THE BIOCHEMISTRY OF HEPATIC FAILURE

BY

A. G. RIDDLE

There are few, if any, metabolic functions of the body in which the liver does not participate. It is not surprising, therefore, that the biochemistry of hepatic failure is an extremely complex one. The liver plays a vital role in carbohydrate, fat and protein metabolism and, in addition, because of its unique anatomical position, provides detoxicating mechanisms to inactivate harmful products of intestinal absorption before they reach the general circulation.

DISTURBANCE OF CARBOHYDRATE METABOLISM

Probably the most critical function of the liver is the control of the normal blood glucose level. Hypoglycaemia is the cause of death in the untreated hepatectomized animal. The maintenance of an adequate blood glucose level depends on the liver maintaining an adequate store of normal glycogen. Hypoglycaemic states associated with liver disease are relatively uncommon in clinical practice but may be observed in acute hepatic necrosis in liver tumours, both before and after resection, in the glycogenoses (Riddell, Davies and Clarke, 1966) and following liver transplantation (Moore et al., 1960). In patients with impaired liver function the stress of an operation may seriously reduce the liver glycogen; it is mobilized to maintain the blood glucose level, leaving insufficient glucose available to the liver to provide for its own metabolic requirements. A glycogen-depleted liver is particularly sensitive to halogenated hydrocarbons, and it is therefore sound clinical practice to ensure a high liver glycogen content prior to operation by oral or parenteral feeding with glucose. Once anaesthesia has been induced there is little if any glycogen storage, however high the blood glucose level is raised (Sunzel, 1963).

HEPATIC COMA

If the hepatectomized animal is maintained by an adequate glucose infusion, it will eventually die after 36-48 hours in coma. The cause of the coma is uncertain but is probably due to ammonia intoxication. In man the neurological disturbances which occur are only partly understood and the causes of the coma are multiple in origin.

This syndrome of hepatic encephalopathy varies from the rapid onset of unconsciousness in acute liver necrosis to a chronic neuropsychiatric illness in cirrhosis of long standing. The neurological disorders which are associated with the syndrome are very variable, but the characteristic neurological abnormality is the occurrence of a "flapping tremor". In this complex syndrome, objective clinical assessment is difficult and serial electroencephalograms are of great value in assessing progress. The characteristic electroencephalographic change is the slowing of alpha rhythm down to the delta range of below 4 c.p.s. This change is best graded by the use of electronic frequency analysis. The technique is not only useful in establishing a diagnosis but also in assessing the effects of treatment; for example, improvement may follow a reduction of the protein content of the patient's diet (Read et al., 1968).

The first observation relevant to the aetiology of hepatic coma was the report of a neurological disorder occurring in dogs following the construction of a portacaval anastomosis. After the construction of the shunt, dogs fed on meat developed lethargy and ataxia and the illness progressed to coma with eventual death. This condition was named "meat intoxication" (Hahn et al., 1893). A comparable state was first described in man by McDermott and Adams (1954). In this case recurrent episodes of coma followed the construction of a portacaval shunt in a patient who, prior to operation, did not have portal hypertension. The shunt was necessitated by removal of a carcinoma of the head of the pancreas, together with part of the portal vein. The condition was given the name of portasystemic encephalopathy by Sherlock and her colleagues (1954), who

A. G. RIDDELL, M.B., B.S., F.R.C.S., Professor of Surgery, University of Bristol.
Artificial shunt or collateral

PROTEIN
UREA
AMMONIUM SALTS

Ingestion of

Protein
Blood
Urea
Ammonium salts

Fig. 1
Diagram showing the concept of portasystemic encephalopathy. (Redrawn from Sherlock, 1968.)

Pointed out that the portasystemic shunt need not be an artificially constructed one, but could be naturally occurring collaterals or through the liver itself, if there were liver cell failure (fig. 1).

It is unusual for encephalopathy to develop if liver function is good but, in rare instances, it will develop in extrahepatic portal hypertension if the shunting is sufficiently great. There appears to be an inconsistency here, in that patients with normal livers withstand shunting well, whereas dogs withstand it poorly. The probable explanation is that the brain tolerates a gradual change, such as occurs when portasystemic shunts develop, but cannot adapt to the sudden production of a shunt such as occurs in the Eck fistula dog or the patient reported by McDermott and Adams (1954).

