Renal function in chronic obstructive jaundice: a micropuncture study in rats

M ARJORIE E. M. ALLISON, N. G. MOSS, MARY M. FRASER, J. W. DOBBIE, C. J. RYAN, A. C. KENNEDY AND L. H. BLUMGART

University Departments of Medicine and Surgery, Glasgow Royal Infirmary, Glasgow, Scotland, U.K.

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Summary

1. We have studied kidney structure and function in female Sprague-Dawley rats with chronic obstructive jaundice after bile-duct ligation and section and in age-matched sham-operated control animals.

2. High bile-duct ligation and section resulted in immediate hyperbilirubinaemia and progressive hepatomegaly with histological evidence of bile-duct proliferation and periportal inflammation and fibrosis.

3. Only 20% of the jaundiced animals developed ascites, but 42% became hypotensive and died during preparation for micropuncture.

4. In the surviving rats there was no significant change in blood pressure, whole-kidney glomerular filtration rate, single-nephron glomerular filtration rate or calculated glomerular capillary hydrostatic pressure from control animals. However, renal plasma flow was increased so that whole-kidney filtration fraction was low. These changes were largely reversed by choledochoduodenostomy.

5. Proximal tubular reabsorption in the jaundiced group was not different from control rats, although the inulin (urine/plasma) ratio was significantly reduced, indicating diminished reabsorption distal to the proximal convoluted tubule. Proximal intratubular hydrostatic pressure was significantly increased in some nephrons.

6. Electron microscopy of the glomeruli from the jaundiced animals revealed evidence of marked increase in activity of both epithelial and endothelial cells.

7. Rats who survive chronic obstructive jaundice for 3–4 weeks have changes in renal function and also structural changes suggestive of diminished glomerular permeability.

Key words: kidney, micropuncture, obstructive jaundice.

Abbreviations: \([P_a]\), arterial plasma protein concentration; \(P_g\), glomerular capillary hydrostatic pressure; \(\pi_o\), oncotic pressure; PAH, \(p\)-aminohippurate.

Introduction

Obstructive jaundice has long been known to increase the risk of acute renal failure after surgery (Clairmont & von Haberer, 1911; Ravdin, 1929; Heyd, 1931; Helwig & Schutz, 1932; Wilbur, 1934; Williams, Elliot & Zollinger, 1960; Funck-Brentano, Mery, Vantelon & Watchi, 1963; Dawson, 1965a; Sørensen, Anderson, Ørnsholt & Skjoldborg, 1971). Changes in kidney structure have been described in obstructive jaundice. Early light-microscopy studies reported degenerative changes in the proximal convoluted tubules together with the presence of pigment casts (Wilbur, 1934; Ayer, 1938). More recently, electron microscopy of the glomeruli has shown fusion of epithelial foot processes, considerable thickening of the basement membranes and black granules in the basement membrane and sub-endothelial space (Sakaguchi, Dachs, Grisham &
In patients with obstructive jaundice and in experimental animals, however, studies of kidney function have given conflicting and inconclusive results (Elsom, 1937; Popper & Schaffner, 1957; Cattell & Birnstingl, 1964; Dawson, 1965b). Some investigators have reported little or no change in renal function (Fajers, 1957; Cattell & Birnstingl, 1964; Dawson, 1968) whereas others have found sodium retention, with ascites and a fall in glomerular filtration rate and renal plasma flow (Gliedman, Carroll, Popowitz & Mullane, 1970; Maroske, Bichler, Naber, Hupé, Muller, Obrowski, Schreiber & Haas, 1971; Better & Massry, 1972).

We have used clearance, micropuncture, light- and electron-microscopy techniques to study kidney structure and single-nephron function in rats who have had obstructive jaundice for 3–4 weeks. Subtle, but consistent, changes in glomerular structure and function and in tubular function were found. There was no evidence in the rats studied that obstructive jaundice of this duration altered proximal fractional reabsorption.

Methods

Obstructive jaundice

Fifty female Sprague–Dawley rats, weighing 150–200 g (Bantin and Kingman Ltd, Grimston, Aldbrough, Hull, North Humberside, U.K.) and fed with regular rat chow (Oxoid 4IB) ad libitum were anaesthetized with ether. The abdomen was opened and the common bile duct was identified, doubly ligated and divided just distal to its formation (Lee, 1972; Wright & Braithwaite, 1962). Neither vitamin K1 (Lee, 1972) nor antibiotics (Yarger, 1976) were given to the animals.

