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Metabolic aspects of hypothermia in the elderly

MRC Trauma Unit, Stopford Building, University of Manchester, Manchester, and Hope Hospital, Salford, Greater Manchester, U.K.

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Summary

1. Plasma concentrations of glucose, lactate, amino acids, non-esterified fatty acids, glycerol, ketone bodies, insulin and cortisol were measured in 43 elderly patients with hypothermia. In 15 of these patients forearm arteriovenous differences were also measured. Core temperatures ranged from 25.9 to 35.5°C.

2. The metabolic state was of mobilization of glycogen and triacylglycerol stores, with high plasma concentrations of lactate and lipid metabolites. The plasma concentration of glucose was raised in those with hypothermia of a short duration (<6 h). In other patients it was low in those with core temperatures around 30°C, but below this temperature it was variable and often high. Concentrations of other metabolites or hormones were not related to core temperature.

3. Plasma concentrations of cortisol were high and positively correlated with those of lactate and glycerol, suggesting active involvement in stimulation of muscle glycogenolysis and of lipolysis.

4. Plasma concentrations of insulin ranged from very low to very high and appeared to depend on the concentrations of both glucose and alanine.

5. Arteriovenous differences were generally small. There was peripheral release of lactate and of amino acids but no overall peripheral uptake of glucose. In nine out of 15 patients there was a significant peripheral release of glucose.

6. No differences in metabolism were observed between patients where the hypothermia appeared accidental and those with an obvious precipitating illness, despite a significantly lower mortality in the former group.

7. It was concluded that therapy should primarily involve rewarming of patients by physical means, without metabolic intervention.

Key words: accidental hypothermia, amino acids, arteriovenous differences, core temperature, cortisol, elderly patients, glucose, glycerol, hypothermia, insulin, ketone bodies, lactate, non-esterified fatty acids.

Introduction

Many people are brought to hospital every year with a low body temperature as the condition responsible for admission. With sufficiently adverse environmental conditions hypothermia can occur at any age but it is particularly likely at the extremes of life. In the elderly there is impairment of thermoregulation (Collins, Doré, Exton-Smith, Fox, MacDonald & Woodward, 1977) and of mobility. Immobility may be due to serious illness such as a cerebrovascular accident or to a simple fall from which the patient is unable to rise, remaining for several hours on the floor of a cold house. In the absence of serious injury or of a pathological condition, the restoration of normothermia is accompanied by a return to the patient's original state, since hypothermia per se does not, for instance, change cerebral function irreversibly (Andjus, Knöpfel, Russell & Smith, 1955).
The temperature in these patients is frequently below the lower limit (35°C) usually studied experimentally in man. The condition is difficult to imitate in laboratory animals where steps (use of anaesthesia, drugs or restraint) have to be taken to inhibit heat production during cooling. Hence these patients can supply unique information about some aspects of metabolism. Most forms of therapy depend on reducing heat loss and rely on the patient's own heat production to restore body temperature. The metabolism of these patients is poorly understood and lack of knowledge could hinder any attempts to improve heat production. We have, therefore, tried to define the biochemical state of the patient with hypothermia and to relate the change in the plasma concentrations of energy-yielding substrates and associated hormones to core temperature and to the duration of the condition.

**Methods**

On arrival in the Accident and Emergency Department the patients were examined and histories taken, usually with the help of ambulance men, relatives, police and others. An accurate picture of the circumstances was often difficult to obtain, but the shorter the time from onset the easier it was to establish the duration of the condition. The core temperature was measured with a zero-gradient aural thermometer (Keatinge & Sloan, 1973) in all but six patients, in whom it was measured rectally. Blood samples, for diagnostic purposes, were taken from an antecubital vein and in some also from a femoral artery. With the extreme constriction of the blood vessels in the skin in these cold patients the venous sample was obtained mainly from muscle. Plasma concentrations of glucose, lactate, non-esterified fatty acids, glycerol, ketone bodies, amino acids, cortisol, insulin and ethanol were measured by methods used before (Stoner, Frayn, Barton, Threlfall & Little, 1979). The methods used for the treatment of hypothermia in these patients have been discussed elsewhere (Yates & Little, 1979). The diagnosis and treatment of other conditions present were carried out by conventional methods. Further blood samples were obtained from 16 patients when normothermia had been restored.

