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THE EFFECT OF A MEAL OF MEAT ON GLOMERULAR FILTRATION RATE IN DOGS AT NORMAL URINE FLOWS

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SUMMARY

1. The exogenous creatinine clearance of conscious dogs has been measured by a method in which no loading doses of water or saline were given. The urine volume was thus in the normal range, 0·1–0·3 ml./min.

2. Under these conditions, the exogenous creatinine clearance of fourteen dogs, measured 17 hr after a meal, was 2·74 ml./min kg^{-1} $\pm$ 0·54 (S.D.). This is about 40 % lower than values usually regarded as 'normal.'

3. A meal of meat, 10 g/kg, increased exogenous creatinine clearance by 12–17 ml./min above the values of 30–50 ml./min found in control experiments, an increase of approximately 40 %.

4. Glycine (10 m-mole) by stomach tube caused increase in creatinine clearance of similar magnitude to that produced by meat. Creatine (50–150 m-mole) had no effect.

5. In discussion reasons are given for believing that the observed increase in exogenous creatinine clearance reflects an increase in glomerular filtration rate. Since this occurs with small doses of meat, increase in glomerular filtration may be important in normal renal function of dogs.

INTRODUCTION

During the early years of the use of clearance methods to define renal function Shannon, Jolliffe & Smith (1932) and Pitts (1935) showed that in the dog a large meal of meat increased xylose clearance and later Moustgaard (1948) found that the inulin clearance was increased. Jolliffe & Smith (1931) found higher creatinine and urea clearance in dogs maintained on a diet containing much meat in comparison to a low protein intake.

For many years dogs in this laboratory have been fed diets of raw beef and biscuit. The beef provides practically all of the solutes excreted in the

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urine. An increase in glomerular filtration rate as the direct result of a meat meal could thus have the practical importance of contributing to the excretion of solutes as they are produced in the body. The purpose of this and following papers is to enquire how far in the dog the increased excretion of urea and electrolytes after a meat meal can be explained by an increase in glomerular filtration rate.

It is first necessary to establish that there is increase in glomerular filtration after a normal meal of meat. The existing evidence is unsatisfactory. Firstly, in the references cited above the dose of meat was 40 g/kg or more; in this paper the dose of 10 g/kg has been used, which is of the same order as the usual daily meal. Secondly, the methods used to measure clearances involved the administration of large doses of water or saline by which the urine flow was increased to 5 ml./min in comparison with the normal urine flow of dogs which rarely exceeds 0·25 ml./min (O'Connor & Potts, 1969); in this paper the urine volume was always below 0·3 ml./min.

Investigation of clearances at normal urine flows has not been previously attempted. It is therefore necessary to describe and justify the procedures by which exogenous creatinine clearances have been measured at intervals over a period of 9 hr without loading doses of water or saline.

Some of the results have been communicated to the Physiological Society (Summerill, 1974).

METHODS

The experiments were performed on adult mongrel bitches well accustomed to life in the laboratory, and trained to accept the experimental procedures. At preliminary aseptic operations the perineum was split to allow easy catheterization and each carotid artery was enclosed in a van Leersum skin loop. The animals were fed at 17.00 hr each day and from 09.00 to 11.00 hr were free in an exercise yard, except on the days, at most twice a week, when experiments were performed. Water was always available except in the exercise yard and during experiments.

In the first groups of experiments, the daily meal consisted of the mixture of meat and 'All-in-One' biscuit described by O'Connor & Potts (1969). In the later experiments the food was lean beef, suet, and a protein-free biscuit (Aminex; Liga Ltd); this allowed a more accurate control of the diet in that a protein allowance was provided by a quota of meat and the food intake could be adjusted to maintain a satisfactory weight by changing the carbohydrate (biscuit) and fat (suet) of the diet. The dogs weighed 14–18 kg and ate 40–60 g protein per day in the form of 180–250 g meat. The energy intake at which body weight was stable was 2–5 MJ per day, depending on the activity of the animal (O'Connor & Potts, 1969).

Large batches of lean raw beef from which all visible fat had been cut away were minced and stored in a deep freeze. Similar batches analysed by Golob (1974) contained 19–23 % protein, 68–73 % water and 0·9–1·2 % fat.

