Renal failure in obstructive jaundice—pathogenic factors

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Summary

In the patient with obstructive jaundice, preliminary dehydration, combined with the toxic effects of free bilirubin and serum bile acids, together with factors which cause inhibition of fibrinolysis, determine a high degree of renal susceptibility to ischaemia. Evidence from animals and man suggests that intravascular coagulation determined by endotoxaemia from the obstructed biliary system occurs at the onset of acute renal failure. Endotoxin is unique in being able to produce all those factors which separately cause a primary increase of renal arteriolar constriction.

THE importance of acute renal failure in association with obstructive jaundice is that this accounts for one-third of surgical cases of acute renal failure (Dawson, 1968), and that 50% of patients who die after surgery for obstructive jaundice do so with acute tubular necrosis (Thal *et al.*, 1971). Clinical observation shows that such patients have usually suffered an incident of shock or hypotension, that the risk is higher in the most deeply jaundiced patients, and that other complications such as infection, perforation or pancreatitis herald a fatal outcome (Anderson, Sørensen and Skjoldborg, 1971). Acute renal failure can also occur in non-icteric patients who have biliary tract calculi and Anderson *et al.* (1971) have attributed this to a focus of sepsis that has precipitated shock.

Histologically, the picture is of focal tubular necrosis with bile staining of both the necrosed cells and tubular casts. Renal cortical necrosis is uncommon. We have also noted evidence of intraglomerular and peritubular capillary fibrin deposits.

The factors involved in the pathogenesis of acute renal failure in obstructive jaundice are summarized in Table 1 and these will be considered individually:

TABLE 1. Potential factors contributing to acute renal failure in obstructive jaundice

1. Dehydration
2. Conjugated bilirubin
3. Bile salts
4. Intravascular coagulation and inhibition of fibrinolysis
5. Endotoxin

Dehydration

Bilirubin itself is a powerful vasodilator and can lead to an obligatory loss of salt and water in the preoperative period (Tohuzlu and Stahl, 1966). In fact blood volume deficits of 1500 ml have been recorded in patients with biliary obstruction.

Conjugated bilirubin

Dawson (1968) has shown a relationship between depth of jaundice and incidence of renal failure. He also showed in Wistar rats, that the presence of obstructive jaundice sensitizes the renal parenchyma to ischaemic damage, but since bile duct ligation in Gunn rats (these are unable to conjugate bilirubin) did not render their kidneys more susceptible to renal ischaemia (Baum, Stirling and Dawson, 1969) it seemed likely that conjugated bilirubin was the sensitizing agent. In fact it has long been known that bilirubin is toxic to cells since it produces uncoupling of oxidative phosphorylation (Cowger, Igo and Labbe, 1965). Binding of circulating bilirubin to albumin prevents this toxicity, and it is only free conjugated bilirubin that is filtered into the urine, allowing access to the tubular cells from within the lumen (Fulop and Sandson, 1967; Fulop, Katz and Lawrence, 1971).

Bile salts

Serum concentrations of bile salts are, of course, raised in obstructive jaundice and Aoyagi and Lowenstein (1968) have shown that rats receiving bile salt infusions develop acute renal failure after 30 min of renal ischaemia, a period of time insufficient to cause renal failure in normal animals.

We have performed bile acid infusions in rabbits and shown that taurocholate, in particular, increases the permeability of the aortic endothelium to Evans' blue. There is a relative preponderance of taurocholate in cholestasis. It is likely that if bile acids damage endothelium they remove the protective fibrinolytic potential which in arteries is normally quite small. It should be noted that taurocholate has a *pKa* of 2.0, glycocholate a *pKa* of 4.0, and the free

bile acids a pK_a of 6.0. Ionization occurs at their carbonyl and sulphonyl groups.

Intravascular coagulation (DIC) and inhibition of fibrinolysis

The fibrinolytic system exists to protect against the intravascular deposition of fibrin. The kidney in particular is rich in plasminogen activator, suggesting that the kidney requires such protection. Clearance of fibrin is also achieved by the reticulo-endothelial system (RES), which includes the Kupffer cells of the liver and the mesangial cells of the kidney (Wardle, 1974a). If DIC does occur in the presence of fibrinolytic inhibition then thrombi in the micro-circulation may result in focal tissue necrosis of vital organs.

Studies of fibrinolysis do show inhibition in obstructive jaundice. It could be that there is diminished release of plasminogen activator from vascular endothelium damaged by bile salts or bilirubin. Certainly also plasmin inhibitors will be raised, since lipoproteins are inhibitors of fibrinolysis. The 'acute phase reactive proteins' α -1-antitrypsin and α -2-macroglobulin are also important antiplasmins.

Endotoxin

Since 1935 it has been known that two spaced doses of endotoxin produce renal cortical necrosis. By manipulation of the dose a spectrum of renal damage can be produced, ranging from cortical necrosis, to glomerular thrombosis, to peritubular capillary thrombosis with the production of focal tubular necrosis. Continuous infusion of smaller doses of endotoxin can produce similar effects, or a single dose of endotoxin will do so if certain preparative manoeuvres are used. These include either the use of cortisone or pregnancy to achieve fibrinolytic inhibition, or blockade of the RES. It is difficult to produce a Schwartzman reaction in the rat but we (Wardle and Wright, 1970) were able to do so in obstructive jaundice using a single dose of endotoxin. We noted a specific inability to clear endotoxin and the rats died of intravascular coagulation.

