THE RELATIONSHIP BETWEEN GLOMERULAR FILTRATION AND SODIUM EXCRETION

by

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INTRODUCTION

According to current views concerning renal function, the glomerular filtrate is a dialysate of blood plasma.(1) Diffusible constituents of plasma pass through the glomerulus to appear in the filtrate in concentrations almost identical to the concentrations in blood plasma while cellular elements and plasma protein are retained in the blood. As the filtrate proceeds along the lumen of the tubule, various constituents are absorbed, and possibly a few physiologic substances are secreted by the tubular epithelium. The fluid within the tubules gradually assumes the composition of bladder urine, largely as a result of differences in rates of absorption of substances from the tubular lumen. In this study, attention is focused on the relationship between the amount of sodium filtered and the amount excreted.

Disturbances of cardiovascular functions frequently are accompanied by marked changes in body hydration and in the volumes of the fluid compartments.(2) For example, in chronic congestive heart failure(3) and in systemic arteriovenous fistula,(4) the total body water, interstitial fluid volume, and plasma volume are found to be considerably elevated. These conditions frequently are associated with a subnormal renal blood flow and a decreased glomerular filtration rate.(5,6) Sodium is the principal constituent of the extracellular fluid and without sodium it is not possible to establish and maintain an elevated extracellular fluid volume. Therefore, it is evident that, in conditions characterized by an increase in extracellular fluid, sodium is being retained in the body. Retention of sodium in the presence of a normal plasma concentration could be accomplished either by a decrease in glomerular filtration or by an

increase in the rate of absorption of sodium from the tubule.

In the normal human, about 125 cc. of water containing about 1100 mg. of sodium are filtered through the glomeruli each minute. By the time this fluid reaches the bladder the water has decreased to about 1.0 cc. and the sodium to about 5 mg.(7) If a subject ingests large quantities of water, or receives glucose in water intravenously, the volume of urine is increased to about 10 to 15 cc. per minute but the actual amount of sodium excreted is changed little, if any.(8) Conversely, a high salt intake will cause a corresponding increase in excretion of sodium in the presence of a normal or decreased water output. On the other hand, in the presence of a decreased pressure in the glomerulus the excretion of both sodium and water is reduced. Measurement of the volume of urine excreted during any time interval provides little or no useful information concerning renal function except in the presence of a very low or a very high water intake.

The kidney is not influenced directly by the volume of any fluid compartment but will respond to changes in composition of the blood and to changes in renal circulation. Changes in the volume of the fluid compartments are accompanied by changes in renal circulation. Since various disturbances of circulation are characterized by a decreased glomerular filtration rate and an increased extra-cellular fluid volume, it is of interest to study the effects of changes in filtration rate on the excretion of sodium. Theoretically, either of two types of result could be obtained. If sodium is absorbed by the tubule at a constant rate, as long as an amount more than the tubule can absorb is presented to it, the ratio of sodium filtered to sodium excreted would be constant at any given filtration rate. On the other hand, if the amount of sodium which the tubular

epithelium can absorb, i.e. the threshold for sodium, is raised or lowered under various conditions, a more complex relationship between the tubular load and the amount of sodium excreted will be observed. In the latter case it should be possible to demonstrate experimentally that different rates of sodium excretion may occur in the presence of a given glomerular filtration rate, or that sodium excretion and glomerular filtration rate may change in opposite directions.

One method of causing a decrease in glomerular filtration rate is to remove from the animal a measured amount of blood. A moderate hemorrhage causes a considerable decrease in renal blood flow and a lesser decrease in glomerular filtration rate.(9) This method has been used in the present study.

REVIEW OF THE LITERATURE

Until recently there has been no experimental work bearing on this problem. During the past few years studies related to the subject, involving patients with congestive heart failure, have been performed. Merrill(5,6) and Mokotoff et al(10) concluded that sodium retention in congestive heart failure is caused by a decreased glomerular filtration rate and not by any increase in absorption of sodium from the tubule. However, Farnsworth(11) came to opposite conclusions, namely, that the positive sodium balance associated with cardiac decompensation is caused by an increased tubular absorption of sodium. Kattus et al(12,13) subjected normal controls and one patient with cardiac failure to a standard exercise test. They found no significant change in either serum sodium level or in glomerular filtration rate during exercise, but sodium excretion was decreased. The retention of sodium, attributable to increased

tubular reabsorption, persisted for an average of 37 minutes after the end of the exercise period.

Selkurt, Hall and Spencer(14) studied glomerular filtration and sodium excretion in anesthetized dogs receiving infusions of saline, mannitol, creatinine and p-amino-hippurate. In their experiments renal blood flow was decreased unilaterally by means of a clamp on the abdominal aorta between the two renal arteries. They concluded that decreases in sodium excretion produced by this method could be explained by decreases in the amount of sodium filtered; however, examination of their data indicates the necessity of qualifying this conclusion. Green and Farah(16) studied the changes in sodium excretion produced by administering saline to anesthetized dogs. They state, "The resultant rise in sodium excretion was found due almost entirely to a decrease in its tubular reabsorption. No consistent change in glomerular filtration rate was demonstrated."

Wesson, Anslow and Smith(15) have recently written a critical review on excretion of strong electrolytes. However, they have not published data related to the problem under consideration here.

No reports have been found concerning studies comparing glomerular filtration and sodium excretion in experimental animals not receiving sodium intravenously.

METHODS

Nine dogs weighing between 6.6 and 14 kg. were used. Eight of these animals received sodium pentobarbital, and one received one-half grain morphine sulfate. All of the dogs were in an adequate state of nutrition and hydration and had received similar diets prior to the experiments. Immediately after anesthetization an intravenous infusion of 5% glucose

in water was started. This infusion was continued, usually at a rate of about 100 drops per minute, until a total of 900 to 1000 cc. was given. The purpose of this infusion was to insure a volume of urine flow sufficient to minimize the effects of the small "dead space" from the distal convoluted tubule to the catheter.

Two techniques of urine collection were used. In dogs 1-4 the abdomen was opened, both ureters were exposed, ligated and severed, and small polyethylene tubes were inserted proximally to the renal pelves. These tubes were allowed to drain into a graduated cylinder or a volumetric flask. In dogs 5-9 no operative procedures were done; an 8-French soft rubber catheter was introduced into the bladder and was allowed to remain in place throughout the experiment. Urine was collected during measured time periods. At the end of each collection period the bladder was rinsed with distilled water. No attempt was made to measure accurately the actual volume of urine produced per unit of time. The urine collected during each successive period was diluted to a definite volume with distilled water, and a small thymol crystal was added to each flask. The concentration of sodium and creatinine per cc. were determined and multiplied by the dilution factor to obtain the totals excreted during each collection period.

Blood for creatinine determinations was collected from the femoral vein or the femoral artery or both. The blood was allowed to clot, the serum removed and a 1:5 filtrate made by mixing one volume of serum with three volumes of water and one volume of 20% trichloracetic acid. This combination was mixed and filtered.

Sodium determinations in experiments 1-7 and 9 were done with a Perkin-Elmer flame photometer using direct intensity sodium standards. The determinations for experiment 8 were done with a Barclay flame photometer

using an internal lithium standard.

The endogenous creatinine clearance was used as a measure of glomerular filtration rate. In order to establish the proper degree of urine dilution, a qualitative creatinine test was devised as follows:

Qualitative Creatinine Test

Reagents:

Creatinine standard: 4 micrograms per cc.

