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THE EFFECTS OF CHANGES IN HAEMATOCRIT ON RENAL FUNCTION

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SUMMARY

1. Acute changes in total body haematocrit were produced in anaesthetized dogs by the rapid infusion of packed red cells, dextran solution or hypertonic mannitol. A reduction of haematocrit resulted in a decrease in filtration fraction, and a rise of haematocrit in an increase in filtration fraction. A direct relationship between water reabsorption (relative to filtered load) and packed cell volume (P.C.V.) was also observed.

2. It is suggested that the changes in filtration fraction accompanying changes in haematocrit are mediated largely by a passive alteration of efferent arteriolar resistance resulting from modifications of blood viscosity.

INTRODUCTION

The regulation of renal blood flow has been the subject of intensive investigation for the past three decades. The resistance to blood flow through the kidney is offered almost entirely by the afferent and efferent arterioles, across which the main pressure drop occurs, and the focus of attention in numerous studies has been the relative importance of these vessels in the control of blood flow and glomerular filtration. The current problems of renal haemodynamics have been informatively reviewed by Thurau (1964), and the present contribution is chiefly concerned with the effects of acute changes in total body haematocrit on renal function.

METHODS

Dogs weighing 10–30 kg were anaesthetized with pentobarbitone (30 mg/kg). A jugular or foreleg vein was cannulated for the infusion of fluids and a femoral artery for blood sampling. Blood pressure was recorded from the other femoral artery by mercury manometer. The ureters were approached through a low abdominal incision and catheterized with polythene tubing.

The animals were hydrated during preparation by an infusion of saline or 5% dextrose solution (200–500 ml.), and during the experiments were breathing spontaneously. After a control period of 20 min the haematocrit was acutely altered by the rapid infusion of 20–30 ml./kg. body wt. of packed cells or dextran solution (6% in normal saline). Later on

in the same dogs the haematocrit was lowered by the intravenous injection of 20 % mannitol solution (4–6 ml./kg body wt.). This produced its effect by haemodilution and probably also by a reduction of individual red cell volume (Lilien, Jones & Mueller, 1963). During the infusions the circulating blood volume was kept as constant as possible by the simultaneous removal of an equal volume of blood (greater in the case of mannitol).

The glomerular filtration rate (G.F.R.) was estimated by the clearance of ^{57}Co-labelled vitamin B_{12} (Nelp, Wagner & Reba, 1964; Ekins, Nashat, Portal & Sgherzi, 1966) and effective renal plasma flow (E.R.P.F.) by the clearance of [^{125}I]orthoiodohippurate ('Hippuran'), both given intravenously by constant infusion after appropriate priming doses. Renal blood flow (R.B.F.) was calculated from E.R.P.F. and packed cell volume (P.C.V.).

Urine collections were made every 2 min throughout the experiments. Arterial blood samples were taken every 4 or 6 min and the haematocrit measured by centrifuging at 3×10^3 rev/min for 30 min. Since relative changes only were being studied, no correction was made for trapped plasma.

All samples were counted in a Packard Autogamma spectrometer (Ekins *et al.* 1966; Brewin, Ekins, Nashat & Portal 1966), and the results calculated by computer.

RESULTS

Increase of haematocrit. The effects of increasing the haematocrit by the infusion of packed cells were studied in three dogs. Results in a representative experiment are illustrated in Fig. 1. In this animal the P.C.V. was raised from 37 to 56 % by an exchange transfusion lasting 12 min. Though an equal volume of blood was removed the procedure was not accomplished without some change in mean blood pressure, which fell from 105 to 90 mm Hg. The feature to be emphasized, however, is the rise in filtration fraction from 0·22 to 0·36 which occurs during the infusion and persists until an injection of mannitol solution was given at 50 min. (The effect of this is discussed later.) The rise is caused by a proportionately greater reduction in E.R.P.F. than in G.F.R.

Reduction of haematocrit. In contrast to Fig. 1, the effects of lowering the haematocrit by an exchange transfusion of dextran are shown in Fig. 2. Here the P.C.V. was reduced from 62 to 43 %, and the blood pressure rose slightly during the procedure from 135 to 145 mm Hg. Notwithstanding this, the filtration fraction fell from 0·34 to 0·27. Again the modification is effected by a greater proportional change in Hippuran clearance than in B_{12} clearance. Similar results were obtained in two other dogs.

