the rise produced by normal rabbit serum was from 15·1 μg./100 ml. to a maximum of 26·1 μg./100 ml. nine days later, an increase of about one-third of that shown by animals treated with antilymphocyte serum.

The "escape" of both the rise in plasma cortisol and the reduction in body weight from initial influence of antilymphocyte serum despite continued injection corresponds with the observations of Waksman *et al.* (1961) that treatment with antilymphocyte serum tended to lose its effectiveness in lowering the white cell count over several days. The same loss of effect was noted by Field and Miller (1961), when sodium salicylate was used to prevent experimental allergic encephalomyelitis in guinea-pigs—an effect which the authors were inclined to attribute to the "stress" of the injections. Even inoculation of saline intraperitoneally had a distinct "protective effect" on the development of allergic encephalomyelitis in guinea-pigs as compared with no treatment at all. Such specific stress reactions are often not taken into account, especially in acute experiments. Field and Metcalf (1955, unpublished results) found that intravenous injection of sterile saline into rabbits will markedly alter the white blood cell picture, often temporarily reversing the normal lymphocyte preponderance in that animal.

In view of these findings it might be rewarding to study the effectiveness of antilymphocyte serum in adrenalectomized animals in order to evaluate what part is played by the "stress" reaction.

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Further Study into Obstructive Jaundice and Ischaemic Renal Damage

British Medical Journal, 1969, **2**, 229–231

Summary: Renal ischaemia for one hour in two groups of Gunn rats, one with and the other without bile-duct ligation, produced comparable reversible renal tubular lesions in both groups. Since Gunn rats have an unconjugated hyperbilirubinaemia, which is unaffected by bile-duct ligation, it seems likely that the high levels of bilirubin glucuronide are responsible for sensitizing the renal tubules to ischaemia, possibly by depressing cell respiration.

INTRODUCTION

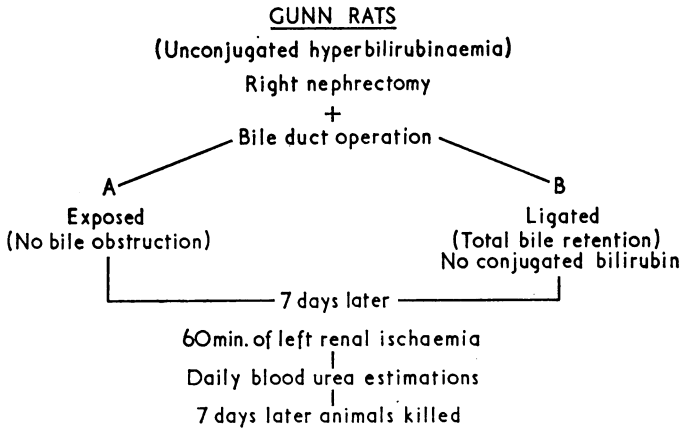
Postoperative renal failure is a well-recognized hazard in patients with obstructive jaundice (Clairmont and von Haberer, 1911; Williams, Elliott, and Zollinger, 1960; Dawson, 1965). With the use of an experimental model in the rat it has been shown that the presence of obstructive jaundice sensitizes the renal parenchyma to ischaemic damage (Dawson, 1964).

The present experiment was designed to try to determine which moiety of retained bile products is responsible for the renal sensitization.

METHOD

The plan of the experiments was similar to that previously reported (Dawson, 1964) except that Gunn rats (Gunn, 1938) were used instead of Wistar rats. The Gunn rat has a congenital absence of enzyme glucuronyl transferase (Carbone and Grodsky, 1957), and consequently has an unconjugated hyperbilirubinaemia which is unaffected by duct ligation.