Experimental protocol. Table 1 is an example. The animal had eaten its usual daily meal at 1700 hr the previous day and had been in its cage with water available until the dose of creatinine was given; thereafter water was not available. The protocol provided for the collection of two half-hour urine samples and one blood sample with the dog lying at rest on the table before the meat, and at 1–2, 3–4, 5–6 hr after the

meat. In addition the urine was collected in the periods 0–1, 2–3, 4–5 hr after the meat when the dog was in a cage in the laboratory. When the dogs were lying quietly on the table, heart rate was always less than 90 beats/min, a useful criterion that the dog was at rest. In control experiments the same procedures were repeated but no meat was given. In some shorter experiments the dog lay on the table for 5 hr after the dose of meat with urine collections made in half-hr periods.

TABLE 1. An experimental protocol, Lassie

08.10 hr	50 ml. 2 % creatinine by stomach tube. Weighed 18·4 kg
09.20	Catheterized; laid on the table on left side
09.30	Bladder washed out; urine discarded
10.00	Urine 1 collected by bladder wash-out.
10.10	Blood sample 1, 5 ml. from right carotid artery
10.30	Urine 2 collected by bladder wash-out. Catheter withdrawn
10.31	Dose of meat eaten; 184 g (10 g/kg)
10.32	Into cage in Laboratory
11.20	Catheterized and laid on left side
11.30	Bladder washed out; urine 3
11.30–12.30	Procedures of 09.30–10.30 repeated to give urine 4, 5 and blood 2
12.31	Into cage
13.20–14.31	Procedures of 11.20–12.31 repeated to give urine 6, 7, 8 and blood 3
15.20–16.31	Procedures of 11.30–12.31 repeated to give urines 9, 10, 11 and blood 4

Urine collection. The bladder was catheterized with a sterile Dowse self-retaining catheter of external diameter 4 mm. To end each collection period the bladder was washed out three times with 10 ml. sterile distilled water and the collected wash-out plus urine used for analysis. Accuracy in measuring creatinine clearances at low urine flows depends on the effectiveness of the wash-out procedure. This was confirmed firstly by noting that if the three stages of the wash-out were performed at exactly 1 min intervals when the urine flow was, say, 0·1 ml./min, the collected volume was 10·1 ml., 10 ml. wash-out plus 0·1 ml. urine. Secondly, if after the ending of a 30 min collection by the usual 3 × 10 ml. wash-out, a further 10 ml. wash-out was collected separately, the creatinine content of the fourth 10·1 ml. collection was only a little more than would be contained in the urine excreted during the 1 min of the fourth wash-out; the amount of creatinine thus estimated as left in the bladder and catheter was 2·3 % ± 2·7 (S.D., $n = 22$) of the creatinine in the 30 min sample. A possible explanation of the success of this method of collecting urine is that the tip of the catheter comes to lie over the ureteric openings with the rugae of the bladder mucosa tightly folded about it and so limiting loss of fluid or urine from this immediate vicinity.

Arterial blood samples. These were drawn by a separate puncture of the carotid artery contained in the skin loop using a needle of 0·66 mm external, 0·3 mm internal diameter connected to a 5 or 10 ml. syringe. The procedure caused no disturbance to the dog and could be repeated many times without damage to the artery. The dead space of the syringe (0·05 or 0·1 ml.) was filled with heparin (5000 i.u./ml.) and 5 ml. blood was usually taken. The small correction of 1 or 2 % has been made to the estimations of plasma concentrations. The collected blood was transferred to a centrifuge tube and spun at 1000*g* for 20 min and the plasma pipetted off for analysis.

Creatinine in urine and plasma. This was determined using the Technicon Auto-Analyser method N-11b (Technicon, 1968); this employs the Jaffe reaction with the

resulting yellow picrate measured at 505 nm. The peaks were recorded twice, the mean of the duplicates giving a value with 95 % confidence limits of ± 1 % as assessed by the method of Kimball (1952). In recovery experiments where known amounts of creatinine were added to plasma the recovery was 100·5 % ± 0·25 (S.E. of mean, $n = 12$).

Where mention is made of other substances in urine or plasma, these were determined by autoanalyser methods of Technicon (1968).

