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CONCEALED GLOMERULAR FILTRATION

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SUMMARY

1. An increase in apparent renal clearances is frequently observed on restoring urine flow after a period of anuria or on increasing it after oliguria. An analysis of such 'peaks' in clearance has been made in experiments on anaesthetized dogs, using two preparations of labelled vitamin B_{12} and urine collections of 1–2 min. [^{57}Co]B_{12} was infused throughout the experiments, while [^{58}Co]B_{12} was given as a single injection during periods of anuria or oliguria induced by noradrenaline infusion, haemorrhage or aortic obstruction.

2. The apparent high clearance in the first minute or two of restored or increased flow is an artifact explained by inclusion in the peak of material filtered earlier, but not excreted. By means of the integrated plasma concentration ratio of the two B_{12} isotopes during the period of low or absent flow, the excess B_{12} in the peak may be reapportioned between the period before the ^{58}Co was injected and the period after it.

3. The findings indicate that filtration may temporarily continue during anuria, but this is concealed as a result of failure of onward flow of filtrate. In oliguria a similar concealment of filtration may result from the cessation of onward flow in some nephrons.

INTRODUCTION

The cessation of urine flow is usually assumed to mean the cessation of glomerular filtration. It is possible, however, that filtration may continue in some or all nephrons, but that reabsorption of the reduced volume of filtrate is so nearly complete that no onward flow results. Similarly, oliguria is commonly taken to reflect a uniform reduction of onward flow in the nephrons. But here a differential reduction of nephron function may be postulated, resulting in a temporary storage of filtered material in some nephrons, while onward flow proceeds in others. If such

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an hypothesis is correct, some or all of the non-reabsorbable molecules filtered during a period of anuria or oliguria would accumulate in the renal tubules, ready for discharge when urine flow was restored. Evidence in support of this concept was provided by the following studies, which afford an explanation of the apparent increase in renal clearances that so frequently accompanies an increase in urine flow.

METHODS

Dogs weighing 10–32 kg were anaesthetized by the intravenous administration of pentobarbitone (30 mg/kg body weight). A jugular or forearm vein was cannulated for the infusion of fluids. One femoral artery was cannulated for recording blood pressure by a mercury manometer and the other for blood sampling. The ureters were approached through a low abdominal incision and catheterized with polythene tubing having a maximal combined volume of 0·4 ml.

The glomerular filtration rate (G.F.R.) was estimated by the clearance of [^{57}Co] vitamin B_{12} (Nelp, Wagner & Reba, 1964) and effective renal plasma flow by [^{125}I] orthoiodohippurate ('Hippuran'), both given by infusion. The doses of radioactivity employed were 2–3 μc of [^{57}Co]B_{12} and 4–6 μc of Hippuran, dissolved in 200 ml. of normal saline or 5% dextrose solution, and infused by a Sigmamotor pump at a rate of 1–2 ml./min. The resulting plasma levels of both isotopes usually lay between 200 and 400 counts/ml./min. During periods of anuria or oliguria the infusion was stopped or slowed so as to maintain the plasma level as constant as possible. In the course of some experiments a rapid intravenous injection of 2–3 μc of [^{58}Co]B_{12} was given to enable further analysis of clearances to be made.

Urine collection periods varied between 1 and 4 min. Volumes of urine were measured gravimetrically. Arterial blood samples were taken at 2–6 min intervals and centrifuged within 30 min of collection. The protein-bound and free fractions of the isotopes were separated by charcoal fractionation and subsequent clearance calculations were based on the free counts only. Urine samples were diluted if necessary to obtain a uniform volume for counting. The activities of the isotopes in 1 ml. of urine or plasma were measured simultaneously in a Packard Auto-Gamma spectrometer, incorporating a 3 in. well-type crystal assembly, using two or three channels as necessary. Calculations of the corrected sample activities were carried out on an Elliott 803 computer, programmed to solve the simultaneous equations derived from the counter results and to calculate the standard errors of the counts.

