ACUTE POST-OPERATIVE RENAL FAILURE IN OBSTRUCTIVE JAUNDICE

Hunterian Lecture delivered at the Royal College of Surgeons of England

on

21st March 1967

by

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Betwixt the urinary secretion and various other functions of the body there exists a connection which presents some remarkable phenomena. The minute relations of these phenomena will probably ever elude our researches.

—ABERCROMBIE, 1821.

WHEN JOHN HUNTER was practising surgery in London during the 18th century abdominal operations were rarely done, and jaundice remained the province of the physician as it had been since the dawn of recorded medicine. Even as late as 1852, Sir George Budd (physician to King's College Hospital) wrote of obstructive jaundice " . . . but when, as is oftener the case, the closure is caused by gall stone or malignant disease, then there is nothing more to be done than to regulate the diet . . . ", and he went on " . . . and to take care to do nothing likely to disorder the action of the kidney, through which the bile finds its way out of the system ".

With the advent of anaesthesia and faith in antisepsis, abdominal surgery blossomed in the later part of the 19th century. By the turn of this century operations for the relief of obstructive jaundice were becoming commonplace and it was soon realized that a jaundiced patient presented special problems—the most obvious one being the haemorrhagic diathesis, which was of course later shown to be due to Vitamin K deficiency (Dam, 1935; Illingworth, 1939).

In 1911, Clairmont and Von Haberer drew attention to a much rarer but none-the-less definite hazard facing a jaundiced patient who undergoes surgery—that is, acute post-operative renal failure. They described five patients, all of whom died of oliguric renal failure soon after an operation for the relief of jaundice due to gall stones. They emphasized that apart from jaundice these patients were in good health with no previous suspicion of renal disease. They postulated that jaundice predisposed to post-operative renal failure. Further case reports soon appeared in the literature and various aetiological factors were invoked, such as toxic anaesthetic agents, trauma of the operation and the direct effect of bile on the kidney (Steinthal, 1911; Stäheli, 1921).

It must be emphasized that oliguric renal failure developing after operation in patients with obstructive jaundice has nothing whatsoever to do with the so-called " hepato-renal syndrome ".

The concept of the " hepato-renal syndrome " was introduced in America (Heyd, 1924) to explain unexpected and unaccountable deaths following operations on the biliary tract. Most of the patients described were in fact *not* jaundiced before the operation. The definition of the syndrome was vague and the published accounts were not supported by detailed laboratory and pathological data. In fact a post-mortem examination was not done in most of the fatal cases reported. By the late 1940s such reports were very infrequent and in 1950 Dunphy and his colleagues pointed out that the hepato-renal syndrome was a generic term for many different causes of post-operative deaths not appreciated in 1924—such as accidental ligation of the hepatic artery, toxic anaesthetic agents, water and electrolyte disorders, oligaemia and overwhelming infection. He concluded that the term is now meaningless and is best avoided.

Since 1911, when Clairmont and Von Haberer first postulated that jaundice might predispose to post-operative renal failure, surprisingly few reports or series have appeared in the literature. But most experienced clinicians would, I think, echo the words of the late Professor Ian Aird, who in 1953 wrote: " There seems no question that renal failure may be precipitated in a jaundiced patient by the operation itself ". It was with this background then that the present work was undertaken.

Three main problems present themselves:

1. Incidence
2. Aetiology
3. Prophylaxis

These problems have been explored by clinical survey, animal experiments and clinical investigations.

CLINICAL SURVEY

Introduction

The incidence of acute post-operative renal failure in obstructive jaundice was examined by clinical survey (Dawson, 1965*b*). A retrospective analysis of the records of 103 consecutive patients with obstructive jaundice undergoing laparotomy from 1956 to 1963 was made. This survey was carried out at two hospitals—St. James' Hospital, Balham, and King's College Hospital. Special note was made of the patient's age, pre-operative bilirubin level, the operative findings, the operative procedure, and the cause of any post-operative deaths.

Results

The results of this survey are shown in Figure 1. The patients have been divided arbitrarily into three groups, according to their pre-operative serum bilirubin level. There were 23 patients with a serum bilirubin below 9 mg. per cent, 49 patients with a pre-operative serum bilirubin between 10 and 19 mg. per cent and 32 patients with a serum bilirubin in excess of 20 mg.

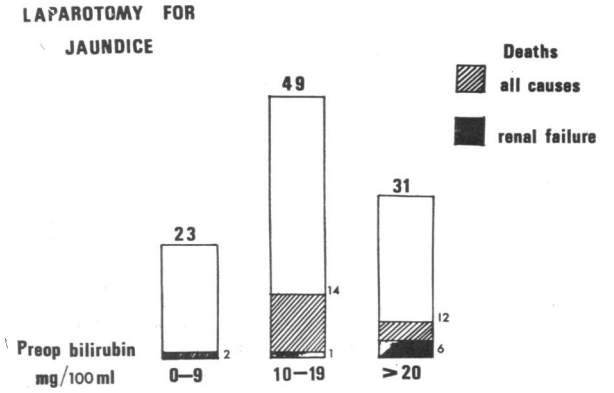


Fig. 1. The results of operation on 103 patients with obstructive jaundice. The patients are grouped together according to the depth of jaundice. Deaths due to renal failure are shown by the height of the solid columns.

per cent. The total deaths are indicated by the height of the hatched columns, and the deaths due to acute renal failure by the height of the solid columns.