Clearance and micropuncture studies were carried out on the 29 long-term survivors 24 ± 9 days later.

In a separate group of eight rats choledocho-duodenostomy was carried out as previously described (Ryan, Than Than & Blumgart, 1977), 13–28 days after bile-duct ligation.

Control rats

Female Sprague–Dawley rats of the same source, age and feeding as the jaundiced rats, had a laparotomy and sham bile-duct ligation carried out under ether anaesthesia. Clearance and micropuncture studies were carried out 34 ± 17 days later.

Clearance studies

The rats were deprived of food but not water overnight before study and were anaesthetized with intraperitoneal sodium pentobarbital, 50 mg/kg body weight. The rats were placed on a thermo-regulated electric blanket to maintain their central body temperature at 36° ± 0.5°C and they were prepared for micropuncture (Gottschalk & Mylle, 1956). An arterial blood sample (30 μl) was immediately obtained for measurement of baseline packed cell volume, plasma urea and protein concentration values.

Both ureters were cannulated with PE10 polyethylene tubing. Blood pressure was recorded continuously from either the carotid or femoral artery with a Statham P23Db transducer (Statham Instruments, Oxnard, CA, U.S.A.).

Sodium chloride solution (154 mmol/l; saline) was given intravenously at the rate of 0.4 ml/100 g body weight per hour, together with [3H]methoxy-inulin and p-[14C]aminohippurate (New England Nuclear Corp.). In those rats in which only intratubular pressure measurements were to be made a priming dose of 80 μCi of [3H]inulin and 4 μCi of p-[14C]aminohippurate was followed by a continuous infusion of [3H]inulin at a rate of 40 μCi h⁻¹ 100 g⁻¹ body weight and p-[14C]aminohippurate at a rate of 4 μCi/h. When proximal tubular fluid collections were to be made, this infusion was increased to 60 μCi of [3H]methoxy-inulin h⁻¹ 100 g⁻¹ body weight.

After 1 h for equilibration three consecutive timed urine collections, each lasting approximately 40 min, were made from each kidney. Blood (30 μl) was taken from the carotid or femoral artery and renal vein at approximately the midpoint of each collection for determination of packed cell volume and protein, inulin and p-aminohippurate concentrations. Clearances were determined as previously described (Allison, Lipham, Lassiter & Gottschalk, 1973). Glomerular filtration rate was calculated separately for the left and right kidneys. Renal plasma flow (RPF) and renal blood flow (RBF) were calculated for the left kidney only, from clearance (C) and extraction (E) of p-aminohippurate: RPF = C_{PAH} E_{PAH}; RBF = RPF/(1 - 0 - packed cell volume). Glomerular filtration rate, C_{PAH}, RPF and RBF have been expressed as ml min⁻¹ g⁻¹ of kidney.
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Single-nephron glomerular filtration rate and percentage reabsorption

These measurements were made in ten rats with obstructive jaundice and 11 sham-operated rats. The kidney was bathed with water-equilibrated mineral oil and timed samples of tubular fluid were obtained from various parts of the proximal convoluted tubule through sharpened siliconized glass pipettes, external tip diameter 8–12 μm, filled with water-equilibrated mineral oil. The number of loops visible on the surface of the kidney beyond the point at which the pipette had been inserted were counted by following the passage of a tiny droplet of mineral oil as it travelled down the nephron. In most instances one to nine loops were visible ‘downstream’. This method of loop identification in the proximal tubule was checked by an ‘upstream’ intratubular injection of isotonic saline coloured with FD and C green dye (Keystone Aniline and Chemical Co., Chicago, U.S.A.) via a pipette of tip diameter about 5 μm. When the position of the pipette had been defined, a long mineral oil block (four to five tubular diameters in length) was injected into the nephron. Tubular fluid was collected by suction, which was adjusted to keep the oil block in place and the tubular diameter constant if this was possible. The sample was placed under water-equilibrated mineral oil on a siliconized watch glass, its volume was measured with a micropipette and it was then transferred into liquid scintillation counting fluid (NE 260, Nuclear Enterprises, Sighthill, Edinburgh, Scotland, U.K.).

