THE EFFECT OF

ACUTE CHANGES IN HAEMATOCRIT IN THE ANAESTHETIZED DOG ON THE VOLUME AND CHARACTER OF THE URINE

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SUMMARY

1. Acute changes in haematocrit were produced by exchange transfusion of dextran-in-saline or packed red cells.

2. There were no significant changes in glomerular filtration rate, blood pressure, central venous pressure, heart rate, respiratory rate, blood volume or extracellular fluid volume following the exchange transfusions.

3. Urine volume increased after haemodilution but decreased after haemoconcentration.

4. The diuresis after haemodilution occurred despite an infusion of ADH or alcohol. Thus it could not be attributed to a change in circulating ADH level.

5. There were two types of diuresis. The 'water diuretic' response was characterized by an increase in free water clearance with a reduction in urinary sodium concentration; the 'sodium diuretic' response by an increase in urinary sodium concentration but no change, or a fall, in free water clearance.

6. The results were related to changes in medullary osmotic gradient found by other workers to occur when medullary blood flow rate is altered.

INTRODUCTION

Recently Nashat, Scholefield, Tappin & Wilcox (1969) have shown that in the anaesthetized dog, acute changes in haematocrit are followed by inverse changes in renal medullary blood flow. In 1960 Thurau, Deetjen & Kramer had found a close relationship between medullary flow and the volume and concentration of urine produced. Thurau (1964) suggested that, at any given ADH level, an increase in medullary flow leads to a reduction in the quantity of water reabsorbed in the collecting duct and the production of increased quantities of a less concentrated urine. Therefore, it seems probable that an acute increase in haematocrit could augment the concentrating ability of the kidney, while haemodilution could limit it. The present experiments were designed to investigate this probability.

METHODS

All observations were made on dogs anaesthetized with pentobarbitone (30 mg/kg) body wt., with maintenance doses of 60 mg as required). Occasionally mongrels were used but the greater number were greyhounds. The weights of the animals varied between 10 and 30 kg.

The blood pressure was recorded from a femoral artery by a mercury manometer. Either one or both ureters were cannulated through an abdominal incision. Urine was collected in weighed disposable polystyrene containers, over 5–30 min intervals. It was measured gravimetrically but without correcting for specific gravity.

Plasma and urine sodium concentrations were measured in an EEL flame photometer. Osmolarities were measured cryoscopically in an Advanced osmometer. The glomerular filtration rate (G.F.R.) was calculated from the clearance of either [⁵⁷Co]eyanocobalamin (vitamin B_{12}) or [¹²⁵I]diatrizoate (Hypaque) given by constant intravenous infusions after appropriate priming doses. Regional distribution of renal blood flow was assessed by the clearance of ¹³⁸Xe as described in a previous paper (Nashat *et al.* 1969). The packed cell volume (P.C.V.) was measured in Wintrobe tubes centrifuged at 3000 rev/min for 30 min.

The haematocrit of the circulating blood was acutely altered by exchange transfusions of 400-600 ml. of packed red cells (P.C.V. around 80%) or 6% dextran (mol. wt. 110,000) in isotonic saline. The exchanges were made either by infusion into a vein while bleeding at the same rate from an artery or by a method similar to that described by Bahlman, McDonald, Dunningham & de Wardener (1967). The exchanges were completed in 10-30 min and were achieved without discernible changes in arterial pressure, mean venous pressure, heart rate or respiration, all of which were recorded continuously using electromanometers (Fig. 1).

As all dogs had a high haematocrit to start with (mean 60.9 ± 0.6 s.E. of mean), the first experimental procedure attempted was an exchange with dextran-in-saline (haemodilution). This was followed either by a transfusion of packed cells (haemoconcentration) or by a further haemodilution. At least 50 min were allowed after each exchange before observations were started. Exchanges were carried out only after the animal had been in a steady state for a minimum of 40 min. The haematocrit was increased in dogs that had previously had one or two exchange transfusions with dextran-in-saline. Only red cells freshly obtained from the animal during earlier exchanges with dextran-in-saline were used. Blood was heparinized and centrifuged at 1000 rev/min for 10 min and about two thirds of the supernatant plasma was removed. In a few experiments the cells were washed once with isotonic sodium chloride solution and infused as an 80 % suspension in saline.

