# CATION AND WATER SHIFTS IN RESPONSE TO PRESSOR AGENTS IN THE CONSCIOUS DOG

by

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## ABSTRACT

The hallmark of essential hypertension is a persistent elevation of blood pressure. Certain changes are associated with the state of hypertension including a derangement of water and electrolytes. Recent work indicates the upset in sodium and water may be causally related to the hypertension. Transitary, acute hypertension may be produced by means of drugs. The drug induced blood pressure rise is accompanied by a disturbance in water and electrolytes. Further work is required to clarify the relationship between shifts in electrolytes and agents that may increase blood pressure (pressor agents).

In order to carry out the programme of research on pressor agents it was necessary to review the fundamental tool, namely the accurate measurement of shifts in water. This review lead to a refinement in the technique of measuring water by infusing inulin.continuously. With nephrectomized animals the inulin dilution technique is a satisfactory method to measure the extracellular space. An equally accurate index of the extracellular space can be provided with an inulin infusion which maintains the extracellular inulin concentration at a constant level.

In the present study the cation and water shifts between cells and the extracellular space associated with two dissimilar pressor agents were observed, using trained, conscious dogs. The pressor agents used were norepinephrine, elaborated by the adrenal medulla and pitressin, elaborated by the posterior pituitary gland. Norepinephrine had no effect, in our hands, on sodium, potassium or water movement. Pitressin had distinct effects, with rapid depression of the extracellular volume and the extracellular sodium concentration, and elevation of the extracellular potassium concentration. The changes caused by pitressin were associated with a pressor response.

TABLE OF CONTENTS

## TABLES & GRAPHS

# INTRODUCTION

## THE EFFECT OF NOREPINEPHRINE ON WATER AND CATIONS

The essential features of the salt and water shifts associated with a norepinephrine infusion are:

1) Cellular uptake of sodium and water and release of potassium are closely associated with a pressor response. These changes likely precede the pressor response.

2) Dibenamine and DHE-45 block both the pressor and the electrolyte responses.

3) A sodium infusion blocks the pressor response.

The cationic shifts have been examined from both the cellular and the extracellular standpoint and the results substantiate one another. Robertson and Peyser (19) in 1951 examined the myocardium of cats after the injection of large doses of epinephrine. In order to increase the cellular sodium and to decrease the cellular potassium significantly, 500 µg of epinephrine was needed.

Tobian and Fox (21) in 1956 showed that these cationic changes were not limited to heart muscle. They examined the effects of a norepinephrine infusion on the arterial smooth muscle of dogs. Twelve trained, conscious dogs were used. One femoral artery was ligated under local anaesthesia and a segment quickly removed. A norepinephrine infusion was begun and the dose was adjusted to elevate and sustain the blood pressure 100mm Hg above the normal base. The infusion was allowed to continue for half an hour and at that time a segment of the opposite femoral artery was similarly excised. Analysis of the arterial segments showed

that the potassium content of the artery had dropped from 8.1 mg/100 Gm solids before, to 5.9 mg/100 Gm solids after infusion. The artery segment gained 1.7 mg of sodium/100 Gm solids in the same interval. The sodium gain was more variable than the potassium loss. The dogs showed considerable individual variation in both the pressor and the cationic responses.

Muirhead, Goth and Jones (15) examined the effects of a norepinephrine infusion on plasma water and electrolytes in anaesthetized dogs. The doses of norepinephrine used were massive. Eleven dogs were given an average of 70 µg/Kg/min of norepinephrine for short periods varying from fifteen to fifty minutes. The plasma sodium concentration became depressed two minutes after the onset of the infusion, returned to normal minutes after termination of the infusion, and was throughout a mirror image of the pressor effect. In the example shown the plasma sodium concentration changed from 145 mEq/L to 130 mEq/L. The plasma potassium concentration showed no distinct relationship to the pressor effect. The radio-sulfate space showed no change. Muirhead et al pointed out that small doses of norepinephrine cause no distinct change in the plasma sodium concentration.