The most striking features of these results is the association of deep jaundice and the development of acute post-operative renal failure. Six of the seven patients who died of acute renal failure had pre-operative serum bilirubin level of more than 20 mg./100 ml. Of all the 28 post-operative deaths, acute renal failure accounted for seven.

Further details of the seven patients who died of acute renal failure are shown in Table I.

In four patients the diagnosis of acute tubular necrosis was confirmed by post-mortem examination, whilst in the remaining three the diagnosis rested upon blood urea levels in excess of 200 mg./100 ml. associated with persistent oliguria. All of these patients underwent a simple bypass operation or merely exploration. Some were comparatively young and in none was there any evidence of unexpected or excessive blood loss, or persistent hypotension.

TABLE I

DETAILS OF SEVEN PATIENTS WHO DIED OF ACUTE RENAL FAILURE

Age	*Sex*	*Pre-Op. Serum Bilirubin mg./100 ml.*	
47	M	29.0	
64	M	22.4	Post-mortem histological
65	M	25.0	confirmation of acute
79	M	26.0	tubular necrosis
64	M	25.8	
74	F	17.8	Persistent oliguria
83	F	21.0	Blood urea = >200 mg./100 ml.

In other words, apart from jaundice there were no predisposing factors for the development of post-operative renal failure.

Discussion

An incidence of seven post-operative deaths from acute renal failure in 103 patients undergoing upper abdominal surgery is many times the expected incidence.

Figure 2 shows the percentage incidence of post-operative renal failure in the present series, compared with two other groups of abdominal operations—partial gastrectomy and biliary tract surgery in patients without jaundice. The former series was reported from St. James' Hospital, Balham (Desmond and Sargeant, 1957), and represents 160 patients who underwent emergency partial gastrectomy for perforated chronic peptic

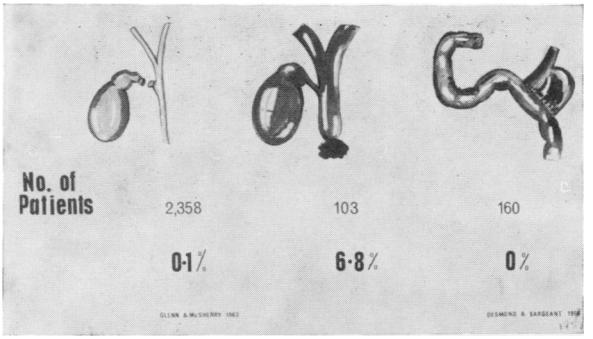


Fig. 2. The incidence of post-operative renal failure in the present series (centre) compared with emergency partial gastrectomy (right) and biliary tract surgery (left).

ulcer. Despite the fact that many of these patients were shocked before resuscitation, none died of acute renal failure, although partial gastrectomy is undoubtedly a greater procedure than any of the operations carried out on the seven jaundiced patients of the present series who died of renal failure. Similarly, in 2,358 operations on the biliary tract in patients without jaundice, there were only three deaths from uraemia and all three of these patients had pre-existing renal disease (Glenn and McSherry, 1963).

Thus the present survey seems to confirm Clairmont's and Von Haberer's original hypothesis—that obstructive jaundice considerably increases the risk of post-operative renal failure. Furthermore, there appears to be a definite association between the depth of jaundice and the development of anuria: the deeper the jaundice, the greater the risk.

ANIMAL EXPERIMENTS

Introduction

To turn now to the aetiology of acute renal failure in obstructive jaundice. Two theoretical possibilities present themselves:

(1) that obstructive jaundice affects the renal parenchyma directly; or

(2) that obstructive jaundice somehow affects circulatory homeostasis, whereby blood flow to vital organs is normally maintained after trauma or haemorrhage.

There was some precedent for the former view, for after the description of the " crush syndrome " during the London blitz (Bywaters and Beall,

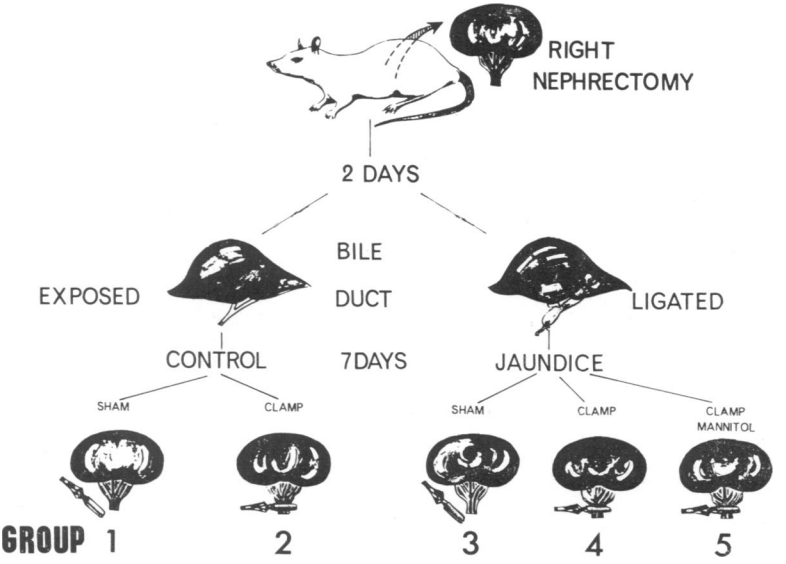


Fig. 3. Plan of the experiments performed on rats.

