

## **Intrarenal distribution of plasma flow in cirrhosis as measured by transit renography: relationship with plasma renin activity, and sodium and water excretion**

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### **Summary**

1. The intrarenal distribution of plasma flow was determined with a technique based on the analysis of the transit time of sodium *o*-[<sup>131</sup>I]-iodohippurate through the kidney in 43 patients with cirrhosis with near-normal total renal perfusion.

2. Twenty-five of the patients had an abnormal pattern of transit times, suggesting a redistribution of plasma flow from outer cortical to juxtamedullary nephrons.

3. Plasma renin activity ranged from below normal to six times normal and high values were found only in patients showing an abnormal pattern of transit times. The latter was also found to be related to sodium retention and a reduced renal capacity to excrete free water.

**Key words:** cirrhosis, plasma renin activity, renal haemodynamics, renography, sodium, water.

### **Introduction**

A number of changes in the renal circulation have been described in cirrhosis. Total plasma flow may occasionally be increased, even to values twice that found in normal subjects (Epstein, Lesser & Berger, 1950), but, more frequently and particularly with advanced disease, an intrarenal vasoconstriction is found (Epstein, Berk, Hollenberg, Adams, Chalmers,

Abrams & Merrill, 1970). Even when total perfusion is normal there may be a redistribution of plasma or blood flow away from the outer cortical to juxtamedullary nephrons, but the validity of the techniques previously used, such as extraction of *p*-aminohippurate (Schroeder, Shear, Sancetta & Gabuzda, 1967) and inert gas washout (Kew, Brunt, Varma, Hourigan, Williams & Sherlock, 1971), have been questioned (Nissen, 1968; Britton, Brown & Bluhm, 1971; Stein, Boonjarern, Wilson & Ferris, 1973). Such a change in intrarenal haemodynamics, however, could be of importance in the pathogenesis of sodium retention; it has been suggested that, because of their shorter length, the outer cortical nephrons might be relative 'salt losers' compared with the longer 'salt-retaining' juxtamedullary nephrons (Goodyer & Jaeger, 1955). Furthermore, renin is secreted chiefly by the afferent arterioles of the outer cortical nephrons (Cook & Pickering, 1958) and studies in laboratory animals have shown that a redistribution of blood flow from outer cortical to juxtamedullary nephrons is associated with an increased renin secretion (Abe, Okahara, Kishimoto, Yamamoto & Ueda, 1973; Kishimoto, Maekawa, Abe & Yamamoto, 1973). This could therefore be the explanation for the high values of plasma renin that have sometimes been observed in patients with cirrhosis in whom total renal plasma flow is not reduced (Schroeder, Eich, Smulyan, Gould & Gabuzda, 1970). In this paper we report measurements of intrarenal plasma flow distribution with a non-invasive technique based on

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an analysis of the transit time of sodium *o*-[<sup>131</sup>I]-iodohippurate through the kidney (Britton & Brown, 1971). The relationship of these measurements to both plasma renin activity and sodium excretion was also investigated. We have included only patients with near-normal total perfusion, determined by clearance of inulin and *p*-aminohippurate, since, when these are low, an elevated plasma renin and sodium retention are almost invariable (Schroeder *et al.*, 1970; Arroyo & Rodes, 1975).

