Summary

1. Hepatic carbohydrate metabolism was studied by an intravenous galactose test in control patients, malnourished non-septic patients, patients with prolonged severe sepsis and patients after recovery from sepsis.

2. Blood galactose half-life was not significantly increased in the septic group despite abnormal liver-function tests, whereas it was approximately doubled in the malnourished patients.

3. The rise in blood glucose after galactose injection was less in both the septic and malnourished groups, as compared with that in the control subjects.

4. Fasting blood glucose, lactate and pyruvate concentrations were similar in all groups, whereas blood ketone bodies were increased in the malnourished and septic groups, and blood alanine was decreased only in the septic group.

5. The changes in hepatic metabolism and function were reversible on recovery from sepsis.

6. It is suggested that alterations in hepatic blood flow and the metabolic fate of galactose within the liver may explain the changes in the metabolic response to galactose observed in malnourished or septic patients.

Key words: alanine, galactose, glucose, ketone bodies, lactate, liver, malnutrition, sepsis.

Introduction

Severe sepsis carries a high mortality and is associated with hepatic damage (Neale, Caughey, Mollin & Booth, 1966; Nunes, Blaisdell & Margaretten, 1970) and malnutrition (Hill, Blackett, Pickford, Burkinshaw, Young, Warren, Schorah & Morgan, 1977). Previous studies of hepatic carbohydrate metabolism in sepsis have not differentiated between the effects of sepsis and malnutrition and have produced variable results, hepatic glucose release having been reported to be either unchanged, increased (Gump, Long, Killian & Kinney, 1974; Gump, Long, Geiger & Kinney, 1975; Long, Spencer, Kinney & Geiger, 1971; Long, Kinney & Geiger, 1976) or decreased (Wilmore, Mason & Pruitt, 1976). The liver is the main site of galactose removal in man (Cohn & Segal, 1973) and intravenous galactose loads have been previously used as a test of hepatic function (Tengström, 1966; Salaspuro & Kesänen, 1973), hepatic blood flow (Tygstrup & Winkler, 1958) and hepatic glucose release (Royle, Kettlewell, Ilic & Williamson, 1978).

We have now attempted to differentiate between the effects of malnutrition and prolonged sepsis on hepatic metabolism, by measuring liver function, fasting blood substrates and the metabolic response to a galactose load in normal and malnourished subjects, and in patients with sepsis, and after recovery from sepsis.

Patients

Seven non-septic malnourished patients with obstructive lesions of the upper gastrointestinal tract were studied, two of whom later died. Malnutrition was shown by a body weight of less than 80% of average body weight (Documenta Geigy, 1970) (Table 1).
Seven patients with major intra-abdominal sepsis (subphrenic or pelvic abscess) of 1–2 weeks' duration were also studied. Sepsis was diagnosed by culture of pus obtained at operation or from discharging abscesses, the organisms being coliform in seven cases, *Pseudomonas* in one and *Staphylococcus aureus* in one. Three of these septic patients died, but four were studied 6–12 weeks later after clinical recovery from sepsis.

Four patients in both the septic and malnourished groups had oesophageal, stomach or colonic carcinomas, but liver metastases were not found either at operation or on liver scan (99mTc). All other patients had non-malignant disease. Nine, non-septic, well-nourished patients of similar age and sex distribution were studied as control subjects (Table 1). None of the patients was oedematous, had diabetes mellitus or received parenteral nutrition or drugs affecting carbohydrate metabolism. None was clinically shocked, dehydrated or had undergone surgery within 1 week of study. The study was approved by the Ethics Committee of the Radcliffe Infirmary, and informed consent was obtained in each case.

### Methods

Weight loss was estimated from average weight tables for age, sex and height (Documenta Geigy, 1970). After a 12 h fast a sample (15 ml) of venous blood was taken via an indwelling cannula without stasis, and 2 ml was immediately deproteinized in 5 ml of cold 10% (w/v) perchloric acid for the enzymic determination of glucose (Stein, 1963), pyruvate and lactate (Hohorst, Kreutz & Bucher, 1959), acetoacetate and 3-hydroxybutyrate (Williamson, Mellanby & Krebs, 1962) and alanine (Williamson, Lopes-Vieira & Walker, 1967). The rest of the sample was heparinized and the plasma used for the estimation of albumin, bilirubin, alkaline phosphatase, glutamate-oxaloacetate transaminase, urea and cholesterol by a Technicon SMA 12/60 Autoanalyzer. Plasma immunoreactive insulin was estimated by a single antibody technique (Albano, Edkins, Maritz & Turner, 1972). After collection of a further 2 ml of blood for basal metabolite measurements, D-galactose (100 ml of 20% solution, w/v) was injected intravenously over 4–6 min via the same cannula. Blood (1–2 ml) was taken via a three-way tap for the estimation of galactose (Kurz & Wallenfels, 1974), glucose and lactate at 10, 15, 20, 25 and 30 min after the galactose injection. Galactose half-life and space was calculated from a semi-logarithmic