Clearances were calculated from simultaneous plasma and urine values when the plasma level was steady, and with application of the appropriate delay time when the level was changing (Ekins, Nashat, Portal & Sgherzi, 1966).

RESULTS AND INTERPRETATION

Anuria and oliguria following noradrenaline infusion

Figure 1 shows the effects of an infusion of noradrenaline on Hippuran and B_{12} clearances, filtration fraction and urine flow. The infusion produced a rise in mean blood pressure from 160 to between 210 and 230 mm Hg, with an increase in filtration fraction and urine flow. On stopping the infusion the resulting fall in blood pressure (to 130 mm Hg) was followed by anuria. After 6 min an injection of 2 μc of [^{58}Co]B_{12} was given intra-

venously. Since this isotope is dealt with by the kidney in an identical manner to $^{57}[Co]B_{12}$ it serves as a convenient marker of glomerular filtration. After a further 12 min of anuria a small quantity of urine was aspirated from one of the ureteric catheters; this was found on analysis to contain $[^{58}Co]B_{12}$ as well as $[^{57}Co]B_{12}$. Immediately afterwards a rapid intravenous injection of 100 ml. 20 % mannitol solution was given, which resulted in a return of urine flow within 2 min.

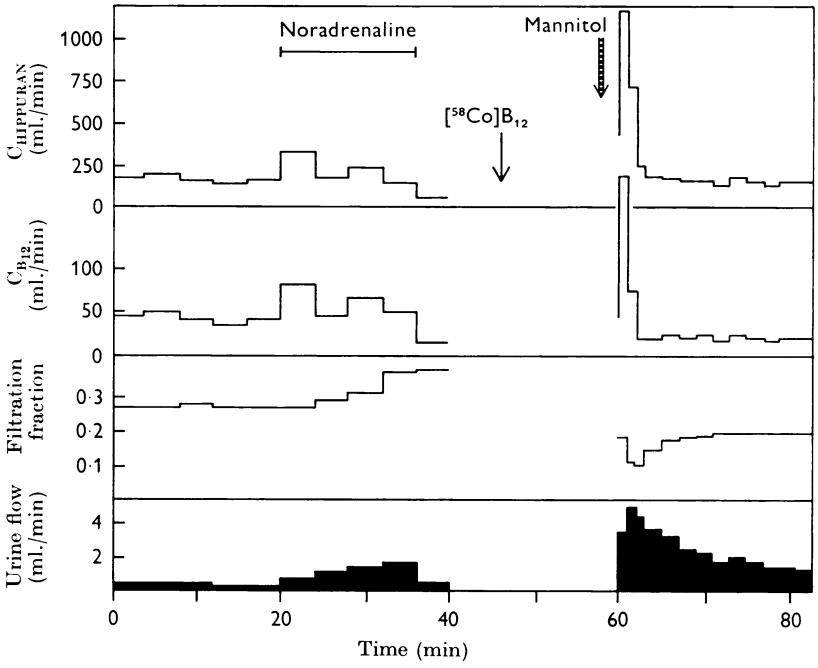

Fig. 1. Dog (female, 14·5 kg). Effects of noradrenaline infusion (20 μg/min in period 20–25 min, 30 μg/min 25–36 min). An increase in filtration fraction and urine flow is seen during the infusion, but on stopping it urine flow ceases. $[^{58}Co]B_{12}$ was injected rapidly at the first arrow. After 14 min anuria flow was restarted by mannitol (second arrow). Note the large peaks in apparent clearance of B_{12} and Hippuran in the first minute after resumption of flow (the ^{57}Co clearance only is shown; for comparison with ^{58}Co clearance see Fig. 2).

The pattern of serial clearances of the two B_{12} isotopes is shown in detail in Fig. 2. The mean ^{57}Co clearance for the control period was 45 ml./min. The urine passed after restoration of flow by mannitol was collected every minute for 3 min, then every 2 min, and contained both $[^{57}Co]$- and $[^{58}Co]B_{12}$, thus enabling the clearances of the two isotopes to be calculated. For this purpose a renal delay time of 2 min was assumed, this being the interval between the injection of mannitol and the first appearance of urine. This correction is necessary for ^{58}Co owing to the

falling plasma concentration of this isotope, though it will only slightly affect the clearance values of ^{57}Co in which the plasma level was maintained by infusion.