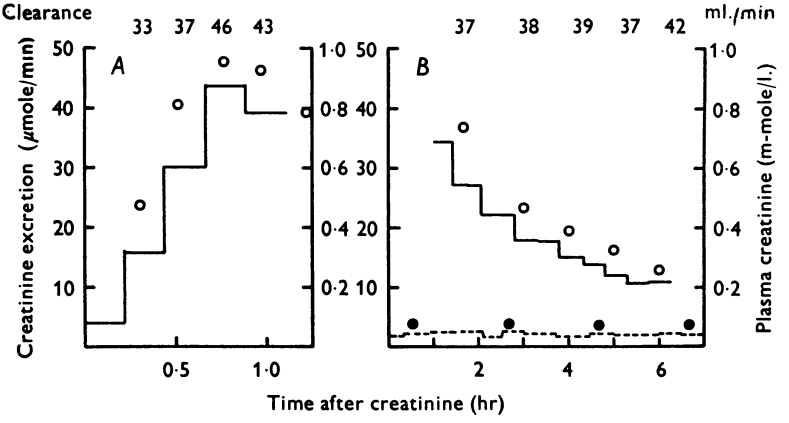

Fig. 1. Two experiments on Cleo in which 1 g (8·8 m-mole) creatinine was given by stomach tube in 50 ml. water at zero time. Abscissa, time after creatinine. Ordinates: rate of excretion of creatinine, μmole/min, —; plasma creatinine, m-mole/l., ○. The points ● and - - - - show plasma creatinine and rate of excretion in an experiment when no creatinine was given. Figures at the top are creatinine clearance, ml./min.

RESULTS

The excretion of creatinine given by stomach tube

Fig. 1*A* shows the plasma creatinine and rate of excretion of creatinine during the 60 min following the administration by stomach tube of 8·8 m-mole creatinine dissolved in 50 ml. water. Plasma creatinine and excretion rose to their maximum about 40 min after the dose and a similar time course was found in experiments on two other dogs. It seems that in the dog creatinine is quickly absorbed from the gut. Fig. 1*B* is an example of a control experiment on the plan of Table 1 where no meat was given and over the experimental period the excretion of creatinine fell in parallel with plasma creatinine concentration. In experiments where no creatinine was given, the measured creatinine concentration of the plasma was 0·07–0·14 m-mole/l. and the excretion 2·0–3·5 μmole/min without significant change during the experimental period. The excretion of exogenous creatinine could be calculated as the difference between the excretion in experiments like Fig. 1*B* and those when no creatinine was given; in ex-

periments on Lassie, Cleo and Cathy 4–5 m-mole of the dose of 8·8 m-mol was excreted in 6 hr after its administration by stomach tube.

In Fig. 2 the rate of excretion of creatinine is plotted against plasma creatinine in a series of five control experiments like Fig. 1*B* performed in one dog while the animal was being fed the same diet. The calculated regression line passes close to zero as it should for a substance filtered at the glomerulus and not re-absorbed or secreted by the tubules. Equally precise regression lines were found in five groups of experiments on four animals with the intercept on the *x*–axis 0·01–0·04 m-mole/l.

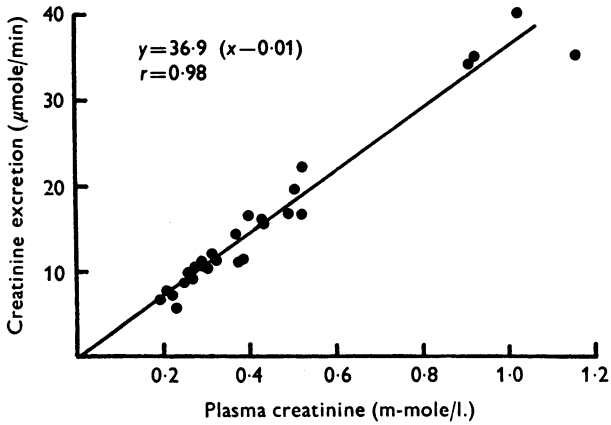

Fig. 2. Lassie. The rate of excretion of creatinine plotted against plasma creatinine in five control experiments.

Creatinine clearance in control experiments

The numbers at the top of Fig. 1*B* are the calculated ratio of creatinine excretion to plasma creatinine (i.e. plasma creatinine clearance). Fig. 1*B* is typical of thirty-one control experiments on eight dogs; control experiments are also shown in Fig. 3. In Table 2 the first column shows the mean creatinine clearance at 10.10 hr of the three dogs most used in these experiments and columns 2, 3, 4 the mean change from initial value on each day. The changes in control experiments were small in comparison with the effects of meat to be described later.