<table>
<thead>
<tr>
<th>Group</th>
<th>Glutamate-oxaloacetate transaminase (μM/l)</th>
<th>Alkaline phosphatase (µmol/l)</th>
<th>Bilirubin (µmol/l)</th>
<th>Cholesterol (mmol/l)</th>
<th>Albumin (g/l)</th>
<th>Estimated weight loss (%)</th>
<th>Weight (kg)</th>
<th>Age (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (9)</td>
<td>46 ± 11</td>
<td>61 ± 8</td>
<td>11 ± 1</td>
<td>4.2 ± 0.5</td>
<td>40 ± 1</td>
<td>2.3 ± 0.5</td>
<td>69 ± 5</td>
<td>60 ± 2</td>
</tr>
<tr>
<td>Malnourished (7)</td>
<td>43 ± 3</td>
<td>19 ± 2</td>
<td>11 ± 1</td>
<td>4.3 ± 0.6</td>
<td>39 ± 3</td>
<td>3.3 ± 0.3</td>
<td>67 ± 4</td>
<td>66 ± 15</td>
</tr>
<tr>
<td>Septic (7)</td>
<td>66 ± 15</td>
<td>22 ± 2</td>
<td>9 ± 2</td>
<td>5.0 ± 0.8</td>
<td>38 ± 1</td>
<td>3.0 ± 0.8</td>
<td>56 ± 4</td>
<td>56 ± 4</td>
</tr>
<tr>
<td>Septic-recovered (4)</td>
<td>23 ± 7</td>
<td>60 ± 21</td>
<td>9 ± 2</td>
<td>5.0 ± 0.8</td>
<td>38 ± 1</td>
<td>3.0 ± 0.8</td>
<td>56 ± 4</td>
<td>56 ± 4</td>
</tr>
</tbody>
</table>

The results are mean values ± sem with the number of patients in each group shown in parentheses. Values which are statistically different from the corresponding value for the control group are indicated: *P < 0.05, **P < 0.01.
Hepatic metabolism in malnutrition and sepsis

TABLE 2. Fasting blood metabolite and insulin concentrations

The results are mean values \( \pm \) SEM with the number of patients in each group shown in parentheses. Values which are statistically different from the corresponding value for the control group are indicated: *\( P < 0.02; **P < 0.01.\)

<table>
<thead>
<tr>
<th>Glucose (mmol/l)</th>
<th>Pyruvate (mmol/l)</th>
<th>Lactate (mmol/l)</th>
<th>L/P ratio</th>
<th>Alanine bodies (mmol/l)</th>
<th>Ketone (mmol/l)</th>
<th>Insulin (munits/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (9)</td>
<td>5.01 ( \pm ) 0.19</td>
<td>0.07 ( \pm ) 0.01</td>
<td>0.65 ( \pm ) 0.09</td>
<td>9.8 ( \pm ) 0.7</td>
<td>0.28 ( \pm ) 0.02</td>
<td>0.18 ( \pm ) 0.05</td>
</tr>
<tr>
<td>Malnourished (7)</td>
<td>4.94 ( \pm ) 0.28</td>
<td>0.07 ( \pm ) 0.01</td>
<td>0.86 ( \pm ) 0.16</td>
<td>10.0 ( \pm ) 0.5</td>
<td>0.28 ( \pm ) 0.03</td>
<td>0.47 ( \pm ) 0.11*</td>
</tr>
<tr>
<td>Septic (7)</td>
<td>5.17 ( \pm ) 0.19</td>
<td>0.08 ( \pm ) 0.01</td>
<td>0.69 ( \pm ) 0.12</td>
<td>8.5 ( \pm ) 0.8</td>
<td>0.16 ( \pm ) 0.02**</td>
<td>0.47 ( \pm ) 0.09*</td>
</tr>
<tr>
<td>Septic-recovered (4)</td>
<td>5.30 ( \pm ) 0.23</td>
<td>0.07 ( \pm ) 0.01</td>
<td>0.59 ( \pm ) 0.03</td>
<td>8.2 ( \pm ) 0.2</td>
<td>0.26 ( \pm ) 0.03</td>
<td>0.30 ( \pm ) 0.12</td>
</tr>
</tbody>
</table>

plot of blood concentration against time. Basal blood metabolite concentrations were calculated from the average of the two basal samples and the mean glucose and lactate changes after galactose injection were calculated from the individual incremental areas under the curves of glucose and lactate plotted against time.