The single-nephron glomerular filtration rate was calculated as: fluid/plasma inulin ratio x tubular flow rate (nl/min), and the percentage reabsorption to the late proximal convolution was calculated as 100[1 – (1/fluid/plasma inulin ratio)].

Absolute reabsorption (nl/min) = fractional reabsorption × single-nephron glomerular filtration rate.

Hydrostatic pressure

This measurement was made in six rats with obstructive jaundice, in two of which no clearances were measured, and in 11 sham-operated control rats. The kidney was bathed with saline heated to 36° ± 1°C to allow use of an electronic servonulling device (Allison, Lipham & Gottschalk, 1972). Sharpened siliconized glass pipettes, tip diameter 3–5 μm, filled with sodium chloride solution (0.5 mol/l) were used and hydrostatic pressure in proximal tubules was measured during free flow and during stop flow after insertion of a castor oil block downstream. Glomerular capillary hydrostatic pressure (Pc) was calculated as the sum of the stop-flow pressure and the afferent onotic pressure (Allison et al., 1972).

Arterial plasma protein concentrations (Pα) were measured before, during and at the end of each experiment by an adaptation of the Lowry technique (Brenner, Falchuk, Keimowitz & Berliner, 1969) with human serum albumin used as standard. Oncotic pressure (πn) was calculated as:

\[ \pi_n = 2.1[P_\alpha] + 0.16[P_\alpha]^2 + 0.009[P_\alpha]^3 \]

[Landis & Pappenheimer (1963) equation, which has been validated for rat plasma (Allison, Wilson & Gottschalk, 1974; Arendshorst, Finn & Gottschalk, 1975)].

At the end of each experiment blood was removed for measurement of serum bilirubin concentration (Brayshaw, 1971). Urine and plasma electrolytes were measured on an IL direct-reading flame photometer (Instrumentation Laboratories, Watertown, Mass., U.S.A.). Plasma urea concentration was determined by a micro-adaptation of the method of Fawcett & Scott (1960). The results are given as mean ± SD. The significance of the differences between mean values for jaundice and control rats was assessed by Student’s t-test.

Microinjection studies

Microinjection experiments were carried out on eight rats with obstructive jaundice and in 14 non-operated control rats as previously described (Gottschalk, Morel & Mylle, 1965). The animals were infused with sodium chloride solution (20 g/l) at a rate of 5-8 ml/h and PE 50 polyethylene catheters were placed in both ureters. A known volume (0.5–3 nl) of [3H]methoxyinulin (New England Nuclear Corp.) coloured with FD and C green or nigrosin was injected slowly over 30–60 s into superficial proximal tubules, and the percentage of the measured injected volume recovered from each kidney over the following 20 min was calculated.

Microscopy studies

At the end of each experiment both kidneys and the liver from each animal were weighed. One-half of the left kidney was fixed in buffered formalin for light-microscopy. Small pieces from the cortex of the left kidney were fixed in 2% or 4% buffered glutaraldehyde for electron microscopy. Sections of the liver from the jaundiced animals were fixed in buffered formalin for light-microscopy.
Results

General characteristics

Ligation and section of the common bile duct was carried out in 50 female Sprague-Dawley rats (Fig. 1). All became jaundiced and survived for 26 ± 10 days, when they were prepared for micropuncture. Ten rats developed ascites, (volume = 0.8–23.7 ml, mean 7.7 ± 8.3 ml). Twenty-one (42%) of the rats died because of hypotension, two before the anaesthesia, the rest during preparative surgery, including nine of the ten rats with ascites.

Clearance, micropuncture or microinjection studies were carried out on the remaining 29 (58% of the jaundiced rats). Table 1 shows features of these survivors, the rats which died and the 15 sham-operated rats. The weight gain was significantly less in the jaundiced rats and their liver weight increased progressively with the duration of jaundice, so that after 5–6 weeks it was 21–26 g. The packed cell volume was lower and the plasma urea concentrations were higher in the two groups of jaundiced rats, compared with the sham-operated rats, but there was no difference in kidney weight or plasma protein concentration between the three groups.