All animals were continuously infused with isotonic saline throughout the experiment at the rate of 1-1.5 ml./min. The infusion was found to have no effect on haematocrit or plasma sodium concentration. In three dogs ethanol was introduced into the stomach at the beginning of the experiment. The dose of pure ethanol given was 0.3-0.5 ml./kg body wt. In another three dogs Pitressin was infused (0.01-0.3 mu./kg.min) throughout the experiment with the saline.

In a limited number of experiments blood volume and extracellular fluid volume were estimated before and after the exchange transfusion using ${}^{51}Cr$ labelled red cells and ${}^{82}Br$ as indicators.

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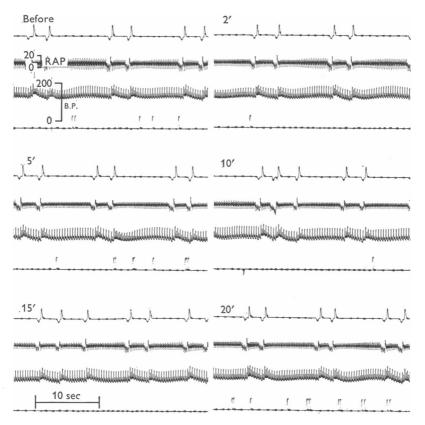


Fig. 1. Records from above downwards, of respiratory rate, right atrial pressure (RAP), arterial pressure (B.P.), and urine drops, before and at various intervals after exchange transfusion of dextran-in-saline. The pressures are not visibly altered and the heart rate remains unchanged at 156 beats/min while rate of respiration varies between 10 and 12 min.

RESULTS

The minute volume of urine increased in thirty-seven of forty-three experiments in which haematocrit was reduced by exchange transfusion with dextran-in-saline. The mean increase was $129 \% \pm 26$ (s.E. of mean). The diuresis started 10-30 min after the beginning of the exchange and reached its peak in 40-80 min (Fig. 2).

In thirteen experiments on ten dogs urine osmolarity (U_{Osm}) and urinary sodium concentration (U_{Na}) were measured. Sodium excretion $(U_{\text{Na}}V)$, osmolar clearance (C_{Osm}) and free water clearance $(C_{\text{H}_2\text{O}})$ were calculated. The results are given in Table 1. The diuresis observed could be classified into two groups according to whether it was accompanied

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by an increase or a decrease in $U_{\rm Na}$ (Fig. 3) and $C_{\rm H_2O}$. Thus in eight experiments, referred to in the Table as 'sodium diuretic', the $U_{\rm Na}$ increased in every instance and was accompanied by a significant percentile increase in $U_{\rm Na}V$ and $C_{\rm Osm}$. In a further series where only $U_{\rm Na}$ was measured $U_{\rm Na}$ increased in five and was reduced in three experiments.

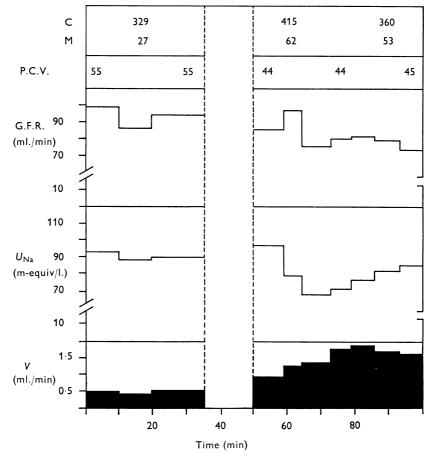


Fig. 2. Acute changes produced in a dog (No. 5) by an exchange transfusion of dextran-in-saline (between the vertical lines). The increase in urine volume is already apparent 15 min after the start of the exchange but reaches its maximum in 40 min. $U_{\rm Osm}$ was not measured in this case but there is a fall in $U_{\rm Na}$. In the top record: C = cortical flow, M = outer medullary flow.

It is noteworthy that there was a difference in the character of the urine between the two groups before the exchange transfusion. In the 'water diuretic' group $U_{\rm Osm}$ was lower and the $U_{\rm Na}V$ and urine volume were higher than in the 'sodium diuretic' group. However, the percentage increase in

urine volume after the exchange transfusion was comparable in the two groups.

After exchange transfusion of red cells the urine volume was invariably reduced in eighteen experiments. The mean reduction was $33\% \pm 5$ (s.e. mean). An immediate reduction in urine volume was commonly observed

TABLE 1. The effect of acute reduction in P.C.V. on the urine. In each experiment: Top line control value (mean of three to four consecutive collections at 10–15 min intervals).