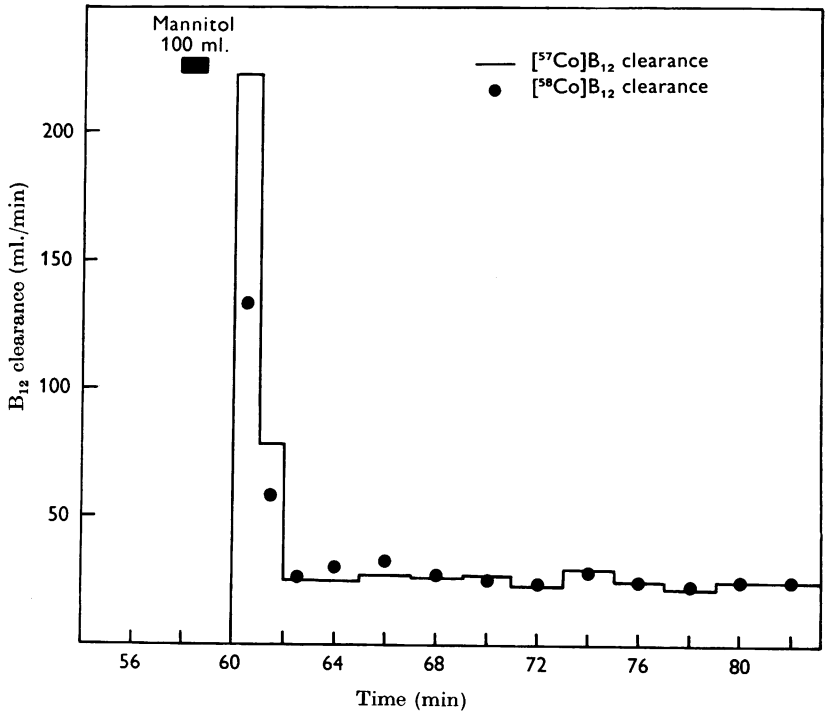

Fig. 2. Detail of same experiment as Fig. 1, comparing the clearances of the two B_{12} isotopes in the period after restoration of urine flow. Note the discrepancy between the two values in the first 2 min, and the close agreement thereafter (^{57}Co, continuous line; ^{58}Co, filled circles).

The striking feature of the clearance pattern is the large peak in apparent clearance of $[^{57}Co]B_{12}$ and the smaller peak in ^{58}Co clearance during the first minute after resumption of flow. The second minute shows smaller peaks, again with a discrepancy between the clearance of the two isotopes. Thereafter close agreement between the two clearances is seen for the remainder of the experiment, the mean value for ^{57}Co being 25·4 and that for ^{58}Co 26·5 ml./min. Such agreement has been regularly observed in comparisons of labelled B_{12} clearances when one is based on a steady and the other on a falling plasma concentration, provided the appropriate correction has been made for renal delay time (Ekins *et al.* 1966).

During the first minute after restoration of flow the calculated ^{57}Co clearance is 223 ml./min and that of ^{58}Co is 133 ml./min, assuming a

delay time of 2 min. This discrepancy is such that the assumption of a longer delay time could only augment the difference by increasing the concentration of ^{58}Co used in the clearance equation. It follows that the apparent high ^{57}Co clearance of 223 ml. does not represent the true value for this particular period (1 min), but is an artifact caused by a dissociation between the volume of urine collected in this period and its corresponding B_{12} concentration. One must therefore conclude that some fraction of the isotope obtained in this period had been filtered earlier. The discrepancy between the size of the peaks may then be explained by the difference in the times during which the two isotopes were available for filtration. By the same argument one may postulate that the ^{58}Co peak is also an artifact and that some of this isotope also had been filtered during the 14 min of anuria since it was injected.