Urine osmolality fell dramatically within 24 h of bile-duct obstruction (jaundice: before 1793 ± 431 mosmol/kg, after 542 ± 187 mosmol/kg; control: before 1823 ± 251 mosmol/kg, after 1388 ± 529 mosmol/kg) and remained low. Water intake was unchanged but sodium and protein intake fell significantly.

After killing all animals were found to have had complete ligation and section of their common bile duct and there was no evidence of recanalization.

Clearance studies

Nineteen of the 29 rats which survived had clearance observations carried out together with tubular fluid collection or measurement of intratubular hydrostatic pressure. We have chosen to use the clearance data from only those 12 rats who received both p-[14C]aminohippurate and [3H]methoxyinulin. Clearance data are given for the left kidney, there being no statistically significant difference between the right and left kidney glomerular filtration rates.

Table 2 gives the clearance data for the left kidney in the 12 rats with obstructive jaundice and in 15 sham-operated control rats. The jaundiced rats had a significantly decreased inulin (urine/plasma) ratio and increased urine flow rate, without a significant alteration in glomerular filtration rate, electrolyte excretion rate or blood pressure. Surprisingly, however, renal plasma flow, renal blood flow and CPAH were all significantly increased over control values. As a result whole-kidney filtration fraction was markedly reduced in chronic obstructive jaundice. EPAH did not differ significantly.

Micropuncture studies

Superficial single-nephron glomerular filtration rate was not significantly different in the jaundiced and control rats (Table 3) whereas calculated glomerular capillary hydrostatic pressure (Pg) was significantly higher in the jaundiced group. There was a wide range of single-nephron glomerular filtration rate values in each group, but the absolute reabsorption rate in each nephron was closely correlated with that nephron's filtration rate, that is, each nephron showed a close degree of glomerulotubular balance. Mean late proximal (fluid/plasma) ratio, calculated on a per rat basis, was not significantly different in the jaundiced and control rats (jaundiced: 1.86 ± 0.36, n = 10; control: 2.06 ± 0.34, n = 8).

Measurements of inulin (fluid/plasma) ratio were also made at different points in the proximal convoluted tubule. In Fig. 2 these have been plotted against the loop number, determined as described in the Methods section. The slope of the regression line for both control and jaundiced animals results is statistically significant, but the lines do not differ significantly from each other.

The distribution of proximal intratubular hydrostatic pressure was not markedly different in animals with obstructive jaundice (Fig. 3).
### TABLE 1. General characteristics of 36 rats with chronic bile-duct ligation compared with those of 15 sham-operated control rats

Mean values ± SD are shown. N.S., Not significant.

<table>
<thead>
<tr>
<th>Days after tie</th>
<th>Body wt. (g)</th>
<th>Liver wt. (g)</th>
<th>Kidney wt. (g)</th>
<th>Packed cell volume (%)</th>
<th>Urea (mmol/l)</th>
<th>Plasma protein (g/100 ml)</th>
<th>Serum bilirubin (μmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jaundiced rats</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Died (n = 21)</td>
<td>29±3</td>
<td>209</td>
<td>16.398</td>
<td>0.9178</td>
<td>43.0</td>
<td>7.3</td>
<td>6.49</td>
</tr>
<tr>
<td>P</td>
<td>±11</td>
<td>±35</td>
<td>±4.60</td>
<td>±0.152</td>
<td>±8.7</td>
<td>±2.2</td>
<td>±1.4</td>
</tr>
<tr>
<td>Surviving rats</td>
<td>24±1</td>
<td>202</td>
<td>13.280</td>
<td>0.8396</td>
<td>45±3</td>
<td>6.9</td>
<td>6.70</td>
</tr>
<tr>
<td>(n = 29)</td>
<td>±9</td>
<td>±34</td>
<td>±4.14</td>
<td>±0.174</td>
<td>±3±0</td>
<td>±2.2</td>
<td>±1.0</td>
</tr>
<tr>
<td>P</td>
<td>N.S.</td>
<td>&lt;0.025</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
</tr>
<tr>
<td>Control rats</td>
<td>34±5</td>
<td>238</td>
<td>7.000</td>
<td>0.8633</td>
<td>48.4</td>
<td>4.1</td>
<td>6.5</td>
</tr>
<tr>
<td>(n = 15)</td>
<td>±17</td>
<td>±35</td>
<td>±0.80</td>
<td>±0.105</td>
<td>±2±4</td>
<td>±1.0</td>
<td>±0.9</td>
</tr>
</tbody>
</table>

### TABLE 2. Clearance data (left kidney) in jaundiced rats and in sham-operated control rats

Mean values ± SD are shown. N.S., Not significant. GFR, Glomerular filtration rate; RPF, renal plasma flow; FF, filtration fraction; C, clearance; E, extraction; PAH, p-aminohippurate; RBF, renal blood flow.

