Effect of portasystemic venous shunt surgery on hyperglucagonaemia in cirrhosis: paired studies of pre- and post-shunted subjects

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SUMMARY The effect of liver disease on glucagon metabolism was examined in nine patients with chronic liver disease who were studied both before and after the creation of a surgical portasystemic shunt. Hepatocellular function did not deteriorate after shunt surgery. However, hepatic perfusion with splanchnic venous blood, as determined by scintisplenopancreatography, decreased after shunt surgery in six subjects but appeared unaltered in three. Basal plasma immunoreactive glucagon (IRG) levels in the pre-shunt cirrhotic group were significantly greater (p <0.005) than in control subjects and further increased (p <0.05) after shunt surgery. Moreover, the increase in basal IRG after shunt was evident only in patients in whom portasystemic shunting was demonstrably increased by surgery. Despite the higher basal IRG levels postoperatively, shunt surgery in the cirrhotics did not alter basal glucose and insulin levels or the glucose and insulin response to a glucose or protein load. Circulating IRG was heterogeneous in the pre-shunt cirrhotic patients: the 9000 molecular weight fraction comprised 27±4%, the 3500 mol. wt. fraction 71±4%, and the >40 000 mol. wt. fraction was minimal. After shunt surgery, the relative proportion of the 9000 mol. wt. fraction of IRG (13±3%) decreased significantly (p <0.05) and this fall was associated with a corresponding increase in the 3,500 mol. wt. fraction (84±4%). It is concluded that, in cirrhosis, hyperglucagonaemia is: (1) dependent on the degree of portasystemic shunting rather than impaired hepatocellular function; (2) predominantly due to increased circulating 3500 molecular weight glucagon; and (3) not a major factor in the pathogenesis of carbohydrate intolerance in liver disease.

Plasma immunoreactive glucagon (IRG) levels are often raised in patients with cirrhosis of the liver (Marco et al., 1973; Sherwin et al., 1974; Soeters et al., 1975) and it has been suggested that the magnitude of this increase is related to the presence of portasystemic shunting of splanchnic venous blood (Sherwin et al., 1974; Soeters et al., 1975). However, the lack of paired studies in patients before and after elective portasystemic shunt surgery has made it impossible to accurately assess the relative roles of hepatocellular dysfunction and portasystemic venous shunting in the pathogenesis of the hyperglucagonaemia.

It has been suggested that hyperglucagonaemia could be an important factor contributing to the increased incidence of glucose intolerance in liver disease (Marco et al., 1973; Sherwin et al., 1974; Sherwin et al., 1978). These studies failed to allow for the fact that IRG is known to circulate as several different sized molecular species with differing biological potencies but identical immunological properties (Valverde et al., 1975; Kuku et al., 1976; Chisholm et al., 1978). Clearly, the heterogeneity of IRG makes it hazardous to speculate as to the physiological importance of hyperglucagonaemia in cirrhotics.

Side-to-side portacaval shunt surgery results in total shunting of splanchnic venous blood past the liver and a decrease in estimated hepatic blood flow (Reynolds et al., 1962). Thus the study of glucose, insulin, and glucagon metabolism in cirrhotics both before and after shunt surgery provides a unique opportunity to investigate the role of hepatocellular dysfunction and portasystemic shunts on glucagon levels and glucose intolerance in cirrhotics.

A group of stable cirrhotic patients were therefore studied both before and after portasystemic shunt surgery by measuring the glucose, insulin, and
glucagon responses to an oral glucose load and a protein meal. Special attention was directed to accurately assessing hepatic function and the extent of portasystemic shunting. To determine the physiological significance of the hyperglucagonaemia in cirrhotics the different molecular weight fractions of IRG before and after shunt surgery were analysed.

**Methods**

**Subjects**

Nine patients were studied: seven males and two females aged between 39 and 57 years, with biopsy-proven cirrhosis of the liver and who had sustained at least one major bleed from endoscopically proven oesophageal varices. The aetiology of the cirrhosis was alcoholic in eight and cryptogenic in one. All subjects were studied both before and after the creation of a surgical portasystemic venous shunt.