1941) experimental evidence was soon produced to show that various circulating pigments, such as haemoglobin, myoglobin and acid haematin, rendered the renal parenchyma much more susceptible to damage from renal vessel clamping (Corcoran and Page, 1945; Badenoch and Darmady, 1948). Experiments were therefore planned in rats (Dawson, 1964):

(1) To compare the effects of renal ischaemia in normal and jaundiced animals.

(2) To see whether an osmotic diuresis established before a period of renal ischaemia in jaundiced animals would in any way modify the outcome.

The second part of these experiments was suggested by the demonstration in recent years that an osmotic diuresis can prevent ischaemic renal damage both clinically and experimentally (Barry *et al.*, 1961; Mueller, 1965).

Experiments on rats

A plan of the experiments is shown in Figure 3.

At the first operation the right kidney was removed. Two days later the animals were subjected to a second operation. In some animals the common bile duct was ligated, whilst in the remainder a sham operation was done. Thus there were two main groups of rats: non-jaundiced and jaundiced.

Seven days later a third operation was done. The left renal pedicle was exposed. In some animals the renal pedicle was occluded for 60 minutes using a small Bulldog clamp; whilst in the others the clamp was laid alongside the pedicle for 60 minutes as a sham operation. Thus there were five groups of animals:

Group 1: non-jaundiced animals with a sham clamping.
Group 2: non-jaundiced animals with 60 minutes of renal ischaemia.
Group 3: jaundiced animals with a sham clamping.

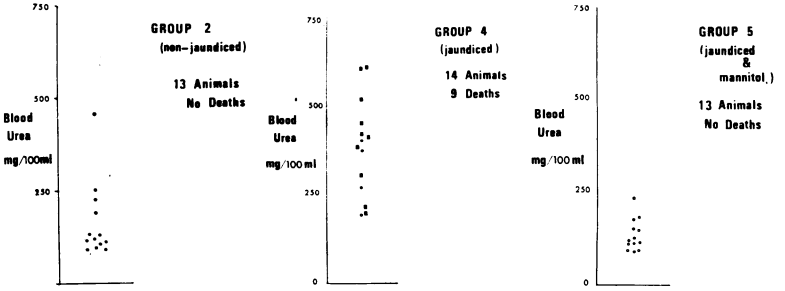


Fig. 4. Maximum levels of blood urea recorded after clamping experiments in rats of Groups 2, 4 and 5. The deaths are indicated by closed squares.

Group 4: jaundiced animals with 60 minutes of renal ischaemia.
Group 5: a further batch of jaundiced rats in which a mannitol diuresis was established immediately before the renal vessel clamping.

Before the clamping experiment blood was taken from the tail vein for estimation of blood urea, and serum bilirubin levels. On the first, second, third, fifth and seventh post-clamping days, blood samples were taken from the tail vein for blood urea estimation. The surviving animals were killed on the seventh day and the left kidney removed and preserved for histological examination. In those animals dying before the seventh day, the kidney was removed as soon after death as possible and preserved for histological examination.

Removal of the right kidney at the first operation was uncomplicated, and all the animals survived. Pilot studies showed that ligation of the common bile duct in the rat carried a considerable immediate mortality rate, but once the animals survived four to five days they continued in good health for several weeks; but the jaundice which appeared on the second day began to fade on the tenth (Haber, 1962). This has been shown

by other workers to be due to recanalization of the duct system (Wright and Braithwaite, 1962). The seventh day, therefore, was chosen for the clamping experiments, as any subsequent deaths were unlikely to be related to the ligation of the common bile duct.

Results

The sham clamping experiments (Groups 1 and 3) produced no rise in blood urea in the days following. In the remainder, the clamping experiments (Groups 2, 4 and 5), the blood urea rose sharply, reaching a peak on the second or third day in most animals before returning to normal values.

The biochemical results of the clamping experiments in groups 2, 4 and 5 are shown in Figure 4. In Group 2, it will be seen that in only one animal did the blood urea rise above 250 mg./100 ml. and none of the 13 animals in this group died. Thus, 60 minutes of renal ischaemia produces only a moderate renal lesion.

TABLE II

SEVERITY OF HISTOLOGICAL LESIONS IN EACH GROUP

Group	*No. of Rats*	*Numbers of animals in each grade*					
		°	+	++	+++	++++	+++++
2	13	—	1	8	3	1	—
3	6	2	4	—	—	—	—
4	14	—	—	—	5	3	4*
5	13	—	—	4	9	—	—

* Kidneys not available for examination in two animals.

In contrast, 60 minutes of renal ischaemia in the jaundiced animals (Group 4) produced severe and lethal effects. Nine of the 14 animals died and in every animal except one the blood urea level rose above 200 mg. per cent.

In the jaundiced animals given mannitol (Group 5) there is a striking contrast. None of the 13 animals died and the post-operative blood urea levels were mostly below 200 mg./100 ml. In fact the results are very similar to those obtained in the non-jaundiced group.

