SESSION I

OCCURRENCE AND MANAGEMENT OF RENAL FAILURE

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Consequences of acute renal failure relevant to hepatic failure

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Summary

The onset of renal failure in patients with liver failure complicates an already deranged metabolic picture and may increase the retention of many potentially toxic substances. The risk to the patient of haemorrhage and infection is aggravated. Dialysis may correct the features of uraemia and, in acute liver failure at least, provide time for kidney as well as liver regeneration.

SIGNIFICANT renal insufficiency is found in 75% of patients dying from liver failure. Whether the liver failure is due to an acute illness (such as fulminant hepatitis) or chronic disease (such as cirrhosis) the occurrence of renal failure carries a grave prognosis (Shear, Keirnerman and Gabuzda, 1965; Wilkinson, Blendis and Williams, 1974) and in a survey of 471 patients with cirrhosis, renal failure was said to be the primary cause of death in 11% (Garceau and Chalmers, 1963). This paper is concerned with the consequences of renal failure in patients with liver disease.

Retention of toxic metabolites

Many metabolites accumulate in blood and tissues of patients with liver failure. As many of them have alternative pathways of excretion via the kidney, the onset of anuria can only lead to further retention. Conjugated bilirubin is water-soluble and partially excreted via the kidney. Plasma concentrations may reach very high levels when renal failure is present (Fulop, Katz and Lawrence, 1971). Conjugated bilirubin is potentially toxic to cellular metabolism (Zetterstrom and Ernster, 1956) and may render the renal tubules more susceptible to ischaemic damage (Baum, Stirling and Dawson, 1969) but many

patients may be jaundiced and yet fully conscious and with normal renal function. In liver failure, bile acids may be rendered more water-soluble by sulphation, possibly by the kidney itself, and renal excretion of sulphated bile acids is 15 times greater than for non-sulphated bile acids (Makino and Shrinozaki, 1974; Stiehl, 1974). These are unlikely to be toxic themselves but the *in vitro* work of Williams and Taylor (1973) has suggested a facilitating role for bile acids, related to their detergent activity, in allowing the entry of respiratory toxins into cells. Aoyagi and Lowenstein (1968) have augmented ischaemic damage to rat kidney tubules with bile acid infusions.

The work of Webster and Gabuzda (1959) has shown that blood levels of ammonia are higher in patients with cirrhosis and renal insufficiency than in patients with cirrhosis and normal kidney function. The recycling of urea via the gut was suggested as the reason but the role of ammonia in the genesis of hepatic encephalopathy is controversial (Schwartz *et al.*, 1953).

Many amino acids accumulate in liver failure and an overspill aminoaciduria occurs. The levels are thus likely to be higher in the anuric patient. The amino acids tryptophan and methionine may depress cerebral function, and Knell and colleagues (1972) have demonstrated their accumulation in patients with acute liver failure.

A potential 'false neurotransmitter' is octopamine. Fischer and Baldessarini (1971) and Lam *et al.* (1973) showed a good correlation between octopamine levels and depth of hepatic encephalopathy. Octopamine is normally excreted by the kidney, and with the onset of renal failure plasma levels rose even further. They also showed a good correlation

between octopamine levels and uraemic encephalopathy in patients with normal liver function. However, although electroencephalographically uraemic and hepatic coma are indistinguishable, there are several clinical differences and it is unlikely that a single agent is the cause of both.

It is unlikely that accumulation of any one metabolite is responsible for the neurological manifestations of liver failure. In this respect, the work of Lascelles and Taylor (1968) on rat brain slice oxygen consumption is relevant: they showed that oxygen consumption was not inhibited by any substance singly, but when bilirubin and bile acids, or plasma from a patient with liver failure, were added to the slices, then brain respiration was depressed.

Sodium and water retention

Fresh frozen plasma is often administered to patients with liver failure in order to correct the synthetic defect of coagulation factors. Up to 2 l/day are sometimes given and in the oliguric patient this may lead to circulatory overload and pulmonary oedema. An additional factor in the pathogenesis of pulmonary oedema may be a direct toxic effect of the uraemic process on the lung capillary permeability to sodium and water (Crosbie, Snowden and Parsons, 1972). Arterial oxygen desaturation may be found in patients with cirrhosis and the further insult of pulmonary oedema is likely to make this even worse.

Cerebral oedema is an important immediate cause of death in fulminant hepatic failure (Ware, d'Agostino and Combes, 1971). Whether or not this is related to sodium and water overload is not known.