### Patients and methods

All 43 patients had histologically proven cirrhosis, which was due to alcohol in 26, active chronic hepatitis in five, primary biliary cirrhosis in four, and was cryptogenic in eight. Thirty-four were male, nine were female, and their ages ranged from 33 to 68 years. At the time of investigation none of the patients had encephalopathy, a history of recent haemorrhage or was receiving either diuretics or corticosteroids, but 28 had ascites. The patients received a sodium intake of 40–50 mmol/day for 5 days. On the fifth day, after an overnight fast, an oral water load of 20 ml/kg body weight was given over 1 h. This was followed by intravenous infusions of inulin and *p*-aminohippurate, given initially as loading doses and followed by constant infusion. The amounts given were calculated to give plasma concentrations of 20–30 and 2–3 mg/100 ml respectively. After allowing 30 min for equilibration, three clearance periods of 30 min were undertaken, with plasma taken for osmolality, inulin and *p*-aminohippurate determinations at the mid-point of each clearance period, and urine obtained for the same estimations at the end of each period by voluntary voiding. Inulin and *p*-aminohippurate were determined by standard techniques (Varley, 1967) and the values given for the clearances were the mean of three periods corrected to a body surface area of 1.73 m<sup>2</sup> (for patients with ascites the surface area was determined later after successful diuretic therapy). Osmolalities were determined by depression of freezing point and the free water clearance was the difference between urine flow rate and osmolar clearance (Smith, 1956) for the period of maximal diuresis. It was expressed as a percentage of the inulin clearance (fractional free water clearance).

### Plasma renin determinations

Before the water load was given, blood samples were taken from the patient, who had been supine for at least 60 min, disodium EDTA being used as anticoagulant. Plasma renin activity was estimated by radioimmunoassay for angiotensin I, the latter being generated by incubating 1 ml of plasma at 37°C for 3 h with BAL, 8-hydroxyquinolone and Tris-HCl buffer. The pH of 6.6 was stable throughout. Recovery of added angiotensin I was quantitative, indicating complete inhibition of angiotensinases and converting enzymes. The generated angiotensin I was estimated by use of a specific antibody (supplied by Dr S. Lader, Wellcome Reagents, Beckenham, Kent, U.K.) and the plasma renin activity was expressed as the angiotensin I generation rate in nmol h<sup>-1</sup> l<sup>-1</sup>. Plasma renin substrate was estimated by incubating 0.5 ml of plasma with 1 munit (Goldblatt) of human renin (MRC Batch no. 68-356) in the presence of angiotensinase inhibitors at pH 6.6 and 37°C for 3 h. This was sufficient to convert all substrate into angiotensin I and aliquots of the incubation mixture were assayed as above for angiotensin I. Results are expressed as μmol of angiotensin I/l of plasma generated by the action of the excess renin.

For healthy control subjects under identical study conditions, including sodium intake and posture, values for plasma renin activity were found to range from 0.92 to 2.96 nmol h<sup>-1</sup> l<sup>-1</sup> (mean value 1.82 ± SD 0.57, *n* = 20). The corresponding range for the substrate was 0.57–0.94 μmol/l (mean value 0.78 ± SD 0.10, *n* = 13).

### Renography technique and analysis

Immediately after the clearance studies, renography was performed with the patient seated and a scintillation detector placed posteriorly over each kidney. The radioactivity recorded is dependent on that present in the kidney and in the non-renal tissue in the field of view of the detector. An estimate of the latter ('blood-background') was obtained from a third counter placed anteriorly over the right infraclavicular region. This detector was also used to determine the plasma disappearance curve for the sodium *o*-[<sup>131</sup>I]iodohippurate (Hippuran). An intravenous bolus of 10 μCi of <sup>131</sup>I-labelled