Alkaline picrate solution: 1 volume 10% sodium hydroxide and 5 volumes 0.04 M picric acid.

Technique:

One cubic centimeter of alkaline picrate solution is added to 2 cc. of the urine dilution, the standard, and a water blank. The colors are compared after 5-10 minutes. The urine is further diluted as necessary to approximate the standard.

Quantitative creatinine determinations were done by the method of Hare and Hare(17:

Reagents:

1) Standard Creatinine Solutions: A stock standard was made containing 1.0 mg. creatinine per cc. in 0.1 N hydrochloric acid. Further dilutions were made as needed. The working standard in most experiments was 4 micrograms per cc. All standards were kept under refrigeration with a small crystal of thymol as a preservative.

2) Oxalic acid. Saturated aqueous solution.

3) Lloyd's reagent. Hydrated aluminum silicate.

4) Alkaline picrate.

5 parts 0.04 M picric acid
1 part 10% sodium hydroxide
12 parts water

This solution was mixed just before use.

Technique:

Five cubic centimeter aliquots of serum filtrate, urine dilution, creatinine standard, and water are pipetted into round-bottomed centrifuge tubes. One-half cubic centimeter of oxalic acid is added, and this is followed by approximately 40 mg. of Lloyd's reagent.

The tubes are agitated for two minutes, centrifuged, and the supernatant discarded. Then 10 cc. of alkaline picrate solution is added to the packed sediment and the mixture is allowed to stand, with occasional shaking, for ten minutes. After centrifugation, the supernatant is transferred to an absorption cell and read in a Coleman Jr. spectrophotometer set at a wave length of 500λ. A reagent blank is used for the 100% transmission setting and readings are made directly from the density scale, where density equals two minus the log of the percent light transmission.

It has been demonstrated that within the range of concentrations of creatinine determined, the optical density is proportional to the creatinine concentration.

RESULTS

Protocols of the experiments are presented below, and the rates of glomerular filtration in cubic centimeters per minute and sodium excretion in mgs. per minute are graphed in the corresponding figures.

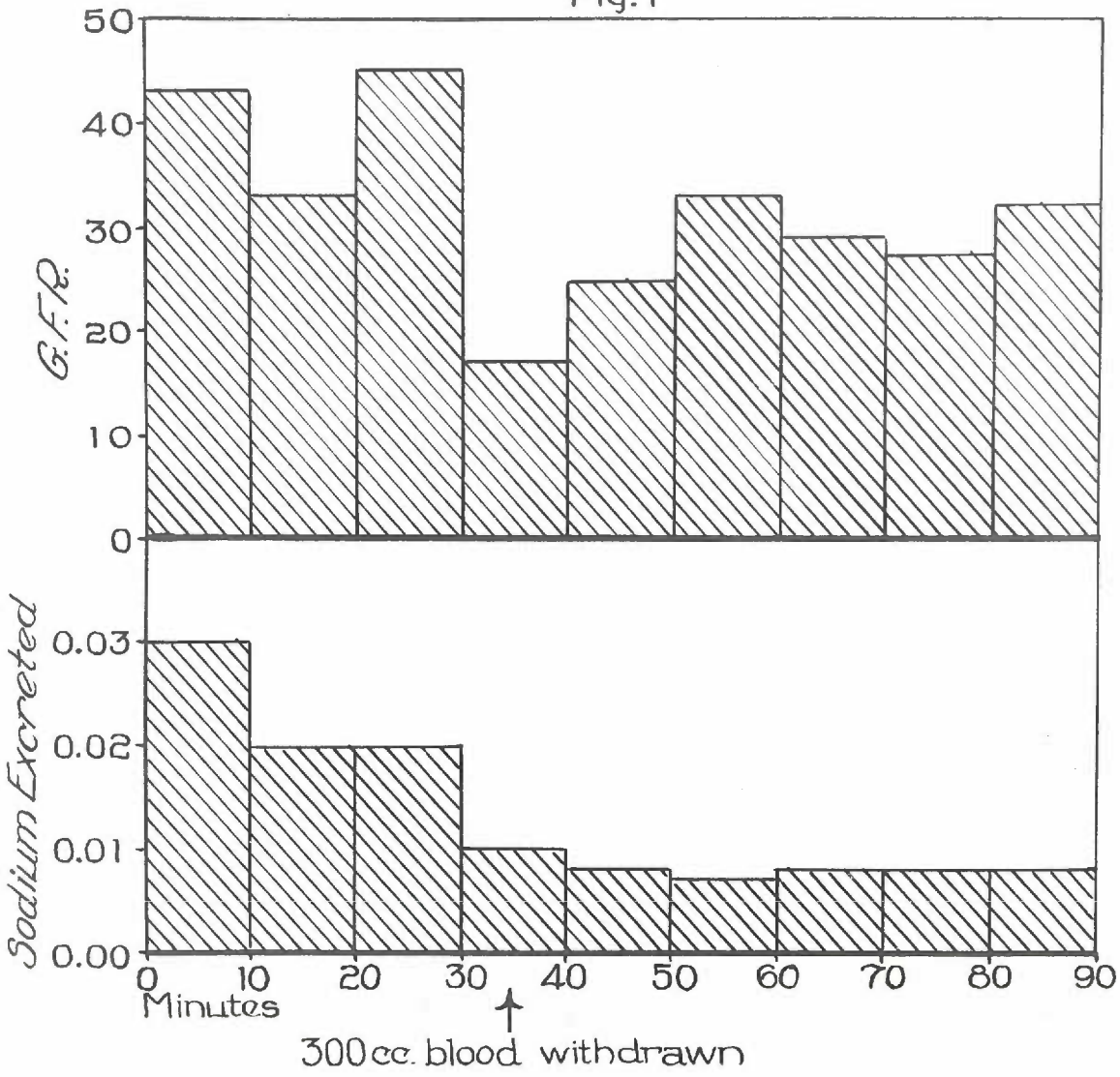
Experiment 1

Female dog, wt. 14 Kg.

Time	
1:45	Nembutal, 7.5 grains, intravenously.
2:00	10 cc. blood were drawn from femoral vein. 1000 cc of 5% Dextrose in water was started intravenously at 200 drops per minute.
2:22	Dextrose infusion was slowed to 60 drops per minute.
2:20 - 2:30	The abdomen was opened in the mid-line; both ureters were transected and catheterized with polyethylene tubes.
2:30	Consecutive urine collection periods were started.
2:45	Nembutal, 2 grains, intravenously.
2:55	The left femoral artery was cannulated.
3:00 - 3:02	300 cc. of blood were withdrawn from the femoral artery.
3:35	10 cc. of blood were drawn from the femoral vein.
3:36	Nembutal, 1 grain, intravenously.
4:00	900 cc. total of Dextrose infusion administered.

Experiment terminated.

