauma. Our results indicate that such measures in no way diminish the catabolic response of muscle tissue. It is true that, faced with a long-term apparently hypercatabolic state or with a patient who will be unable to feed normally for some time, intensive nutrition with high-energy regimens will be of value since nitrogen balance should be improved (Peaston, 1968).

The effect of environmental temperature on the metabolic response to trauma is a relatively recent finding. The first observation of a reduction in what Cuthbertson has defined as the 'flow' phase (Cuthbertson, 1942) was made by Caldwell in 1962. This report showed that an ambient temperature of 30°C reduced negative nitrogen balance and mortality in rats with severe scalding injury. These observations have been confirmed by Barr and others (1968) and Davies and Liljedahl (1970) for man with similar results.

The initial suggestion of Caldwell (1962) was that the warmer environment provided the heat required to evaporate the water that is continuously lost from burned skin and thus relieved the body of a heat burden which can easily exceed 3000 Cal. (12.5 MJ.) per day (Moyer and Butcher, 1967). This may be part of the value of the warmer environment to patients with burns, but it in no way accounts for the similar effect of temperature on the metabolic response to long bone injury in the rat (Campbell and Cuthbertson, 1967) or the results for man reported in the present paper. Unfortunately our experiments do not allow us to draw conclusions about the mechanisms involved. We do know that the corticosteroid response is not affected by the higher temperature, at least in the rat (Tilstone and Roach, 1969) and we feel that more evidence is needed before Caldwell's more recent suggestion (Caldwell, 1970) that the thyroid is definitely concerned can be accepted.

Johnston and others have been studying the effect of exposure to 30°C on the metabolic response to trauma in patients undergoing elective abdominal surgery. They have recently reported their conclusions (Spivey and Johnston, 1972) and state that temperature does not affect the metabolic response in these patients but point out that the catabolic response to such trauma is usually minor. This agrees with our results from the less severely injured subgroup, but our overall results and those mentioned above from workers dealing with burns injuries quite clearly show that a reduced metabolic response can be achieved by increasing the ambient temperature to 30°C. A beneficial clinical response also seems clear in the burns cases, although we can put forward no conclusions at all about the progress of the long bone injuries other than that it is not impaired. Improved superficial wound healing in rats has already been reported by us (Cuthbertson and Tilstone, 1967).

The parallel observations on some of our cases made by Fleck and Ballantyne (1971) in respect of the behaviour of the plasma proteins following injury indicate that at 28-30°C, there is a hormonal disturbance with a diminished rise in acute phase reactants and a diminished fall in plasma-albumin concentration.

Davies (1970), following up the close correlation between the increased rate of nitrogen excretion and the increase in resting metabolic rate both in fractures and burns, has, with his Swedish collaborators (Barr and others, 1968), further demonstrated the beneficial effect of a warm environment (32°C) on protein metabolism. They have shown that the catabolism of plasma albumin and IgG was increased as the severity of the burns increased and with burns the catabolic rate of these two proteins was reduced by nursing the patients at 32°C.

Campbell and Cuthbertson (1967) and Cuthbertson and others (1968) observed a 15-30 per cent fall in voluntary food intake in the rat at an environmental temperature of 30°C, but we have not found a significant fall in intake in our human patients. However, in an earlier report (Tilstone and Cuthbertson, 1970) we did consider the possible combined effects of the slight increase in intake of energy together with possibly reduced heat loss at 30°C on urine nitrogen at 30°C., and concluded this to be still significant. Similarly, the loss of nitrogen, which amounts to about 0.55 g. per day for a sedentary man in a comfortable environment (Calloway, Odell, and Margen, 1971), would not be expected to differ at 30°C., to an extent which would compensate for the reduced excess nitrogen excretion.

Patients vary in the intensity and duration of their response to injury, particularly in terms of heat production (Kinney, Long, and Duke, 1970). Involved in this is the effective circulating blood-volume, the integrity of the particular reaction of the neuro-endocrine system, the nutritional state in respect of its energy reserves, and the effect of environmental temperature.

Following moderate to severe injury there is first the 'ebb phase' of diminished heat production corresponding with the 'shock' period. This depression, as Threfall (1970) has pointed out, is not due to lack of oxygen supply but possibly is effected through changes in the thermoregulatory mechanism. The changes characteristic of tissue hypoxia in experimental animals do not tend to occur until the point
when death seems certain. When the metabolic tide 'turns' the increased heat production of the 'flow phase' is apparently brought about through changes in the sites of thermogenesis. The application of heat during this stage in experimental animals has an adverse effect on survival, possibly due to their low thermal capacity. Man has a much greater thermal capacity and heat may be advantageous at an earlier stage than we have applied it, once appropriate blood transfusions have been effected. Cases involving brain damage, however, are an exception.

During the 'flow phase' when heat production and oxygen consumption are increased the hyperglycaemia and glycosuria usually disappear. When the environmental temperature is brought up to thermoneutrality for man, i.e., 28–30°C, the need for increased oxidation of protein and for carbohydrate intermediates and the products of their oxidation is also reduced (Kinney and others, 1970). The increased body temperature associated with moderate to severe injury-traumatic fever—does not appear to be affected by the thermal environment.

The increases in urinary potassium, zinc, and creatine as well as nitrogen at normal ward temperature lend further emphasis to the view that following trauma the major change in metabolism in the 'flow phase' is increased catabolism rather than diminished anabolism.

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