human albumin was first given to determine the ratio of radioactivity counts between each kidney and the infraclavicular region so that a blood-background subtraction from the kidney curves could be made throughout the renogram, the latter being performed after 100  $\mu$ Ci of sodium *o*-[ $^{131}$ I]iodohippurate also given intravenously. Methods for the mathematical analysis of the curves obtained, from which the transit time of hippuran is determined, are given in detail elsewhere (Britton & Brown, 1971; Britton, Brown, Cruz, Chang, Ralphs & Myers, 1976). In principle this is derived from the uptake and removal functions of iodohippurate by the kidney by a process called 'deconvolution'. The uptake component is equivalent to the integral of the plasma disappearance curve since the kidney is the only source of iodohippurate removal, and the removal component the difference between uptake component and kidney content curve, the latter being the renogram with blood-background subtracted. Two independent methods were used for performing the deconvolution. The first, after Bradley, Nickel & Leifer (1952), uses an algorithm, which extracts the contribution from each discrete transit time in ascending order. The second carries out a least-squares fit of a given set of transit times to the iodohippurate output curve, which is the differential of the removal component, an IBM subroutine (DAPFS) being used. These two methods are subject to different errors and results were accepted only when the difference between them was less than 10%. The analysis was based on the mean of the two values from the kidney from which the highest radioactivity counts were recorded. Using this technique, Britton & Brown (1971) have shown that the frequency distribution of tracer transit times through the kidney is bimodal. Normally the most rapid transit mode has a peak time of about 2½ min and the second of 5 min. In control subjects on a sodium intake of 40–50 mmol/day we have found that 54–90% of total radioactivity is present in the first mode, which is similar to the 50–86% reported by Britton & Brown for a slightly lower sodium intake of 20 mmol/day. The first mode most probably represents transit of the fraction of iodohippurate flowing in tubular fluid through the shorter outer cortical nephrons and the delayed one the transit of iodohippurate through the longer juxtamedullary nephrons. Since the

secretion of iodohippurate into a nephron is proportional to its plasma flow, the area of each mode of the frequency distribution curve for transit times will be proportional to the plasma flow to each nephron population. This interpretation has been confirmed by comparing the results of transit renography in rabbits with the microsphere technique, a more direct method for measuring intrarenal haemodynamics (Wilkinson, Bernardi, Britton, Brown, Pearce, Jenner & Williams, 1976a).

In the presentation of the results the percentage of total radioactivity present in the first transit mode, i.e. percentage flow to outer cortical nephrons, is given. This figure was also used to calculate effective plasma flow to the outer cortical nephrons from the *p*-aminohippurate clearance.

Results are shown  $\pm$  SD where appropriate.

## Results

A continuous spectrum of percentage radioactivity in the first of the two modes was found (Fig. 1), but the patients were divided into two

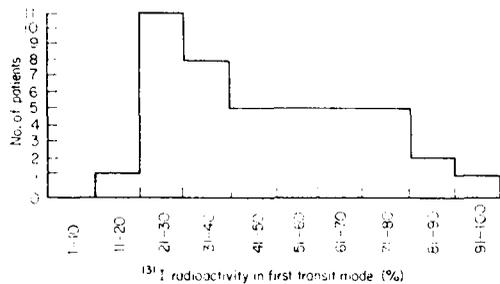


FIG. 1. Histogram of the percentage total radioactivity in the first of the two transit modes of sodium *o*-[ $^{131}$ I]iodohippurate.

groups: (a) 18 patients with > 50% radioactivity in the first mode as was found in normal subjects (Fig. 2a) and (b) 25 patients in whom the pattern of transit times was reversed, with a reduced radioactivity of between 18 and 47% to the first mode (Fig. 2b). Total renal perfusion, as assessed from clearances of inulin (80–228 ml/min), and *p*-aminohippurate (322–1115 ml/min), were similar in the two groups and each group included patients with and without ascites (Fig. 3).