Fig. 1

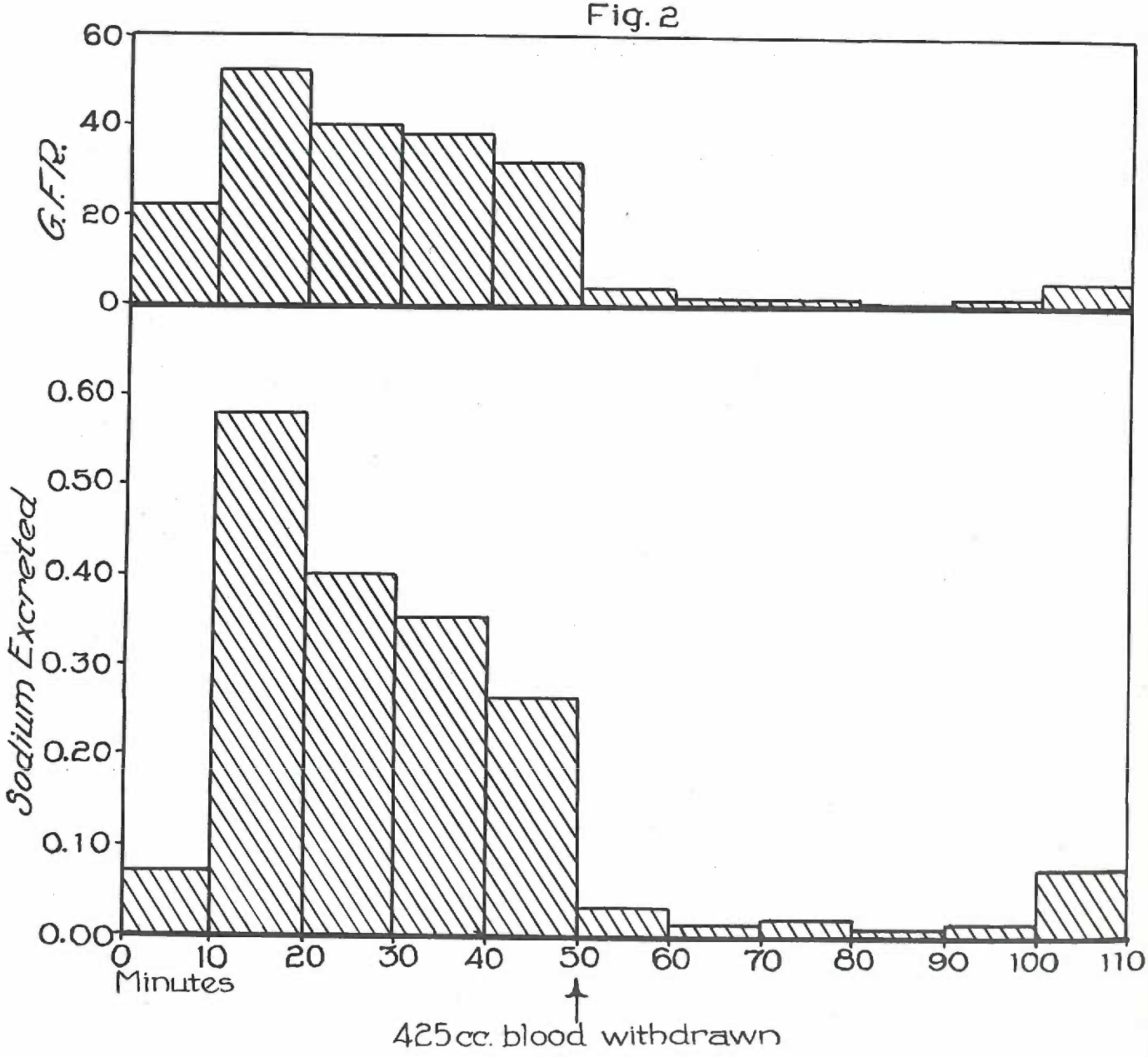

50
40
30
20
10
0
G.F.R.
0.03
0.02
0.01
0.00
Sodium Excreted
0
10
20
30
40
50
60
70
80
90
Minutes
300 cc. blood withdrawn

Experiment 2

Female dog, wt. 14 Kg.

Time	
1:00	Nembutal, 8 grains intravenously.
1:10	10 cc. of blood were drawn from the femoral vein. 1000 cc. 5% Dextrose in water was started intravenously at 120 drops per minute.
	The abdomen was opened. Both ureters were isolated and catheterized. The femoral artery and vein were exposed bilaterally.
1:50	Dextrose infusion slowed to 60 drops per minute (600 cc. administered).
2:00	Nembutal, 2 grains intravenously.
2:10	Urine collections started.
2:45	An 18 g. needle was put in the left femoral artery with a poor flow of blood.
2:50	Cannula put in femoral artery and opened.
3:03	Blood flow slowing, 400 cc. removed.
3:06	Cannula clogged, total of 425 cc. blood removed.
4:00	Experiment terminated.

Fig. 2


60
40
20
0
G.F.R.
0.60
0.50
0.40
0.30
0.20
0.10
0.00
Sodium Excreted
0
10
20
30
40
50
60
70
80
90
100
110
Minutes
425 cc. blood withdrawn

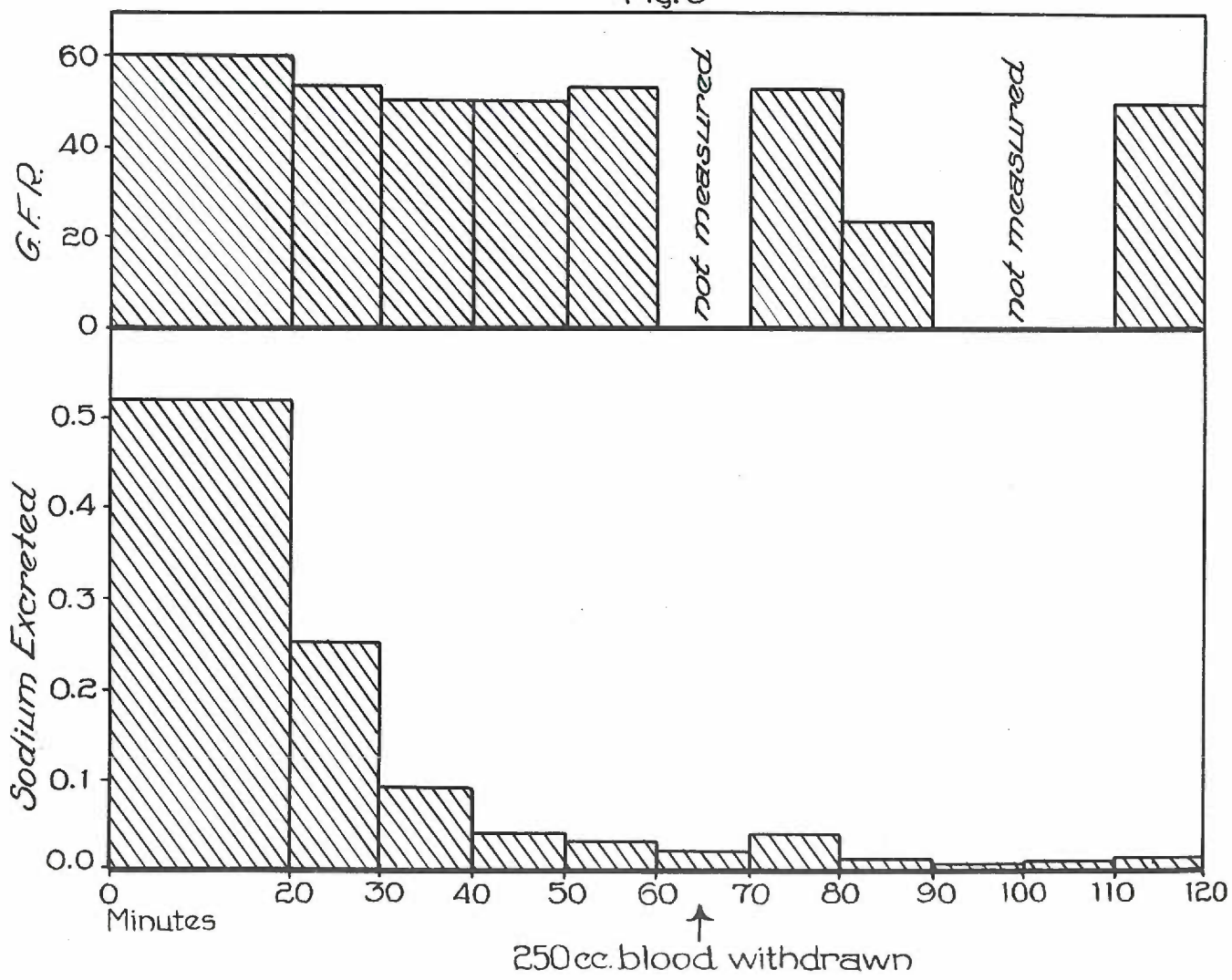
Experiment 3

Female dog, wt. 13 Kg.