In Fig. 1*A* it seems that the first clearance determined during the rising phase of plasma creatinine and excretion might be lower than those obtained later after a dose of creatinine and that determined at the peak of plasma creatinine might be higher. Because of these doubts, the practice was to follow the protocol of Table 1 by which at least an hour had elapsed after the dose of creatinine before taking the first blood samples. The 10.10 hr values in Table 2 were with this delay.

Where no creatinine was given, the clearance of endogenous creatinine was not significantly different from the values in the same dog after administration of creatinine. In calculating exogenous creatinine clearances no correction has been made for endogenous creatinine.

TABLE 2. The exogenous creatinine clearance of three dogs at 10.10 over approximately 2 years; mean, S.D. and number of observations are given in column 3. Columns 4, 5, 6 show the change from the 10.10 hrs value when clearances were measured at approximately 12,10. 14.10 and 16.10 hrs in control experiments in the plan of Table 1; mean, S.E. of mean and number of observations

Dog	Weight (kg)	Creatinine clearance at 10.10 hr ml./min (mean ± S.D.)	Change in creatinine clearance, ml./min (mean ± S.E. of mean) at 12.10 hrs	14.10 hr	16.10 hr
Lassie	17·0–18·5	39·5 ± 4·2 (45)	−0·1 ± 1·8 (8)	−2·5 ± 1·8 (8)	−2·9 ± 3·0 (5)
Cathy	13·5–14·5	32·7 ± 5·6 (45)	−0·1 ± 1·8 (7)	−1·4 ± 1·4 (6)	+2·7 ± 0·4 (5)
Cleo	14·0–15·0	46·4 ± 8·3 (47)	−3·7 ± 2·1 (8)	−3·9 ± 1·6 (9)	−5·7 ± 2·9 (6)

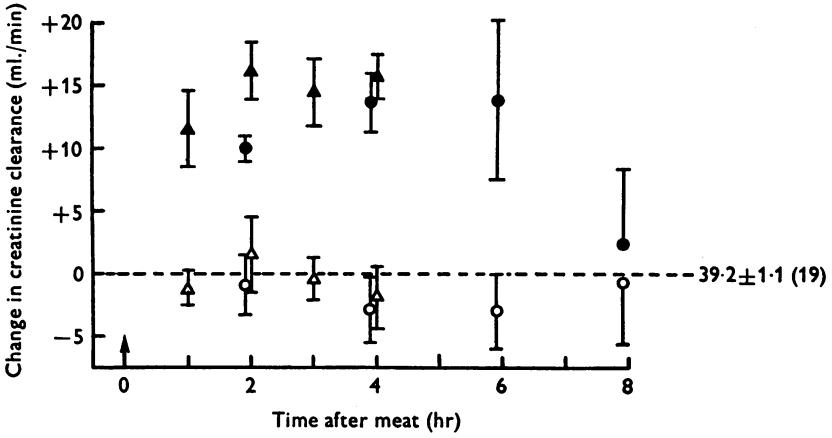

Fig. 3. Lassie. The effect on exogenous creatinine clearance of meat 10 g/kg. Meat was given at zero time on abscissa in hr. Ordinate is change in creatinine clearance from the initial value on each day at 10–10.30 hr, before the meat. The means and 1 S.E. of mean are shown in two series of experiments by different symbols: ● and ▲ are the means of three and seven experiments in which meat was given; ○ and △ five and four interspersed control experiments. The mean initial creatinine clearance was 39·2 ml./min ± 1·1 (S.E. of mean, n = 19).

The effect of meat

Meat always caused an increase in exogenous creatinine clearance; Fig. 3 shows the mean changes in creatinine clearance in control and meat experiments in two series on the one animal. In all meat, 10 g/kg was given

in thirty-three experiments on eight dogs with always similar increase in creatinine clearance, the results in the three animals used extensively being collected in Table 3. The increase in exogenous creatinine clearance after 10 g/kg meat, in comparison with control experiments (Table 2) was about 15 ml./min, 40 %. The clearance had increased at measurements 1 hr after the meat and appeared to be falling 6 hr after the meal. There were, however, too few observations to define the changes beyond 6 hr. In experiments where no creatinine was given, meat increased the endogenous creatinine clearance in the same way. The urine volume at 4 hr after the meat rose to 0·22 ± 0·05 ml./min (mean and S.D. of experiments in Table 3) in comparison to 0·12 ± 0·04 ml./min in control experiments of Table 2.