Plasma renin activity ranged from 0.05 to

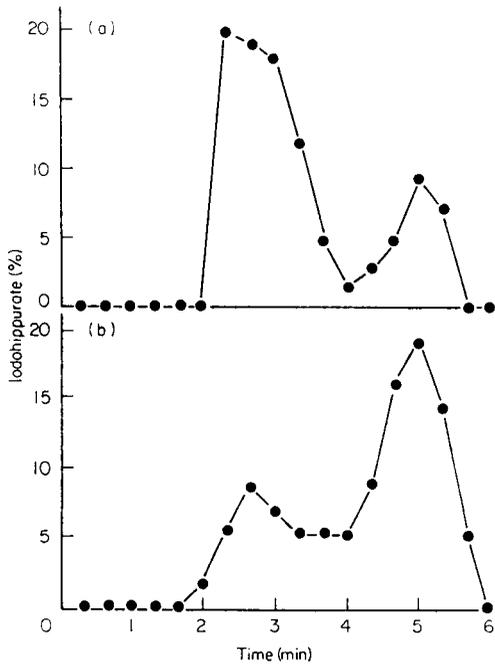


FIG. 2. Frequency distribution curves of transit times of sodium *o*-[<sup>131</sup>I]iodohippurate (Hippuran) through the kidney. (a) Normal pattern with >50% total radioactivity in the first mode. Sodium excretion, 84 mmol/24 h; plasma renin activity, 0.38 nmol h<sup>-1</sup> l<sup>-1</sup>. (b) Redistribution pattern with <50% total radioactivity in the first mode. Sodium excretion, 5 mmol/24 h; plasma renin activity, 3.17 nmol h<sup>-1</sup> l<sup>-1</sup>.

17.92 nmol h<sup>-1</sup> l<sup>-1</sup>. In all cases with a normal transit analysis, it was either normal or reduced; the mean value (0.65 ± 0.53 nmol h<sup>-1</sup> l<sup>-1</sup>) was significantly lower than found in control subjects (*P* < 0.001). Renin substrate concentrations in this group (0.89 ± 0.22 μmol/l) were comparable with control values. An elevated plasma renin activity was found in 10 patients (mean value 7.45 ± 4.71 nmol h<sup>-1</sup> l<sup>-1</sup>), and in each instance was associated with reduced radioactivity in the first transit mode (33 ± 8%) (Fig. 3). These patients had a reduced renin substrate concentration (0.59 ± 0.33 μmol/l). There were also 15 patients with an abnormal pattern of transits (32 ± 8% of total radioactivity in the first mode) in whom plasma renin activity was not increased (mean value 1.4 ± 0.86 nmol h<sup>-1</sup> l<sup>-1</sup>) although these values were significantly higher (*P* < 0.005) than in the patients with a normal transit analysis. Values for renin substrate in this group were higher (0.66 ± 0.21 μmol/l) than in the patients with an elevated plasma renin activity, although the difference was not statistically significant.

Overall there was a statistically significant inverse correlation between effective plasma flow to the outer cortical nephrons and log plasma renin activity (*r* = 0.58, *P* < 0.001) (Fig. 4).

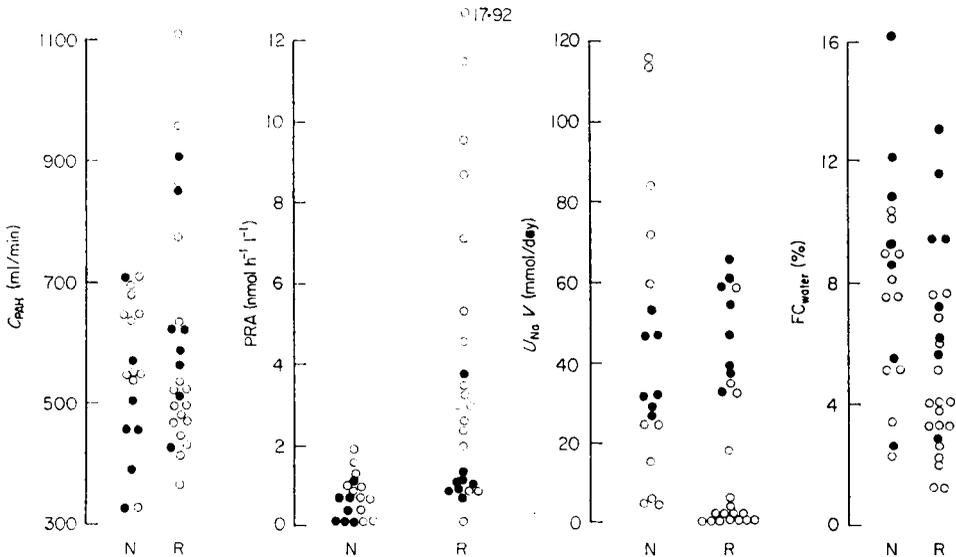


FIG. 3. Comparison of *p*-aminohippurate clearance (*C*<sub>PAH</sub>), plasma renin activity (PRA), sodium excretion (*U*<sub>Na</sub> *V*), and fractional free water clearance (*FC*<sub>water</sub>) in patients in whom the frequency distribution curves of transit times of sodium *o*-[<sup>131</sup>I]iodohippurate were normal (N) or showed a redistribution pattern (R). ● = No ascites; ○ = ascites.