Time	
10:00	Nembutal, 7 grains, intravenously.
10:05	1000 cc. 5% Dextrose intravenously started.
	The abdomen was opened. Both ureters were catheterized and the femoral artery and vein exposed.
10:30	Urine collections started.
10:35	10 cc. of venous blood were drawn.
11:21	Nembutal, 2 grains, intravenously.
11:35 - 11:40	250 cc. of blood were drawn from the femoral artery.
11:50	1000 cc. 5% Dextrose finished.
12:30	Urine collections were terminated.
12:35	10 cc. of venous blood were drawn.

Experiment terminated.

Fig. 3


G.F.R.
60
40
20
0
not measured
not measured
Sodium Excreted
0.5
0.4
0.3
0.2
0.1
0.0
0
20
30
40
50
60
70
80
90
100
110
120
Minutes
250 cc. blood withdrawn

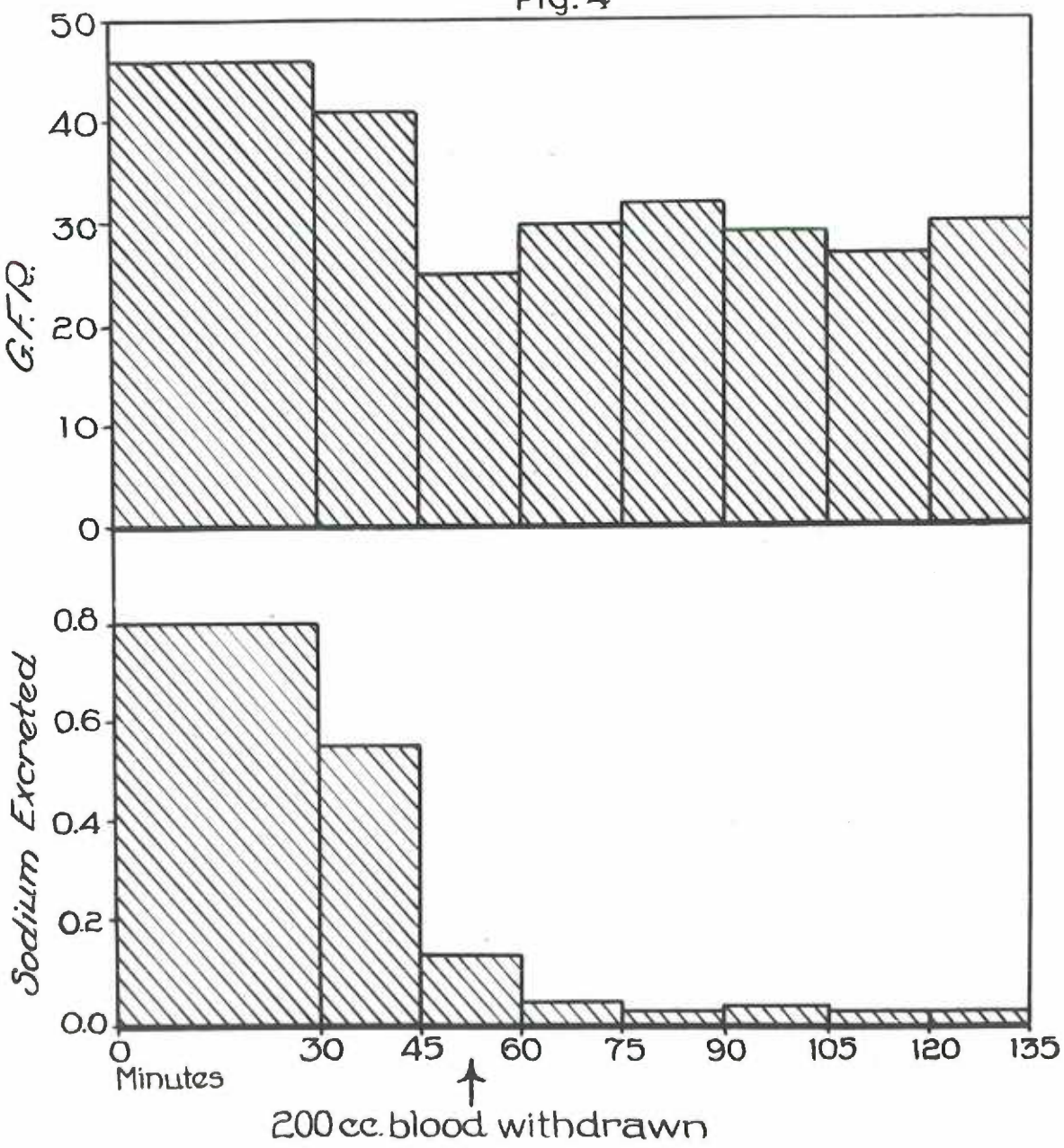
Experiment 4

Female dog, wt. 14 Kg.

Time	
12:30	Nembutal, 7 grains intravenously slowly, after induction with open drop ether. The abdomen was opened. Both ureters were isolated and catheterized and the femoral artery and vein exposed.
1:00	Urine collections started.
1:05	1000 cc. of 5% Dextrose started intravenously.
1:50	200 cc. of blood were drawn from the femoral artery.
2:10	Nembutal, 2 grains, intravenously.
3:15	Urine for the 15-minute period from 3:00 - 3:15 appeared smoky.
3:20	Urine contained gross blood - not saved. 10 cc. of venous blood were drawn.

Experiment terminated.