Hyponatraemia is common in cirrhosis (Shear *et al.*, 1965) and in fulminant hepatic failure, even when glomerular filtration rate is normal or near normal. Unless rigid fluid restriction is employed in the management of such patients if they develop renal failure, plasma sodium concentration will fall even more. Hyponatraemia may itself cause encephalopathy with EEG changes very similar to those found in hepatic failure (Pampiglione, 1973).

Reversal of some metabolic consequences of hepatic failure with onset of renal failure

Extreme alkalosis and hypokalaemia are common occurrences with acute and chronic liver failure. Hypophosphataemia has been described in acute liver failure (Knell *et al.*, 1972). With the onset of oliguria, these changes frequently reverse and phosphate and potassium retention, together with acidosis, then dominate the metabolic picture. However, it cannot be said that this reversal has any beneficial effect to the patient.

Haemorrhage

Patients with liver failure, either acute or chronic,

are at risk from haemorrhage, particularly from the gastrointestinal tract.

The factors involved in its pathogenesis include a synthetic defect of coagulation factors, disseminated intravascular coagulation, oesophageal varices, and mucosal haemorrhages induced by endotoxins (Wilkinson *et al.*, 1974a).

Uraemia is also associated with a tendency to bleeding (Shackman and Perkasch, 1964) and may be caused by a functional defect of platelets. Platelets in uraemia have been shown to possess low factor 3 levels, reduced adhesion *in vitro* and reduced ADP-mediated aggregation (Horowitz *et al.*, 1967, 1970). These changes are reversible with dialysis. Thus, the onset of anuria in patients with liver failure is likely to worsen the risks of haemorrhage.

Infection

Infection is an important cause of death in patients with acute renal failure (Montgomerie, Kalmanson and Guze, 1968). The mechanisms involved include impaired cell-mediated immunity, phagocytic activity and reticulo-endothelial function. Life threatening infections are also a common feature of patients with cirrhosis and fulminant hepatic failure (Udhoji and Weil, 1965; Mummery, Bradley and Jeffries, 1971) so again the effects of hepatic and renal impairment are likely to be additive.

Effect of uraemia on hepatic regeneration

Chen and Leevy (1973) have shown that uraemia inhibits replication of experimentally injured hepatocytes in the rat. If this also applies to man, then uraemia might impede recovery from liver failure, especially that due to fulminant hepatitis.

Therapeutic considerations

The management of renal failure when it supervenes in patients with liver disease must follow the lines of treatment in any other setting. However, a number of modifications need to be made: for example, diuretics are often used in the early stages in management of acute renal failure, but renal vein ammonia concentrations are probably increased by some diuretics (Gabuzda and Hall, 1966) and so, theoretically at least, their use is undesirable. Also, frusemide is hepatotoxic when given to mice in high doses (Mitchell, Potter and Jollow, 1973) but the relevance of this in man is unknown.

Oral neomycin is used to modify bowel flora in liver failure, but approximately 2% of this is absorbed. In anuria, serum levels may become high enough to cause both nephrotoxicity and also ototoxicity (Kunin *et al.*, 1960). Other antibiotics commonly used, such as gentamicin, need drastic reduction in dosage schedules, and daily plasma levels are helpful in management.

Haemodialysis with a cuprophane membrane or peritoneal dialysis may have a number of roles to play in patients with liver failure. Firstly, dialysis removes ammonia efficiently (Kiley *et al.*, 1958) and has been said to accelerate the recovery from hepatic coma in patients with cirrhosis (Keynes, 1968). However, for the removal of toxins and reversal of coma in acute liver failure, for example, it has had an inadequate trial. Secondly, with dialysis against a bath of appropriate hydrogen ion and sodium ion concentration, hyponatraemia and alkalosis may be corrected. Thirdly, for the correction of the uraemic syndrome and support of patients with a reversible kidney lesion, dialysis has an important part to play. Two patients in grade 4 hepatic encephalopathy from acute liver failure due to paracetamol poisoning treated recently in this department, became anuric. One patient was comatose for 6 days and the other for 8 days and neither recovered consciousness until liver function had recovered. Both received treatment with charcoal haemoperfusion while unconscious, and both received peritoneal dialysis, and in one case haemodialysis was also used. The duration of oliguria was 6 weeks in each instance before kidney function returned. Experience with dialysis in cirrhotic patients, however, has yielded no long-term survivals (Parsons, Wilkinson and Weston, 1975).

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