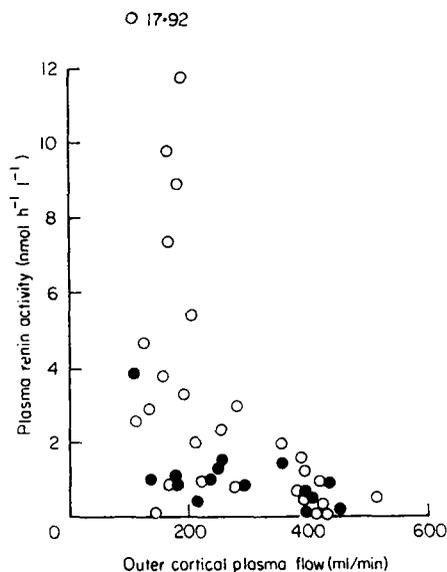


FIG. 4. Relation between effective plasma flow to outer cortical nephrons and plasma renin activity. ● = No ascites; ○ = ascites.

Changes in plasma renin activity also shared a significant inverse relationship with plasma sodium concentrations ( $r = -0.64$ ,  $P < 0.001$ ), which ranged from 122 to 142 mmol/l, but plasma sodium was normal ( $\geq 135$  mmol/l) in four of the 10 patients with a raised plasma renin activity. There was no relationship with values for plasma potassium (range 2.9–3.7 mmol/l).

#### Relation of transit times to sodium and water excretion

On the day of investigation, in spite of a constant sodium intake of 40–50 mmol, the renal sodium excretion showed a wide range of values from 1 to 114 mmol. The patients with a positive balance were accumulating ascites whereas those in whom this was negative were undergoing a spontaneous loss of ascites. Sodium excretion was unrelated to the clearances of inulin and *p*-aminohippurate ( $r = 0.04$ ,  $r = 0.05$  respectively).

In the patients with an abnormal pattern of iodohippurate transit times the renal sodium excretion was significantly lower than for those in whom this was normal ( $22 \pm 24$  mmol/24 h,  $44 \pm 34$  mmol/24 h respectively;  $P < 0.025$ ), but a number of patients with normal sodium

excretion had an abnormal transit analysis (Fig. 3).

Fractional free water clearance, values for which ranged from 1.2 to 16.1%, was also significantly lower in patients with an abnormal pattern of iodohippurate transits,  $5.3 \pm 3.3\%$ , as compared with  $7.9 \pm 3.5\%$  for patients with a normal pattern ( $P < 0.025$ ).

#### Discussion

The reversal of the normal pattern of transit times through the kidney, even when total perfusion was little affected, suggests that plasma flow is redirected from outer cortical to juxtamedullary nephrons. A raised plasma renin activity was found only in patients who showed this redistribution. Renin is secreted by the afferent arterioles of the outer cortical nephrons and a reduced plasma flow to this compartment might lead to a reduction in pressure within the afferent arterioles, the proposed location of the baroreceptors that mediate renin release, and result in increased renin secretion. An alternative possibility is that the outer cortical ischaemia is secondary to local formation of angiotensin II as a result of renin release (Itskovitz & McGiff, 1974). This seems unlikely, however, since a number of patients (15 of 25) with evidence for a reduced flow to the outer cortical nephrons had normal or even reduced values for plasma renin activity.