TABLE 3. The changes in exogenous creatinine clearance of three dogs when meat was given at 10.30 hr in the protocol of Table 1. The values are the differences from the value at 10.10 hr each day, when the clearance was measured at 12.10, 14.10, 16.10 hr, approximately 1½, 3½, 5½ hr after the meat. The mean, S.E. of mean and number of observation is shown

	Change in creatinine clearance, ml./min (mean ± S.E. of mean)		
	at 12.10 hr	14.10 hr	16.10 hr
Lassie	+ 14·1 ± 1·8 (10)	+ 15·2 ± 1·4 (10)	+ 13·9 ± 6·4 (3)
Cathy	+ 13·4 ± 2·3 (8)	+ 13·9 ± 1·9 (9)	+ 11·4 ± 2·7 (6)
Cleo	+ 5·0 ± 2·2 (9)	+ 8·5 ± 3·4 (8)	0 ± 2·6 (5)

The fact of increased xylose, creatinine or inulin clearance reported after large doses of meat by Shannon *et al.* (1932), Pitts (1935) and Moustgaard (1948) has thus been extended by the observation of a similar change in exogenous creatinine clearance after a 'normal' meal of 10 g/kg meat and with the urine flow within the normal range of 0·1–0·25 ml./min.

The effect of amino acids on creatinine clearance

Fig. 4 shows that 100 m-mole glycine given by stomach tube caused increase in creatinine clearance comparable in magnitude to that produced by meat. The increase was of shorter duration than after meat; in three experiments in which clearances were measured 2, 4, 6 hr after glycine in the protocol of Table 1, the creatinine clearance was increased by 3–7 ml./min. Measurements of urea in plasma and urine showed these to be raised from 1 hr after glycine indicating the rapid deamination of the amino acid.

In contrast when in four experiments on two dogs 50–100 m-mole creatinine was given by stomach tube there was no increase in exogenous creatinine clearance and no increase in plasma urea or urea excretion; creatine is not deaminated and there was no increase in creatinine clearance.

The composition of plasma after meat

Meat produced no fall in plasma protein concentration or packed cell volume, so that the increased creatinine clearance cannot be attributed to the effect of these factors on glomerular filtration. In connexion with the investigations of the excretion of individual substances, the plasma concentrations of urea, PO_4, SO_4, K were measured in some experiments. Only plasma urea increased considerably after the meat; there was a small increase in PO_4 and no significant change in the other measurements. The observed changes in plasma do not account for the increase in creatinine clearance.

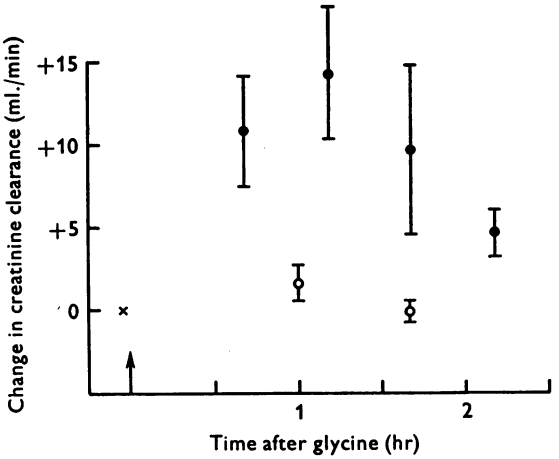

Fig. 4. The effect on creatinine clearance of 7·5 g glycine in 100 ml. water given by stomach tube at zero time. Plotting as in Fig. 3. ● is the mean of four experiments on two dogs and ○ the mean of four interspersed control experiments.

DISCUSSION

The main result in this paper is that an amount of meat similar to that forming a usual daily ration caused in dogs a substantial increase in creatinine clearance. Previously this has only been known with very large doses of meat and as pointed out by O'Connor (1962) its significance to normal renal function has remained uncertain.

It is always presumed that increase in exogenous creatinine clearance in the dog indicates increase in glomerular filtration rate. However, it might be argued particularly at the normal low urine flows of this work, that meat affects creatinine clearance by altering the flow or composition of fluid in the distal parts of the nephron to allow effective secretion of creatinine or to reduce an existing re-absorption. But the following points

go against this suggestion: (i) xylose and inulin clearances also increase after meat (Shannon *et al.* 1932; Pitts, 1935; Moustgaard, 1948); (ii) in control experiments creatinine excretion is directly proportional to plasma creatinine (Fig. 2), i.e. creatinine clearance is independent of plasma concentration as is required of a substance which is not secreted nor reabsorbed in the tubules. Shannon (1936) found that inulin and creatinine clearances were identical in the dog at low urine flows. Endogenous creatinine clearance is also increased; (iii) urea clearance increases in parallel with creatinine clearance (O'Connor & Summerill, 1976); (iv) after meat plasma SO_4 does not increase, but the excretion of SO_4 increases by an amount equal to the increase in filtered load calculated from creatinine clearance (W. J. O'Connor and R. A. Summerill, in preparation). Together these points strongly support the conclusion that the increase in exogenous creatinine clearance after meat records a real increase in glomerular filtration.