Statistical methods were based on those described by Snedecor & Cochran (1967). The statistical distributions of the concentrations of the amino acids tested (see Table 1) and of cortisol, glycerol, insulin, lactate and total ketone bodies (acetoacetate and β-hydroxybutyrate) were positively skewed (P < 0.05) but this asymmetry was reduced on transformation to logarithms, in general agreement with the results of Foster, Alberti, Hinks, Lloyd, Postle, Smythe, Turnell & Walton (1978) in normal subjects. These variables have been treated throughout this paper as lognormally distributed. The concentration of non-esterified fatty acids and the β-hydroxybutyrate/acetoacetate ratio were not skewed and have been treated as normally distributed. The plasma concentration of glucose was non-linearly related to core temperature (Fig.

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>Mean</th>
<th>2 SD range</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactate* (mmol/l)</td>
<td>41</td>
<td>2.79</td>
<td>0.60–12.90</td>
<td>0.46–0.97*</td>
</tr>
<tr>
<td>Non-esterified fatty acids (mmol/l)</td>
<td>40</td>
<td>1.13</td>
<td>0.16–2.11</td>
<td>0.15–0.89</td>
</tr>
<tr>
<td>Glycerol* (mmol/l)</td>
<td>39</td>
<td>0.256</td>
<td>0.073–0.894</td>
<td>0.033–0.139*</td>
</tr>
<tr>
<td>Total ketone bodies* (mmol/l)</td>
<td>8</td>
<td>0.241</td>
<td>0.071–0.820</td>
<td>0.024–0.840*</td>
</tr>
<tr>
<td>β Hydroxybutyrate/acetoacetate</td>
<td>17</td>
<td>1.17</td>
<td>0.08–17.84</td>
<td>0.024–0.840*</td>
</tr>
<tr>
<td>Cortisol* (μmol/l)</td>
<td>42</td>
<td>1.18</td>
<td>0.37–3.79</td>
<td>0.7–4.3*</td>
</tr>
<tr>
<td>Insulin* (m units/l)</td>
<td>41</td>
<td>8.8</td>
<td>1.1–70.8</td>
<td>1.9–12.3*</td>
</tr>
<tr>
<td>Total amino acids* (mmol/l)</td>
<td>36</td>
<td>2.40</td>
<td>1.37–4.21</td>
<td></td>
</tr>
<tr>
<td>Alanine* (mmol/l)</td>
<td>36</td>
<td>0.259</td>
<td>0.092–0.726</td>
<td>0.170–0.385*</td>
</tr>
<tr>
<td>Glutamine* (mmol/l)</td>
<td>36</td>
<td>0.60</td>
<td>0.29–1.23</td>
<td></td>
</tr>
<tr>
<td>Branched-chain amino acids* (mmol/l)</td>
<td>36</td>
<td>0.36</td>
<td>0.12–1.03</td>
<td></td>
</tr>
</tbody>
</table>

* Results calculated after logarithmic transformation of data.
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1) and did not conform to either of these distributions. Non-parametric methods have therefore been used where practicable for calculations involving plasma concentrations of glucose. For multiple correlations involving this variable, parametric methods have been used but the results were not affected by the choice of normal or lognormal distribution. All two-variable correlations, involving other variables, were calculated by both distribution-free (Kendall's rank correlation method) and parametric methods and results were always similar.

In order to compare our results with those in subjects with normothermia we have where possible used the data of Foster et al. (1978) for the 61–75 year age group (Table 1) although our patients were, on average, somewhat older.