Both this latter finding and the significantly reduced values for plasma renin activity in patients with an apparently normal intrarenal distribution of plasma flow require explanation. Plasma renin activity is a function of the concentrations of both renin and its substrate. In liver disease the latter may be reduced because of impaired hepatic synthesis (Schroeder *et al.*, 1970). However, in the present series, substrate deficiency could not account for either of these findings. It is therefore possible that renin secretion was being suppressed. Total exchangeable sodium and extracellular fluid volume (Roberti, Traverso, Vesin, Viguie & Blanchon, 1966), plasma volume (Liebermann & Reynolds, 1967) and blood volume (Traverso, Raynaud, Blanchon, Roberti, Vesin & Viguie, 1966) are all usually increased in cirrhosis, whether or not ascites is present, and could be responsible for this.

In addition to being related to a change in

intrarenal plasma flow distribution, plasma renin activity was also inversely related to plasma sodium concentration. The mechanism whereby hyponatraemia increases renin secretion is probably related to sodium delivery to the macula densa of the distal tubule (Davis & Freeman, 1976). Patients with cirrhosis and hyponatraemia may have hypertrophy and hyperplasia of the juxtaglomerular apparatus (Reeves, Lowenstein & Sommers, 1963).

Whether a redistribution of plasma or blood flow to the longer juxtamedullary nephrons is ever a cause of sodium retention has been a subject of much debate (Horster & Thurau, 1968; Stein, Ferris, Huprich, Smith & Osgood, 1971; Blanz, Wallin, Rector & Seldin, 1972; Bruns, Alexander, Riley & Levinsky, 1974). Although the present findings in general support the hypothesis that a redistribution of plasma flow is important in this respect, in the same group of patients we have found a much closer relationship between aldosterone concentrations and sodium excretion (unpublished work). The relation between intrarenal distribution of plasma flow and sodium excretion may therefore be fortuitous, the reduced flow to the outer cortical nephrons stimulating renin secretion, which in turn is likely to increase the secretion of aldosterone.

The reduced capacity of the kidney to excrete free water when plasma flow to the juxtamedullary nephrons appeared to be increased, was also of interest. The latter might result in an increased hydrostatic pressure in the capillaries around the ascending limb of the loop of Henle of these nephrons, the effect of which might be to reduce sodium chloride reabsorption and therefore free water generation. Other factors known to modify free water clearance in cirrhosis include the amount of filtered solute (Shear, Hall & Gabuzda, 1965) and the degree of proximal tubular reabsorption of sodium (Schedl & Bartter, 1960).

The stimulus to a redistribution of plasma flow within the kidney must remain conjectural. One possibility is endotoxaemia. Endotoxins are normally absorbed from the gut into the portal circulation and removed by the Kupffer cells of the liver (Ravin, Rowley, Jenkins & Fine, 1960), and with the development of a collateral circulation might escape into the systemic circulation. Large quantities of endotoxin, as detected by the *Limulus* lysate assay,

have been implicated as a cause of renal failure in patients with cirrhosis (Wilkinson, Moodie, Stamatakis, Kakkar & Williams, 1976b), but there is indirect evidence from the antibody titres to endotoxins present in the peripheral blood that a low-grade endotoxaemia may occur when renal failure is not present (Bjørneboe, Prytz & Ørskov, 1972; Triger, Alp & Wright, 1972). Small amounts of endotoxin, at least in rats, may cause a redistribution of blood flow from outer cortical to juxtamedullary nephrons (Grün, Liehr, Thiel & Rasenack, 1976).