A schematic plan of the experiment is shown:



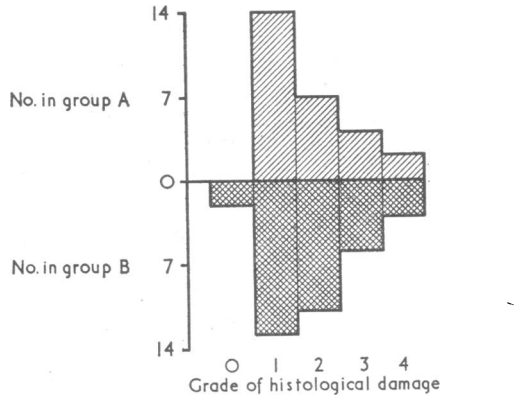
The right kidney was removed in all animals. In group A the common bile duct was only exposed, and in group B it was ligated as high as possible, close to the junction of the right and left hepatic ducts. Ether anaesthesia was used throughout. Seven days later the left renal pedicle was clamped for 60 minutes in both groups. Only those animals recovering from this second procedure were included; those that obviously died from rupture of the dilated common duct were excluded. Daily samples of tail vein blood were taken after the clamping experiment and blood urea levels estimated. The animals were killed on the seventh day and the left kidney was examined histologically, the degree of damage being graded 0 to 5 (Dawson and Stirling, 1964) without knowledge of the biochemical results (0=no change, 5=gross tubular necrosis and calcification).

Effect of Clamping Experiment on Blood Urea Levels (mg./100 ml.) in the Two Groups of Rats. (Results are shown as Mean and Standard Error of Mean for Each Group)

Group	No. of Animals	Deaths	Blood Urea Levels							
			Preoperative	Days Postoperative						
				1	2	3	4	5	6	7
A	28	2 (7%)	57 ± 3	159 ± 11	148 ± 13	80 ± 6	90 ± 20	89 ± 11	62 ± 6	71 ± 3
B	40	9 (22·5)	58 ± 2	160 ± 11	165 ± 16	96 ± 21	78 ± 7	83 ± 9	56 ± 6	61 ± 3

RESULTS

There were 28 rats in group A (sham ligation of common duct) and 40 in group B. Two deaths occurred in group A and nine in group B. The blood urea results are shown in the Table and the histological gradings in the Chart. The histological results for one batch of five animals in group B are not available and do not appear in the Chart.



Grade of histological change found in the left kidneys of the two groups of animals (Group A=Control. Group B=Bile duct ligation).

After clamping there was a rise in blood urea, reaching a peak on the first or second day and falling towards normal values by the sixth day. There was no statistical difference on any day between the values in groups A and B, and the grade of histological damage was also similar, the peaks being in grade 1.

The renal papillae of both right and left kidneys were packed with bile pigment in the extracellular space, and this was associated with damage to the overlying epithelium. Frank papillary necrosis was also seen in many of the left kidneys whose pedicle had been clamped, but this was unrelated to the grade of tubular damage in other areas.

The only reported difference between the bile of Wistar and Gunn rats is the absence of conjugated bile in the latter variety, thus these experiments show the effect of retention of all bile constituents *except conjugated bilirubin*. Both groups of animals had an unconjugated hyperbilirubinaemia, of course, which equilibrates at about 7 mg./100 ml. of plasma, probably by excretion of unidentified products across the intestinal mucosa (Blanc and Johnson, 1959).

There is no significant difference between the renal lesion in groups A and B measured by changes in blood urea levels and histological damage. There were more deaths in group B than in group A ; the animals having their ducts ligated were not nearly as fit and did not thrive as well as those having the sham operation, but the deaths were not apparently due to uraemia.

Previous experiments with Wistar rats have shown that 60 minutes of renal ischaemia after a seven-day occlusion of the bile duct produces a very severe renal lesion, which was fatal in 60% of animals (Dawson, 1964). But the present experiments in Gunn rats show no difference after ligation of the common bile duct ; thus it seems likely that it is the high levels of bilirubin glucuronide, and not the bile salts, unconjugated bilirubin, or other retained bile products that render the renal tubular cells more sensitive to ischaemia. It is of great interest that recent work (Powell, Dunnicliff, and Billing, 1968) has shown that the shortened red cell life in obstructive jaundice is also related to the retention of conjugated bilirubin in the plasma. In contrast, it has recently been shown that the infusion of bile salts (sodium cholate and taurocholate) produces sensitization of the renal parenchyma to ischaemic damage, whereas the infusion of a solution of bilirubin had no such effect (Aoyagi and Lowenstein, 1968). These infusion experiments, however, probably do not reproduce the effect of bile-duct obstruction, as the bilirubin is not conjugated, and the plasma and tissue levels of bile salts are not known to be of the same order and ratio as those found with duct obstruction.