<table>
<thead>
<tr>
<th></th>
<th>Urine flow rate (ml min⁻¹ g⁻¹ of kidney)</th>
<th>Indin U/P ratio</th>
<th>GFR (ml min⁻¹ g⁻¹ of kidney)</th>
<th>RPF (ml min⁻¹ g⁻¹ of kidney)</th>
<th>FF</th>
<th>C_FAN (ml min⁻¹ g⁻¹ of kidney)</th>
<th>E_FAN (ml min⁻¹ g⁻¹ of kidney)</th>
<th>RBF (ml min⁻¹ g⁻¹ of kidney)</th>
<th>Sodium excretion (μmol min⁻¹ g⁻¹ of kidney)</th>
<th>Potassium excretion (μmol max⁻¹ g⁻¹ of kidney)</th>
<th>Blood pressure (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jaundiced rats</td>
<td>2.95±0.76</td>
<td>247</td>
<td>0.639</td>
<td>4.153</td>
<td>0.17</td>
<td>3.255</td>
<td>0.755</td>
<td>7.342</td>
<td>0.0-2567</td>
<td>0.5614</td>
<td>98±3</td>
</tr>
<tr>
<td>(n = 12)</td>
<td>±1.22±0.11</td>
<td>±0.12</td>
<td>±0.174</td>
<td>±1.31</td>
<td>±0.06</td>
<td>±0.67</td>
<td>±0.08</td>
<td>±2±42</td>
<td>±0.2792</td>
<td>±2529</td>
<td>±12±6</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>N.S.</td>
<td>&lt;0.025</td>
<td>&lt;0.05</td>
<td>&lt;0.005</td>
<td>N.S.</td>
<td>&lt;0.05</td>
<td>N.S.</td>
<td>N.S.</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Control rats</td>
<td>1.99±0.77</td>
<td>344</td>
<td>0.643</td>
<td>2.935</td>
<td>0.24</td>
<td>2.086</td>
<td>0.788</td>
<td>5.474</td>
<td>0.13±05</td>
<td>0.5±10</td>
<td>102±1</td>
</tr>
<tr>
<td>(n = 15)</td>
<td>±0.77</td>
<td>±0.07</td>
<td>±0.23</td>
<td>±1.08</td>
<td>±0.03</td>
<td>±0.79</td>
<td>±0.069</td>
<td>±1.754</td>
<td>±6.149</td>
<td>±0.247</td>
<td>±12±4</td>
</tr>
</tbody>
</table>
TABLE 3. Whole-kidney and single-nephron glomerular filtration rate and calculated glomerular capillary hydrostatic pressure ($P_g$) in jaundiced and control rats

Mean values ± SD are shown. N.S., Not significant. GFR, Glomerular filtration rate.

<table>
<thead>
<tr>
<th></th>
<th>GFR $\left(\text{ml min}^{-1} \text{g}^{-1} \text{of kidney}\right)$</th>
<th>Single-nephron GFR $\left(\text{nl/min}\right)$</th>
<th>$P_g$ $\left(\text{mmHg}\right)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jaundiced rats</td>
<td>$0.697 \pm 0.17$</td>
<td>$18.8 \pm 5.5$</td>
<td>$55.1 \pm 5.0$</td>
</tr>
<tr>
<td>($n = 10$)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control rats</td>
<td>N.S.</td>
<td>N.S.</td>
<td>$&lt;0.025$</td>
</tr>
<tr>
<td>($n = 11$)</td>
<td>$0.660 \pm 0.15$</td>
<td>$19.5 \pm 6.2$</td>
<td>$49.6 \pm 4.5$</td>
</tr>
</tbody>
</table>

Fig. 2. Inulin (fluid/plasma) ratio in different loops (nos. 1–9) of the proximal convoluted tubule in control (○) and jaundiced (●−●) rats. Loop position was determined by visual observation of an injected oil droplet. Loops no. 7 and no. 8 represent the late proximal convolution, as determined by the injection of lissamine green.