Urine was collected for 24 h for measurement (Technicon Autoanalyzer) of urinary urea excretion.

Comparisons were made by unpaired \( t \)-test, except when variances were non-homogeneous as determined by the \( F \) test, when the Mann–Whitney \( U \) test was used.

Results

Weight loss was present in the malnourished, the septic and the septic-recovered patients (Table 1). Liver-function tests (Table 1) were abnormal in the septic patients, but these changes reversed on recovery from sepsis. Urea concentration was unchanged in septic and malnourished patients, suggesting that there was no severe dehydration.

Basal concentrations of blood glucose, pyruvate, lactate, lactate/pyruvate ratio and insulin were similar in all groups (Table 2). Blood ketone body concentrations were, however, increased in both septic and malnourished patients, whereas alanine was decreased in the septic group only, increasing again on recovery from sepsis. Urea excretion was low in both malnourished (158 \( \pm \) 33 mmol/24 h) and septic (281 \( \pm \) 60 mmol/24 h) patients compared with patients with multiple fractures (Williamson, Farrell, Kerr & Smith, 1977).

Blood galactose concentrations (Fig. 1) and half-life (Table 3) were markedly increased in the malnourished compared with control patients.

![Graph showing blood galactose concentrations and half-life](image)

**Fig. 1.** Blood galactose concentrations (mean values \( \pm \)SEM) after intravenous injection in control (\( \bullet, n = 9 \)), malnourished (\( \Delta, n = 7 \)) and septic (\( \Theta, n = 7 \)) patients. For clarity the larger SE values only of the control or septic group are shown. *\( P < 0.05; **P < 0.01, \) malnourished compared with control.

TABLE 3. Metabolic response to galactose infusion

The results are mean values \( \pm \) SEM with the number of patients in each group shown in parentheses. Values which are statistically different from the corresponding value for the control group are indicated: *\( P < 0.05; **P < 0.01.\)

<table>
<thead>
<tr>
<th>Group</th>
<th>Galactose removal, ( t_{9.5} ) (min)</th>
<th>Glucose increase (mmol/l)</th>
<th>Lactate increase (mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (9)</td>
<td>13.9 ( \pm ) 1.0</td>
<td>0.69 ( \pm ) 0.11</td>
<td>0.22 ( \pm ) 0.08</td>
</tr>
<tr>
<td>Malnourished (7)</td>
<td>32.2 ( \pm ) 5.5**</td>
<td>0.34 ( \pm ) 0.07*</td>
<td>0.04 ( \pm ) 0.03</td>
</tr>
<tr>
<td>Septic (7)</td>
<td>17.1 ( \pm ) 1.9**</td>
<td>0.36 ( \pm ) 0.09*</td>
<td>0.05 ( \pm ) 0.02</td>
</tr>
<tr>
<td>Septic-recovered (4)</td>
<td>13.6 ( \pm ) 3.0</td>
<td>0.85 ( \pm ) 0.14</td>
<td>0.16 ( \pm ) 0.09</td>
</tr>
</tbody>
</table>
nourished patients, as compared with the other groups, but the mean rises in glucose and lactate after the galactose injection were lower than normal in both the malnourished and septic patients (Table 3). Blood galactose half-life was similar in the septic patients and after recovery from sepsis, but glucose and lactate increases were greater after recovery from sepsis (Table 3). The estimated galactose space \((L)\) did not differ significantly between the control subjects \((9.6 \pm 1.1)\), the malnourished \((12.0 \pm 1.2)\), the septic \((11.3 \pm 0.6)\) or septic-recovered \((9.2 \pm 0.6)\) patients.

**Discussion**

Abnormal liver-function tests have previously been reported in both sepsis (Neale et al., 1966; Nunes et al., 1970) and malnutrition (McLean, 1962). Our septic patients had more abnormal liver-function tests than our malnourished patients. These tests are non-specific, and do not indicate the integrity of hepatic metabolic pathways.