Bottom line: value in steady state after exchange transfusion (mean of four to six collections at 5–10 min intervals).

Experiments marked @: the exchange was carried out during constant infusion of Pitressin; experiments marked *: the exchange was carried in dogs that had been given ethanol.

P values were calculated by the Student *t* test for deviation of the mean changes from zero in each group $(\bar{x} - 0)$ and for differences between mean changes in the two groups $(\bar{x}_1 - \bar{x}_2)$

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_		V	$U_{\rm Na}$	$U_{\rm Na}V$	$U_{\rm Osm}$	C_{0sm}	$C_{\rm H_2O}$
\mathbf{Dog}		(ml./	(m-	(equiv/	(m-	(ml./	(m]./
no.	P.C.V.	min)	equiv/l.)	min)	osmole/l.)	min)	min)
			Group I.	Sodium diu	retic		
16 @	66	0.44	44	20	1337	1.99	-1.54
0	52	1.05	73	87	1067	3.49	-2.43
17	63	0.74	4	3	1224	3 .00	-2.22
	48	0.93	45	36	1353	4.19	-3.26
18@	64	0.35	10	3	1172	1.36	-1.01
0	48	1.00	63	72	791	2.38	- 1·38
19*	63	0.33	41	14	1282	1.34	-1.01
	48	0.50	121	61	1186	1.88	- 1·38
20	58	0.10	5	1	1080	0.86	-0.58
	40	0.30	15	5	1143	1.30	-0.96
20	41	0.31	38	11	1225	1.61	-1.20
	28	1.73	121	215	747	4.45	-2.54
21	62	0.27	15	4	1214	1.09	-0.82
	51	0.37	32	12	1085	1.34	-0.97
22*	58	0.22	20	4	1505	1.10	-0.88
	42	0.46	54	25	1210	1.86	-1.40
Mean change		+150%	+315%	+755%	-14%	+ 69 %	-0.63
s.E. of mean		$\pm 53\%$	$\pm 120\%$	$\pm 223 \%$	±7%	±18%	± 0.15
$P(\bar{x}-0)$		< 0.01	< 0.02	< 0.005°	< 0.1	< 0.004	< 0.002
Group II. Water diuretic							
		0.00	•		723	1.47	-0.83
14*	59 50	0.63	77 47	52 94	334	1·47 1·85	-0.33 -0.20
14*	50 57	2·04 0·91	47 63	94 71	334 386	1.85	-0.20 -0.18
14+	57 38	2.08	63 67	145	380 314	1.10	+0.18 +0.30
15	38 57	2·08 0·86	110	94	607	1.19	-0.86
15	40	1.30	70	94 91	440	$1.03 \\ 1.85$	-0.55
17	40	1.30	42	57	1190	5·43	-4.06
17	40	1.33	11	20	890	5.31	-3.52
23	56	0.85	289	245	1125	3.04	-2.21
20	39	2.51	112	274	585	4.55	-2.03
Mean change		+127%	-41%	+ 31 %	-34%	+29%	+0.43
s.E. of mean		±43%	$\pm 15\%$	$\pm 29\%$	±8%	$\pm 14\%$	± 0.09
$P(\bar{x}-0)$		$\frac{1}{2}$ 0.01	$\frac{1}{5}$ 0.03	$\frac{1}{<} 0.20$	< 0.008	< 0.05	< 0.0025
$P(\bar{x}_1 - \bar{x}_2)$.)	< 0.3	< 0.01	< 0.01	< 0.05	< 0.1	< 0.001
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during the exchange, but the main reduction started after 20-30 min, and the lowest value was reached in 80-100 min (Fig. 4). The effect of haemo-concentration on $U_{\rm Na}$, $U_{\rm Osm}$, $U_{\rm Na}V$, $C_{\rm Osm}$ and $C_{\rm H_{2}O}$ is shown in Table 2.

Exchange transfusions were also made against a background of continuous infusion of Pitressin in three experiments. The dose infused varied between 0.010 and 0.030 mu./kg.min. In two instances a typical sodium diuretic response was obtained but in the third, water clearance increased

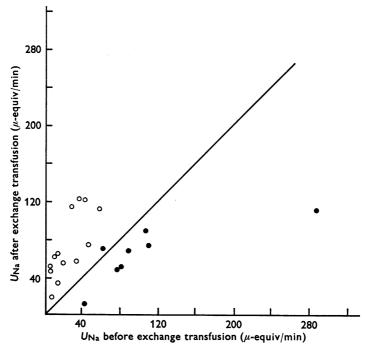


Fig. 3. A composite graph showing the effect of exchange transfusion with dextran-in-saline on the urinary concentration of sodium $(U_{\rm Na})$. Continuous line is a line of no change. The graph is drawn from data presented in Table 1. Open circles represent changes in animals from the 'sodium diuretic' group; filled circles, the results from animals in the 'water diuretic' group.

from 0 to +1.26 ml./min, but $(U_{\rm Na})$ increased from 38 to 55 m.equiv/l. The urine volume increased from 1.50 to 3.60 ml./min. This experiment could not be included in either diuretic categories in Table 1.