Histological examination showed all the right kidneys to be normal. In Group 1, non-jaundiced animals undergoing a sham clamping, the left kidneys were also normal. The renal tubular damage found in the left kidneys of the other groups showed a close correlation with the biochemical disturbance just described. The degree of damage has been graded from 0 (no change) to 5 (gross tubular necrosis and calcification) (Dawson and Stirling, 1964).

The results are shown in Table II.

In Group 2, that is renal ischaemia without jaundice, moderate histological lesions were seen in the renal tubules, the majority of the changes being in the second grade.

In Group 3, jaundice alone with no ischaemia, a very mild tubular lesion was found, consisting of a little loss of cell outline and bile pigment within

the tubular cells (Grade 1). There was no biochemical disturbance in this group.

In Group 4, that is renal ischaemia with jaundice, severe histological damage was found in this group (Grades 3, 4 and 5).

In Group 5, renal ischaemia, jaundice and mannitol, again the renal lesion is much less severe, the majority being in Grade 3.

In the animals of Group 5, mannitol probably exerts its protective effect in two ways:

(i) It causes a more rapid return of effective renal blood flow immediately after release of the clamp (Selkurt, 1945).

(ii) It prevents the accumulation of high concentration of toxic substances within the renal tubular lumen.

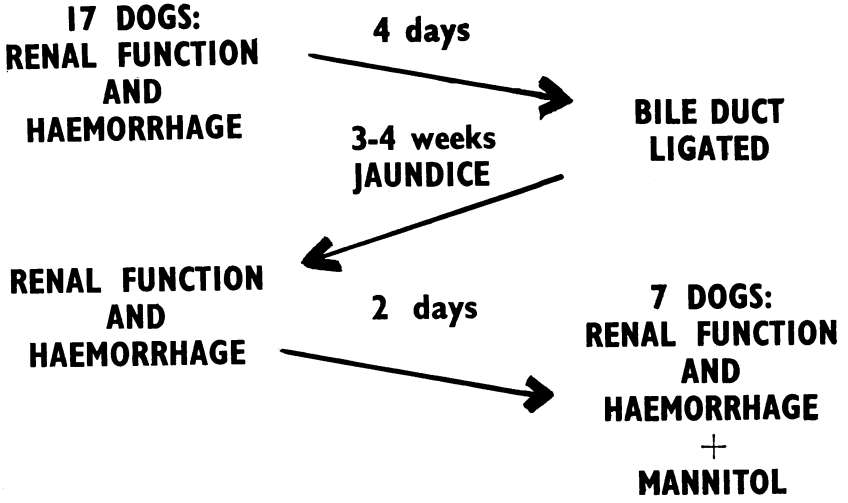


Fig. 5. Plan of the experiments performed on the 17 dogs.

This accumulation of toxic substances such as pigment or ammonia within the tubular lumen is held by some workers to be responsible for the renal tubular damage (Mueller, 1965; Wickham and Sharma, 1965).

These experiments just described, then, certainly show that obstructive jaundice does affect the renal parenchyma. It renders it more sensitive to damage by ischaemia.

But does obstructive jaundice affect circulatory homeostasis? In 1960, experiments were described which suggested that it does (Williams *et al.*, 1960). Jaundiced dogs were more easily rendered hypotensive following haemorrhage than were normal dogs. In normal dogs a blood loss of 54.2 ml./Kg. body weight was required to produce the same hypotension. No changes in blood volume were found which might explain these results. The authors concluded that obstructive jaundice induced a state of func-

tional hypovolaemia and recommended that jaundiced patients be given one to two units of blood before operation to anticipate their increased sensitivity to haemorrhage.

The implications of these observations are so important that further studies to confirm the findings seemed appropriate.

Experiments were devised:

First, to test the effect of a comparable haemorrhage on renal function in normal and jaundiced dogs.

Secondly, to test the therapeutic value of a mannitol diuresis initiated before such a haemorrhage (Dawson, 1966).

The plan of the experiments is shown in Figure 5.

Experiments on dogs

Seventeen adult mongrel bitches were used. In each of these experiments the effect of a comparable haemorrhage on renal function and blood pressure was observed. In the first instance when the dogs were normal,

TABLE III

THE EFFECT OF BILE DUCT LIGATION IN THE DOG

(*Mean and S.E.M. in* 17 *dogs before and* 3–4 *weeks after ligation of the common bile duct*)

	Normal	*Jaundice*
Serum bilirubin	0.5 mg./100 ml.	4.4 mg./100 ml.
Body weight	15.1 Kg.	12.8 Kg.
Haematocrit	39.5	35.5
Blood pressure	129.5 ±10.1	113 ±9.3
Estimated renal blood flow ..	130.3 ±34.7	125.2 ±45.0
Glomerular filtration rate ..	26.8 ±2.3	24.2 ±2.3

in the second after three to four weeks of jaundice and in the third after a mannitol diuresis had been established. The third experiment was done in only seven out of 17 dogs.

A few days after the first experiment the common bile duct was ligated and the animals were given penicillin to prevent cholangitis.

Renal function studies were done similarly in each of the experiments. After measuring basal clearances of para-amino-hippurate and creatinine over four periods of 15 minutes, an acute arterial haemorrhage of a volume of 20 ml. of blood per Kg. body weight was carried out.

Over the next hour the clearances were measured in four 15-minute periods. Serial measurements of the blood pressure and haematocrit were made in all the experiments.