Effects of mannitol infusion. The immediate effects of an hypertonic mannitol injection were studied in six animals. Two phases were evident:

(i) a peak in the apparent clearances of both Hippuran and B_{12}, often reaching, and sometimes exceeding, twice the control value, lasting 2–4 min, and always related to the commencement of the diuresis; this is attributable to the rapid removal of material filtered and secreted earlier, but not excreted in the urine (Brewin *et al.* 1966).

(ii) an increase in E.R.P.F. and a decrease in G.F.R., resulting in a fall in the filtration fraction (these effects regressed as the mannitol was excreted).

These changes are illustrated in the latter half of Fig. 1. At 50 min 60 ml. of 20 % mannitol were injected rapidly. Within 2 min the haematocrit fell from 56·5 to 48 %, with a concurrent reduction in the filtration

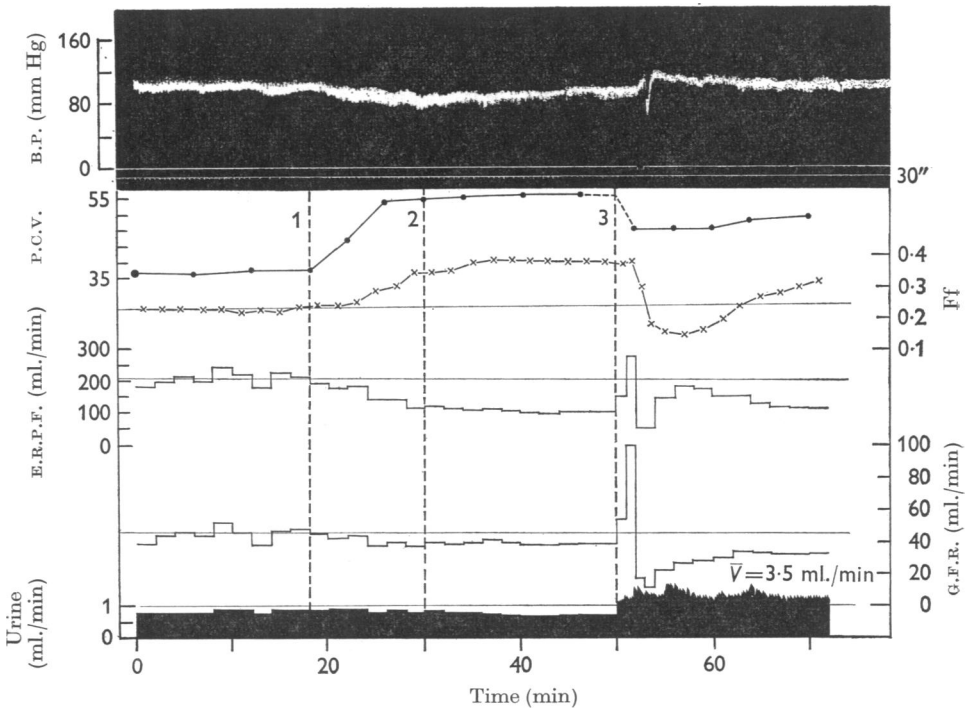

Fig. 1. Acute changes produced in dog by an exchange transfusion of packed cells (between vertical lines 1 and 2) and by a rapid injection of 20 % mannitol (at line 3). Clearance periods were 2 min throughout. Note the increase in filtration fraction (Ff) as the P.C.V. is increased, and its sudden reduction when the P.C.V. is rapidly lowered by mannitol. The horizontal straight lines are reference lines to facilitate interpretation. $\bar{V}$, mean urine flow.

fraction from 0·36 to a minimal value of 0·14. This was caused partly by an increase in Hippuran clearance and partly by a fall in B_{12} clearance. This reduction of filtration fraction after a substantial dose of mannitol was a constant finding, and occurred despite the transient increase in blood pressure often seen after the injection; it tended, moreover, to be greater when the preceding P.C.V. was high.

Relation of P.C.V. *to filtration fraction.* The relation between haematocrit and filtration fraction in six experiments is shown in Fig. 3, where it is evident that a direct relationship between the two parameters exists. In relation to any given haematocrit an injection of hypertonic mannitol reduced the filtration fraction to a greater extent than did an exchange

transfusion of dextran. This is shown by the hatched areas in Fig. 3, which lie consistently below the black areas on the filtration fraction axis. This may be explained by the greater reduction of total blood viscosity produced by the mannitol.