Treatment with ethanol (0.3-0.5 ml./kg) before the exchange transfusion did not modify the diversis produced.

The G.F.R. was measured before and after exchange transfusion in twenty-one cases. After twelve exchanges with dextran-in-saline there was a significant reduction (P < 0.05) in only three cases. The mean fall

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in the series was $8 \pm 5 \%$ (s.E. of mean). After nine exchanges with packed cells there was a significant rise (P = < 0.05) in one experiment, a significant fall (P = < 0.05) in one but no significant change in the other seven. The mean fall in the series was $4 \pm 6.5 \%$ (s.E. of mean; Table 3).

Plasma sodium concentration and osmolarity were little affected by the

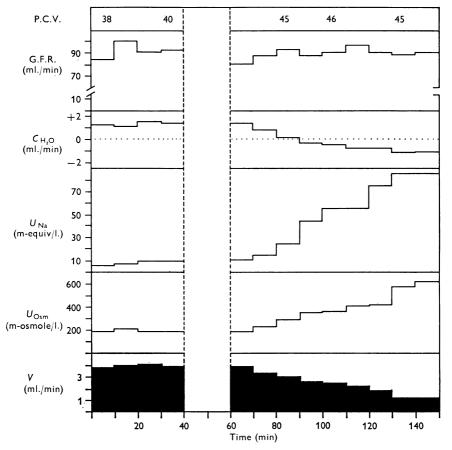


Fig. 4. Acute changes produced in a dog (No. 11) by an exchange transfusion of packed red cells (between the vertical lines). The urine volume begins to fall 30 min after the exchange and reaches its lowest value in 90 min. The reduction in volume is accompanied by an increase in $U_{\rm 0sm}$, $U_{\rm Na}$, and a reduction in free water clearance.

exchange transfusions of dextran-in-saline. The mean $(P_{\rm Na})$ before the exchanges was $146 \cdot 7 \pm 1 \cdot 3 \%$ (s.E. of mean) and $146 \cdot 2 \pm 1 \cdot 2$ (s.E. of mean) after, the mean fall being $0 \cdot 2 \pm 0 \cdot 5 \%$ (s.E. of mean). $(P_{\rm Osm})$ fell from $313 \cdot 3 \pm 3 \cdot 0$ (s.E. of mean) to $311 \cdot 6 \pm 2 \cdot 5$ (s.E. of mean), a mean reduction of $0 \cdot 5 \pm 0 \cdot 5 \%$ (s.E. of mean). The blood volume was measured before and

after haemodilution in five cases. There was an average reduction of $4.8\% \pm 4.1$ (s.E. of mean) after the exchange transfusion. Bromine space was measured twice, being 8070 and 6044 ml. before and 7920 and 5775 ml. after, a mean reduction of 3.2%.

With haemodilution the renal medullary flow increased but the cortical flow remained unchanged. The effects of acute changes in P.C.V. on the intrarenal distribution of blood flow were described in detail in a previous paper (Nashat *et al.* 1969).

TABLE 2. The effect of acute increase in P.C.V. on the urine. In each experiment:Top line: control value (mean of four to six consecutive collections at 5-10 minintervals).

Bottom line: value in steady state after exchange transfusion (mean of three to four collections at 10–15 min intervals.)

Experiments marked *: the exchange was carried out in dogs that had been given ethanol; mean changes and s.e. of mean are expressed as percentages.

Changes in $C_{\rm H_2O}$ are presented as absolute values.