Results

Forty-three patients (11 male) with core temperatures between 25.9 and 35.5°C were examined. Their ages ranged from 53 to 97 years (median 81). Clinical and biochemical information about these patients has been deposited as Clinical Science Table no. 80/1 with the Librarian, The Royal Society of Medicine, 1 Wimpole Street, London W1M 8AE, from whom copies may be obtained on request. Unlike in some series of patients with hypothermia (Maclean, Murison & Griffiths, 1973) in many of ours (22) there was no clear precipitating illness and their hypothermia could be traced to a simple fall from which they could not rise. In the 21 other patients there was a wide range of significant pathological conditions, some of which clearly played a major part in the development of hypothermia. These differences were reflected in the mortality rates, for 16 of these 21 died whereas only seven of the 22 patients with 'accidental' hypothermia died (P < 0.01; \( \chi^2 \) test), despite a greater average age (P < 0.01; Wilcoxon's two-sample rank test).

Three other patients with hypothermia were...
excluded. In one, there was a large pituitary chromophobe adenoma which pressed on and deformed the hypothalamus, another died from leukaemia very shortly after arrival and, in a third, ethanol was detected in the plasma. This was the only patient in whom ethanol was found in the plasma; there were no known patients with chronic alcoholism or other drug abusers in the series.

Our patients differed from others described elsewhere (Maclean et al., 1973; Maclean, Griffiths, Browning & Muriison, 1974) in that most had not been neglected. This was shown by the short duration of the cooling period in many of them, the absence of gross clinical malnutrition and the relatively normal concentration of the plasma proteins (deposited Table 80/1).

**Substrate and hormone concentrations**

Plasma concentrations of glucose ranged from 1·07 to 21·3 mmol/l (Fig. 1). In patients with hypothermia of less than 6 h duration plasma concentrations of glucose were greater than in patients with hypothermia of longer duration, when compared over an intermediate temperature range (Fig. 1). In patients with hypothermia of more than 6 h duration plasma concentrations of glucose were lowest in those with core temperatures around 30°C. The existence of a minimum value was confirmed by fitting a parabolic regression of plasma concentration of glucose on core temperature. The fit was significant (P < 0·05 by F-test) and better than by linear regression (P < 0·05 by F-test), and the curve showed a minimum at 31·6°C. Below a core temperature of 29°C plasma concentrations of glucose were variable but usually high.

Plasma concentrations of lactate (Table 1) were above the normal range (Foster et al., 1978) in all but two patients. The concentrations were not related to core temperature, or to the duration of the hypothermia.

Concentrations of lipid metabolites (non-esterified fatty acids, glycerol and ketone bodies) were also elevated (Table 1) but again were unrelated to core temperature. Only the total ketone-body concentration was affected by the duration of hypothermia, being higher in those with hypothermia of longer duration (Wilcoxon's two-sample rank test for <6 h vs >6 h; P < 0·05). The mean β-hydroxybutyrate/acetoacetate ratio was towards the upper end of the normal range.

As concentrations of amino acids other than alanine are not given by Foster et al. (1978), we have compared our data with means and standard errors calculated for age 80 years using the regressions of amino acid concentration on age given by Armstrong & Stave (1973). The concentrations of glutamine and branched-chain amino acids shown in Table 1 agreed closely with those derived from their data. The concentration of alanine in our patients was lower (P < 0·001) but agreed with that found by Foster et al. (1978).

Plasma concentrations of cortisol were high in all patients (Table 1), sometimes extremely so (range 0·54–4·31 μmol/l). They were not related to core temperature or to the outcome. Plasma concentrations of insulin ranged from very low to very high (<1–88 munits/l).

For none of the measured variables was there a significant difference between patients with other diseases and those in whom the hypothermia was accidental (Wilcoxon's two-sample rank test; P > 0·1 for each).

**Arteriovenous differences**

Arteriovenous differences for glucose, lactate, non-esterified fatty acids and amino acids were small (Fig. 2), so that the general pattern of results described above was the same whether arterial or venous samples were used. There was a significant peripheral output of lactate but no significant uptake of glucose in the group as a whole. The significance of individual arteriovenous differences for glucose was examined, based on the precision of plasma-glucose estimation (coefficient of deviation 0·5%). Of the 15 measured arteriovenous differences for glucose, five showed significant peripheral uptake (each P < 0·01) but nine showed significant output (each P < 0·001).