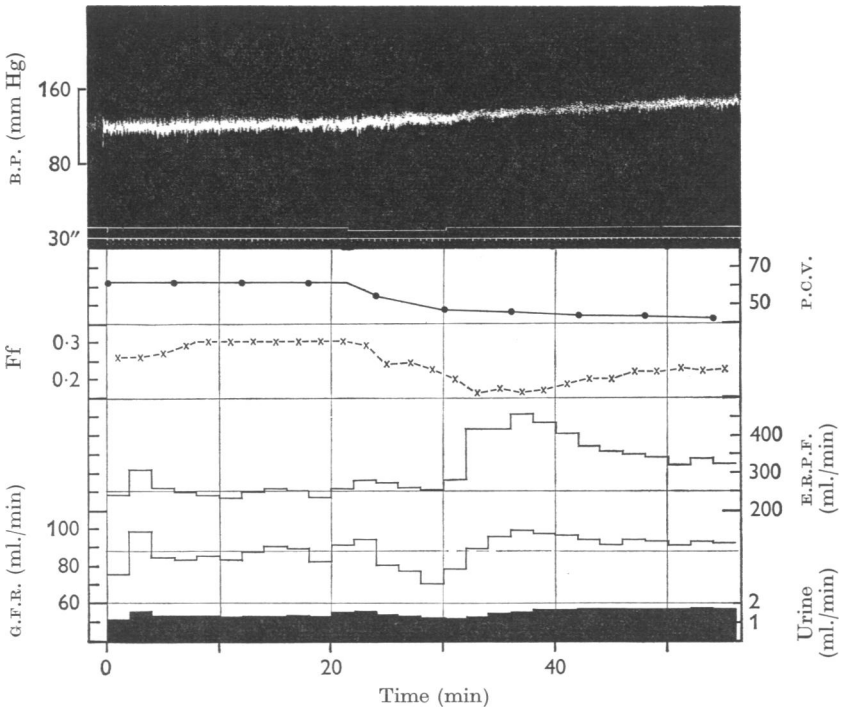

Fig. 2. Acute changes produced in dog by an exchange transfusion of dextran (between 20–30 min). The fall in P.C.V. is accompanied by a decrease in filtration fraction. Reference lines as in Fig. 1.

P.C.V. *and water reabsorption.* We have found some correlation between P.C.V. and water reabsorption by the renal tubules. Thus an increase in P.C.V. was accompanied by an increase in water reabsorption relative to the filtered load ($V \times 100/C_{B_{12}}$) in two out of three experiments and a decrease in P.C.V. by a relative decrease in water reabsorption in three out of four experiments. This is shown in Table 1. The fraction ($V \times 100/C_{B_{12}}$) is, of course, a measure of the degree of concentration in the urine of a substance that is neither reabsorbed nor secreted by the tubules.

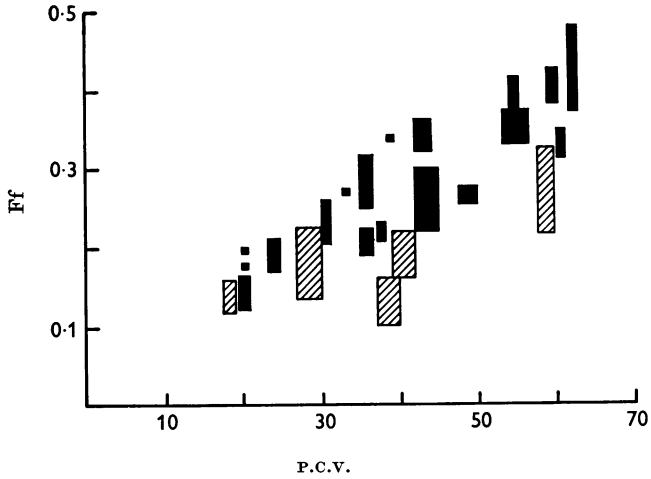

Fig. 3. Composite graph showing data from six dog experiments in which the P.C.V. was acutely altered by the rapid intravenous injection or infusion of packed red cells, dextran or hypertonic mannitol. The width of the blocks indicates the ranges of P.C.V. during stable periods of the experiments, and the height the range of filtration fractions observed at the same times. The hatched areas are observations obtained after mannitol injections.