Fig. 4

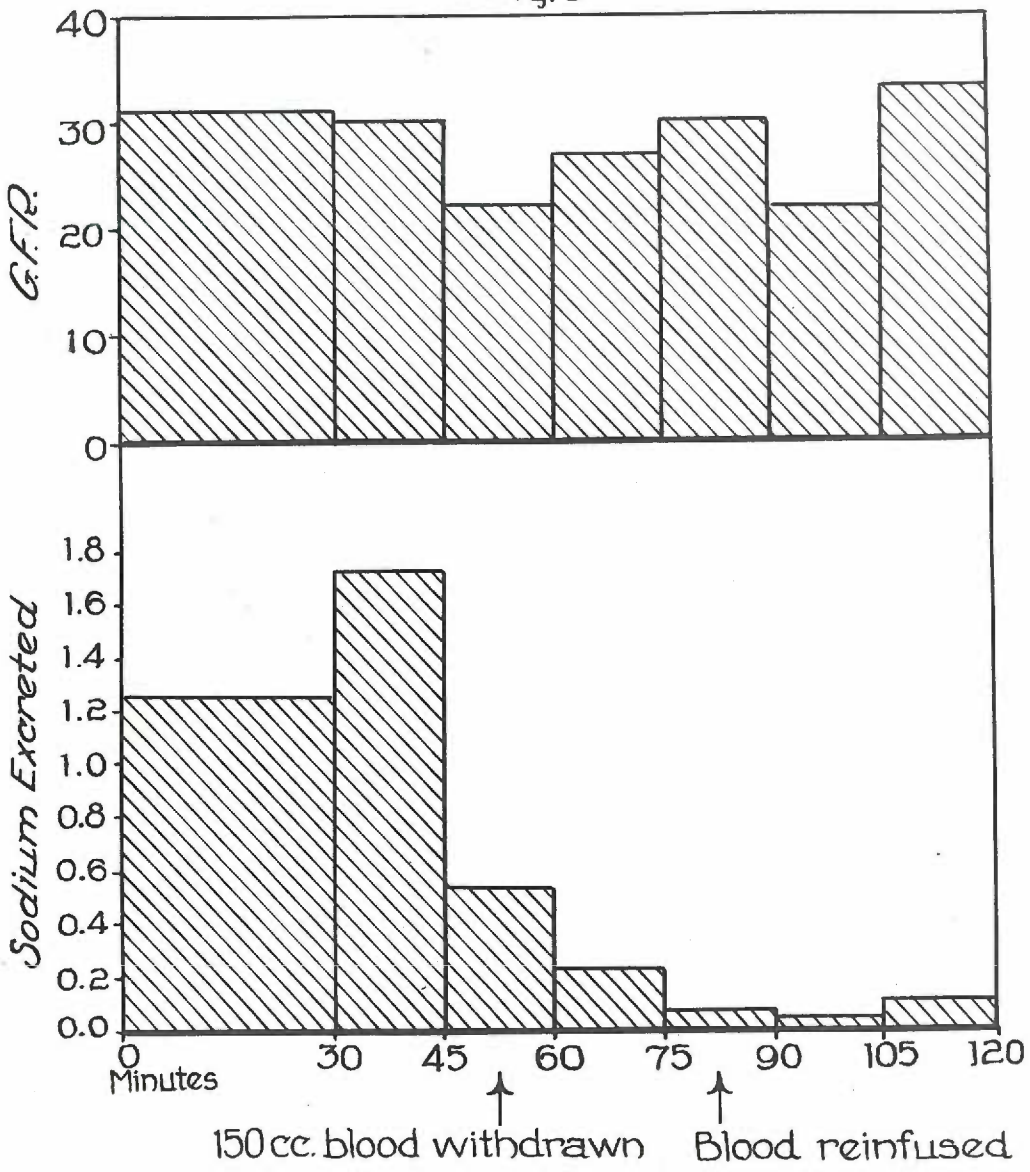

50
40
30
20
10
0
G.F.R.
0.8
0.6
0.4
0.2
0.0
Sodium Excreted
0
30
45
60
75
90
105
120
135
Minutes
200 cc. blood withdrawn

Experiment 5

Female dog, wt. 8 Kg.

Time	
1:15	Nembutal, 4.5 grains intravenously.
1:30	1000 cc. of 5% Dextrose in water started intravenously. An indwelling 8 French soft rubber catheter was inserted through the urethra. The bladder was rinsed with distilled water.
1:30	Nembutal, 1 grain intravenously.
1:45	Urine collections started. At the end of each collection period the bladder was rinsed with distilled water. The femoral artery was exposed and cannulated.
2:40	150 cc. of arterial blood were drawn into a flask containing heparin.
2:50	10 cc. of venous blood were drawn.
3:00	1000 cc. of Dextrose infusion completed. Infusion of the heparinized blood was started at about 100 drops per minute.
3:00 - 3:15	Urine for this period appeared hazy with small blood clots.
3:20	Re-infusion of 150 cc. heparinized blood completed. One grain Nembutal intravenously.
3:30	10 cc. of venous blood were drawn. Urine appeared clear with no trace of blood.
3:45	Experiment terminated.

Fig. 5

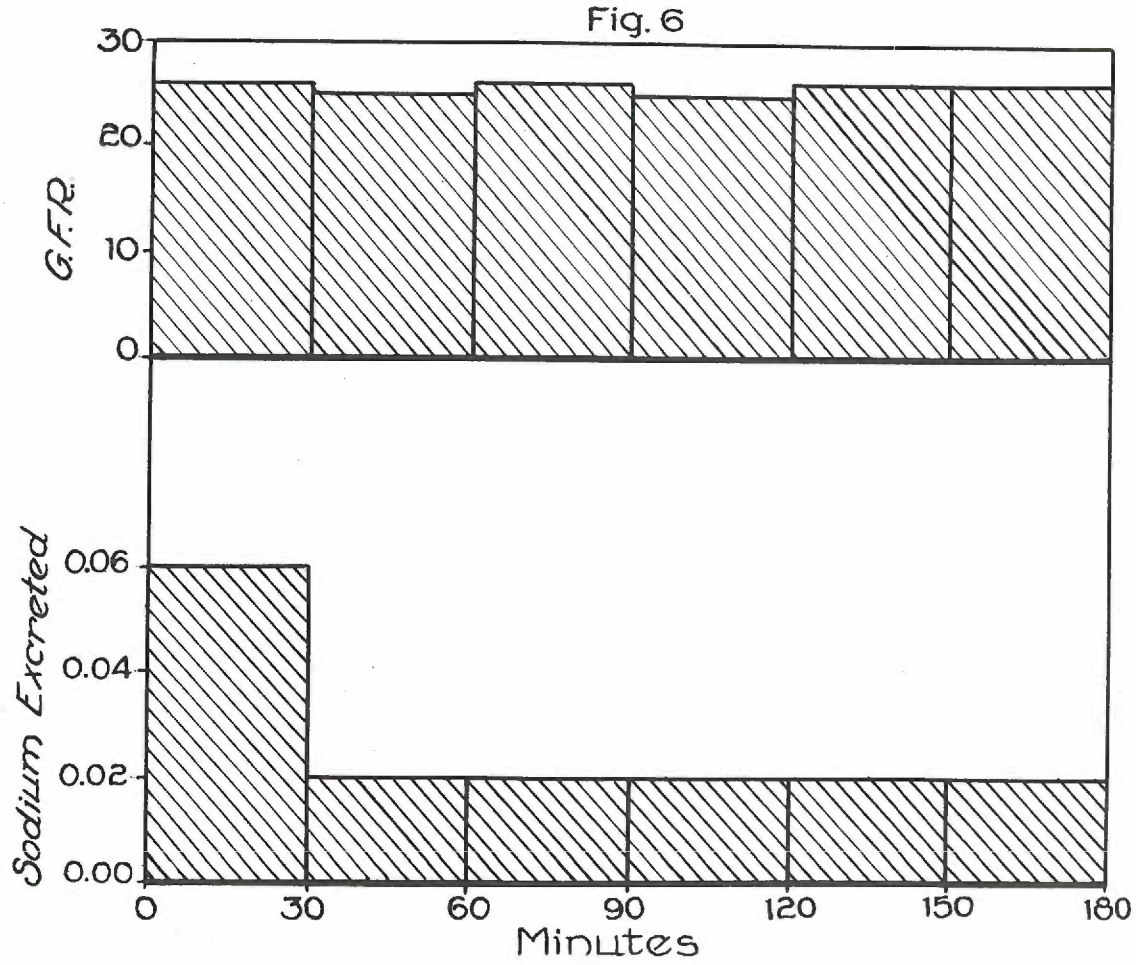

G.F.R.
40
30
20
10
0
Sodium Excreted
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0
Minutes
30
45
60
75
90
105
120
150 cc. blood withdrawn
Blood reinfused

Experiment 6

Male dog, wt. 13 Kg.