All but one were within 15% of their ideal body weight (Metropolitan Life Insurance Company Tables, 1959). Eight had a mesocaval interposition graft (Drapanas, 1972), and one a distal lienorenal shunt (Warren et al., 1967). No patient had clinical evidence of pancreatitis and the serum potassium was normal in all at the times of study. There was no clinically detectable ascites or infection and no patient was on potentially diabetogenic drugs. All patients had normal fasting blood glucose levels before operation. Pre- and postoperative studies were undertaken at a time when the patient was fully ambulant and had been on a standard diet, without alcohol, for at least five days. There was no clinical or biochemical evidence of deteriorating liver function, recent blood loss, infection, or fever. Studies were performed in the week before elective operation and between two and eight weeks postoperatively.

The control group, all within 15% of their ideal body weight, consisted of six healthy volunteers, five males, and one female aged between 22 and 34 years. There was no clinical or biochemical evidence of liver disease or a family history of endocrine disease.

Informed written consent was obtained from all control and cirrhotic subjects before they took part in the study.

**Assessment of Hepatic Status**

This assessment consisted of standard liver function tests (Table 1), antipyrine kinetics, and scintisplenoporoportography.

The half life of antipyrine was determined in control and cirrhotic subjects, both pre- and post-shunt, from the plasma concentrations of antipyrine, three, six, 12, 24, 48, and 72 hours after the ingestion of 600 mg antipyrine dissolved in water. Plasma clearance of antipyrine is dependent upon hepatocellular function and is not appreciably altered by changes in hepatic blood flow or renal function (Branch et al., 1973; Harman et al., 1977).

Scintisplenoporoportography was performed both before and after shunt surgery in the cirrhotic subjects (Dudley et al., 1977). This demonstrated patency of the shunt in all operated patients and constituted qualitative evidence of the extent of hepatic perfusion by splenic venous blood (Kashiwagi et al., 1974; Dudley et al., 1977).

**Experimental Studies**

Subjects were maintained on a diet, containing at least 200 g carbohydrate and 120 g protein, and supplemented by 50 mmol potassium per day for at least five days before each study. All studies were performed in a randomised fashion after an overnight (12–15 hours) fast, with at least a one day interval between studies. Subjects were recumbent for at least 20–30 minutes before each study. Blood samples for blood glucose and plasma IRI and IRG were collected at regular intervals during each study from an indwelling butterfly needle placed in an antecubital vein. For hormone estimations, 4.5 ml blood was placed in chilled heparinised tubes containing 5000 KIU aprotinin (Trasylol, Bayer.

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**Table 1** Liver function of cirrhotic patients before and after shunt surgery (mean ± sem)

<table>
<thead>
<tr>
<th>Groups</th>
<th>Body wt (kg)</th>
<th>Total serum bilirubin (μmol/l)</th>
<th>Serum albumin (g/l)</th>
<th>Prothrombin time (%)</th>
<th>AST† (IU/l)</th>
<th>Half-life Antipyrine (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrhotics</td>
<td></td>
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<tr>
<td>Pre-shunt</td>
<td>76.6 ± 3.2</td>
<td>23 ± 3</td>
<td>37 ± 2</td>
<td>79 ± 5</td>
<td>50 ± 5</td>
<td>24.6 ± 1.2</td>
</tr>
<tr>
<td>Post-shunt</td>
<td>74.2 ± 3.3</td>
<td>23 ± 3</td>
<td>34 ± 2</td>
<td>78 ± 5</td>
<td>52 ± 5</td>
<td>26.2 ± 1.4</td>
</tr>
<tr>
<td>Normal subjects</td>
<td>56–83 (range)</td>
<td>&lt; 20</td>
<td>35–48</td>
<td>60–100</td>
<td>&lt; 50</td>
<td>8–17</td>
</tr>
</tbody>
</table>

* T½: half-life of plasma clearance of antipyrine.
† AST: aspartate aminotransferase.
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Pharmaceuticals), promptly centrifuged at 4°C and plasma stored frozen at −20°C until time of assay.