P values were calculated using the Student t test for deviations from zero $(\bar{x}-0)$

Dog no.	P.C.V.	V (ml./ min)	U _{Na} (m- equiv/l.)	U _{Na} V (equiv/ min)	U _{o.m} (m- osmole/l.)	C _{osm} (ml./ min)	C _{H2O} (ml./ min)
11	42	4.00	9	36	190	2.50	+1.50
	46	2.05	68	121	459	2.75	-0.84
13	43	0.22	16	3	1210	0.87	-0.71
	49	0.19	32	6	1420	0.88	-0.69
14*	38	3 ·84	69	265	221	2.66	+1.18
	48	2.82	83	236	265	2.33	+0.48
14*	46	2.82	84	236	265	2.35	+0.48
	48	$2 \cdot 30$	95	221	287	2.08	+0.22
17	34	1.79	20	52	890	5.31	-3.52
	43	1.58	56	100	1120	5.86	-4.51
Mean chan s.e. of mean $P(\bar{x}-0)$		-24 % ±8 % < 0.02	+194% $\pm134\%$ <0.15	+82% $\pm50\%$ <0.1	+42% $\pm28\%$ <0.12	-1% $\pm 5\%$ > 0.4	$-0.72 \pm 0.33 < 0.05$

DISCUSSION

A definite increase in urine volume was observed in almost every experiment in which the haematocrit was acutely reduced by exchange transfusion with dextran-in-saline. This occurred without a rise in G.F.R.

There were two types of diuresis. One, a 'water diuresis,' was characterized by an increase in free water clearance and relatively minor changes in sodium output; the other a 'sodium diuresis' in which there was a massive increase in sodium output and a reduction in free water clearance.

The fact that two types of responses followed the same experimental procedure emphasizes the complexity of the situation and the importance of conditions prevailing at the time of the experiment. Thus when the urine osmolarity was high or sodium output low before haemodilution, a water diuresis was not produced.

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An acute increase in haematocrit by exchange transfusion of packed red blood cells produced one type of response in all experiments. This was reduction in urine volume and water clearance without profound changes in sodium output. In these cases too there were no significant changes in G.F.R.

> TABLE 3. The effect of exchange transfusions of dextran-in-saline or packed red cells on G.F.R.

Grou	p I. Following ex	change transfusion of de	xtran-in-saline
Dog no.	Animal wt.	G.F.R. before	G.F.R. after
1	30	86 ± 2.02 (10)	93 ± 1.48 (13)
2	26	91 ± 2.42 (10)	95 ± 2.80 (11)
3	12	27 ± 1.53 (10)	20 ± 1.67 (10)
4	24	31 (3)	23 (3)
5	29	111 ± 2.03 (9)	91 ± 3.03 (11)
		108 ± 2.95 (10)	97 (3)
6	21	96 ± 2.00 (5)	81 ± 2.17 (12)
7	26	44	55 (2)
13	26	42 ± 2.49 (6)	34 ± 3.25 (8)
		23 ± 2.97 (6)	19 (4)
14*	29	44 ± 3.59 (5)	49 ± 10.87 (6)
19*	27	84 (4)	78 (3)

Mean change $-8\% \pm 5.0$ (s.e. of mean)

	Group II. Following	exchange transfusion	or packed cens
8	11	20 ± 1.25 (5)	16 ± 0.93 (5)
9	30	163 ± 3.63 (9)	146 ± 10.42 (10)
10	10	45 ± 1.54 (9)	38 ± 0.47 (11)
5	29	91 ± 3.03 (11)	108 ± 2.95 (10)
7	26	57 (2)	57 (2)
11	24	92 ± 2.84 (17)	91 ± 1.30 (7)
12	32	73 ± 2.72 (16)	71 (4)
13	26	34 ± 3.25 (8)	23 ± 2.97 (6)
14*	29	25 (2)	32 ± 3.83 (11)
		Mean change – 4%	$\pm 6.5\%$ (s.e. of mean)

Group II. Following exchange transfusion of packed cells

All values are mean \pm s.E. of mean of *n* consecutive observations made at 5–15 min intervals. s.E. of mean was not calculated when the value of *n* was below 5.

Experiments marked (*) indicate that the exchanges were carried out in animals that had been given ethanol.

The changes in urine volume occurred without detectable changes in B.P., mean venous pressure, heart rate or respiration. Nor were they accompanied by measurable changes in blood volume or extracellular fluid volume.