Time	
11:15	Nembutal, 8 grains intravenously.
11:25	1000 cc. of 5% Dextrose in water were started intravenously.
11:30	A urethral catheter was inserted and the bladder was washed with distilled water.
	Urine collections started.
11:45	10 cc. of venous blood were drawn.
12:30	Nembutal, 2 grains intravenously.
	2 grains Nembutal injected into Dextrose infusion bottle.
2:00	1000 cc. of Dextrose infusion completed.
2:30	Experiment terminated.

Fig. 6


30
20
10
0
G.F.R.
0.06
0.04
0.02
0.00
Sodium Excreted
0
30
60
90
120
150
180
Minutes

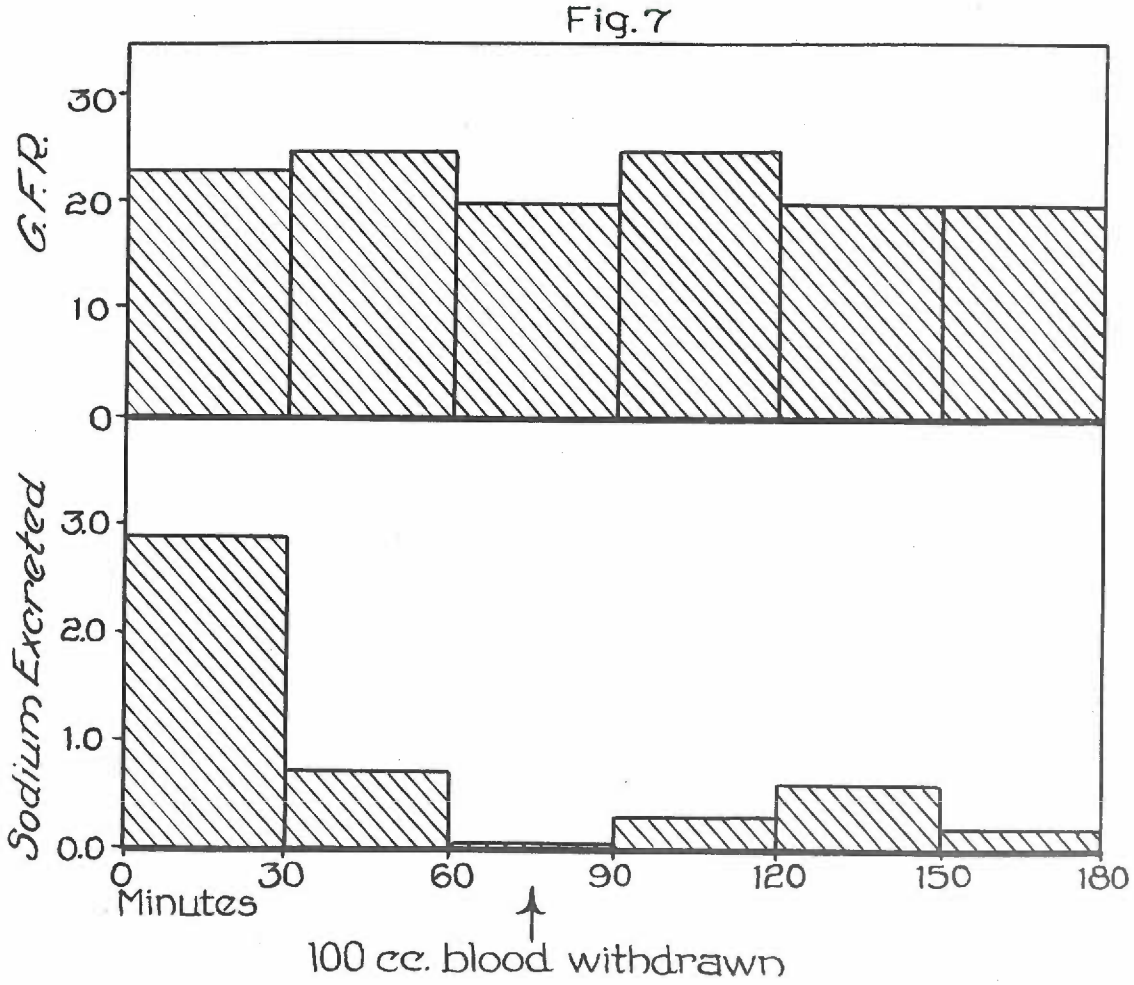
Experiment 7

Male dog, wt. 6.6 Kg.

Time	
12:00	Nembutal, 4 grains intravenously. A bilateral posterior kidney exposure was done with complete adrenalectomy. Wounds closed.
1:00	Nembutal, 1 grain intravenously. 1000 cc. of 5% Dextrose in water started. The bladder was catheterized and rinsed with distilled water.
1:20	Urine collections started. The femoral artery and vein were exposed.
2:40	100 cc. of blood were drawn from the femoral artery.
2:45	Nembutal, 1 grain intravenously.
3:45	1000 cc. of Dextrose infusion finished. Nembutal 1 grain intravenously. 10 cc. of venous blood were drawn.
4:20	Dog died.

Experiment terminated.

Fig. 7


G.F.R.
30
20
10
0
Sodium Excreted
3.0
2.0
1.0
0.0
0
30
60
90
120
150
180
Minutes
100 cc. blood withdrawn