We used an intravenous galactose load to test liver function (Tengström, 1966; Salaspuro & Kesäniemi, 1973), and to measure hepatic glucose release (Royle et al., 1978). The half-life of galactose depends on its distribution, and on the activity of the enzymes responsible for its metabolism, and on hepatic blood flow. The estimated galactose space was similar in all our four groups of subjects, and blood galactose removal did not appear to be related to liver-function tests, nor to a change in hepatic redox state \((\text{lactate/pyruvate ratio})\) as occurs after ethanol intake (Salaspuro & Kesäniemi, 1973). A decrease in blood galactose removal (Alleyne & Scullard, 1969) and reduced cardiac output with increased recirculation time (Alleyne, 1966) have both been previously reported in malnourished children, implying that a reduction in hepatic blood flow may explain the prolongation of galactose half-life which we have found. Alteration in cardiac output may also modify the metabolic response in sepsis (Clowes, O'Donnell, Ryan & Blackburn, 1974).

The rise in blood glucose and lactate concentrations after galactose injection was low in both septic and malnourished patients, as compared with those in control subjects and after recovery. The blood glucose concentrations reflect a balance between hepatic release and peripheral uptake, and similarly blood lactate concentrations depend upon peripheral production and hepatic metabolism. A reduction in hepatic glucose release after galactose was more likely than an increase in peripheral uptake in the septic and malnourished patients, as blood lactate did not markedly increase in either group, and both septic (Gump et al., 1974; Wilmore et al., 1976) and malnourished patients (Smith, Edgar, Pozefsky, Chhetri & Prout, 1975) are glucose intolerant. Decreased hepatic glucose release in the malnourished patients may have been due to the slower removal of galactose from the blood, but this does not explain the small increases in glucose and lactate in the septic patients.

Decreased glucose release in the septic patients was not due to a high basal plasma insulin concentration, as occurs in the fed state (Royle et al., 1978), nor to decreased glucose 6-phosphatase (EC 3.1.3.9) activity, as there was no fasting hypoglycaemia, and administration of galactose to patients with a deficiency of this enzyme results in hyperlactataemia (Schwartz, Ashmore & Renold, 1957) which was not observed in our patients.

The results of the galactose infusion in the septic patients therefore suggest that galactose carbon was used for increased synthesis of hepatic glycogen or fat. This may also have occurred in the malnourished patients, despite their slow removal of blood galactose as an increase in deposition of both glycogen and fat in the liver has been demonstrated in malnourished rats (Weinkove, Weinkove & Pimstone, 1976) and children (Waterlow & Weisz, 1956; Alleyne & Scullard, 1969).

Alanine, unlike galactose, is a major glucose precursor in man (Felig, 1973). However, the rise in blood glucose concentration after an intravenous alanine infusion was less in infected patients with burns, as compared with non-infected patients with burns, which also suggests that hepatic glucose production is reduced in sepsis (Wilmore et al., 1976). Our study implies that these changes in hepatic carbohydrate metabolism are reversible on recovery from sepsis.

Our findings that fasting blood glucose and lactate were unchanged, together with low alanine and increased ketone body concentrations in the septic patients, differ from those studies of sepsis which report increased blood glucose, lactate and alanine (O'Donnell, Clowes, Blackburn, Ryan, Benotti & Miller, 1976; Wilmore et al., 1976) and low ketone body concentration in humans (O'Donnell et al., 1976) and rats (Neufeld, Pace & White, 1976). This may be due to differences in the nature, severity and duration of the infection, and also in the nutritional state of the patients (Beisel, 1972). Our septic patients were poorly nourished, with prolonged sepsis, and were not in a hypercatabolic state, as indicated by the low urinary urea excretion. Decreased blood alanine and increased ketone body concentrations reflect the increased gluconeogenesis of the liver in response to the hypermetabolic state of the septic patient.
concentrations have been previously reported in prolonged experimental starvation (Owen, Felig, Morgan, Wahren & Cahill, 1969; Felig, Owen, Wahren & Cahill, 1969), whereas blood alanine concentration has been reported to be unchanged in malnutrition (Smith, Pozefsky & Chhetri, 1974), as we have found. This may be due to an increased intake of carbohydrate in malnutrition, as compared with experimental starvation (Adibi, 1968) or may result from a reduced hepatic blood flow with consequent decreased hepatic removal of alanine.

In conclusion, the metabolic responses to prolonged major infection appear to be similar to those of malnutrition in man, although the decreased hepatic release of glucose after administration of galactose demonstrated in our study may result from different mechanisms, such as a reduction in hepatic blood flow in malnutrition, and alteration in hepatic metabolism in sepsis. Changes in hepatic function and metabolism in sepsis appear to be reversible, even before normal body weight is regained.

Acknowledgments

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References