After large meat meals, associated with the increase in glomerular filtration rate Moustgaard (1948) found increased hippodin clearances and van Slyke, Rhoads, Hiller & Alving (1934) similarly calculated an increase in renal blood flow by the application of the Fick principle to the excretion of urea. In contrast Fronek & Fronek (1970) and Vatner, Franklin & van Citters (1970) using implanted flowmeters found no changes in renal blood flow after meat. Increased renal blood flow would indicate dilatation of the renal arterioles as the mechanism producing increased creatinine clearances. As yet, however, increase in renal blood flow after meat has not been clearly established.

Since Pitts (1935, 1944) and Moustgaard (1948) demonstrated that individual amino acids or protein hydrolysates by intravenous, I.V., infusion or by stomach tube could increase clearances, it has been accepted that amino acids or substances derived from them acted as dilators of renal arterioles producing increased renal blood flow and increased filtration. The doses of amino acids were, however, very large. In this paper a more reasonable dose of glycine by stomach tube produced (Fig. 4) increase in creatinine clearance of the same order as produced by meat. This adds support to the possibility that the increased glomerular filtration after meat is due to the entry into the circulation of amino acids. Moustgaard (1948) found that the amino acid concentration in peripheral blood rose and fell again within an hour of I.V. infusion of a hydrolysate of casein, whereas the increase in renal plasma flow and glomerular filtration lasted 3–4 hr. The renal effects are not therefore produced directly by the amino acids but are associated more with the time of their deamination. In accordance with this suggestion, creatine which is not deaminated caused no increase in glomerular filtration.

Although the deamination of amino acids yielded by meat seems to provide sufficient explanation for the recorded increase in clearances, several other possibilities can be suggested. For example, Liang (1971) has presented and discussed evidence for a reflex from the portal circulation to the kidney, but Rhoads, van Slyke, Hiller & Alving (1934) and Moustgaard (1948) found that with a large meat meal increase in glomerular filtration rate occurred in denervated kidneys. During digestion polypeptide hormones from the gut and also insulin enter the circulation; these are examples of many factors which might affect the kidney. It has been found, however, that meals low in protein do not increase clearances (Shannon *et al.* 1932; Pitts, 1935) and the effect is therefore regarded as specific to protein.

Table 2 gives the normal creatinine clearances for the three dogs used for most of these experiments, and creatinine clearances have also been determined by the same procedure in eleven other dogs. Comparison with other data can be best made by expressing the creatinine clearance/kg body weight. For fourteen dogs the mean in our laboratory has been 2·74 ml./min kg^{-1}, S.D. of deviation $\pm$ 0·54, range 2·2–4·2. This is lower than 'normal' clearances reported; by Houck (1948), 4·3 ml./min kg^{-1}, range 2·2–8·3 in seventy-five dogs; by Dupré & Coxon (1958), mean 5·2, range 3·5–6·1 in four dogs; by Stamler, Katz & Rodbard (1949) mean 4·8, six dogs. It thus seems that the values here reported as normal are about 40% lower than other reports.

Our measurements were made at normal urine flow of 0·1–0·3 ml./min, the use of doses of water or I.V. infusions of saline being avoided. The higher values of other authors may be due to the large doses of water or infusion by which the urine volume was raised to diuretic rates. Ramsay & Coxon (1967) found that the inulin clearance was less (3·33 $\pm$ 0·59 ml./min kg^{-1}) if no saline infusion was used, but still used water to raise the urine volume above 2·5 ml./min. In that the average of 2·74 ml./min kg^{-1} was obtained at normal urine flow it may be more correctly regarded as normal than those higher values obtained after large amounts of water or saline. A second factor which could affect 'normal' clearances is the diet and the time after the last meal. Meat, and possibly other protein food, increases glomerular filtration for many hr. No useful comparison is however possible as the examples in the literature do not state the dietary regime with sufficient accuracy.

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