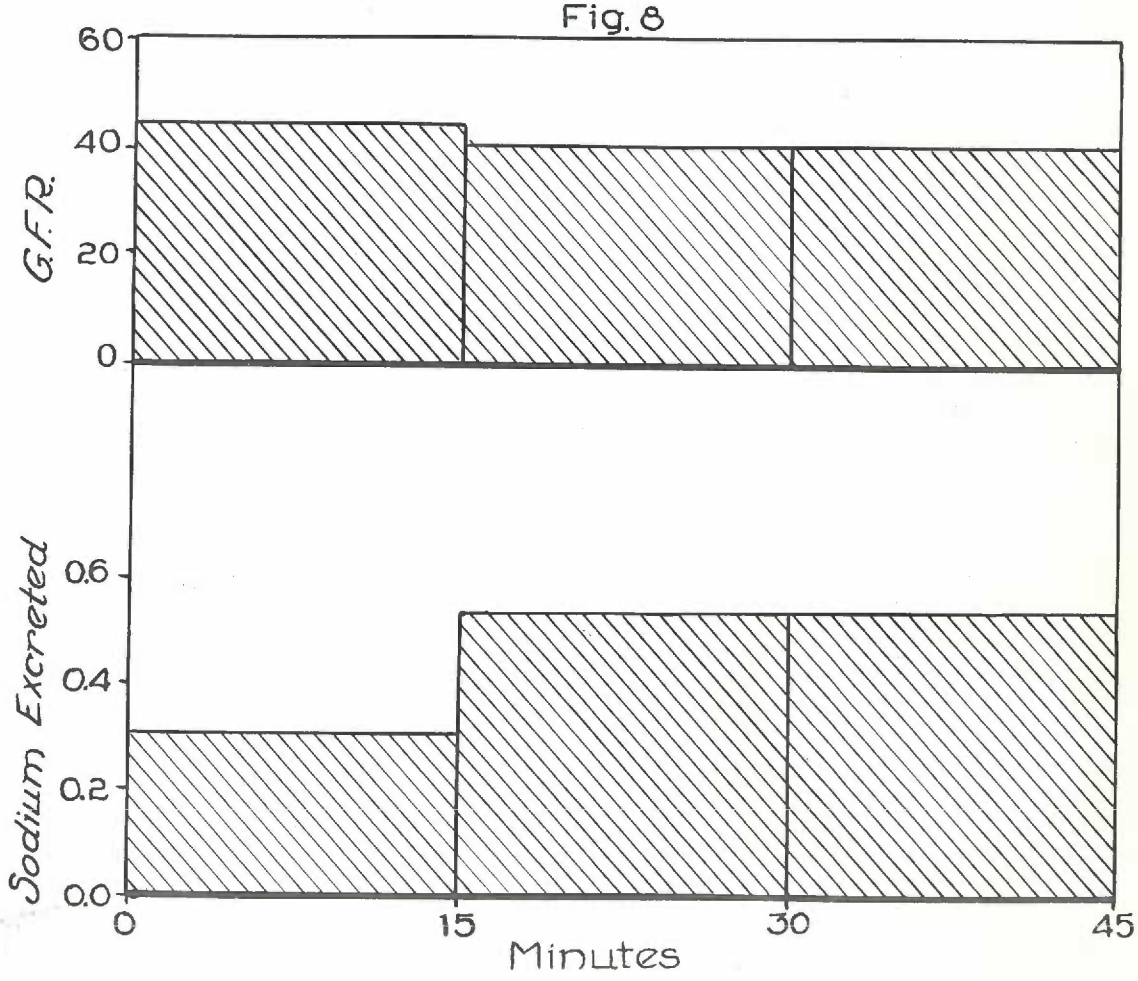
Experiment 8

Male dog, wt. 12 Kg.

Time	
10:30	Morphine sulfate, 0.5 grain, subcutaneously. The animal was tied loosely on a table. A urethral catheter was inserted into the bladder and the bladder was rinsed with distilled water.
12:00	Urine collections started.
12:45	10 cc. of blood were drawn from the femoral artery.

Experiment terminated.

Fig. 8

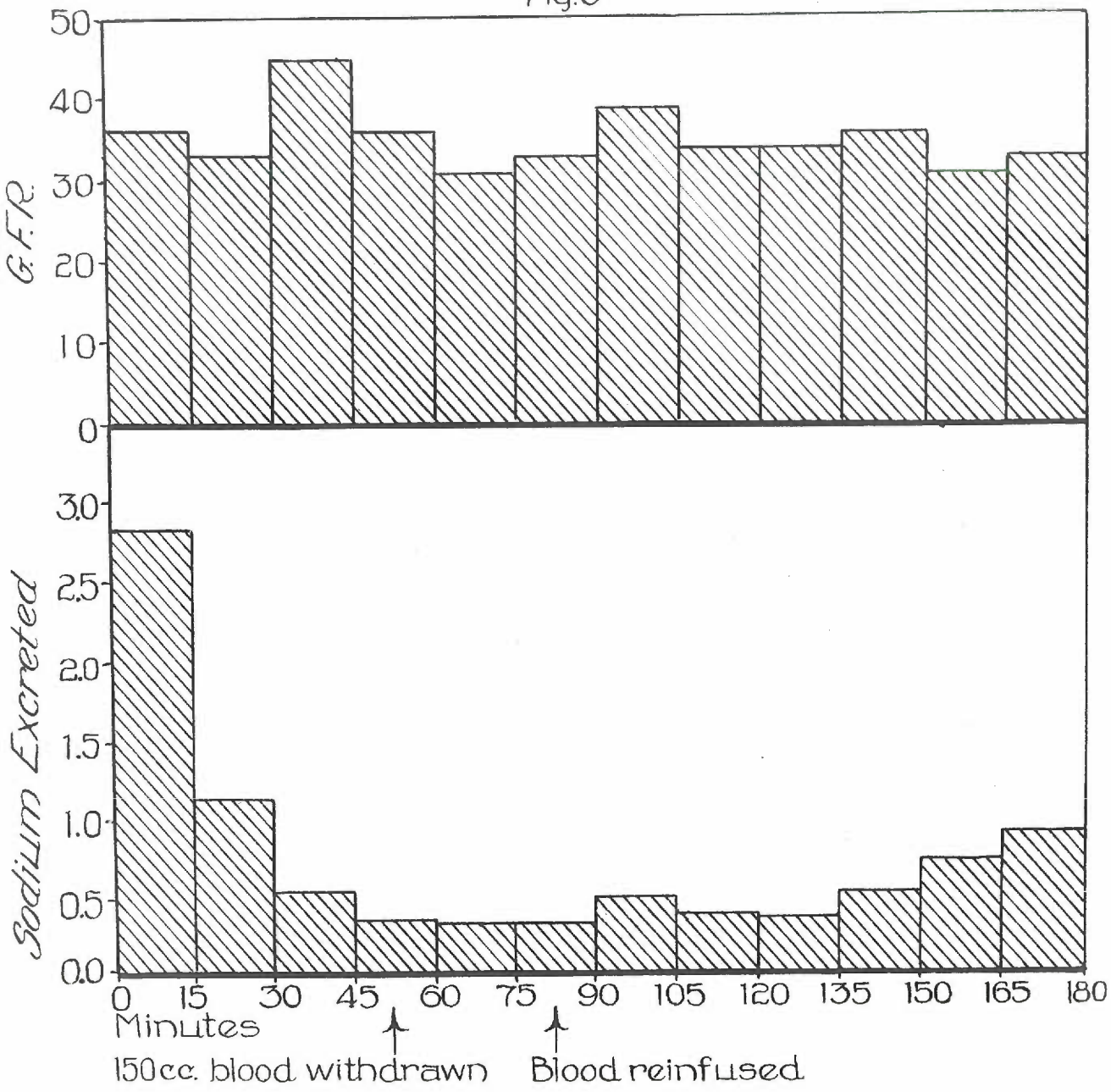


Experiment 9

Female dog, wt. 12 Kg.

Time	
10:15	Nembutal, 6 grains intravenously. The animal showed considerable respiratory depression, but maintained good circulation. A slight Trendelenburg position was maintained throughout the experiment.
10:30 - 11:05	A right lateral kidney incision was made and the adrenal gland removed.
11:05 - 11:35	The left adrenal gland was removed.
11:15	1000 cc. of 5% Dextrose in water was started intravenously.
12:00	A catheter was inserted into the bladder. The bladder was rinsed with distilled water and urine collections were started.
12:20	The left femoral artery and vein were exposed.
12:25	10 cc. of venous blood were withdrawn.
12:52 - 12:53	150 cc. of arterial blood were withdrawn into a bottle containing heparin.
1:13	Nembutal, 0.5 grain intravenously.
1:17 - 1:37	The 150 cc. of heparinized arterial blood were reinfused.
1:55	The animal was shivering mildly, possibly a pyrogen reaction.
2:05	Nembutal, 0.5 grain intravenously.
2:50	10 cc. venous blood withdrawn.
3:00	Experiment terminated.