A number of questions relating to endotoxaemia in obstructive jaundice require answers.

Is the functional capacity of the RES impaired?

Clearances of aggregated albumin suggest that it is. The RES cells could be functioning below par on account of lipid ingestion because of an accumulation of unconjugated bilirubin as noted by Schaffner, Popper and Steigmann (1950) or because of exposure to endotoxin. Kupffer cells are in a unique position for dealing with antigens that enter from the bowel, and endotoxin which is presented in

this manner need not elicit a pyrogenic response (Greisman and Woodward, 1970).

Is DIC demonstrable in human obstructive jaundice?

In using the radiofibrinogen catabolism test the fibrinogen catabolic rate is often doubled before classical coagulation factor assays become abnormal. This is the most practical and at the same time most sensitive test for monitoring low grade DIC. In obstructive jaundice the synthesis of prothrombin and other factors is impaired. However, we have shown that radiofibrinogen catabolism shows increased turnover whatever the cause of the obstruction. In an occasional case post-operative acceleration of catabolism has been linked to endotoxaemia. It is doubtful whether operation *per se* alters the fibrinogen catabolic rate (Wardle, 1974b).

Is endotoxin demonstrable in obstructive jaundice?

Results using the Limulus assay indicate that some 25% patients have transient endotoxaemia and that the figure rises to 75% in the immediate post-operative period (Wardle, 1974b). These figures are supported by data using a platelet nitroblue tetrazolium reduction assay.

What is the origin of endotoxin?

In the dog, bacteria can be cultured from the portal venous blood and this will explain why the dog with obstructive jaundice becomes anuric and hypotensive and always gets cholangitis. In man, it is certain that the bile duct must be obstructed for bacteria to multiply. Bacteria are cultured from the gall bladder bed in 80% cases of human cholecystitis and 15% of the organisms are anaerobes. Much clinical evidence suggests that when acute renal failure occurs, there is a focus of infection or endotoxaemia from the bowel.

What is wrong with the endotoxin clearing mechanisms?

There is insufficient knowledge of the body defences against endotoxin. If there is antibody, then complexes may be formed and cleared by the Kupffer cells; however there could still be intraportal coagulation. It is certain that endotoxin becomes bound to an α -1-lipoprotein, and that final inactivation is achieved by an α -1-globulin, which is heat labile. Both proteins have non-specific esterase activity of the organophosphate resistant type (Skarnes, 1970) and they function efficiently only when the ionic calcium is low. These non-specific esterases are diminished in chronic rather than acute disorders of the liver (Waterlow, 1950). Furthermore experiments with obstructive jaundice in the rat show also some diminution of esterase

activity. C5- and C6-deficient animals are highly susceptible to endotoxin, but it is not certain that complement does inactivate endotoxin, for if it does it must do so by means other than the usual sequential pathways (Johnson and Ward, 1972). However, depletion of complement components does not prevent the Shwartzman reaction (Bergstein and Michael, 1974) and endotoxin is anticomplementary.

Endotoxin is also inactivated within the phagocytic cells of the liver and spleen (Farrar and Corwin, 1966). This function is impaired when there is fatty or other pathological change in the liver.

What are the properties of endotoxin that make it so lethal?

Endotoxin is a polyanion assembled from three units like a nuclear warhead. In some animals as little as 0.15 ng/kg is toxic (Watson, 1971), and this is certainly comparable to the levels found using the Limulus assay in man. However, we do not yet know what is the danger level in man: my estimate is that 1 ng/ml plasma is sufficient to cause lethal effects. At any rate endotoxin has a multiplicity of sinister biological effects which include activation of coagulation at the same time as inhibition of fibrinolysis, reticulo-endothelial blockade, activation of the complement and kinin systems, direct metabolic injury to cells and usually profound vasoconstriction and tissue ischaemia. It is vasoconstriction within the liver that limits the clearance of large doses of endotoxin.

What are the renal effects of endotoxin?

Small doses of endotoxin just sufficient to cause a pyrogenic response produce vasodilation, which is probably due to the associated release of kinins. Larger doses cause vasoconstriction. Endotoxin in primates produces neurogenic vasoconstriction, catecholamine release, renin-angiotensin activation and DIC (Selymer, Reynolds and Swan, 1973). Thus, it is capable of causing all those primary factors which induce the initial increase of renal vascular resistance that heralds renal cortical ischaemia (Table 2). Much evidence is quite consistent with the hypothesis that endotoxin is the cause of the majority of cases of acute renal failure in man,

in other words, they are Shwartzman equivalents. Added to this is the knowledge that should renal tubular cell metabolism be already impaired on account of say, volume depletion or jaundice, then even low grade endotoxaemia could deal the final blow to tubular cell metabolism.

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TABLE 2. Mechanism of acute renal failure

Onset of increased renal vascular resistance	Persistence of increased renal vascular resistance
Neurogenic vasoconstriction	Endothelial swelling
Catecholamines	Sludged red cells
Renin-angiotensin	White cells and platelets
DIC	Fibrin thrombi
Volume depletion	