Friedman, Butt and Friedman (8) also showed that the plasma sodium concentration in dogs does not change in response to small doses of norepinephrine. They observed, however, that a measurable change in the total extracellular sodium occurred in anaesthetized dogs with one-tenth the dose of norepinephrine used by Muirhead et al. In addition, they showed that total extracellular potassium rose coincidentally with the pressure change. Eight anaesthetized nephrectomized dogs were given

from 3 - 6.5 µg/Kg/min of norepinephrine by infusion. Plasma sodium concentration did not change but inulin space decreased so a fall in total extracellular sodium was calculated. The curves for total extracellular sodium formed mirror images of the blood pressure.

Friedman et al noted that the cationic changes may precede the pressor effect. Since they had found similar cationic changes with pressor agents other than norepinephrine they advanced the theory that the cationic changes were causally related to pressor effects. Support for this contention was provided by the demonstration of suppression of the pressor response by infusion of sodium. Friedman et al (11) pointed out that the agent responsible for this pressor response suppression is the sodium ion. In a rat a sodium infusion blocked the pressor response to both norepinephrine and pitressin. Moreover, the amount of sodium required to block the pressor response corresponded to the amount lost from the extracellular space with the infusion of the pressor agent.

The results of experimental work on the rat by Friedman, Friedman and Nakashima (9) using a norepinephrine infusion were similar to the results described for the dog. They stressed the rapidity with which these changes occur in the rat and found it necessary to establish hypotension prior to the infusion to detect an early shift of water.

The rise of the plasma potassium concentration in response to an epinephrine infusion has been recognized for some time. This was first observed by D'Silva (6,7). He felt that the rise of the plasma potassium concentration was due to the glycogenolytic effect of epinephrine

on the liver. Obrien, Murphy and Meek (17) have shown that dibenamine blocks the potassium shift as well as the pressor response to epinephrine. This has also been shown by Friedman, Friedman and Nakashima (10) in regard to both sodium and potassium. Since dibenamine blocks the pressor response but not the glycogenolytic action of epinephrine (Nickerson and Goodman (16) ), D'Silva's contention is probably in error. Friedman believes the rise in extracellular potassium is in part a loss from the cells and it is in part due to concentration from the extracellular water loss. Certainly an adequate source of potassium has been demonstrated in arterial smooth muscle and in the myocardium. The rise of the plasma potassium concentration in response to a norepinephrine infusion in the work of Muirhead et al was slow, slight and slow to return to normal. In the work of Friedman et al, in dogs and rats, the rise of total extracellular potassium coincided closely with the blood pressure rise but the change was not as rapid as the change in the total extracellular sodium.

THE EFFECT OF PITRESSIN ON WATER AND CATIONS

Studies of the effect of the posterior pituitary gland on blood pressure and cation shifts have resolved around -

1) Supraoptico-hypothalmic lesions

2) Stimulation of the supraoptico-hypothalamic tract.

3) Infusion and injection of pitressin

The observations of Friedman, Webber, Scherrer, and Friedman (12) have important implications for our work. They produced lesions of the supraoptico-hypothalamic tract in rats and observed changes in salt and water distribution which are the reverse of those found in association

with a pitressin infusion. A pitressin infusion produces a fall in the extracellular water and sodium concentration and a rise in extracellular potassium. They were able to show that these changes were not renal in origin since they could be produced in the bilaterally nephrectomised rat.

Oliver and Shafer (18) were the first to describe the pressor effect of posterior pituitary hormone. Kölls and Geiling (14) were the first to observe the hormone's action in the conscious dog. These latter workers, using Armour's liquid pituitary, noted the rise in mean and diastolic blood pressure and the sudden bradycardia that follows the blood pressure rise. Scherrer and Friedman (20) have described a sustained blood pressure rise following electrical stimulation of the posterior hypothalamic area.

The studies of Friedman, Butt and Friedman (8) have direct application to our work and will be dealt with in some detail. Their experiments were performed on anaesthetized dogs, using small and large doses of intravenous pitressin. In the first experiment 12 mU/Kg/min of pitressin was infused for twenty minutes. Plasma sodium concentration fell from 146.5 mEq/L to 143.8 mEq/L while plasma potassium concentration rose from 4.89 mEq/L to 5.11 mEq/L. Diastolic pressure rose 40 mm Hg in this period. In the second experiment 50 mU/Kg/min of pitressin was infused for seventeen minutes. In this case bilateral nephrectomy had been previously performed. Extracellular sodium (product of inulin space and plasma Na) fell from 28.79 mEq/Kg to 28.13 mEq/Kg. Extracellular potassium rose from 0.8 mEq/Kg to 0.9 mEq/Kg. The diastolic pressure rose 30 mm Hg in this period. In the third experiment 200 mU/Kg/min of pitressin was infused for ten minutes. Plasma sodium concentration

fell from 147.2 mEq/L to 141.7 mEq/L while plasma potassium concentration rose from 4.7 mEq/L to 5.19 mEq/L.