Results

The mean values for the basal results in the 17 dogs before and after three to four weeks' jaundice are shown in Table III.

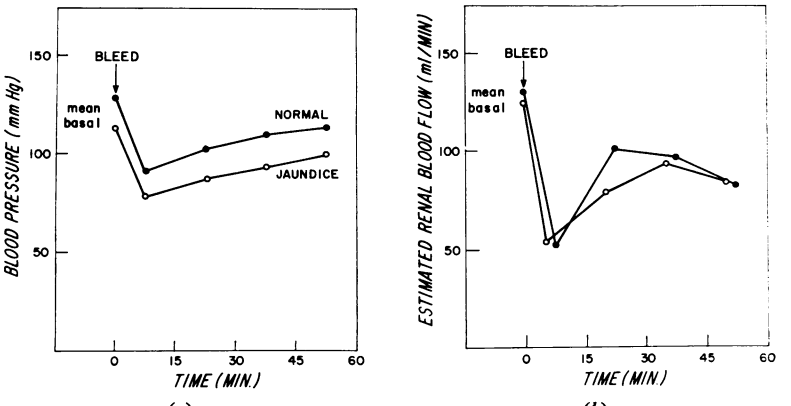
Complete biliary obstruction was confirmed at autopsy in all the animals.

Despite three to four weeks' obstruction, the mean level of bilirubin was only 4.4 mg./100 ml. This is somewhat lower than that recorded by other workers, whose values usually range between 5 to 10 mg./100 ml. But

despite many weeks' complete biliary obstruction the serum bilirubin levels in the dog never approached those met with in jaundiced patients (Mann and Bollman, 1925; MacGregor, 1953).

The dogs' mean weight fell from 15.1 kilo to 12.8 kilo, and the mean haematocrit values from 39.5 to 35.5. These changes have previously been noted and may be related to the almost total anorexia which overtakes the dogs after ligation of the bile ducts (MacGregor, 1953).

The most important finding was that the mean resting blood pressure of the dogs fell from 129.5 when they were normal to 113 after three to four weeks' jaundice. Basal renal function, as measured by the estimated renal blood flow and glomerular filtration rate, is unchanged before and three to four weeks after jaundice. And this is in keeping with other workers' results.



(*a*) (*b*)

Fig. 6. (*a*) The effect of a haemorrhage (20 ml./Kg. body weight) on the mean arterial pressure in 17 dogs before (●—●) and after 3–4 weeks of jaundice (O—O). (*b*) The effect of a haemorrhage (20 ml./Kg. body weight) on the mean levels of estimated renal blood flow (ml./min.) in 17 dogs before (●—●) and after 3–4 weeks obstructive jaundice (O—O).

Figure 6 (*a*) shows the behaviour of the mean blood pressure of the 17 dogs before and immediately after haemorrhage. The closed circles represent the values before duct ligation, when the animals were normal; the open circles—three to four weeks after duct ligation—when they were jaundiced. It will be seen that the curves run parallel. The values in the jaundiced dogs were persistently 85 per cent of the normal. Homeostasis in the jaundiced dogs appears normal but merely geared to the lower initial blood pressure.

Figure 6 (*b*) shows the behaviour of the estimated renal blood flow before and after haemorrhage. The closed circles represent the values in the normal dogs before duct ligation; but the open circles, the values when the dogs were jaundiced three to four weeks after duct ligation.

There was no statistical difference between any of these pairs of results.

Figure 7 (*a*) shows the mean values of glomerular filtration rate in the 17 dogs before and after haemorrhage; the closed circles are the values before duct ligation, and the open circles three to four weeks after duct ligation. Again, there is no difference in the response to a comparable haemorrhage before and after obstructive jaundice.

Discussion

Thus, the renal response to a comparable haemorrhage in dogs before and after three to four weeks of jaundice is unchanged. If jaundiced dogs really do behave as though they were hypovolaemic, then a much greater and more persistent depression of renal function would have been

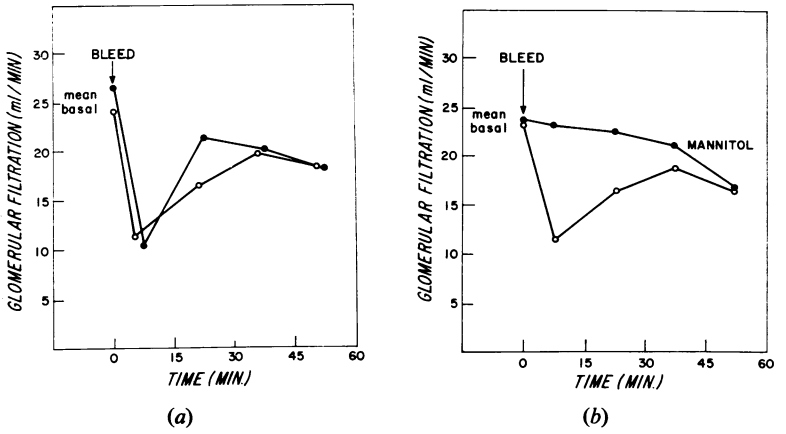


Fig. 7. (*a*) The effect of a haemorrhage (20 ml./Kg. body weight) on the mean levels of glomerular filtration rate (ml./min.) in 17 dogs before (●—●) and after 3–4 weeks of obstructive jaundice (O—O). (*b*) The effect of a haemorrhage (20 ml./Kg. body weight) on the glomerular filtration rate (ml./min.) in seven dogs with (●—●) and without (O—O) mannitol.

expected in these experiments. What then is the explanation of the discrepancy between the results of these experiments and the results obtained by previous workers (Williams *et al.*, 1960)?