Oral glucose tests
One hundred grams of glucose was administered orally, over one to two minutes to eight cirrhotic subjects before and after shunt surgery and to the six controls. Blood was obtained at −10, 0, 30, 60, 90, 120, and 180 minutes and analysed for glucose, IRI, and IRG.

Protein meals
A 225 g lean steak was eaten over 10–15 minutes by eight cirrhotics, before and after shunt surgery, and six control subjects. Blood was obtained at −10, 0, 30, 60, 90, 120, and 180 minutes for estimation of glucose, IRI, and IRG.

GEL FILTRATION
0.8 ml plasma samples were gel filtered through 55 × 0.9 cm Sephadex G 200 superfine (Pharmacia Fine Chemicals, Sydney, Australia) columns. Samples were eluted under gravity at a flow rate of 2 ml/h, at room temperature with a barbital/sodium chloride 0-15 M buffer, pH 7-4, containing 0.1% 'glucagon-free' human serum albumin (Behringwerke, Australia) and 100 KIU/ml aprotinin. 0.8 ml fractions were collected and assayed in total (Chisholm et al., 1978).

Columns were calibrated using porcine proinsulin (approximate mol. wt. 9000) and cytochrome C (approximate mol. wt. 11300) for each run; additional calibration between every four runs was performed using glucagon (mol. wt. 3485) or 125I-glucagon, porcine insulin (mol. wt. 4777), or 115T1-insulin and 131I-Na. Percentage recovery of immunoreactive glucagon from the column was calculated from the total glucagon-like immunoreactivity eluted from the column (including that of the void volume) and the total IRG applied originally to each column. Each immunoreactive peak diluted in parallel with the standard glucagon curve confirming immunological identity.

ANALYTICAL METHODS
Blood glucose was determined by autoanalyser, using the glucose oxidase method (Gochman and Schmitz, 1972). Plasma IRG was measured by radio-immunoassay, using a 'pancreatic glucagon-specific' (C-terminal reacting) anti-serum (kindly donated by Dr S. R. Bloom) as previously described (Alford et al., 1976; Alford et al., 1977). Non-specific interference by plasma is very low for this assay using the RCS 5 antiserum (Alford et al., 1977) and there were no correction factors were applied (Weir et al., 1975). All samples from one individual's pre- and postoperative tests were included in the same assay. Plasma IRI was measured by radio-immunoassay, employing dextran-charcoal separation of bound and free fractions (Albano et al., 1972). Antipyrine was assayed by the method of Brodie et al. (1949) after chloroform extraction from plasma. Serum albumin, total bilirubin, aspartate aminotransferase, urea, creatinine, creatinine clearance, and prothrombin time were measured by standard techniques.

Statistical analyses were made using Student's t test and linear regression analysis.

RESULTS
Of the eight patients who subsequently had a mesocaval interposition graft, preoperative scintisplenoportography clearly demonstrated hepatic perfusion with splenic venous blood in six. In the other two, although a patent portal vein was demonstrated by angiography, there was no demonstrable hepatic perfusion with splenic venous blood during the preoperative scintisplenoportography. Postoperatively, scintisplenoportography demonstrated the complete diversion of splanchnic venous blood through the shunt into the systemic venous system in all patients with mesocaval interposition grafts (Dudley et al., 1977). The ninth patient was subjected to a distal lienorenal shunt. Preoperative scintisplenoportography revealed hepatic perfusion with splenic venous blood and presumably this persisted postoperatively because of the selective nature of the variceal decompression provided by this type of shunt (Warren et al., 1967). Thus hepatic perfusion with splanchic venous blood was definitely decreased after shunt surgery in six subjects but may not have been substantially altered in three subjects.

Despite these gross haemodynamic changes in portasystemic blood flow, pre- and postoperative values of serum bilirubin, aspartate aminotransferase albumin and prothrombin time were similar (Table 1). The half life of antipyrine was significantly prolonged in all cirrhotic subjects (range T 1/2 19–30 hours, mean 25:8 ± 1.6 versus normal subjects, range T 1/2 6–18 hours, mean 11:8 ± 1:5, P < 0.001). Shunt surgery did not significantly alter the half life of antipyrine in the cirrhotic group (Table 1). Blood urea, creatinine, and creatinine clearance were also unaffected by shunt surgery.