The cause of hepatic coma
The nature of the cerebral intoxicant, derived from the alimentary tract, is not known precisely but the most widely investigated substance has been ammonia. The concept of ammonia intoxication, while not fitting all the observed facts, provides a rational theoretical basis for the prevention and therapy of hepatic coma. So far no other substance has been identified which can be shown to produce neurological changes. However, it is almost certain that other substances are involved which have yet to be isolated.

Hepatic coma may be induced in cirrhotic patients by the oral administration of a high protein diet, ammonium salts, urea or methionine. The symptoms may be relieved by giving the patients oral antibiotics, of which neomycin is the most effective, or by reducing the alimentary flora by the operation of colonic exclusion. These two sets of observations suggest that the intestinal flora liberate a toxic product from nitrogenous material. It has, moreover, been demonstrated that the urea in the blood seeps out into the stomach and intestine and is then broken down to ammonia which is reabsorbed.

There is very little free NH₃ in the blood; at pH 7.4 almost all is in the form of NH₄⁺. Tissue cells are relatively impermeable to NH₄⁺ but are permeable to gaseous NH₃. As the pH rises NH₄⁺ dissociates forming more NH₃, which then enters the tissue cells.

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\text{NH}_4^+ + \text{HOH} \rightleftharpoons \text{NH}_3 + \text{OH}'
\]

The concentration of ammonium varies in different parts of the vascular tree, being highest in portal vein blood and above the normal systemic venous level in the renal vein (fig. 2). In hepatic coma there is an increased A-V difference indi-
eating an increased uptake of \( \text{NH}_3 \) by brain and muscle.

There is a significant correlation between the mental state in hepatic coma and blood levels of ammonium. The arterial concentration correlates better than the venous concentration. The correlation is most striking in patients who have been given a nitrogen or ammonium load. The correlation is poor in patients who develop spontaneous coma; in these patients, other ill-defined factors come into play.

The mechanism by which ammonia affects the brain cells is only in part understood. Figure 3 shows the principal biochemical abnormalities that have been shown to be present in hepatic coma. The most acceptable theory is that of Bessman and Bessman (1955), which suggests that \( \alpha \)-ketoglutarate is siphoned off by combining with ammonia to form glutamic acid and then glutamine. This would limit the rate of the citric acid cycle with consequent depression of glucose metabolism and ATP synthesis.

Patients in hepatic coma are often alkalotic and have hypokalaemia. The transfer of ammonia across cell membranes is increased when the blood pH rises. This may explain why any potent diuretic may precipitate hepatic coma by producing electrolyte disturbance and also by increasing the ammonia output from the kidney into the renal vein.

**MANAGEMENT OF PATIENTS WITH LIVER DISEASE**

The anaesthetist's role in the management of patients with liver disease will be to attempt to prevent the onset of hepatic coma rather than to treat an established case. In managing these patients at the time of operation the following list of precipitating factors may be of value.

Hepatic coma may be precipitated by:

1. anoxia and hypovolaemia;
2. electrolyte disorders, particularly alkalaemia and hypokalaemia;
3. blood in the gut acting as an effective high protein diet;
4. narcotics, particularly morphine;
5. abdominal paracentesis;
6. stored blood having a high ammonia content.

**ASCITES**

Ascites may complicate any form of cirrhosis and its occurrence implies the presence of liver failure with associated portal hypertension. Starling (1895) first suggested that formation of interstitial fluid was governed by a balance between the capillary filtration pressure and the colloid osmotic pressure of the plasma. The colloid osmotic pressure of the plasma is largely related to the concentration of the plasma albumin. Since albumin synthesis is reduced in liver disease, the colloid osmotic pressure of the plasma is reduced. While there is not

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**Fig. 3**

The metabolic pathways involved in ammonia metabolism. Substances which have been found to be increased in patients with hepatic coma are shown in capitals. (Zieve, 1966.)
a direct correlation between the plasma albumin level and the formation of ascites, patients in whom ascites occurs have a diminished serum albumin plus a raised portal pressure (Cherrick et al., 1960).

A raised portal venous pressure by itself does not lead to the development of ascites. In patients with extrahepatic portal obstruction ascites does not occur, unless, following severe haemorrhage, there is depletion of the plasma albumin. As the patient recovers and albumin is resynthesized the ascites will disappear. The main significance of portal hypertension is, in the presence of hypoalbuminaemia, to cause localization of the additional extracellular fluid to the peritoneal cavity, rather than the interstitial space in general.