The mode of excretion of bilirubin glucuronide by the kidney is undecided, but most is probably filtered through the glomerulus (Fulop, Sandson, and Brazeau, 1964). Unconjugated bilirubin is so tightly bound to albumin that it is virtually undialysable (Fulop *et al.*, 1964), but conjugated bilirubin is less firmly bound, especially in the presence of bile salts, and is then ultrafiltrable (Fulop and Sandson, 1967). Its presence in renal tubular fluid may account for the entry of bile pigment into the tubular cells of the Wistar rats with obstructive jaundice (Dawson and Stirling, 1964) and for its absence in those of the Gunn rat.

Bilirubin glucuronide may even be toxic to the tubular cells in the absence of ischaemia, since mild tubular lesions are seen in Wistar rats with obstructive jaundice. Furthermore, Antoine and Neveu (1968) demonstrated renal antigens in the urine of patients with conjugated hyperbilirubinaemia, presumably derived from damaged renal tubules.

Ischaemic anoxia is likely to increase capillary and cell membrane permeability, and this in turn increases the concentration of bilirubin glucuronide in the tubular cells where it would be hydrolysed by lysosomal glucuronidase to free bilirubin. Zetterström and Ernster (1955) showed that bilirubin uncouples oxidative phosphorylation in mitochondria and decreases the cellular respiratory rate. More recently Cowger, Igo, and Labbe (1965) confirmed this in tissue culture and showed bilirubin to be an electron transport inhibitor. It would therefore appear that ischaemic anoxia by increasing the intracellular concentration of bilirubin would further depress cell respiration, so further increasing the anoxia.

An interesting incidental finding of this study was the occurrence of papillary necrosis in both groups of Gunn rats. Odell, Natzschka, and Storey (1967) have already shown that the renal papillae of the Gunn rat contains 80 times more bile pigment than other tissues, and demonstrated that there is inability to secrete a concentrated urine. The pigment may interfere with the blood flow to the loop of Henle and the collecting tubules. The blood supply to the papillae via the vasa recta is at best tenuous, so that one hour's ischaemia could easily precipitate papillary necrosis.

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Medical Memoranda

Fulminating Meningococcal Septicaemia Presenting with Subarachnoid Haemorrhage

British Medical Journal, 1969, **2**, 231–232

Meningococcal infection usually presents as acute bacterial meningitis (cerebrospinal fever), but there are many other less common clinical manifestations. One of the least common is an acute septicaemia with shock and a generalized purpuric rash.

Andrewes (1906) described the first proved case of meningococcal septicaemia. His patient, a 53-year-old doctor, became ill during the night; at midday on the next day he developed spots on the face and later became covered in a haemorrhagic rash; at 6 p.m. he died. An organism identical with the meningococcus was grown in culture, and at necropsy haemorrhages were noted in the adrenals, skin, intestines, and meninges; there was no evidence of meningitis. Waterhouse and Friderichsen described further cases and their names became attached to the syndrome. Banks (1948) preferred to call it the "adrenal type" of fulminating meningococcal infection; the postmortem finding of adrenal haemorrhage suggested that adrenal insufficiency might be the cause of the hypotensive collapse, and early reports of the successful use of cortisone gave some support to this view (Nelson and Goldstein, 1951). Nevertheless, laboratory evidence of cortisone deficiency has not been forthcoming. Steroids may fail to prevent death, and maintenance therapy with cortisone is not required in survivors. Adrenal haemorrhage is not always found in patients whose clinical course has been typical (Daniels, 1948).