The glucose arteriovenous difference was not related to the plasma concentrations of glucose or insulin, nor to core temperature or the duration of the hypothermia. The arteriovenous difference for lactate, however, was strongly correlated with its venous plasma concentration (Fig. 3), indicating that the latter was being determined mainly by variations in the rate of production. Lactate output appeared to be stimulated by both cortisol and insulin, since the arteriovenous difference was negatively related to amino acid arterio-
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Glucose
Lactate
Total amino acids
Non-esterified fatty acids
Alanine
Glutamine
Branched-chain amino acids

Arteriovenous difference (mmol/l)

Fig. 2. Arteriovenous differences in patients with hypothermia. Samples were taken from a femoral artery and an antecubital vein. The difference shown is arterial concentration—venous concentration (i.e. positive values represent peripheral uptake). Symbols are as in Fig. 1. $P$, Significance of the difference of the mean from zero assessed with the paired $t$-test.

Fig. 3. Relationship between arteriovenous difference and venous concentration of lactate in initial plasma samples from patients with hypothermia ($r = -0.85, P < 0.001$). Symbols are as in Fig. 1. Concentration of lactate is given on a logarithmic scale for reasons given in the text. The regression line shown is the line of best fit for all patients. Positive values represent peripheral uptake and negative values release.

Relationships between metabolites

The wide spread of the initial concentrations of most plasma constituents in these patients made the relationships between them more informative than might be expected in normal subjects. In none of these correlations was there any indication that either the cause or duration of the hypothermia affected the relationship (Figs. 3 and 4). Some of these relationships might have been expected in normal subjects, and their occurrence in our patients indicates that at least some aspects of metabolism were qualitatively unaffected by the hypothermia per se (Table 2). Other correlations shown were more unexpected, and some of those expected were not found. Plasma concentrations of glucose, for instance, were unrelated to those of any other substrate or hormone except insulin and (weakly) lactate. The concentration of insulin appeared to depend on both glucose and alanine concentrations, since it was positively correlated with each of these, and these relationships were additive (three-variable correlation: $n = 36, r = 0.69, P < 0.001$). Plasma amino acid concentrations were generally correlated one with another and with the total amino acid concentration, but alanine was the only one related to the plasma concentrations of lactate (Fig. 4) and insulin, and the ratio of venous differences, significantly so for total amino acids ($n = 10, r = -0.66, P < 0.05$) and branched-chain amino acids ($n = 10, r = -0.87, P < 0.001$).
TABLE 2. Correlations between concentrations of plasma constituents in initial samples from patients with hypothermia

Product–moment correlation coefficients between plasma concentrations of the variables in single venous samples from patients with hypothermia are shown. All concentrations except those of glucose and non-esterified fatty acids (NEFA) were converted to logarithms for reasons given in the text. Only significant correlations considered relevant to the discussion in the text are presented. The correlations between plasma concentrations of glucose and those of insulin and lactate were significant by Kendall’s rank correlation method (\(r = 0.25, P < 0.01\); \(r = 0.74, P < 0.001\) respectively).

<table>
<thead>
<tr>
<th>Variables</th>
<th>No. of patients</th>
<th>(r)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>Insulin</td>
<td>40</td>
<td>0.43</td>
</tr>
<tr>
<td>Glucose</td>
<td>Lactate</td>
<td>41</td>
<td>0.21</td>
</tr>
<tr>
<td>Alanine</td>
<td>Insulin</td>
<td>36</td>
<td>0.54</td>
</tr>
<tr>
<td>Lactate</td>
<td>Insulin</td>
<td>40</td>
<td>0.57</td>
</tr>
<tr>
<td>Lactate</td>
<td>Cortisol</td>
<td>40</td>
<td>0.52</td>
</tr>
<tr>
<td>Lactate</td>
<td>Alanine</td>
<td>36</td>
<td>0.75</td>
</tr>
<tr>
<td>Lactate</td>
<td>Alanine/total amino acids</td>
<td>36</td>
<td>0.74</td>
</tr>
<tr>
<td>NEFA</td>
<td>Glycerol</td>
<td>38</td>
<td>0.36</td>
</tr>
<tr>
<td>NEFA</td>
<td>Total ketone bodies</td>
<td>25</td>
<td>0.67</td>
</tr>
<tr>
<td>Glycerol</td>
<td>Cortisol</td>
<td>38</td>
<td>0.54</td>
</tr>
<tr>
<td>Glycerol</td>
<td>Lactate</td>
<td>39</td>
<td>0.60</td>
</tr>
</tbody>
</table>

Fig. 4. Relationship between plasma alanine and lactate concentrations in initial samples from patients with hypothermia (\(r = 0.75, P < 0.001\)). Symbols are as in Fig. 1. Both concentrations are given on a logarithmic scale for reasons given in the text. The regression line shown is the line of best fit for all patients.