TABLE 1. The effect of P.C.V. on the percentage of glomerular filtrate excreted as urine ($V \times 100/C_{B_{12}}$)

Experiment no.	Exchange transfusion	P.C.V. range	$V \times 100/C_{B_{12}}$*	P†
33*b*	Packed cells	32–33	2·81 ± 0·08 (7)	—
		39–43	2·69 ± 0·08 (10)	0·01
43	Packed cells	55	0·52 ± 0·03 (9)	
		58–64	0·44 ± 0·04 (10)	0·001
46	Packed cells	37–38	1·82 ± 0·03 (9)	
		55–57	1·96 ± 0·14 (11)	0·025
27	Dextran	40–42	3·89 ± 0·44 (8)	
		34–36	5·05 ± 0·34 (10)	0·001
45	Dextran	62	1·52 ± 0·04 (10)	
		43–46	1·71 ± 0·09 (13)	0·001
47	Dextran	43–44	0·84 ± 0·05 (10)	
		33–36	0·89 ± 0·13 (11)	0·3
48	Dextran	35–37	2·09 ± 0·21 (10)	
		19–21	2·64 ± 0·09 (10)	0·001

In each experiment; top line—control values, bottom line—values, after exchange transfusion.

* Mean ± S.D. of (n) consecutive observations made at 2–4 min intervals.

† Obtained by the Student t test for differences between means.

DISCUSSION

Our observations led us to reconsider the role of the afferent and efferent arterioles and to review some of the data of earlier workers. The following remarks rest on two assumptions about which there is little dissension among renal physiologists: (i) all the blood perfusing the renal parenchyma passes through the glomeruli, and (ii) the pressure in the glomerular capillaries, and hence the filtering force, is determined by the proximal pressure head (systemic blood pressure), the plasma protein osmotic pressure, and the resistances of the afferent and efferent arterioles.

The part played in renal function by the afferent and efferent arterioles has been the subject of much experiment and discussion (Winton, 1937; Lamport, 1941; Selkurt, 1946; Forster & Maes, 1947; Selkurt, Hall & Spencer, 1949; Gertz, Mangos, Braun & Pagel, 1965). The conclusion finally to be drawn from the observations of these workers is that the efferent arteriole plays relatively little part in the regulation of renal blood flow and glomerular filtration, a view the more superficially acceptable owing to the remoteness of this vessel from the systemic pressure head.

It may be suggested, however, that insufficient emphasis has been given in the past to the effect of blood viscosity on the resistance of the efferent vessel. The effect on renal function of changes in the corpuscular volume of the circulating blood was studied in dogs by Spencer (1951). In both acute and somewhat less acute experiments a rise in the P.C.V. by the infusion of red cells caused no significant change in blood pressure, R.B.F., G.F.R. or total renal resistance. The increase in haematocrit, on the other hand, was clearly correlated with the filtration fraction, which rose as the packed cell volume was elevated, owing to a relative reduction in the renal plasma flow. Spencer concluded that the maintenance of renal blood flow despite the markedly increased blood viscosity indicated a dilatation in the renal vascular circuit; the increase in filtration fraction suggested the afferent arteriole as the main site of reduced resistance.

A gradual increase in haematocrit was produced in four dogs by Marshall, Hanna & Specht (1952) by subjecting the animals to low barometric pressure for 6 hr daily. The experiments covered periods of 6–10 weeks at each simulated altitude. Clearance studies showed an approximate doubling of blood flow through the kidneys. The filtration fraction rose in every case, though a decline from its peak value was observed during the final increment in haematocrit. Conversely, the acute reduction of P.C.V. in dogs by bleeding resulted in an increase in E.R.P.F. and a fall in filtration fraction (Share, 1952), while the production of chronic anaemia by repeated bleeding resulted in a rise in R.B.F., though no consistent change in filtration fraction (Paterson, 1951).

The clinical counterpart of these experiments is provided by studies of renal function in patients with polycythaemia or anaemia, though here one is observing only the chronic effects of altered haematocrit. In the polycythaemia of cyanotic congenital heart disease (Scott & Elliott, 1950) and in primary polycythaemia (de Wardener, McSwiney & Miles, 1951) R.B.F. was raised above the normal, and filtration fraction increased. In both these reports the authors relate the augmented filtration fraction to the even greater viscosity of the blood traversing the efferent arterioles. In anaemia, on the other hand, there is a marked reduction of R.B.F. and a fall in filtration fraction (Bradley & Bradley, 1947).