BASEL GLUCAGON, INSULIN, AND GLUCOSE LEVELS
Plasma glucagon levels in the fasting state were significantly (P < 0.005) higher in pre-shunt cirrhotics (198 ± 25 pg/ml) than in the normal control group (53 ± 13 pg/ml) (Fig. 1). Further rises of basal plasma glucagon levels occurred (P < 0.05) after
shunt surgery. However, in the three cirrhotic patients in whom pre- and postoperative scinti-splenopanography was unable to demonstrate any substantial alteration of hepatic perfusion with splenic venous blood, basal glucagon levels did not change (Δ basal IRG after surgery = 23 ± 21 pg/ml).

In contrast, in the six cirrhotic patients in whom a post-shunt decrease in hepatic perfusion with splenic venous blood was demonstrated, basal IRG rose significantly (Δ basal IRG after surgery = 264 ± 62 pg/ml) (p < 0.005). There was no correlation between indices of hepatocellular function such as routine liver function tests and the half life of antipyrine and the change in pre- and post-shunt basal IRG concentrations.

As expected, basal insulin levels were also significantly higher (p < 0.01) in pre-shunt cirrhotics, as compared with the control group. Basal insulin levels were not significantly changed by shunt surgery (Fig. 1). Fasting blood glucose concentrations were similar in control, pre- and postoperative cirrhotic groups (Fig. 1).

**Response to Oral Glucose**

Plasma glucagon levels were suppressed by oral glucose in both cirrhotic and control groups. The nadir was reached later (p < 0.05) and suppression was prolonged in the preoperative cirrhotic patients (Fig. 2) and this trend was further exaggerated (p < 0.01) in the post-shunt cirrhotic group (control vs pre-shunt cirrhotic vs post-shunt cirrhotic: 50 ± 10 vs 100 ± 20 vs 145 ± 20 min) (Fig. 2). The fall in plasma glucagon after glucose administration was significantly (p < 0.02) greater in the pre-shunt cirrhotic group (155 ± 30 pg/ml) as compared with controls (50 ± 13 pg/ml). The decrement was greatest (p < 0.005 vs control) in the post-shunt cirrhotic group (305 ± 65 pg/ml).

Plasma insulin levels were significantly higher in the preoperative cirrhotic compared with the control group throughout the test (Fig. 2). The creation of a surgical portasystemic shunt had no effect on the basal insulin levels. After glucose ingestion, insulin levels and the incremental rise of plasma insulin appeared higher in the shunted patients (Fig. 2) but was not significantly different from the pre-shunt cirrhotics.

Glucose tolerance was impaired in pre-shunt cirrhotic patients. Shunt surgery caused no further deterioration of glucose tolerance (Fig. 2).
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Shunt surgery did not significantly alter the insulin response (25 ± 6 μU/ml) to the protein meal (Fig. 3). Blood glucose levels did not rise significantly after the protein meal in the control, pre- or post-shunt cirrhotic groups (Fig. 3).

**Fig. 2** Effect of an oral glucose load on IRG, IRI, and blood glucose levels in normal subjects (N=6) and cirrhotics (N=8), both pre- and post-shunt. Mean values ± SEM are shown. The asterisks represent statistically significant differences between the control and cirrhotic groups at a given time and the crosses statistically significant differences between the pre- and post-shunt cirrhotic patients.

**Fig. 3** Effect of a protein meal on IRG, IRI, and blood glucose levels in normal subjects (N=6) and cirrhotics (N=8) both pre- and post-shunt. Mean values ± SEM are shown. The asterisks represent statistically significant differences between the control and cirrhotic groups at a given time and the crosses statistically significant differences between the pre- and post-shunt cirrhotic patients.

**Response to Protein Meal**

Plasma glucagon levels rose significantly as a result of protein loading and attained peak levels at a similar mean time (between 90–120 minutes) in the pre- and post-shunt cirrhotic and control groups (Fig. 3). Glucagon levels were at all times higher in the pre-shunt cirrhotics than in the controls. After shunt surgery, glucagon levels rose further and remained significantly higher than the pre-shunt levels throughout the test (Fig. 3). The increase in plasma glucagon above basal levels (Δpg/ml), was greatest in the post-shunt cirrhotic group (483 ± 116 pg/ml) as compared with the pre-shunt cirrhotic (338 ± 86 pg/ml, P < 0.01) and the control (186 ± 66 pg/ml, P < 0.05) groups.