It is reasonable to assume that the true clearance during this first minute differs but little from the mean clearance of the isotopes after the peak. If this value (26 ml./min) is deducted from the apparent peak value of each isotope we are left with an excess ^{57}Co clearance of 197 ml. (223 – 26) and an excess ^{58}Co clearance of 107 ml. (133 – 26). But since the clearance of the two isotopes must be identical during any given period, the total ^{57}Co clearance for the 14 min between the administration of the ^{58}Co and the restoration of urine must also be 107 ml. The mean clearance for this period is therefore 107/14 or 7·6 ml./min. This leaves a ^{57}Co clearance of 90 ml. unaccounted for (197 – 107); if this were filtered during the 6 min of anuria before the injection of ^{58}Co, the mean clearance for this period would be 15 ml./min. In this calculation the excess B_{12} in the second minute after restoration of flow has been ignored for simplicity. Were it included, the clearance values for the period of anuria would be somewhat greater.

An important objection to this line of argument arises from the fact that the ^{58}Co plasma concentration was falling as a result of the injection of this isotope as a single dose. Since it is postulated that filtration was proceeding during the period of anuria, the validity of ^{58}Co clearances becomes questionable owing to the uncertainty of the correct plasma level to use in the clearance equation. A delay time of 2 min is clearly not appropriate in a situation where the ^{58}Co obtained in the first urine of resumed flow could have been filtered at any time during the preceding 14 min. Another approach to the problem was therefore adopted.

If the continuation of filtration during anuria be conceded, then the plasma concentration of either isotope appropriate in the clearance formula for the first minute of resumed flow ('peak' urine) must be a mean of the plasma concentration throughout the period of anuria. After injection of the $[^{58}Co]B_{12}$, moreover, the ratio of the mean plasma concentrations of

the two isotopes must be reflected in the 'peak' urine. Thus we may write

$$\bar{P}_{58}/\bar{P}_{57} = (U_{58}.V)/(U_{57}.V).$$

where $\bar{P}$ represents the mean plasma concentration during the period of anuria, U the concentration in the 'peak' urine, V the volume of the 'peak' urine, and the suffixes 57 and 58 the two isotopes. From this it follows that the fraction of ^{57}Co in the 'peak' urine filtered after the administration of ^{58}Co is given by $(\bar{P}_{57}.U_{58}/\bar{P}_{58}$. The fraction of ^{58}Co filtered before the ^{58}Co injection may then be obtained by subtracting the quantity found above from the total ^{57}Co filtered during the period of anuria. Calculated in this way, the mean B_{12} clearance for the period after the ^{58}Co injection becomes 5·6 ml./min and for the period before ^{58}Co administration 20 ml./min. These figures differ from the values given earlier only because in the recalculation the mean ^{58}Co plasma level over the period of anuria was employed instead of the level 2 min before the 'peak' urine.

In the above analysis the excess clearance in the 'peak' urine has been distributed only over the period of anuria. This is probably an unjustifiable procedure, for some of the [^{57}Co]B_{12} in the 'peak' urine may have been filtered before urine flow ceased, and the clearance in the period before the anuria must thus have been underestimated. To this extent therefore the distribution of the excess B_{12} is arbitrary, though the validity of the argument remains unaffected.

Figure 3 shows the urine flow and [^{57}Co]B_{12} clearance in an experiment in which a noradrenaline infusion resulted not in complete anuria, but in a reduced urine flow of between 0·1 and 0·2 ml./min. A single injection of [^{58}Co]B_{12} was given during the oliguria, followed 12 min later by 100 ml. of mannitol. A large peak in apparent clearance again accompanied the first 2 min period of increased urine flow. In this case the clearance of the two isotopes showed no discrepancy in the peak period because the excess ^{57}Co present in the tubules before the ^{58}Co injection had appeared in the urine before the mannitol was given.