Alanine to total amino acids was highly correlated with the plasma concentration of lactate.

Plasma lipid metabolites (glycerol, non-esterified fatty acids and total ketone bodies) were correlated one with another as expected. The plasma concentration of glycerol was also correlated with those of cortisol and lactate (the relationship between glycerol and lactate not being mediated solely through their common relationship with cortisol; \(r_{\text{partial}}\) for glycerol against lactate at constant cortisol = 0.44, \(P < 0.01\)).

Changes on rewarming

When normothermia had been restored 12 h–3 days after the initial sampling, there was a general return to normal (Table 3); the plasma concentrations of lactate, amino acids and lipid metabolites were falling, along with the \(\beta\)-hydroxybutyrate/acetocacete ratio, and the variance in the plasma concentration of glucose was decreasing (\(F\)-test; \(P < 0.005\)) as the patients tended towards normoglycaemia. The relationship between plasma concentrations of lactate and alanine was maintained during rewarming, the change in concentration of alanine being correlated with that in lactate (\(n = 14, r = 0.59, P < 0.05\)), and the change in concentration of insulin was again dependent on the changes in both glucose and alanine concentrations (three-variable correlation: \(n = 14, r = 0.63, P < 0.05\)). The changes in plasma concentrations of the lipid metabolites were related (e.g. glycerol and non-esterified fatty acids, \(n = 15, r = 0.57, P < 0.05\); total ketone bodies and non-esterified fatty acids, \(n = 9, r = 0.78, P < 0.05\)) and a changing plasma concen-
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Venous blood samples were taken during hypothermia ('Initial') and 0-5-3 days later when the patient was normothermic ('Rewarmed'). Plasma concentrations of the variables shown were determined as described in the text. The significance of the changes was assessed by the paired t-test.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Initial</th>
<th>Rewarmed</th>
<th>Mean</th>
<th>SD range</th>
<th>Mean</th>
<th>SD range</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (mmol/l)</td>
<td>16</td>
<td>16</td>
<td>7-40</td>
<td>3.69-11.11</td>
<td>5.47</td>
<td>3.84-7.10</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Lactate* (mmol/l)</td>
<td>16</td>
<td>16</td>
<td>2.54</td>
<td>1.24-5.19</td>
<td>1.70</td>
<td>1.16-2.51</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Non-esterified fatty acids (mmol/l)</td>
<td>15</td>
<td>15</td>
<td>1.24</td>
<td>0.90-1.58</td>
<td>0.77</td>
<td>0.40-1.36</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Glycerol* (mmol/l)</td>
<td>16</td>
<td>16</td>
<td>0.265</td>
<td>0.152-0.463</td>
<td>0.15</td>
<td>0.071-0.321</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total ketone bodies* (mmol/l)</td>
<td>9</td>
<td>9</td>
<td>0.86</td>
<td>0.20-3.69</td>
<td>0.25</td>
<td>0.04-1.60</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>β-Hydroxybutyrate/acetocacetate</td>
<td>9</td>
<td>9</td>
<td>3.82</td>
<td>2.61-5.03</td>
<td>2.11</td>
<td>1.19-3.02</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cortisol* (μmol/l)</td>
<td>15</td>
<td>15</td>
<td>1.09</td>
<td>0.75-1.57</td>
<td>1.08</td>
<td>0.68-1.72</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Insulin* (m-units/l)</td>
<td>16</td>
<td>16</td>
<td>7.2</td>
<td>2.1-24.4</td>
<td>8.2</td>
<td>2.4-28.2</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Total amino acids* (mmol/l)</td>
<td>12</td>
<td>12</td>
<td>2.32</td>
<td>1.78-3.01</td>
<td>1.81</td>
<td>1.50-2.18</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Alanine* (mmol/l)</td>
<td>14</td>
<td>14</td>
<td>0.224</td>
<td>0.150-0.334</td>
<td>0.155</td>
<td>0.104-0.231</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Glutamine* (mmol/l)</td>
<td>14</td>
<td>14</td>
<td>0.582</td>
<td>0.445-0.762</td>
<td>0.530</td>
<td>0.401-0.700</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Branched-chain amino acids* (mmol/l)</td>
<td>14</td>
<td>14</td>
<td>0.348</td>
<td>0.211-0.575</td>
<td>0.219</td>
<td>0.156-0.308</td>
<td>&lt;0.02</td>
</tr>
</tbody>
</table>