In attempting to make a synthesis of both experimental and clinical data one encounters discrepancies between the short and long term effects of altered haematocrit on renal function. It is, however, not surprising that the immediate changes in the parameters studied should be short-lived, and that a fairly rapid readjustment of renal haemodynamics ensues. In brief it would appear that an increase of P.C.V. (increased blood viscosity) results in an immediate fall in R.B.F. and E.R.P.F., but an increase in filtration fraction. As adjustment occurs (the mechanism is unknown) the R.B.F. increases, and E.R.P.F. and filtration fraction tend to return towards normal. In our own experiments the R.B.F. returned to the control level within 10–20 min, although E.R.P.F. and filtration fraction remained altered. The opposite pertained when the haematocrit was reduced. Here the initial increase in R.B.F. and E.R.P.F., with reduced filtration fraction, gave way to a reduction of R.B.F. and a trend of E.R.P.F. and filtration fraction towards normal values.

Such events undoubtedly reflect the working of different control mechanisms, of which either afferent tone or efferent resistance related to blood viscosity may be the dominant influence at different times. The facts observed indicate strongly that changes in efferent resistance resulting simply from an altered haematocrit play a significant part in regulating the filtration fraction, both in acute and chronic disturbances.

The afferent arteriole is so sited as to act as the prime regulator of blood flow through the kidney. The resistance which it offers is modified by various mechanisms, the most important of which is its tone in the face of variation in blood pressure (the myogenic theory of the autoregulation of renal blood flow). However, once the blood reaches the glomerulus its distribution between filtrate and post-glomerular blood will be determined by the resistance offered by the efferent arteriole. This division of the blood into two channels which later fuse again may be deemed the chief function of the efferent vessel, which achieves its effects by either maintaining or dissipating the pressure head in the glomerulus. It seems to us unlikely that this vessel should respond differently to neurogenic, hormonal or

other stimuli from the afferent arteriole, yet the formation of urine under varying conditions demands that they act independently. One way in which they may do so relates to the viscosity of the blood perfusing them. The structure of the two vessels is not identical: the efferent vessel in the majority of nephrons is smaller in calibre and longer than the afferent (Maximow & Bloom, 1957). It follows that any change in the haematocrit of renal arterial blood will produce a greater change in resistance at the efferent than at the afferent arteriole. This difference in the two resistances is magnified by the fact that owing to the removal of glomerular filtrate the viscosity of the blood traversing the efferent vessel is always greater than that traversing the afferent. The curve relating viscosity (or resistance) to P.C.V. is not linear, but of such a shape that a given change in P.C.V. produces a greater change in viscosity in the higher range of P.C.V. than in the lower range (Whittaker & Winton, 1933). The efferent arteriole therefore functions on the steep part of the curve, while the afferent functions on the flatter portion.

Winton (1937), in considering the effect of altered haematocrit on efferent resistance, took as a starting point a change in renal perfusion pressure which in turn modified filtration fraction, viscosity of post-glomerular blood, and efferent resistance. One may shift the emphasis by assuming a constant perfusion pressure, but a change in haematocrit of the blood entering the glomerulus (i.e. a change in total body haematocrit). If this is reduced, the resistance offered by the efferent arteriole falls and the filtration fraction is likewise decreased. Conversely, if the haematocrit is raised the filtration fraction rises too. Though resistance at the afferent arteriole must also be modified by the change in blood viscosity, it is still, for the reasons given above, the efferent resistance which largely determines the filtration fraction. In this way homeostasis of the G.F.R. may be effected in face of a changing haematocrit by a passive mechanism which need not involve any alteration in calibre of either afferent or efferent arterioles.

In this context the simultaneous fall in G.F.R. and filtration fraction following a mannitol injection is of special significance, for it is difficult to explain it except on the basis of a reduction in efferent resistance. The rise in blood pressure and the fall in plasma protein concentration that accompany the injection must both increase the effective filtering force, and so tend to increase the filtration fraction. Since the exact opposite occurs there must be a potent factor operating in the reverse sense, and reduction of the blood viscosity would appear the most likely explanation.