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#### References

- ABE, Y., OKAHARA, T., KISHIMOTO, T., YAMAMOTO, K. & UEDA, J. (1973) Relationship between intrarenal distribution of blood flow and renin secretion. *American Journal of Physiology*, **225**, 319–323.
- ARROYO, V. & RODES, J. (1975) A rational approach to the treatment of ascites. *Postgraduate Medical Journal*, **51**, 558–562.
- BJØRNEBOE, M., PRYTZ, H. & ØRSKOV, F. (1972) Antibodies to intestinal microbes in serum of patients with cirrhosis of the liver. *Lancet*, **i**, 58–60.
- BLANZ, R.C., WALLIN, J.D., RECTOR, F.C. & SELDIN, D.W. (1972) Effect of variation in dietary NaCl intake on intrarenal distribution of plasma flow in the rat. *Journal of Clinical Investigation*, **51**, 2790–2795.
- BRADLEY, S.E., NICKEL, J.F. & LEIFER, E. (1952) The distribution of nephron function in man. *Transactions of the Association of American Physicians*, **65**, 147–158.
- BRITTON, K.E. & BROWN, N.J.G. (1971) *Clinical Renography*. Lloyd-Luke, London.
- BRITTON, K.E., BROWN, N.J.G. & BLUHM, M.M. (1971) Xenon washout. *Lancet*, **ii**, 822.
- BRITTON, K.E., BROWN, N.J.G., CRUZ, F., CHANG, H.C., RALPHS, D. & MYERS, M. (1976) Deconvolution analysis of dynamic curves. In: *Information Processing in Scintigraphy: Proceedings of IVth International Conference*, pp. 244–260. Ed. Raynaud, C. & Todd-Pokropek, A. Orsay, Paris.
- BRUNS, F.J., ALEXANDER, E.A., RILEY, A.L. & LEVINSKY, N.G. (1974) Superficial and juxtamedullary nephron function during saline loading in the dog. *Journal of Clinical Investigation*, **53**, 971–979.
- COOK, W. & PICKERING, G. (1958) Location of renin within kidney. *Journal of Physiology (London)*, **143**, 78p–79p.
- DAVIS, J.O. & FREEMAN, R.H. (1976) Mechanisms regulating renin release. *Physiological Reviews*, **56**, 1–56.
- EPSTEIN, M., BERK, D.P., HOLLENBERG, N.K., ADAMS, D.F., CHALMERS, T.C., ABRAMS, H.L. & MERRILL,