* Results calculated after logarithmic transformation of data.

Discussion

The metabolic state in these patients was of high concentrations of most energy-yielding substrates, probably due to mobilization of body fuel stores. The high plasma concentrations of non-esterified fatty acids, glycerol and ketone bodies indicated lipolysis of adipose tissue triacylglycerol with conversion of non-esterified fatty acids into ketone bodies in the liver. The high plasma concentrations of lactate were due to breakdown of muscle glycogen, as shown by their correlation with the forearm lactate arteriovenous difference and by the absence of consistent peripheral glucose uptake. Rapid muscle glycogenolysis can lead to release of free glucose from muscle (Wicklmayr & Dietze, 1978) and this was probably responsible for the peripheral glucose output in some of our patients. There was also peripheral net proteolysis as shown by the significant release of amino acids.

The high plasma concentrations of glucose in patients with hypothermia of short duration and in those whose core temperatures had not fallen below about 34°C, probably reflected mobilization of liver glycogen stores. This agrees with the progressive increase in hyperglycaemia with falling core temperature seen during rapid cooling in man (Alexander, 1945). At lower core temperatures the changes in plasma concentrations of glucose became more complicated and presumably reflected an altering balance between production and utilization. Low plasma concentrations of glucose were seen in patients with core temperatures around 30°C, but below a temperature of 29°C hyperglycaemia reappeared, as noted by others in patients with profound hypothermia (Laufman, 1951). These results thus show more order than do previous reports on accidental hypothermia (Nicolas, Nicolas, Heurte, Baron, Rodineau & De Lajartre, 1974; Ledingham & Mone, 1978; reviewed by Maclean & Emslie-Smith, 1977) and fit in with the hypothesis, arising from experimental work on man and animals (Wynn, 1954, 1956; Bickford & Mottram, 1960; Fuhrman & Fuhrman, 1963), that there is severe impairment of glucose utilization and oxidation below a core temperature of around 30°C, although glucose production can still occur.

Although the main stimulus for the mobilization of both adipose tissue triacylglycerol and muscle glycogen probably would have been the sympatho-adrenal response, our results suggest that the high plasma concentrations of cortisol also played an active role, since plasma concentrations of cortisol were correlated positively with those of glycerol and lactate as well as negatively with the arteriovenous difference for the latter. These observations are in general agreement with previous work showing that glucocorticoid treatment potentiates catecholamine-stimulation of lipolysis (Goodman, 1970) and of muscle glycogenolysis (Scllaeffer, Chenoweth & Dunn, 1969; Miller, Exton & Park, 1971), although the latter effect of glucocorticoids has been described as permissive only (Miller et al., 1971). The apparently more
active role in our patients may reflect the extremely high plasma concentrations of cortisol reached in some, although the elevation of free cortisol concentrations will have been reduced, to some extent, by the increased affinity of binding to corticosteroid-binding globulin at low temperatures (Sandberg & Slaunwhite, 1971).

The observation of net muscle proteolysis was surprising and the stimulus is uncertain from our results, but the lack of peripheral glucose uptake may have been involved, as glucose is an inhibitor of muscle protein breakdown (Fulks, Li & Goldberg, 1975). Low plasma concentrations of insulin also contributed in some patients as shown by the negative relationship with amino acid arteriovenous differences. Cortisol did not appear to be involved, as its plasma concentration was not related to amino acid output, and high concentrations of circulating catecholamines would have tended to suppress muscle proteolysis (Garber, Karl & Kipnis, 1976).