Another mechanism for the production of ascitic fluid is an increased production of lymph by the liver. Experimentally, occlusion of hepatic veins causes a great increase in the production of hepatic lymph and in cirrhosis the thoracic duct is dilated and the lymph flow increased. This increased lymph production may be reduced by side-to-side portacaval anastomosis. Some of the increased liver lymph weeps from the surface of the liver into the peritoneal cavity. This extra source of ascitic fluid may account in part for the poor correlation between the plasma albumin level and occurrence of ascites in patients with cirrhosis.

The outpouring of fluid into the peritoneal cavity causes a general depletion of body fluid. This latter effect results in an increased secretion of aldosterone which, in itself, leads to sodium retention. The conservation of sodium by the cirrhotic patient with ascites leads to an increase in the amount of extracellular fluid and, consequently, an increase in the ascites.

In the past repeated paracenteses to withdraw the ascitic fluid have been practised. This leads to depletion of protein, particularly albumin. Ascites can be reduced or resolved by the skilled use of diuretics and this renders the use of paracentesis unnecessary.

RENAL MANIFESTATIONS

It is perhaps appropriate to discuss renal failure in association with liver failure at this point. Patients with cirrhosis commonly die in a state characterized by hypotension, oliguria and a rising blood urea. The clinical manifestations of uraemia are not present, and the syndrome is due to failing kidney perfusion due to hypotension. Terminal hyponatraemia is also frequent and may be precipitated by the use of diuretics or paracentesis. The combination of azotaemia, hyponatraemia and hypotension is normally fatal regardless of treatment.

In the 1920s the term "hepato-renal syndrome" was introduced to explain the renal failure that might follow operations on the biliary tree in patients who were not necessarily jaundiced. The term hepato-renal syndrome should be abandoned, as it described a variety of conditions including hepatic artery ligation, the effects of toxic anaesthetic agents, water and electrolyte disorders, oligoemia and overwhelming infections. However, renal failure may follow operations for the relief of obstructive jaundice, and there is a correlation between the depth of the jaundice and the incidence of postoperative renal failure. This disorder is due to failure of circulatory homeostasis and also increased sensitivity of the renal parenchyma to decreased renal perfusion in patients with hyperbilirubinaemia. The risk of renal failure developing after operations for the relief of obstructive jaundice can be reduced by a prophylactic infusion of mannitol (Dawson, 1968).

BLOOD CHANGES

Another aspect of severe liver failure is the profound haematological changes that may occur. In patients with portal hypertension there is often evidence of "hypersplenism": anaemia, leucopenia and thrombocytopenia. The changes are, however, only in part corrected by splenectomy, and some other factor related to the liver disease is also responsible. Since the liver is the main site of protein synthesis, it follows that severe liver failure will result in abnormalities in the coagulation mechanism. Fibrinogen deficiency is rarely a cause of haemorrhage in patients with chronic liver disease, but may occur after hepatic resection or liver transplantation.

In obstructive jaundice there is vitamin K deficiency which will result in failure of the liver to synthesize prothrombin and factor VII. In patients with cirrhosis there may be failure of synthesis of these factors, even in the presence of an adequate vitamin K intake. Another common
deficiency in chronic liver disease, which will affect the one-stage prothrombin test, is factor V deficiency. At operation prothrombin and factor VII deficiencies may be corrected by giving stored blood, while platelet and factor V deficiencies will necessitate giving fresh blood.

The administration of large volumes of citrated blood to the patient with liver disease will pose an additional problem, since these patients metabolize citrate poorly and are liable to develop citrate intoxication. Intravenous calcium supplements should therefore be given when large volumes of blood require replacement.

Plasma fibrinolysins are frequently increased in patients with cirrhosis and this may lead to increased postoperative bleeding after portacaval anastomosis. Unless a donor liver can be transplanted in almost perfect condition, the development of severe fibrinolysis is inevitable. This disorder in liver function appears to be the most significant change that follows liver anoxia. The effects of the fibrinolysins produced may be controlled by the administration of epsilon amino-caproic acid during the operation. It is, however, less effective in controlling the established fibrinolytic syndrome than if used prophylactically.

**OTHER PROBLEMS**

**Hypoxaemia.**

In patients with severe cirrhosis a reduced arterial oxygen saturation is a relatively frequent occurrence and in a few patients cyanosis is present. Various mechanisms are responsible for this finding. Porta-pulmonary anastomosis and other extra-alveolar right-to-left shunts across the lung may occur (Mellemgaard et al., 1963). In a few instances it is due to pulmonary arteriovenous anastomosis (Rydell and Hoffbower, 1956). Recently patients who had portacaval anastomoses of long standing were investigated for breathlessness on exertion. These patients were shown to have a defect in gas transfer, possibly due to the overperfusion of lung tissue with respect to its ventilation. The breathlessness could be relieved by administering oxygen (Cotes et al., 1968).