In the dog the cation and water changes produced by a pitressin infusion are more defined than the changes produced by an infusion of norepinephrine. With pitressin these changes are like the pressor response, slower to appear. Similar changes have been shown in the rat by Friedman et al with pitressin. They point out that the magnitude of the cation and water change is greater with pitressin than with norepinephrine for a comparable pressor response.

As observed with a norepinephrine infusion, the administration of sodium ions as sodium phosphate or sodium acetate will abort or suppress the normal pressor response to a pitressin infusion. The amount of sodium required approximates the amount the drug normally displaces.

THE INULIN INFUSION TECHNIQUE

The measurement of changes in extracellular volume in the conscious animal depends on an infusion of inulin which maintains the extracellular inulin concentration at a constant level.

The merits of inulin as an accurate measure of extracellular space are well known and a subject of many investigations (1, 2, 3, 4). One of the main disadvantages of inulin is its rapid excretion by glomerular filtration. This property prevents a uniform distribution of inulin in the extracellular space after a single injection and has limited its usefulness to the nephrectomized animal.

In 1949 Gaudino and Levitt (3) described a constant inulin infusion procedure for use in trained, conscious dogs. Using the recovery

technique they were able to measure inulin space that corresponded closely to the inulin space measured in the same dog after nephrectomy. Gaudino and Levitt observed that with a steady infusion of an inulin solution equilibration is reached in about two hours. A state of equilibration was inferred from steady plasma inulin concentrations. They noted that the state of equilibration was maintained in one dog up to twelve hours, whereas with nephrectomized dogs both the radio-sulphate space and the inulin space begin to rise after six hours. This rise is presumably a pathological water shift. Inulin equilibration in the extracellular space two hours after the onset of an infusion has been confirmed by other workers (1, 2, 4).

Thus it has been shown that inulin achieves complete distribution and equilibration in the extracellular space in two hours and that this state can be maintained for long periods by a constant inulin infusion. Changes in the volume of the extracellular space would be reflected by increases and/or decreases of inulin concentration. This being so, it should be possible to ascertain the direction of water movement in the extracellular space in response to various drugs such as norepinephrine and pitressin.

## EXPERIMENTAL

PURPOSE - The aim of the present work was twofold:

(1) To establish a workable index for changes of extracellular fluid volume in the conscious dog.

(2) To determine the effect of two dissimilar pressor agents on that index and on plasma sodium and potassium in the conscious dog.

METHODS AND MATERIALS -

Two healthy female labradors were used throughout and they were well at the finish of these experiments. Both dogs were a year and a half old at the beginning of the work and were weighed at that time.

Dog D weighed 24.8 Kgms.

Dog M weighed 23.4 Kgms.

They were placed in an outdoor compound daily and were exercised, in addition to this, two to three times weekly. They were familiarized with experimental handling over a three month period. This familiarization was greatly facilitated by similar training during the year prior to this experiment.

In every instance the dogs were in an 18-hour post-absorptive state and allowed water ad lib. During experiments the dogs, loosely restrained, rested supine on a board. They assumed this position voluntarily and showed no inclination to struggle. The hind limbs were used for infusion, injection and sampling.

In the first phase of the work the constancy of serial inulin values in the extracellular space during constant inulin infusion was determined. For this purpose a constant infusion apparatus was set up to deliver inulin solution at the rate of 0.75 ml/min. The rate was irregular within any thirty second interval but varied only $\pm$ 0.03 ml/30 seconds. The rate varied from day to day but was constant for each experiment. The small volume of infusion was used in order to avoid undue expansion of the extracellular fluid volume. This small volume necessitated the use of a fairly concentrated inulin solution. A 10% inulin solution of 40 ml was diluted with 60 ml of saline to give an inulin solution of

40 mg/ml. This solution permitted the controlled administration of 30 mg inulin per minute. A loading dose of 10 ml of 10% inulin solution was given initially over a ten second interval. In the earlier experiments to be described this loading dose of inulin was too high and accounted for high plasma levels with a steep falloff.