The plasma insulin response was significantly greater (P < 0.05) in the pre-shunt cirrhotics (26 ± 8 μU/ml) than in the controls (8 ± 3 μU/ml) (Fig. 3).

**Gel Filtration Patterns of IRG**

Individual and mean data for five pre- and post-shunt fasted cirrhotic patients (with recoveries) are presented in Table 2. It was not technically possible to accurately fractionate plasma samples from normal subjects because of the uniformly low IRG values obtained in such subjects with our assay and RCS5 antiserum (Alford et al., 1977). The mean recovery for 18 cirrhotic plasma samples was 110 ± 11% and for control subjects 97 ± 11%.

Three major peaks were detected: peak A (emerging in the void volume, mol. wt. > 40000) was minimal in both cirrhotic groups; peak B (eluting in region of proinsulin marker, approximate mol. wt. 9000) was significantly increased (P < 0.03)
in the pre-shunt cirrhotic subjects (27±4%) compared with the post-shunt group (13±3%); and peak C (eluting in the region of the standard glucagon and 125I glucagon markers, approximate mol. wt. 3500) was the major fraction of IRG. This latter peak was greater in the post-shunt than in the pre-shunt group, but the difference was not significant (84±4% versus 71±4%, 0.1 > P > 0.05).

Gel filtration of plasma from two pre- and post-shunt cirrhotic subjects, after the protein meal, demonstrated that the protein induced rise in plasma IRG was due mainly to the rise in peak C IRG. Thus, the Δ IRG peak B/peak C increments were -43/ +304 and -1/ +113 pg/ml pre-shunt, and +45/ +372 and +7/ +172 pg/ml post-shunt respectively. In the control group (n=6) 87±5% of the total plasma IRG post-protein meal was also peak C glucagon.

The suppression of glucagon concentration in two pre- and post-shunt cirrhotics by a glucose load could again almost entirely be accounted for by the decrease in peak C IRG. Thus, the Δ IRG peak B/peak C decrements were 3/99 and 19/153 pg/ml pre-shunt, and 44/225 and 38/98 post-shunt respectively.

Table 2  Distribution of glucagon immunoreactivity in fasting state in five pre- and post-shunt cirrhotic subjects

<table>
<thead>
<tr>
<th>Group</th>
<th>Peak A</th>
<th></th>
<th>Peak B</th>
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<th>Peak C</th>
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<th>Recovery</th>
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<tr>
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<tr>
<td>pre-shunt</td>
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<tr>
<td>W.O.</td>
<td>0</td>
<td>0</td>
<td>30</td>
<td>20</td>
<td>120</td>
<td>80</td>
<td>140</td>
<td>138</td>
</tr>
<tr>
<td>R.D.</td>
<td>0</td>
<td>0</td>
<td>47</td>
<td>38</td>
<td>77</td>
<td>62</td>
<td>138</td>
<td></td>
</tr>
<tr>
<td>R.A.</td>
<td>3</td>
<td>6</td>
<td>16</td>
<td>33</td>
<td>30</td>
<td>61</td>
<td>80</td>
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</tr>
<tr>
<td>L.W.</td>
<td>10</td>
<td>3</td>
<td>61</td>
<td>19</td>
<td>250</td>
<td>78</td>
<td>125</td>
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<tr>
<td>C.K.</td>
<td>7</td>
<td>2</td>
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<td>26</td>
<td>238</td>
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<tr>
<td>W.O.</td>
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<td>14</td>
<td>45</td>
<td>12</td>
<td>277</td>
<td>74</td>
<td>133</td>
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<tr>
<td>R.D.</td>
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<td>1</td>
<td>54</td>
<td>17</td>
<td>260</td>
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<td>17</td>
<td>67</td>
<td>81</td>
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<td>L.W.</td>
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Discussion

This study clearly establishes that the hyperglucagonaemia of cirrhosis is accentuated by the portasystemic shunting of splanchnic venous blood. A significant rise in basal IRG after shunt surgery was evident only in cirrhotic subjects in whom an increased shunting of splanchnic venous blood past the liver could be demonstrated to follow drive of the A cell, whereas in the post-shunt cirrhotics both delayed clearance and increased secretion may be responsible (Alford et al., 1979).