Anuria or oliguria produced by haemorrhage or mechanical reduction of renal artery pressure

Similar peaks in clearance have been observed following the anuria produced by haemorrhage. Figure 4 illustrates such an experiment. The animal was bled rapidly (about 500 ml.) and the resulting anuria was terminated after 14 min by an injection of mannitol. In the first minute of resumed flow the apparent clearances of the two isotopes are 150 ml. for ^{57}Co and 63 ml. for ^{58}Co. The true clearance during the minute of the peak is taken as 15 ml., this being the mean clearance after the peak. Redistribution of the excess ^{57}Co clearance using the mean plasma ratio

method described above gives a clearance of 112 ml. in the 3 min of anuria before the ^{58}Co injection, and 23 ml. in the 11 min after it. Again it is likely that filtration in the period immediately preceding the cessation of urine flow was underestimated, and that filtration actually tailed off somewhat in the manner shown by the interrupted line in Fig. 4.

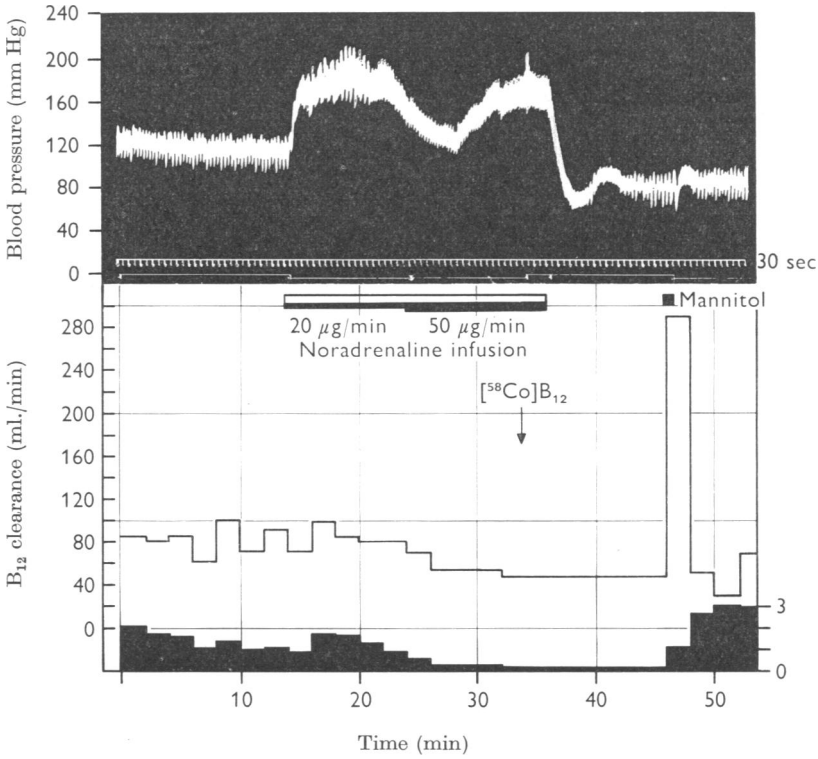

Fig. 3. Dog (male, 15 kg). Effects of noradrenaline infusion on blood pressure (recorded from femoral artery), B_{12} clearance and urine flow. [^{58}Co]B_{12} injected at arrow. Anuria was not produced, but a large peak in clearance occurs when urine flow is increased by mannitol. The ^{58}Co clearances in this case are similar to the ^{57}Co values, and are omitted.

In a further haemorrhage experiment the injection of ^{58}Co was delayed till 6 min after the urine flow had stopped. Though a peak in the ^{57}Co clearance was again seen on inducing a mannitol diuresis, the ^{58}Co clearance was much smaller and hardly differed from the subsequent post-peak values (Table 1). In this case therefore it was concluded that little if any filtration took place after the ^{58}Co was injected.