After the leg had been prepared and local anaesthetic injected the vein selected for infusion was cannulated with a No. 19 short bevel needle. A vein in the opposite hind limb was similarly cannulated and used for serial blood samples. Clotting in the needle was avoided by attaching a 2 ml syringe with heparin solution to the sampling needle and injecting a small amount in the interval between sampling. The first ml of sampled blood was always discarded. The blood was centrifuged immediately and the plasma drawn off, appropriately diluted and stored. Plasma inulin concentration was measured by the method of Hagishi and Peters (5).

Timed urine specimens were collected. The bladder was cleared of urine by two washouts of ten ml of tap water each, followed by thirty ml of air. The delay time was set at six minutes and though this is open to criticism it is not important since the same delay time was used in all experiments.

Drugs were always administered by single injection in the sampling needle. The intra-arterial pressure was recorded from the right femoral artery.

The inulin used was: Solution Purified Inulin. (U.S. Standard Products Co.)

The Norepinephrine used was: Levophed (Winthrop Stearns)

The Pitressin used was: Pitressin (Parke Davis & Co.)

## OBSERVATIONS

### INULIN INFUSION TECHNIQUE

The first seven experiments deal with the development of a method to maintain plasma inulin values at a constant level. The first three experiments in this group were spoiled due to faulty apparatus and are therefore not presented.

In experiment IV the priming dose of inulin, 1.3 grams was given at 10:35 A.M. The sustaining dose of inulin was begun simultaneously and continued for three and one-half hours. Blood samples were taken at approximately fifteen minute intervals after thirty minutes of infusion. The results are presented in Table I and Figure I. The large priming dose resulted in early, high levels of plasma inulin. The observed variation in the plasma inulin concentration was calculated on the figures obtained after two hours of infusion. In experiment IV the variation from the mean was $\pm$ 0.875 mgm% plasma inulin.

In experiment V the priming dose of inulin, 1.3 grams was given at 11:30 A.M. The sustaining dose of inulin was given simultaneously and continued for five hours. Blood samples were taken at approximately fifteen minute intervals after one hour of infusion. The results are presented in Table II and Figure II. The large priming dose again resulted in early, high plasma inulin levels. The period from the onset of the infusion to two hours after the onset is considered to be the equilibration time. The plasma inulin levels in this period were not included in the calculation of variation. In experiment V the variation from the mean was $\pm$ 1.0 mgms% plasma inulin.

In experiment VI the priming dose of inulin, 1.0 grams was given at 10:30 A.M. The sustaining dose of inulin was given simultaneously and continued for four and one-half hours. Blood samples were taken every fifteen minutes after fifty minutes of infusion. The results are presented in Table III and Figure III. The equilibration time is shortened, probably due to the modified priming dose. The observed variation from the mean was ± 1.25 mgms% plasma inulin. All the figures for plasma inulin concentration were taken into account. The priming dose of 1.0 grams of inulin was used for all succeeding experiments.

In experiment VII the priming dose of inulin, 1.0 grams was given at 11:30 A.M. The sustaining dose of inulin was given simultaneously and continued for three and one-half hours. Blood samples were taken every fifteen minutes after forty minutes of infusion. At 12:40 P.M. and 1:40 P.M. the period within two fifteen minute intervals was examined with blood samples taken every three minutes. The urine excreted during these two intervals was collected and the inulin excretion is presented in Table IV. The results of the plasma inulin concentration are presented in Table IV and Figure IV. The observed variation from the mean was ± 1.5 mgm% plasma inulin. The plasma inulin concentration in the three minute intervals showed the same constancy as the plasma inulin concentration in the fifteen minute intervals.

In experiments IV and V, 1.3 grams of inulin was used as a loading dose. In Experiments VI and VII this was reduced to 1.0 gram. In Experiments IV and V, the observations on variation from the mean were begun after 2 hours of inulin infusion. The period between the onset of the infusion and two hours after the onset was considered to

be the equilibration time. The observed variations in the plasma inulin concentration are shown for each experiment. In Experiments VI and VII the equilibration point was shortened, probably due to the modified loading dose. In Experiments IV, V, and VI the samples are fifteen minutes apart. In Experiment VI the fifteen minute intervals were examined on two occasions by sampling every three minutes. This was considered a prerequisite to later experiments involving acute water shifts. The greatest variation from the mean plasma inulin concentration over several hours was 1.5 mgm % plasma inulin. The plasma inulin concentration in the three minute intervals showed the same constancy as the plasma inulin concentration in the fifteen minute intervals.