The amino acid most consistently released was alanine, probably reflecting its production from pyruvate by transamination with other amino acids (Felig, 1973). This could explain in part the marked correlation between plasma concentrations of alanine and lactate (Fig. 4), as with the correlation between concentrations of pyruvate and alanine found in normal subjects by Felig & Wahren (1971). However, the lack of correlation between the plasma concentration of alanine and its arteriovenous difference suggests that other factors reinforced the relationship between lactate and alanine concentrations. There may have been substrate competition for hepatic uptake and perhaps a common inhibition by insulin of this process (Claus & Pilkis, 1976), as suggested by the positive correlation of each with plasma concentrations of insulin, although whether this occurs in man is uncertain (reviewed by Rabin, Mueller, Lacy & Liljenquist, 1979). A further reason for the relationship between plasma insulin and alanine concentrations might have been stimulation of pancreatic insulin secretion by alanine. This would account for the apparent dependence of insulin on both alanine and glucose concentrations, since the effects of alanine and glucose are complementary in this respect (Müller, Faloona & Unger, 1971; Gerich, Charles & Grodsky, 1976).

The role of impairment of hepatic blood-flow and oxygenation as a common mechanism for elevation of the plasma concentrations of the various substrates and hormones is difficult to assess, but it is unlikely to have been a major factor. The plasma $\beta$-hydroxybutyrate/acetoacetate ratio, which is to some extent a reflection of hepatic redox state, was not grossly elevated, and the observed pattern of correlations between metabolite and hormone concentrations suggests that these were determined more by variation in production rates than in rates of clearance. One exception was the plasma cortisol, concentrations of which were elevated in some patients beyond the range attained in normal subjects on maximal stimulation by ACTH (Eik-Nes, Sandberg, Nelson, Tyler & Samuels, 1954), showing that cortisol removal, which occurs mainly in the liver (Peterson, 1971), must have been impaired.

There has been much discussion on methods of treatment of hypothermia (Lloyd, Mitchell & Williams, 1976; Stine, 1977; Editorial, 1978; Editorial, 1978) but apart from the work of Maclean et al. (1974) little attention has been paid to metabolic aspects. Our results do provide some pointers in this field. With such high endogenous plasma-cortisol concentrations there would be no reason for giving glucocorticoids, a point previously made by others (Mills, 1974; Maclean & Emslie-Smith, 1977). Measurement of the blood-glucose concentration is important as it may well be beneficial to give glucose to the hypoglycaemic patient for the needs of the central nervous system (Maclean & Emslie-Smith, 1977), but other than for this, such treatment is unnecessary as the glucose may remain in the extracellular space creating osmotic problems (Wynn, 1954). This was illustrated in one of our patients with a core temperature of 28.0°C given 50 g of glucose, in whom the plasma concentration of glucose rose to 28 mmol/l and remained at that value for 10 h (despite intravenous injection of 10 units of soluble insulin) and the serum concentration of sodium dropped to 118 mmol/l. Injection of sufficient insulin may lower the hyperglycaemia, as it does in animals with hypothermia (Wynn, 1954; Bickford & Mottram, 1960) but since endogenous insulin did not appear to promote glucose uptake into peripheral tissues at any core temperature, this effect may simply reflect inhibition of hepatic output.

The metabolic state in the patient with hypothermia is thus of a mobilization of body fuels under the influence of cold-induced increases in adrenal medullary and cortical activity. The biochemical state of the patients was dominated by the low body temperature since no differences were found between those with significant underlying disease and those without. Preliminary measurements of the metabolic rate, made by indirect calorimetry, in four of our patients showed that this was reduced as expected from
the effects of temperature on reaction rates. Under these circumstances minimizing heat loss, with or without provision of an external heat source, will lead to a steady increase in body temperature, thus removing the stimuli for the metabolic abnormalities, and we suggest that there is no need for metabolic intervention in this process.

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