The most likely explanation seems to be simply the lowered resting blood pressure of the dogs after three to four weeks of jaundice. One might expect that it would take a greater volume of blood to reduce the arterial pressure from 130 mm. down to 60 mm. of mercury, which was the situation in these dogs when they were normal, than it would to reduce the blood pressure from 113 down to 60 mm. of mercury, which was the situation in these 17 dogs when they were jaundiced.

Figure 7 (*b*) shows the results obtained in the seven jaundiced dogs who had the haemorrhage experiment repeated after a mannitol diuresis was

initiated. The open circles represent the mean values of these seven dogs when they were not given mannitol.

After the haemorrhage there is an abrupt fall in the glomerular filtration rate which climbs back towards normal values over the next hour. The closed squares represent the mean values in the same seven dogs two days later when the haemorrhage experiment was repeated following a mannitol diuresis. The expected fall in glomerular filtration rate is largely prevented.

The value of a mannitol diuresis before haemorrhage in the jaundiced dogs is obvious. The expected fall in estimated renal blood flow and glomerular filtration rate was largely prevented. Similar results have been obtained by other workers using non-jaundiced animals (Peters and Brunner, 1963).

In these experiments the action of mannitol is almost certainly renal, and not due to any expansion of the plasma volume, as the same fall in blood pressure was observed in the seven dogs with and without mannitol.

Following haemorrhage in man or experimental animals there is a period of oliguria or anuria which has been ascribed to renal vasoconstriction (Phillips *et al.*, 1946). But if an osmotic diuresis is established before a period of haemorrhage, then this oliguria or anuria is diminished or prevented—perhaps by an effect directly on the renal vasculature (Braun and Lilienfield, 1962), or perhaps by an effect on blood viscosity (Lilien *et al.*, 1963). This action of mannitol was different from that obtaining in the rat experiments already described, in which mannitol mitigated the effects of a known period of renal ischaemia.

The beneficial action of mannitol in preventing renal damage appears to be twofold:

(1) It decreases the likelihood of renal ischaemia after haemorrhage or trauma.

(2) Secondly, it decreases the renal damage caused by any renal ischaemia which actually does occur.

The present experiments on dogs lend no support to the hypothesis that obstructive jaundice affects the circulatory homeostasis. But a much more important lesson to be learnt is that the dog is a very poor experimental animal on which to base a study of the problems of obstructive jaundice met with in man, for the following reasons:

(1) When jaundiced, the dog becomes anaemic and man does not.

(2) The dog becomes hypotensive and man does not.

(3) The dog develops cholangitis unless given penicillin, whereas man rarely does so.

(4) Finally, and most important of all, the dog does not develop deep jaundice, and, as we have already seen, it is only the deeply jaundiced patients who develop post-operative renal failure.

CLINICAL INVESTIGATIONS

Introduction

The aim of these studies was to see whether operation had a different effect on renal function in jaundiced patients from that usually observed in non-jaundiced patients undergoing abdominal surgery.

Daily sequential renal function studies were made on 15 jaundiced patients before and after operation, and the results were compared with those obtained from 12 non-jaundiced patients undergoing operations of comparable magnitude (Dawson, 1965*a*). These control patients were undergoing either cholecystectomy or partial gastrectomy. These operations were chosen because the incisions used, the handling of the viscera, length of the operation, were all comparable with the usual procedures carried out in a patient with obstructive jaundice.

In a third group of seven deeply jaundiced patients, a mannitol diuresis was begun immediately before operation and maintained for 48 hours after

TABLE IV

THE PRE-OPERATIVE FINDINGS IN THE 12 CONTROL AND 15 JAUNDICED PATIENTS (MEAN VALUES)

	Control (12)	*Jaundice* (15)
Age (yrs.)	54	67*
Hb. (%)	94	87
Systolic B.P. (mm. Hg) ..	150	170*
Blood urea (mg./100 ml.) ..	27	27
Creat. clear. (ml./min.) ..	64	93*
Length optn. (min.) ..	96	86
Blood loss (ml.)	187	164

* $p = <0.05$

operation. Renal function studies were made as in the two larger groups and the results compared with those found in the 15 jaundiced patients not given mannitol.

A careful physical examination was carried out on every patient studied, with special reference to their height, weight and blood pressure. During the operation regular blood pressure recordings were made; the blood loss was estimated by weighing the swabs, and a record made of the anaesthetic drugs used, the operative findings, the operative procedure and the length of the operation.

Twenty-four-hour urine samples and between 10 and 15 ml. of blood were taken in each day during the study. This enabled the following investigations to be done:

1. The 24-hour urine volume and specific gravity.
2. The serum creatinine.
3. The urinary creatinine.
4. The 24-hour endogenous creatinine clearance.
5. The blood urea.
6. The haemoglobin and packed cell volume.
7. The urine sodium concentration.