- J.P. (1970) Renal failure in the patient with cirrhosis: The role of active vasoconstriction. *American Journal of Medicine*, **49**, 175-185.
- EPSTEIN, F.H., LESSER, G.T. & BERGER, E.Y. (1950) Renal function in decompensated cirrhosis of the liver. *Proceedings of the Society for Experimental Biology and Medicine*, **75**, 822-824.
- GOODYER, A.V.N. & JAEGER, C.A. (1955) Renal response to non-shocking haemorrhage: Role of autonomic nervous system and the renal circulation. *American Journal of Physiology*, **180**, 69-74.
- GRÜN, M., LIEHR, H., THIEL, H. & RASENACK, U. (1976) Effekt einer Endotoxämie auf die renale und intrarenale Hamodynamik bei Ratten mit und ohne portokavale Anastomose. *Zeitschrift für Gastroenterologie*, **14**, 285-297.
- HORSTER, M. & THURAU, K. (1968) Micropuncture studies on the filtration rate of single superficial and juxtamedullary glomeruli in the rat kidney. *Pflügers Archiv für die Gesamte Physiologie*, **301**, 162-181.
- ITSKOVITZ, H.D. & MCGIFF, J.C. (1974) Hormonal regulation of the renal circulation. *Circulation Research*, **34-35** (Suppl. I), 1-65-1-73.
- KEW, M.C., BRUNT, P.W., VARMA, R.R., HOURIGAN, K.G., WILLIAMS, H.S. & SHERLOCK, S. (1971) Renal and intrarenal blood flow in cirrhosis of the liver. *Lancet*, **ii**, 504-510.
- KISHIMOTO, T., MAEKAWA, M., ABE, Y. & YAMAMOTO, K. (1973) Intrarenal distribution of blood flow and renin release during renal venous pressure elevation. *Kidney International*, **4**, 259-266.
- LIEBERMANN, F.L. & REYNOLDS, T.B. (1967) Plasma volume in cirrhosis of the liver: its relation to portal hypertension, ascites and renal failure. *Journal of Clinical Investigation*, **46**, 1297-1308.
- NISSEN, O.I. (1968) The extraction fraction of *p*-aminohippurate in the superficial and deep venous drainage area of the cat kidney. *Acta Physiologica Scandinavica*, **73**, 329-338.
- RAVIN, H., ROWLEY, D., JENKINS, C. & FINE, J. (1960) On the absorption of bacterial endotoxin from the gastrointestinal tract of the normal and shocked animal. *Journal of Experimental Medicine*, **112**, 783-792.
- REEVES, G., LOWENSTEIN, L.M. & SOMMERS, S.C. (1963) The macula densa and juxtaglomerular body in cirrhosis. *Archives of Internal Medicine*, **112**, 122-129.
- ROBERTI, A., TRAVERSO, H., VESIN, P., VIGUIE, R. & BLANCHON, P. (1966) Etude du Na et du K échangeables et des liquides extracellulaires dans les cirrhoses éthyliques. *Semaine des Hôpitaux de Paris*, **42**, 1714-1718.
- SCHEDL, H.P. & BARTTER, F.C. (1960) An explanation for and experimental correction of the abnormal water diuresis in cirrhosis. *Journal of Clinical Investigation*, **39**, 248-261.
- SCHROEDER, E.T., EICH, R.H., SMULYAN, H., GOULD, A.B. & GABUZDA, G.J. (1970) Plasma renin level in hepatic cirrhosis. *American Journal of Medicine*, **49**, 186-191.
- SCHROEDER, E.T., SHEAR, L., SANCETTA, S.M. & GABUZDA, G.J. (1967) Renal failure in patients with cirrhosis of the liver. III. Evaluation of intrarenal blood flow by *para*-aminohippurate extraction and response to angiotensin. *American Journal of Medicine*, **43**, 887-896.
- SHEAR, L., HALL, P.W. & GABUZDA, G.J. (1965) Renal failure in patients with cirrhosis of the liver. II. Factors influencing maximal urinary flow rate. *American Journal of Medicine*, **39**, 199-209.
- SMITH, H.W. (1956) *Principles of Renal Physiology*. Oxford University Press.
- STEIN, J.H., BOONJAREERN, S., WILSON, C.B. & FERRIS, T.F. (1973) Alterations in intrarenal blood flow distribution. Methods of measurement and relationship to sodium balance. *Circulation Research*, **32-33** (Suppl. I), 1-61-1-71.
- STEIN, J.H., FERRIS, T.F., HUPRICH, J.E., SMITH, T.C. & OSGOOD, R.W. (1971) Effect of renal vasodilatation on the distribution of cortical blood flow in the kidney of the dog. *Journal of Clinical Investigation*, **50**, 1429-1438.
- TRAVERSO, H.D., RAYNAUD, C.L., BLANCHON, P., ROBERTI, A., VESIN, P. & VIGUIE, R. (1966) Etude des clearances de l'inuline et du PAH, du débit cardiaque, du Na et du K échangeables et des liquides extracellulaires au cours de l'évolution de la cirrhose du foie. *Revue Internationale d'Hépatologie*, **16**, 1377-1398.
- TRIGER, D.R., ALP, M.H. & WRIGHT, R. (1972) Bacterial and dietary antibodies in liver disease. *Lancet*, **i**, 60-63.
- VARLEY, H. (1967) *Practical Clinical Biochemistry*, 4th edn. Heinemann, London.
- WILKINSON, S.P., BERNARDI, M., BRITTON, K.E., BROWN, N.J.G., PEARCE, P.C., JENNER, R. & WILLIAMS, R. (1976a) Validation of 'transit renography' as a method for determining the intrarenal distribution of blood flow. *Clinical Science and Molecular Medicine*, **50**, 13P.
- WILKINSON, S.P., MOODIE, H., STAMATAKIS, J.D., KAKKAR, V.V. & WILLIAMS, R. (1976b) Endotoxaemia and renal failure in cirrhosis and obstructive jaundice. *British Medical Journal*, **ii**, 1415-1418.