Figure 5 shows a large peak in clearance in an experiment in which renal artery pressure was lowered by inflating a balloon in the aorta above

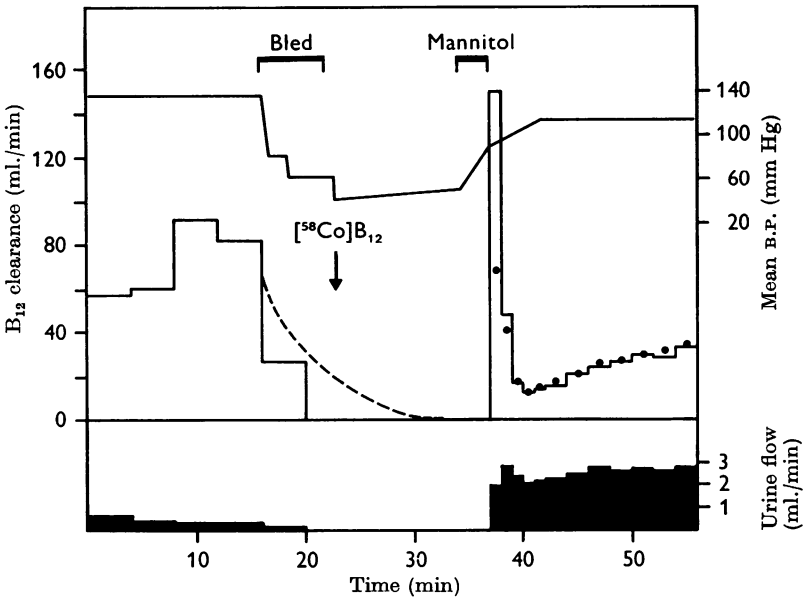

Fig. 4. Dog (male, 17 kg). Effects of haemorrhage on B_{12} clearance. The animal was bled 500 ml. during period shown by the signal. ^{58}Co was injected after 3 min anuria (arrow). A peak in the apparent clearance of both isotopes occurs when urine flow is restored by mannitol (^{57}Co, continuous line; ^{58}Co, filled circles). The interrupted line indicates a possible mode of decline of filtration during and after bleeding.

TABLE 1. B_{12} clearances before and after anuria produced by haemorrhage

Time (min)	^{57}Co clearance (ml./min)	^{58}Co clearance (ml./min)
0–12	66	—
12–30	Anuria	
30–32	71	25
32–34	19	21
34–36	14	15
36–38	12	14

the origins of the renal vessels. Mean urine flow was reduced from 0·54 to 0·06 ml./min. On releasing the balloon a peak in apparent clearance more than twice the control value occurred when urine flow was restored to its former level.

DISCUSSION

The validity of renal clearance under changing conditions has rightly been questioned, especially when urine flow is small or inconstant. Smith (1951) commented on a 'suspicious increase' of clearances when urine flow was suddenly increased, and Schmidt-Nielsen (1958) applied the terms 'exaltation' and 'abatement' to the rise and fall of urea clearance that accompanied alterations of flow. For this reason a period of equi-

libration is often allowed after any change in experimental conditions before the definitive period for clearance measurements is started. Since the duration of urine collections commonly employed is 15 min or longer the sequence of events at the time of a change in conditions has tended to escape analysis. In a recent study of filtration rate using labelled vitamin B_{12} and 2 min urine collections (Ekins *et al.* 1966) we were impressed by the frequency and magnitude of the peaks in the apparent clearance of the vitamin in a variety of conditions in which urine flow was suddenly increased or restored.