Control rats: $r = 0.59$, $P < 0.01$; jaundiced rats: $r = 0.61$, $P < 0.01$.

However, a very small number of nephrons with raised hydrostatic pressure (up to 34 mmHg) were found in all jaundiced rats examined. Mean intratubular hydrostatic pressure was significantly higher in the jaundiced rats (jaundice: $16.7 \pm 2.4$ mmHg, $n = 6$; control: $12.4 \pm 1.0$ mmHg, $n = 11$, $P < 0.001$).

There was no evidence of a significant trans-tubular leak of $[^{3}H]$methoxyinulin in either group, the percentage of microinjected inulin recovered from the left kidney being $93.5 \pm 3.7\%$ ($n = 7$) in obstructive jaundice and $98.4 \pm 7.0\%$ ($n = 14$) in control rats.

Choledochoduodenostomy was carried out 13–28 days after bile-duct ligation and the rats were studied 12–28 days thereafter. Complete relief of obstructive jaundice occurred in four out of eight of the animals in which this was attempted, with a resultant fall in serum bilirubin to $6.32 \pm 2.74 \mu$mol/l and a return of liver weight to values not significantly different from control. In these rats plasma urea concentration, packed cell volume, renal plasma flow and filtration fraction were not significantly different from the values in control animals (Table 4).

In the remainder only partial relief of obstructive
jaundice was obtained, as judged by mildly elevated bilirubin concentration, a continuing elevation of blood urea, and moderate elevation of liver weight.

**Histology**

Light-microscopy of the kidneys from rats with obstructive jaundice revealed pigmented granules in glomeruli, tubules and tubular casts. The Bowman's space of many of the glomeruli contained granular debris. Mild degenerative changes with focal dilatation were seen in some of the proximal convoluted tubules.

**Electron microscopy**

Immersion fixation studies of the kidneys of rats with obstructive jaundice revealed reproducible and definite changes in the glomeruli 20–30 days after obstruction (Fig. 4 and Fig. 5). The most striking abnormality was the evidence of increased activity of both epithelial and endothelial cells, which showed increased density of the cytoplasm, closely packed organelles and a rough endoplasmic reticulum. The basement membrane appeared muddy and the three layers were not clearly delineated.

**Discussion**

Obstructive jaundice is simply produced in the rat and its effects on liver structure and function are well recognized (Cameron & Oakley, 1932; Cameron & Hasan, 1958; Sasaki, 1960; Ryan et al., 1977). The mortality rate in experimental obstructive jaundice is about 35% (Sasaki (1960) and C. J. Ryan (personal communication)). In the present study 42% of the jaundiced rats became severely hypotensive and died either before or during preparation for micropuncture. Only 20% of the rats developed ascites, a much lower incidence than reported by Bank & Aynedjian (1975) and Yarger (1976) in studies on male Sprague–Dawley rats. However, in earlier studies in rats and dogs ascites was a late and inconstant development (Gliedman et al., 1970; Mulland & Gliedman, 1970; Better & Massry, 1972). These differences may be related to variations in sodium intake, as our animals took only about 60% of their pre-operative sodium intake whereas those of Bank & Aynedjian (1975) and Yarger (1976) continued on a fixed sodium intake.

Definite, reproducible and reversible changes in renal function were detected after 3–4 weeks of total biliary tract occlusion. Whole-kidney glomerular filtration rate, single-nephron glomerular filtration rate and afferent arteriolar oncotic pressure were not significantly different in the jaundiced and control groups of rats. Two other factors determining glomerular filtration rate (i.e.

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**Table 4. Effect of complete relief of obstructive jaundice on plasma urea concentration, renal plasma flow and filtration fraction**

Mean values ± SD are shown. N.S., Not significant.