8. A microscopic examination of a freshly spun specimen of urine each day.
9. The serum bilirubin level in a jaundiced patient.

Results

Before comparing the results of the post-operative investigations in the 15 jaundiced and the 12 control patients, it is first important to establish that these two groups of patients were indeed comparable; so that any difference in the post-operative results could only be related to the presence of obstructive jaundice.

Table IV shows the comparison of the mean values of the pre-operative investigations in these two groups of patients. There were in fact some slight but not highly significant differences: the jaundiced group was slightly older, slightly more hypertensive and the resting pre-operative endogenous creatinine clearance was also higher.

TABLE V

THE POST-OPERATIVE FINDINGS IN THE 12 CONTROL AND 15 JAUNDICED PATIENTS (MEAN VALUES)

	Control	*Jaundice*
Absolute drop creat. clear. (ml./min.) ..	23	57*
Percentage drop creat. clear. (ml./min.) ..	31	63*
Urine flow period max. drop (ml./min.) ..	.26	.33
Lowest Na^+ concentration urine (mEq./l) ..	26	19
Max. S.G. urine	1022	1021

* $p = <0.02$

But there was no difference with respect to the other investigations: the haemoglobin levels, blood urea levels, the length of the operation, the blood loss sustained at operation. Nor was there any difference between the anaesthetic drugs used or the fluctuations in blood pressure under anaesthesia.

A fall in endogenous creatinine clearance after operation was observed in all 15 jaundiced patients and in 10 out of the 12 control patients. In some of the patients it lasted 48 or even 72 hours after the operation.

Table V shows the mean values of the post-operative results in the 15 jaundiced and 12 control patients. The fall in creatinine clearance was significantly greater in the jaundiced group than in the control, whether it be expressed as an absolute drop or a percentage drop. By expressing the drop as a percentage of the resting level, the variation from patient to patient in the pre-operative values of the creatinine clearance is compensated for. There was no difference between the two groups in respect to the other post-operative investigations; especially important the urine flow over a period of maximum fall in creatinine clearance. There was no difference between the two groups, so it is unlikely that back diffusion was causing erroneous clearance values. The minimum sodium concentration achieved and the maximum specific gravity of the urine were comparable.

It is unlikely that the greater drop in the post-operative creatinine clearance, found in the jaundiced group, was in fact related to the minor pre-operative differences in age and blood pressure, because no statistical correlation could be found between the percentage post-operative fall in creatinine clearance and either age or the pre-operative blood pressure. In contrast, however, a very strong correlation was found between the pre-

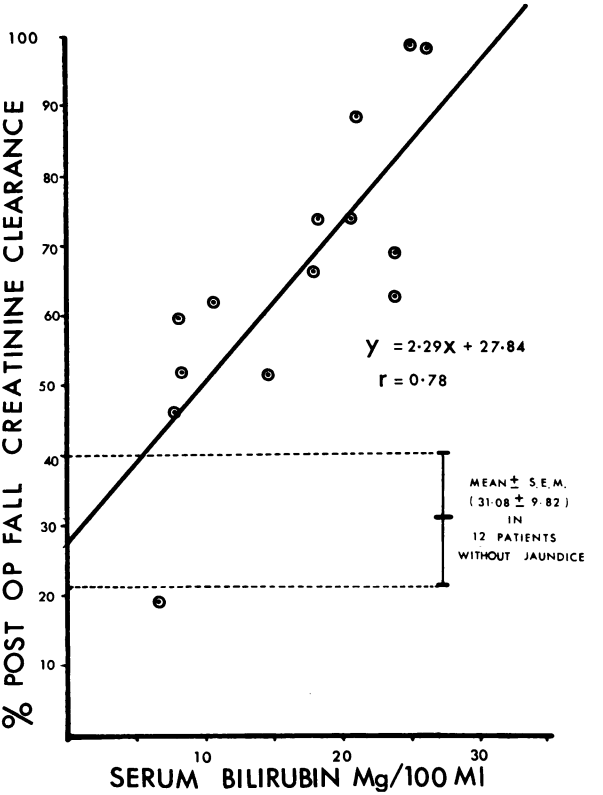


Fig. 8. The correlation between serum bilirubin level and the percentage post-operative fall in creatinine clearance.

operative serum bilirubin level (shown along the horizontal scale) and the percentage post-operative fall in creatinine clearance (shown on the vertical scale) in Figure 8.

Each of the 15 patients studied is shown by a closed circle. The deeper the jaundice, the greater the fall. The validity of this regression line is further confirmed by the fact that when it is extrapolated towards the zero point it predicts a mean fall of 28–29 per cent in creatinine clearance in a non-jaundiced patient. This value is almost identical with the mean actually observed in the 12 control patients (31.09).