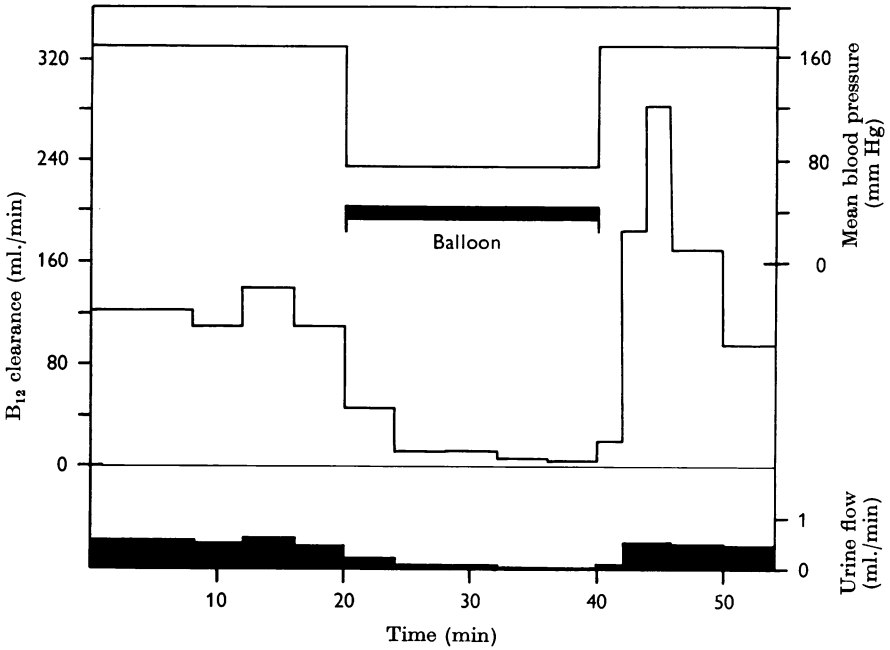

Fig. 5. Dog (male, 32 kg). Effects of lowering renal artery pressure by inflation of a balloon in the aorta above the origins of the renal vessels. Blood pressure (shown schematically above) was recorded from femoral artery and is assumed to reflect the renal artery pressure. Note the peak in apparent [^{57}Co]B_{12} clearance when urine flow is restored on release of the balloon. (^{58}Co was injected at 29 min; subsequent clearance values are similar to ^{57}Co, and are omitted.)

The transience of these peaks and the frequent lack of a physiological explanation for them indicated that they did not represent the true clearance during the periods in question, but were the result of a dissociation between the increased volume of urine and its appropriate B_{12} concentration. Once they were accepted as artifacts it followed that some of the B_{12} recovered must have been filtered at an earlier period, and therefore that the clearance had at some previous time been under-

estimated. The term 'concealed filtration' may reasonably be applied to this filtration which continues but which is not immediately detectable.

In the above experiments the peaks in apparent clearance were most striking after the anuria produced by a noradrenaline infusion. The analysis of ^{58}Co and ^{57}Co excretion by means of the isotope ratios provides strong evidence for the continuation of filtration during the period of anuria, as does the finding of ^{58}Co in the ureteric catheter during this period. The possibility of tubular secretion of B_{12} must, however, be considered. The cyanocobalamin molecule, though smaller than inulin, is some 5 times larger than that of creatinine, and there is no evidence at present in favour of its secretion by the tubules (Nelp *et al.* 1964). Moreover, under the conditions of the present experiments the oliguria or anuria is accompanied by a high concentration of B_{12} in the filtrate, so that passage of the substance across the tubular cells would have to take place against a very high gradient. In circumstances in which filtration might reasonably be expected to have stopped, no peak in clearance was seen. An example of this is shown in Table 1, where no peak in ^{58}Co clearance occurred on resumption of flow.

Peaks identical in timing, though smaller, were observed in the anuria following haemorrhage. Their possible occurrence in this context was considered by Peters & Brunner (1963) when studying the effects of mannitol on urine flow in post-haemorrhagic hypotension. These authors demonstrated that urine flow could be restarted by a mannitol infusion at systemic blood pressures between 35 and 50 mm Hg, findings which we have confirmed on many occasions. The question arose whether the diuretic action of mannitol in these conditions was due to the addition of osmotically active particles to a small amount of filtrate actually being formed during the anuria, or whether the agent started filtration *de novo*. In discussing this, Peters & Brunner favoured the latter mechanism and pointed out that if filtration had continued during the anuria, the first urine to appear on restoring flow would be expected to contain a large quantity of clearance substance. This they failed to observe. The pattern of clearances illustrated above, however (Fig. 4, Table 1), shows how such an increase would be masked by a pooled 10 or even 5 min urine collection, and supports the view that filtration may continue at a reduced level for a while after the cessation of urine flow. Further evidence for this was provided by Coelho & Bradley (1964) who studied the tubular maximum (T_m) of glucose and diodrast in graduated haemorrhagic hypotension in dogs. They found a progressive diminution of tubular function as blood pressure and G.F.R. were reduced, and suggested that this might be ascribed to the cessation of function in successive fractions of the nephron population as filtration pressure fell. Though it is probable that mannitol

exerts its diuretic action in these circumstances by its haemodynamic and mechanical effects (Lilien, Jones & Mueller, 1963), a contributory osmotic effect on pre-formed (or 'concealed') filtrate is by no means unlikely.