**Metabolic effects.**

The damaged liver will fail to metabolize drugs adequately so that serious overdosage may readily occur. The cirrhotic patient will inactivate adrenal steroids poorly and this may lead to overdosage after quite small amounts.

**Fall in serum albumin level after resection.**

Certain problems of liver surgery are relevant to the problems of liver failure. An important one is the management of patients after massive liver resection, such as right hepatic lobectomy. Probably the most important change is the rapid fall in serum albumin levels which, if unsupported, leads to generalized anasarca, hypovolaemia and reduced tissue perfusion. Death will occur unless adequate infusions of serum albumin are given over the first 5–7 days after the operation, and the patient may require as much as 100 g of albumin a day. During the first 24 hours after hepatic lobectomy there will be hypoglycaemia and bleeding tendencies which can be corrected with glucose and fresh blood transfusions respectively.

**ASSESSMENT OF LIVER FUNCTION**

From the point of view of the practising anaesthetist, the most important aspect of liver disease is the pre-operative assessment of liver function. Since jaundice is perhaps the commonest presenting symptom of severe liver disease, it is convenient to deal first with bilirubin metabolism.

Bilirubin is derived from haem in the cells of the reticulo-endothelial system. Bilirubin itself is insoluble in water and carried in the plasma by attachment to albumin. How the bilirubin enters the liver cells is unknown. In the liver cells it is carried by a macromolecule that is distinct from albumin. At the microsomes it is conjugated to glucuroniode to form water-soluble bilirubin, which then passes into the bile canaliculi. The bilirubin glucuroniode then passes down the intestine and in the colon some bilirubin is converted to sctecobilinogen. A small proportion of sctecobilinogen is then reabsorbed into the blood stream and excreted in the urine by the kidney.

Jaundice may arise as a result of various disorders along this metabolic pathway (fig. 4). Theoretically, it may be due to four different mechanisms. Firstly, there may be an increased bilirubin load on the cell; secondly, there may be disorders in which the bilirubin cannot pass across the cell membrane or cell transport is disturbed;
thirdly, there may be a failure of conjugation at microsomal level; or, fourthly, there may be defective canalicular excretion or mechanical obstruction in the biliary tree.

The differential diagnosis of jaundice may be simple or can be highly complex requiring many investigations including liver biopsy. The full investigation of a patient with liver disease is beyond the scope of this article, but this section will review briefly simple liver function tests which may be used for assessing the patient preoperatively. No battery of liver function tests, however comprehensive, can replace careful clinical assessment of the patient. The presence of ascites usually indicates severe liver damage, whereas jaundice alone has not the same grave prognostic significance, particularly among surgical patients.

BIOCHEMICAL TESTS

After the estimation of conjugated and unconjugated bilirubin in the serum, the other important investigation is the study of the serum proteins. Albumin is synthesized exclusively in the liver as also are fibrinogen and prothrombin, whereas the immunoglobulins are synthesized by the plasma cells anywhere in the body. Consequently, in chronic liver disease, the serum albumin tends to fall while immunoglobulins tend to be increased.

The bleeding tendencies which occur in severe liver disease may need complex investigation, but the one-stage prothrombin test is a highly reliable screening test which measures not only prothrombin but also factors V, VII, X and fibrinogen.

Of the serum enzyme studies the serum alkaline phosphatase is the most valuable, in that it is increased in cholestasis and therefore aids in the diagnosis of this disease complex. Of the other enzyme studies available, the determination of serum glutamic oxalo-acetic transaminase (SGOT, aspartate transferase) is the most generally useful. It is present in large quantities in the heart, liver, kidney and skeletal muscle. If the cells are damaged the enzyme is released into the blood. Very high values are found in liver necrosis and myocardial infarction. Since the clinical differentiation of these two diseases is straightforward, the SGOT estimation is a valuable method for determining liver cell necrosis. It is particularly useful in determining whether liver cell damage is occurring in the non-icteric forms of hepatitis. The SGPT (serum glutamic pyruvate transaminase—alanine transferase) is also increased in liver failure. This matter is fully discussed elsewhere in this issue (Taylor, 1969).

This review of liver failure has, of necessity, been brief and aspects of the problem which are particularly related to anaesthetics have been stressed. For a comprehensive review of liver disease the reader is referred to Sherlock (1968).

REFERENCES


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