There are several reasons to believe that under our experimental conditions ADH could not be responsible for the changes in free water clearance. All experiments were performed in anaesthetized animals. Plasma sodium concentration, plasma osmolarity, blood volume and extracellular fluid volume are factors known to affect ADH release. These were not measurably different following the exchange transfusions. Furthermore, the diuresis occurred after haemodilution in animals receiving an infusion of ADH, and in those previously given ethanol into their stomachs. Alcohol is an inhibitor of ADH release (Goodman & Gilman, 1965). The process of exchange transfusion with dextran-in-saline necessarily involves the removal of a fraction of the animal's own plasma, and the dilution of the remaining plasma ADH. But this cannot be an important cause of the diuresis because exchange transfusions of identical volumes of washed red blood cells invariably produced an antidiuresis.

The osmotic gradient between the renal medulla and the collecting ducts is recognized as being of importance in determining the rate at which solute free water is reabsorbed from the tubular fluid. The degree of osmotic gradient actually established depends upon the balance between the rate at which solutes are deposited into the region by the thin loops of Henle and the rate at which they are removed by blood flow in the vasa recta.

Thurau (1964) predicted, from a mathematical model, that the maximum osmolarity achieved in the region is inversely proportional to a value that lies between the blood flow rate and its square. Thus even a small change in blood flow may have pronounced effects on the osmotic gradient. In a previous publication (Nashat *et al.* 1969) we have shown that, under identical conditions of exchange transfusion, the blood flow rate to the outer medulla increased following a fall in haematocrit and decreased following a rise. Measurements in the isolated perfused kidney demonstrated that the inner medulla behaved similarly. Thus an explanation for the free water diuresis following haemodilution and the antidiuresis following haemoconcentration is apparent. The alteration in medullary blood flow rate may influence the kidney's ability to reabsorb solute free water by modifying the medullary osmotic gradient.

Evidence to link an increased medullary blood flow rate with a washout of solutes from the dog's renal medulla has been provided by Elpers & Selkurt (1963). They found that an infusion of albumin solution increased medullary blood flow rate; this was accompanied by a rise in the quantity of solute removed from the kidney into the renal vein. This process began soon after the albumin infusion started and was complete in about 45 min.

It has been argued that the production of urine of osmotic pressures below that of plasma cannot be accounted for on the basis of a washout of the medullary gradient (MacDonald & de Wardener, 1965). However, Clapp & Robinson (1966) have found that in the dog, even in antidiuresis, the distal tubular fluid remains hypotonic in relation to plasma. In the presence of ADH the collecting ducts still have a finite permeability to water; thus at high rates of flow in the collecting ducts there may not be sufficient time for the hypotonic fluid to be concentrated. Indeed in our experiments water clearance became positive only when urine flow rates exceeded 2 ml./min.

The instances in which haemodilution was followed by no change or a decrease in free water clearance (sodium diuresis) are more difficult to understand. These experiments were preceded by a control period in which urinary sodium output was low, urine osmolarity was high or a combination of the two. We are at present unable to account for the increase in sodium output. But according to the model proposed earlier there are two possible explanations for the failure to increase free water clearance. On the one hand, these conditions may be associated with a particularly high rate of deposition of solute in the medulla. A rise in medullary blood flow rate should then be accommodated without a large decrease in osmotic gradient. On the other hand, there may be a particularly low rate of removal of solute from the medulla. The absolute increase in flow might then be insufficient to dissipate the gradient.

There is tentative evidence from experiments on rats which suggests that both mechanisms could be operative. Landwehr, Schnermann, Klore & Giebisch (1968) have found that a rise in G.F.R. increases the rate at which sodium is extruded from the loops of Henle. Recently Thurau & Horster (1968) have produced evidence that the G.F.R. of juxtamedullary nephrons is greatly increased in salt depletion without appreciable change in total G.F.R. These nephrons are important for the generation of the osmotic gradient in the dog's kidney. Although the total G.F.R. in 'sodium diuretic' experiments was not increased, it is not possible to exclude a rise in juxtamedullary G.F.R., and so in the rate of deposition of solutes in the medulla.

Fourman's (1964) evidence may be construed as suggesting the operation of the second mechanism. She has found that the concentration of urine may be accompanied by a reduction in blood flow through the vasa recta. Under these conditions it is possible that the increase in flow as a result of haemodilution may be insufficient to wash away the gradient. Without direct evidence, the possibility that the increase in outer medullary flow, observed following haemodilution, may not be accompanied by a comparable increase in inner medullary flow, under *all* circumstances, could not be excluded.

The quantitative significance of the effects described may be questioned. It may be argued that under natural conditions only minor changes in haematocrit are expected. However, it suffices to remember that the various homoeostatic mechanisms involved in the regulation of urine volume act together under natural conditions, and may magnify each others effects.

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