We have considered so far the effect of alterations of haematocrit on the filtration fraction. If variations in the filtration fraction are a means of maintaining an adequate volume of filtrate despite changes in the volume

of plasma perfusing the kidney, the next enquiry should logically be into the subsequent fate of the filtrate itself. How much of it is reabsorbed and how much leaves the body as urine? Is there any mechanism by which an increase in haematocrit (produced physiologically by water deprivation) could result in an increase of water reabsorption? Our results indicate, though they do not prove, that there is a relationship between P.C.V. and water reabsorption (Table 1). The recent findings of Nashat, Scholefield & Tappin (1967) that renal medullary blood flow in the isolated perfused kidney of the dog is viscosity dependent may explain how this relationship is effected if the results obtained in the isolated perfused kidney were to apply to the intact animal.

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REFERENCES

BRADLEY, S. E. & BRADLEY, G. P. (1947). Renal function during chronic anaemia in man. *Blood* **2**, 192–202.

BREWIN, E. G., EKINS, R. P., NASHAT, F. S. & PORTAL, R. W. (1966). Concealed glomerular filtration. *J. Physiol.* **187**, 603–614.

DE WARDENER, H. E., MCSWINEY, R. R. & MILES, B. E. (1951). Renal haemodynamics in primary polycythaemia. *Lancet* **ii**, 204–206.

EKINS, R. P., NASHAT, F. S., PORTAL, R. W. & SGHERZI, A. M. (1966). The use of labelled B_{12} in the measurement of glomerular filtration rate. *J. Physiol.* **186**, 347–362.

FORSTER, R. P. & MAES, J. P. (1947). Effect of experimental neurogenic hypertension on renal blood flow and glomerular filtration rate in intact denervated kidneys of unanaesthetised rabbits with adrenal glands demedullated. *Am. J. Physiol.* **150**, 534–540.

GERTZ, K. H., MANGOS, J. A., BRAUN, G. & PAGEL, H. D. (1965). Pressure in the glomerular capillaries of the rat kidney and its relation to arterial blood pressure. *Pflügers Arch. ges. Physiol.* **288**, 369–374.

LAMPORT, H. (1941). Formulae for afferent and efferent arteriolar resistance in the human kidney: an application to the effects of spinal anaesthesia. *J. clin. Invest.* **20**, 535–544.

LILIEN, O. M., JONES, S. G. & MUELLER, C. B. (1963). The mechanism of mannitol diuresis. *Surgery, Gynec. Obstet.* **171**, 221–228.

MARSHALL, L. H., HANNA, C. H. & SPECHT, H. (1952). Renal function in the dog during increased blood viscosity produced by simulated altitude exposure. *Am. J. Physiol.* **171**, 499–505.

MAXIMOW, A. A. & BLOOM, W. (1957). *A Textbook of Histology*. London: W. B. Saunders and Co.

NASHAT, F. S., SCHOLEFIELD, F. R. & TAPPIN, J. W. (1967). The effect of viscosity on the blood flow in the isolated kidney of the dog. *J. Physiol.* **191**, 124–125*P*.

NELP, W., WAGNER, H. N. & REBA, R. C. (1964). Renal excretion of vitamin B_{12} and its use in measurement of glomerular filtration rate in man. *J. Lab. clin. Med.* **63**, 480–491.

PATERSON, J. C. S. (1951). Effect of chronic anaemia on renal function in the dog. *Am. J. Physiol.* **164**, 682–685.

SCOTT, H. W. & ELLIOTT, S. R. (1950). Renal haemodynamics in congenital cyanotic heart disease. *Johns Hopkins Hosp. Bull.* **86**, 58–71.

SELKURT, E. (1946). The relation of renal blood flow to effective arterial pressure in the intact kidney of the dog. *Am. J. Physiol.* **147**, 537–549.

SELKURT, E., HALL, P. W. & SPENCER, M. P. (1949). Influence of graded arterial pressure decrement on renal clearance of creatinine, *p*-aminohippurate and sodium. *Am. J. Physiol.* **159**, 369–378.

SHARE, L. (1952). Primary effects of acute oligocythaemia on renal function. *Am. J. Physiol.* **171**, 159–163.

SPENCER, M. P. (1951). Renal haemodynamics in experimental polycythaemia. *Am. J. Physiol.* **165**, 399–406.

THURAU, K. (1964). Renal haemodynamics. *Am. J. Med.* **36**, 698–719.

WHITTAKER, S. R. F. & WINTON, F. R. (1933). The apparent viscosity of blood flowing in the isolated hind limb of the dog and its variation with corpuscular concentration. *J. Physiol.* **78**, 339–369.

WINTON, F. R. (1937). Physical features involved in the activities of the mammalian kidney. *Physiol. Rev.* **17**, 408–435.