The peaks in apparent clearance demonstrable on a sudden increase of urine flow may bear a similar interpretation to the post-anuria peaks. It may be argued, however, that in oliguria (whatever its cause) a steady state will eventually be reached in which the quantity of B_{12} filtered in unit time will equal the quantity obtained at the collecting site, so that the true clearance will be manifest. None the less, the excess output of B_{12} apparent on an increase in flow must have been filtered in an earlier period, and if this can be delineated the excess material may be re-distributed accordingly. The greater the peak in clearance and the shorter the period of oliguria, the greater must have been the underestimation of the clearance during this time. The B_{12} filtered but not collected is stored in the renal 'dead space'. The storage of clearance substances in the kidney at low urine flows (less than 0·4 ml./min. 100 g. of kidney) was demonstrated by Balint, Fekete & Forgacs (1964). After infusing inulin and *p*-amino-hippuric acid (PAH) for an hour, during which renal blood flow was measured by a direct method, they removed the kidney, ground it and measured its content of inulin and PAH. They found that the excess material recovered accounted almost quantitatively for the underestimation of the conventionally calculated clearances. The exact site and volume of this storage space are not known, but in the present context we take it to include all areas between the glomeruli and the collecting site. The studies of Bojesen (1949) on the volume of the renal pelvis indicate that this decreases linearly with urine flow, and approximates to the minute volume. It seems likely that the smaller tubular spaces behave similarly, and that during anuria or extreme oliguria the total dead space is very small.

Since the original direct observation of intermittent nephron function in the frog's kidney by Richards & Schmidt (1924) support has accumulated for the idea that glomerular filtration is not an 'all or nothing' phenomenon. The evidence for the diversity of nephron structure and function was reviewed by Bradley & Wheeler (1958). The present findings are best explained by a grading of nephron function, which is not recognizable in a steady state experiment, but which manifests itself when conditions are rapidly changed.

The common factor in the apparent peaks in clearance described above is the temporary storage of B_{12} in the kidney, associated with continuing water reabsorption and a consequent increase in the urine/plasma B_{12} ratio. When the balance of filtration and reabsorption is altered in such a way as to reduce the volume of onward flowing filtrate, the mean transit time of filtrate through the tubules will eventually be prolonged, until

anuria ensues and the transit time is infinite. Owing to differences in the structure or perfusion of nephrons, however, the rate of flow of filtrate is not uniform, with the consequence that while onward flow continues in some nephrons (manifest filtration), in others it is reduced or halted, even though filtration itself temporarily continues (concealed filtration). This explains the accumulation of B_{12} during a limited period of oliguria, with the associated underestimation of clearance and the appearance of the 'peak' when urine flow is increased. The same argument applies to anuria in which onward flow of filtrate is totally halted, despite the temporary formation of a reduced volume of filtrate. The process of concealed filtration is necessarily a transient phenomenon, for the capacity of the tubules to harbour non-reabsorbable molecules is limited.

A somewhat similar situation pertains during occlusion of the ureters (stopflow). Here again, filtration may continue despite the absence of urine flow (Taylor & Ullman, 1961), and studies of glucose T_m have suggested a progressive drop-out of functioning nephrons as intra-ureteric pressure is raised (Malvin, Kutchai & Ostermann, 1964; Selkurt, Deetjen & Brechtelsbauer, 1965). Under these conditions, as in those discussed above, the net filtering force at the glomeruli is reduced.

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