Attention has recently turned to disseminated intravascular coagulation as a possible mechanism of the shock, thrombosis of vessels, adrenal necrosis and haemorrhage, and renal cortical necrosis which occur in meningococcal septicaemia and in other clinical states known to be accompanied by disseminated intravascular coagulation (Margaretten and McAdams, 1958; McKay, 1965), That this occurs is evidenced by the demonstration of fibrin thrombi at necropsy (Ferguson and Chapman, 1948) and by thrombocytopenia and diminished levels of fibrinogen and factors V and VIII in severe cases (McGehee *et al.*, 1967).

We report a case of fulminating meningococcal septicaemia to record a rare presentation, subarachnoid haemorrhage, which obscured the diagnosis and to discuss the implication of this to the pathogenesis and treatment of the disorder.

CASE REPORT

A 20-year-old Irish woman, on holiday in London, was admitted to hospital on 10 February 1968. A history was obtained from a friend of a sore throat and cold-like symptoms for one week. On the day of admission she awoke with a headache, which was severe and persisted throughout the day, and for which she took various remedies. The friend was with her during the day but went out for an hour in the evening. She returned to find the patient collapsed, semiconscious, and covered with a red blotchy rash.

On examination she was shocked with a systolic blood pressure of 60 mm. Hg and a pulse rate of 120/min. There was a generalized purpuric rash (Fig. 1). She was verbally inaccessible and resisted any kind of attention. There was neck stiffness and positive Kernig's and Brudzinski's signs. Her temperature was 96·8° F. (36° C.).

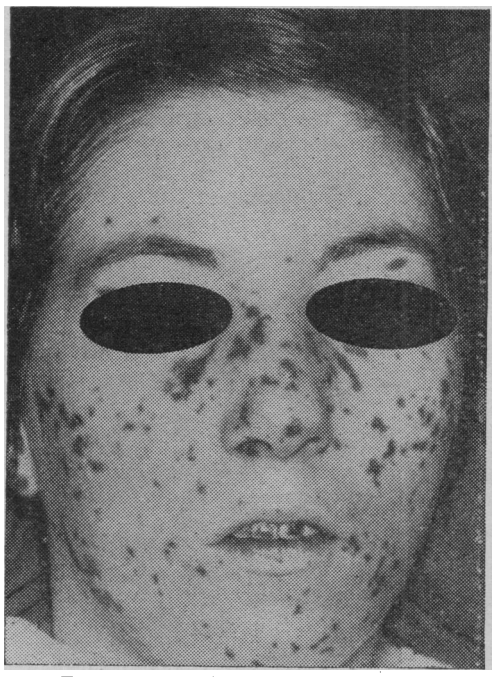

FIG. 1.—Purpuric lesions on the face.

Lumbar puncture revealed heavily blood-stained fluid with no excess of white blood cells. Blood was taken for cultures and intravenous fluid therapy was instituted.

After admission she remained hypotensive and anuric for 24 hours but had a diuresis after administration of mannitol. The rash persisted, the lesions becoming a deep purple colour. Over the upper thighs several large confluent lesions were produced (Fig.2). The skin of both big toes was noted to be black but remained warm. All peripheral pulses were palpable. Her general condition improved slowly.

Investigations on the third day of the illness were as follows: haemoglobin 98%, W.B.C. 10,200/cu. mm. (79% neutrophils, which appeared "very toxic"; many were vacuolated, and one contained diplococci), platelets 55,000, fibrinogen 650 mg./100 ml. (normal 200–400 mg./100 ml.), and plasminogen 0 (normal 2–4 units). A Synacthen (tetracosactrin) test was carried out on the twelfth day of the illness, and showed a normal adrenal response. Immunoglobulins were also normal.

There was no growth from the spinal fluid, but on the fourth day a meningococcus was isolated from the original blood culture. Treatment was started with penicillin and sulphadimidine, and her condition continued to improve slowly.