Heterogeneity of IRG was detected in the cirrhotic subjects, the major immunoreactivity of the basal fasting samples residing in the 3500 mol. wt. peak C.

When the percentage IRG present in peak C is used to estimate the mean basal value of 'true' glucagon in the two cirrhotic groups, the pre-shunt
value (141 pg/ml) becomes even more clearly separated from the post-shunt cirrhotics (331 pg/ml). These values are still significantly higher than the total non-fractionated IRG value of the control group 53 ±13 pg/ml (p <0.01). After the oral glucose load and the protein meal the changes in total IRG predominantly reflected changes in the absolute levels of the 3500 mol. wt. IRG.

27 ±4% of total basal IRG in plasma of pre-shunt cirrhotic subjects resided in peak B IRG (mol. wt. 9000). This is considerably in excess of that reported in the literature for basal samples from healthy subjects (Kuku et al., 1976; Jaspan and Rubenstein, 1977). After shunt surgery peak B IRG in basal plasma fell significantly: and this fall was associated with a corresponding rise of peak C. As the absolute concentration of peak B IRG was not altered by shunt surgery (Table 2), the observed percentage fall in peak B IRG post-shunt probably only reflects the dilutional effect of increased amounts of the 3500 mol. wt. IRG rather than any change in the metabolism of peak B IRG.

Peak A IRG (mol wt. >40 000) represented less than 5% of total IRG. The small amount of peak A IRG contrasts with reports from other laboratories (Kuku et al., 1976; Valverde and Villanueva, 1976, Jaspan and Rubenstein, 1977) and probably reflects the 'specific' qualities of RCS5 antiserum and the very low plasma interference factor with this assay (Alford et al., 1977).

These results clearly indicate that the hyperglucagonaemia of cirrhosis is largely due to an absolute increase of the small 3500 mol. wt. IRG, presumably the biologically active fraction (Chisholm et al., 1978). However, despite the increase in 3500 mol. wt. glucagon, this study could not demonstrate a major role for endogenous hyperglucagonaemia in the pathogenesis of the impaired glucose tolerance of patients with chronic liver disease. This is based on the following observations: firstly, basal glucose and insulin concentrations were not altered by the creation of the surgical shunt, despite the significantly higher post-shunt glucagon levels. Secondly, portasystemic shunt surgery did not result in either deterioration of glucose tolerance or a change in the insulin levels after a standard glucose load, despite the development of marked post-shunt hyperglucagonaemia. Thirdly, during the protein meal studies, glucose levels were unaltered by shunt surgery, despite the resultant increase in glucagon concentrations in the presence of unchanged insulin levels. Furthermore, the recent reports of a diminished glycaemic response to infusion of exogenous glucagon in cirrhotics with surgical portasystemic shunts (Davies et al., 1976; Sherwin et al., 1978), the evanescent action of glucagon on the liver (Feliz et al., 1976), and the necessity for severe insulinopaenia to exist before the hyperglycaemic action of glucagon is manifest (Feliz et al., 1976), all argue against a major pathogenic role for glucagon in the glucose intolerance of cirrhotic subjects. The apparent failure of glucagon to impair glucose tolerance in cirrhosis may also be related to the fact that a major portion of pancreatic venous blood is bypassing the liver, the prime site of glucagon action (Exton et al., 1971).

In conclusion, this study has clearly demonstrated that the hyperglucagonaemia of cirrhosis is largely dependent on the degree of portasystemic shunting of splanchnic venous blood past the liver rather than impaired hepatocellular function. In addition, glucagon does not appear to be a major factor in the pathogenesis of carbohydrate intolerance in liver disease, despite the fact that circulating glucagon in cirrhotics is predominantly of the biologically active 3500 molecular weight species.

References