<table>
<thead>
<tr>
<th></th>
<th>Plasma urea (mmol/l)</th>
<th>Renal plasma flow (ml min⁻¹ g⁻¹ of kidney)</th>
<th>Filtration fraction</th>
</tr>
</thead>
</table>
| Choledochoduodenostomy  
(n = 4)                   | 4-4                  | 3-59 ± 0-5                                 | 0-22 ± 0-02         |
| Control rats          
(n = 15)                 | 4-1 ± 1-0            | 2-94 ± 1-1                                 | 0-24 ± 0-03         |
| Jaundiced rats        
(n = 12)                | 7-0 ± 2-8            | 4-15 ± 1-31                                | 0-17 ± 0-06         |

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![Fig. 3. Distribution of proximal intratubular free-flow hydrostatic pressure (mmHg) in six rats with obstructive jaundice (stippled blocks) and 11 age-matched sham-operated control rats (open blocks).](image)
FIG. 4. Electron micrograph (original x 17 500) of glomerulus from sham-operated control rat. The three layers of the basement membrane are clearly delineated and the epithelial and endothelial cells appear quite normal with no evidence of increased cytoplasmic activity. The normal fenestrated endothelial configuration is clearly visible, as are the epithelial foot processes.

$p_s$ and proximal intratubular hydrostatic pressure), although significantly different in the two groups, cancel each other out. However, there is an increase in whole-kidney renal plasma flow and hence renal blood flow, calculated from the clearance and extraction of p-aminohippurate in the jaundiced group. As a result whole-kidney filtration was significantly reduced in obstructive jaundice. In previous studies there has been a fall in total renal plasma flow (Gliedman et al., 1970; Bank & Aynedjian, 1975; Yarger, 1976) with evidence of redistribution of flow from cortex to inner medulla (Yarger, 1976).

However, there are two reasons why we believe
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FIG. 5. Electron micrograph (original × 17,500) of a glomerulus from a rat with obstructive jaundice. There is an increase in activity of both epithelial and endothelial cells, with marked endothelial cell swelling. The basement membrane appears muddy and the three layers are not clearly delineated.

that there was a rise in renal plasma flow in our jaundiced rats. First, the increase in renal plasma flow disappeared on successful reversal of the obstructive jaundice by choledochoduodenostomy. Secondly, calculation of the renal plasma flow by the clearance and extraction of inulin, rather than $p$-aminohippurate, also showed renal plasma flow to be significantly increased in obstructive jaundice. Inulin is excreted solely by a process of glomerular ultrafiltration (Gutman, Gottschalk & Lassiter, 1965) and there was no evidence of increased transtubular permeability to inulin in the jaundiced rats. The structural changes we observed in the glomeruli were very similar to those reported by Sakaguchi et al. (1965) and Arhelger et al. (1970). It is interesting that similar
changes have recently been reported by others in the early stages of acute renal failure from the intrarenal infusion of noradrenaline (Cox, Baehler, Sharma, O’Dorisio, Osgood, Stein & Ferris, 1974; Stein & Sorkin, 1976), angiotensin (Hornych, Beaufils & Richet, 1972) or uranyl nitrate (Stein, Gottschalk, Osgood & Ferris, 1975). However, others have been unable to confirm these findings (Blantz, 1975). It is possible, however, that the fall in filtration fraction which we observed might reflect a decrease in glomerular permeability in obstructive jaundice.

In contrast to two recent kidney micropuncture studies (Bank & Aynedjian, 1975; Yarger, 1976), we found no significant change in fractional or absolute reabsorptive rate in the proximal convoluted tubule in the jaundiced rats. However, none of our animals had ascites whereas this was a prominent feature in the previous studies.

Although there was no change in proximal tubular reabsorption there must have been a reduced reabsorption at more distal sites as the jaundiced rats had a significantly raised urine flow rate and reduction in insulin (urine/plasma) ratio. In fact urine osmolality fell significantly within 24 h of bile-duct obstruction, despite no increase in water intake in comparison with control rats, and this could be due to a decreased concentrating ability. A marked fall in urinary concentrating ability in dogs with chronic obstructive jaundice was described by Better & Massry (1972) and ascribed to a fall in sodium content of the inner medulla and a fall in protein consumption. Unconjugated bilirubin was later shown to be a cause of the fall in urinary concentrating ability in the Gunn strain of rat.

Near half our jaundiced rats died before precise renal function studies could be made. Our observations of subtle but consistent changes in glomerular structure and function and in tubular function apply, therefore, only to the hardy survivors. The cause of these changes and the reason for the high mortality rate remains unknown.

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Renal function in obstructive jaundice