Fig.9


G.F.R.
50
40
30
20
10
0
Sodium Excreted
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0 15 30 45 60 75 90 105 120 135 150 165 180
Minutes
150cc. blood withdrawn
Blood reinfused

Creatinine clearances before hemorrhage varied in the nine animals from 22 cc. per minute to 60 cc. per minute. Since the purpose of the experiments was to produce variations in filtration rate during measured time periods in order to determine what effects on sodium excretion would be elicited, "spontaneous" variations in each animal as well as variations between animals were not undesirable. Part of the variation was due to differences in weight of the animals, and probably part was due to variations in depth of anesthesia. Since Nembutal is a vasodilator agent, large doses would be expected to decrease disproportionately the resistance to blood flow in arterioles normally having a higher tonus than the renal arterioles and thus cause a decrease in renal blood flow(18,19)

Sodium excretion before hemorrhage varied from 0.02 mgs. per minute to 1.73 mgs. During the first control period in each of two adrenalectomized dogs, about 2.9 mg. of sodium were excreted per minute. The low rate of sodium excretion in some of the animals prior to removal of blood, when the glomerular filtration rate is at near-normal levels, indicates that a mechanism for retention of sodium, consisting of an increased rate of sodium absorption by the tubule, has been elicited. In experiments 1, 2, 6, 7 and 9, where sodium excretion dropped markedly before the glomerular filtration rate was decreased by hemorrhage, it is possible that the sodium retention mechanism was elicited by operative trauma or by changes in circulation or respiration produced by Nembutal.

Controlled arterial hemorrhage, varying in amounts from 100 cc. to 425 cc., caused a decrease in glomerular filtration rate ranging from 10% to 98%. Sodium excretion, if not already at a low level, invariably

was markedly decreased following hemorrhage. Although glomerular filtration rate tended to recover after hemorrhage, and in experiment 5 was re-established at control levels by infusion of the blood which previously had been withdrawn, sodium excretion in none of the experiments ever reached the control level or ever showed a consistent upward trend during the remainder of the experiment.

In figures 3, 5, 6, 7, 8 and 9 it is shown that when glomerular filtration rate was at the same level at different periods during the experiment, the levels of sodium excretion were widely separated.

In experiments 7 and 9 dogs which had had both adrenal glands removed before urine collections were begun, and which were showing high rates of sodium excretion consistent with lack of adrenal cortical hormones, showed an acute drop in sodium excretion comparable to that in the dogs with adrenal glands intact. The rate of sodium excretion remained depressed in spite of a restoration of glomerular filtration rate to control levels. Therefore, in these experiments also, the failure to excrete sodium is related not only to decreased filtration but to an increased rate of absorption of sodium by the tubules. In these animals the secretion of adrenal cortical hormone, regardless of its blood level at the time, could not have been increased following the hemorrhage. Therefore, the increase in absorption of sodium by the tubule was related to some mechanism other than an increase in adrenal cortical activity. It is well known that adrenal cortical hormone is capable of causing an increased rate of absorption of sodium from the renal tubule;(20,21) however, these experiments indicate that there is an additional potent influence on the tubular absorption of

sodium. The nature of this mechanism is not known. It would appear, since the mechanism can be elicited by hemorrhage, that a decrease in blood flow or pressure in the kidney or elsewhere can evoke the mechanism. Once sodium retention is induced, it persists for a considerable period after the restoration of the glomerular filtration rate.

DISCUSSION

The tubular transport mechanism can remove from the tubular lumen only a certain specific quantity of a substance per unit of time. Ordinarily, a substance which, when presented in small amounts to the tubular epithelium, is completely removed from the tubular urine, and when presented in large amounts is not completely removed, is called a threshold substance. Actually, there is a threshold for any substance which is transported by the cells of the tubule. The load of the substance presented to the tubular epithelium and the amount of the material excreted are the important measurements in determining changes in threshold. The load varies with changes in either blood concentration or glomerular filtration rate. Therefore, the sodium load may be altered by a change in plasma concentration or in glomerular filtration rate; and a decrease in sodium excretion, theoretically, could be produced by one or more of three mechanisms: 1) decreased plasma concentration, 2) decreased glomerular filtration rate, 3) increased tubular absorption.

According to the present theories, the absorption of sodium in the proximal convoluted tubule is considered to be an active obligatory function whereby about 87% of the filtered sodium is absorbed.

The remaining 13% passes on through the thin loop of Henle to the distal convoluted tubule(15). The activity of the transport mechanism of the distal tubular epithelium may be considered to vary through a range from zero activity, i.e. no further absorption of sodium, to maximal activity, i.e. the maximum capacity of an adaptive mechanism to absorb sodium. If this theory is correct, changes in distal tubular transport capacity would determine changes in the level of the renal threshold for sodium.

Regardless of the locus of sodium reabsorption, the renal threshold for sodium normally is at a slightly lower level than the tubular sodium load(14,15). If the tubular sodium load is decreased or if the renal threshold is raised, the sodium excretion rate will be decreased. These two mechanisms are not incompatible, and the present experiments have shown that both can operate simultaneously. Selkurt et al(14) concluded that the reduction in sodium excretion which they observed following aortic occlusion was due not to a change in threshold but to the decreased tubular sodium load. However, evaluation of the one experiment for which they present complete data indicates that following the release of the aortic occlusion there is an increased tubular absorption of sodium. When glomerular filtration rate was restored to a previous level, sodium excretion was not restored.

In a preliminary report of experiments by Elkinton et al(22) normal human subjects were subjected to tilting from the horizontal in order to change renal dynamics. This procedure caused a decrease in renal plasma flow, glomerular filtration rate, and sodium excretion. Sodium excretion failed to return to control levels when renal plasma flow and glomerular filtration rate were restored. They concluded that

sodium excretion appears to be determined by changes in tubular transfer rather than by changes in glomerular filtration.

SUMMARY

The relationship between glomerular filtration rate and the rate of sodium excretion was studied in nine dogs. Eight received Nembutal and one was unanesthetized. Each animal was hydrated with intravenous dextrose in water during the experiment, but received no sodium. Reductions in glomerular filtration rate were produced by withdrawal of measured amounts of blood. In some cases the blood was re-infused. Urine was collected for measured periods, and dilutions and calculations were made on a time basis. Sodium was determined by means of a flame photometer, and endogenous creatinine clearance was used as a measure of glomerular filtration rate.

Sodium excretion rate was decreased following a depression of the glomerular filtration rate by hemorrhage. The decreased sodium excretion rate persisted throughout the experiment even after restoration of the filtration rate to control levels. In the latter case, the amount of sodium reabsorbed by the tubules, which is the difference between the amount of sodium filtered and the amount excreted, was increased.

In several experiments sodium excretion rate was markedly decreased prior to withdrawal of blood and remained decreased for the duration of the experiment. In such cases the sodium retention may have been initiated by administration of Nembutal or by operative trauma and possibly is related in part to liberation of adrenal cortical hormone.

In two animals an increase in tubular absorption of sodium was observed after bilateral adrenalectomy. This result would indicate that an increased output of adrenal cortical hormone is not essential for sodium retention even though it is probable that adrenal cortical hormone is partly responsible when the adrenal glands are intact.

The dissociation of the rates of filtration and excretion of sodium supports the conclusion that there is no simple causal relationship between the two functions.

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