To turn now to the third group of patients studied—the seven deeply jaundiced patients given mannitol. There were no pre-operative differences between these seven patients and the 15 jaundiced patients already described. But the results of the post-operative investigations showed a significant difference. The excessive post-operative fall in endogenous creatinine clearance was largely prevented. This is shown in Figure 9, which again shows the serum bilirubin level plotted against the post-operative fall in creatinine clearance. The closed circles represent the

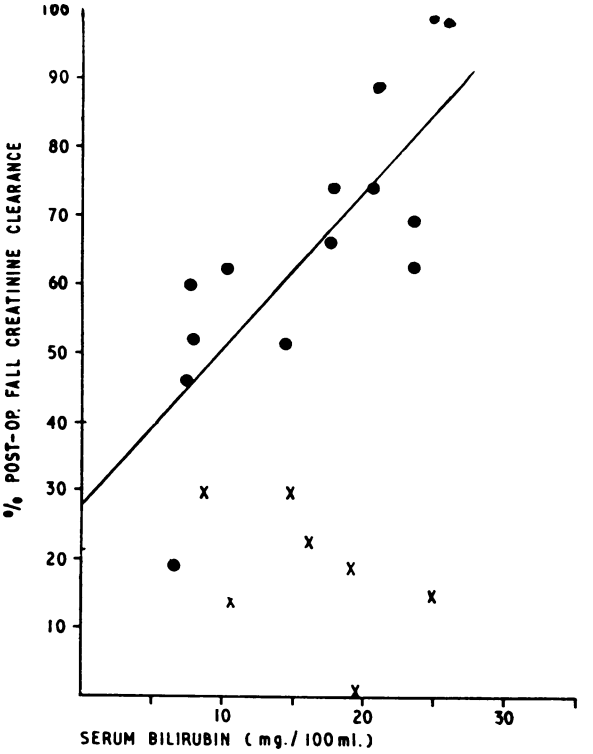


Fig. 9. The effect of a mannitol infusion in seven patients (X) in preventing the expected post-operative fall in creatinine clearance (● = 15 patients not given mannitol).

15 jaundiced patients not given mannitol. The crosses represent the seven patients who were given mannitol—the difference is easily seen. The effect of deep jaundice is prevented. The expected fall in creatinine clearance did not take place.

Discussion

The results of all these observations, therefore, strongly suggest that the presence of obstructive jaundice does modify the effect of operation on renal function.

The endogenous creatinine clearance is a good guide to the glomerular filtration rate, although it is not an exact measure (Brod and Sirota, 1948). A fall in endogenous creatinine clearance almost certainly signifies a decrease in effective renal blood flow (Selkurt *et al.*, 1949). A similar post-operative drop in creatinine clearance has recently been reported in patients undergoing aortic surgery (Luck and Irvine, 1965).

A fall in renal blood flow lasting for 24–48 hours after operation is not readily explained, but it probably results from a summation of various factors:

1. The anaesthetic agents.
2. Blood loss.
3. The traction on viscera.
4. The pain of the wound.
5. Sequestration of fluid in the operative site.
6. Unrecognized acidosis.

Why such a fall should be greater in jaundiced patients is even less readily explained. No significant alteration in blood volume has been found amongst patients with obstructive jaundice (Ellison *et al.*, 1953; Cattell and Birnstingl, 1967). Hence one returns to the hypothesis that the presence of deep jaundice somehow affects circulatory homeostasis. Although such a mechanism could not be demonstrated in the dog experiments already described, the depth of jaundice in these animals did not nearly approach the levels of icterus at which patients show a significant deviation from normal findings.

The effect of a mannitol diuresis in the seven jaundiced patients is striking. It prevented the expected fall in glomerular filtration rate and presumably the renal blood flow following operation.

Acute post-operative renal failure almost certainly follows a period of decreased renal blood flow. Hence the routine prophylactic use of mannitol in deeply jaundiced patients undergoing operation seems appropriate, as it appears to maintain the glomerular filtration rate and the renal blood flow over the critical early post-operative days.

Any patient with pre-operative serum bilirubin level of more than 15 mg./100 ml. should certainly receive a prophylactic mannitol infusion.

The regimen which has been found satisfactory is as follows:

500 ml. of a 10 per cent solution of mannitol is infused, beginning one to two hours before operation.

After the operation the urine flow should be maintained at more than 1 ml. per minute over the next 48 hours using 5 per cent mannitol; between a half and one litre per 24-hour period is usually required.

SUMMARY

1. Incidence

Obstructive jaundice increases the risk of the development of post-operative renal failure. The deeper the jaundice, the greater the risk.

2. Aetiology

Obstructive jaundice appears to predispose to post-operative renal failure in two ways:

(i) It renders the renal parenchyma much more sensitive to damage by ischaemia.

(ii) It is associated with an excessive reduction in the renal blood flow following operation. The deeper the jaundice, the greater this reduction in blood flow.

3. Prophylaxis

A mannitol diuresis has been shown to be of considerable prophylactic value in maintaining the renal blood flow and diminishing ischaemic renal damage in both jaundiced patients and jaundiced animals.

ACKNOWLEDGEMENTS

The investigations which were the basis of this lecture would not have been possible but for the help I received from many people, but especially I should like to mention all the surgeons of St. James' Hospital, Balham, and King's College Hospital, for allowing me to study their patients; Mr. J. B. Woods, Chief Technician in the Biochemistry Laboratory at St. James' Hospital for his help with the clinical investigations; Dr. George Stirling, Senior Lecturer in Morbid Anatomy at King's College Hospital Medical School, for his help with the interpretation of the histological material; and Professor J. G. Murray at King's and Professor W. V. McDermott, Jr., at Harvard University, under whose auspices the animal work was done.

Figures 6 and 7 have been produced from the *British Journal of Surgery* and Figures 8 and 9 have been produced from the *British Medical Journal*, by kind permission of the Editors.

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