TABLE I

| EXPERIMENT IV | INULIN INFUSION | | DOG M |
|---|---|---|---|
| Sample | Time | | In. mg% |
| | Start 10:35 | | |
| 1 | 11:00 | | 37.0 |
| 2 | 11:18 | | 36.25 |
| 3 | 11:34 | | 35.75 |
| 4 | 11:54 | | 35.75 |
| 5 | 12:12 | | 37.0 |
| 6 | | -spoiled- | |
| 7 | 12:46 | | 30.75 |
| 8 | 12:59 | | 32.5 |
| 9 | 1:14 | | 32.25 |
| 10 | 1:30 | | 31.25 |
| 11 | 1:44 | | 31.25 |
| 12 | 1:52 | | 30.75 |
| 13 | 2:00 | | 31.75 |

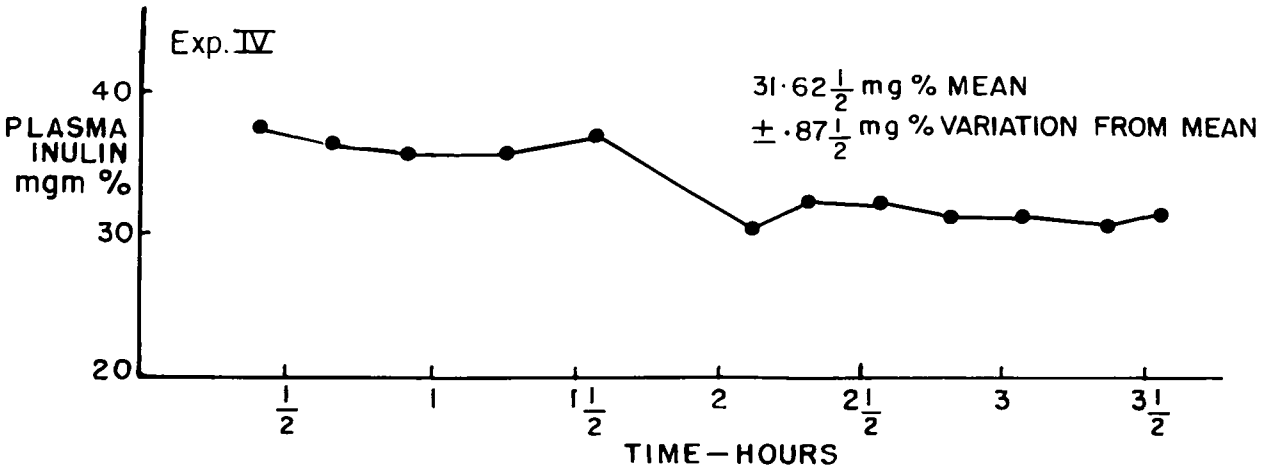
Exp. IV
40
PLASMA
INULIN
mgm %
30
20
31·62½ mg % MEAN
±·87½ mg % VARIATION FROM MEAN
½
1
1½
2
2½
3
3½
TIME—HOURS

Figure 1

TABLE II

EXPERIMENT V — INULIN INFUSION — DOG D

| Sample | Time | In. mg% |
|---|---|---|
| | Start 11:30 | |
| 1 | 12:25 | 44.0 |
| 2 | 12:42 | 35.75 |
| 3 | 1:02 | 33.0 |
| 4 | 1:20 | 30.5 |
| 5 | 1:35 | 30.5 |
| 6 | 1:51 | 28.0 |
| 7 | 2:09 | 26.0 |
| 8 | 2:26 | 24.5 |
| 9 | 2:42 | 24.5 |
| 10 | 3:00 | 25.75 |
| 11 | 3:15 | 26.5 |
| 12 | 3:30 | 26.0 |
| 13 | 3:45 | 25.5 |
| 14 | 4:02 | 25.75 |
| 15 | 4:17 | 25.0 |
| 16 | 4:30 | 25.0 |

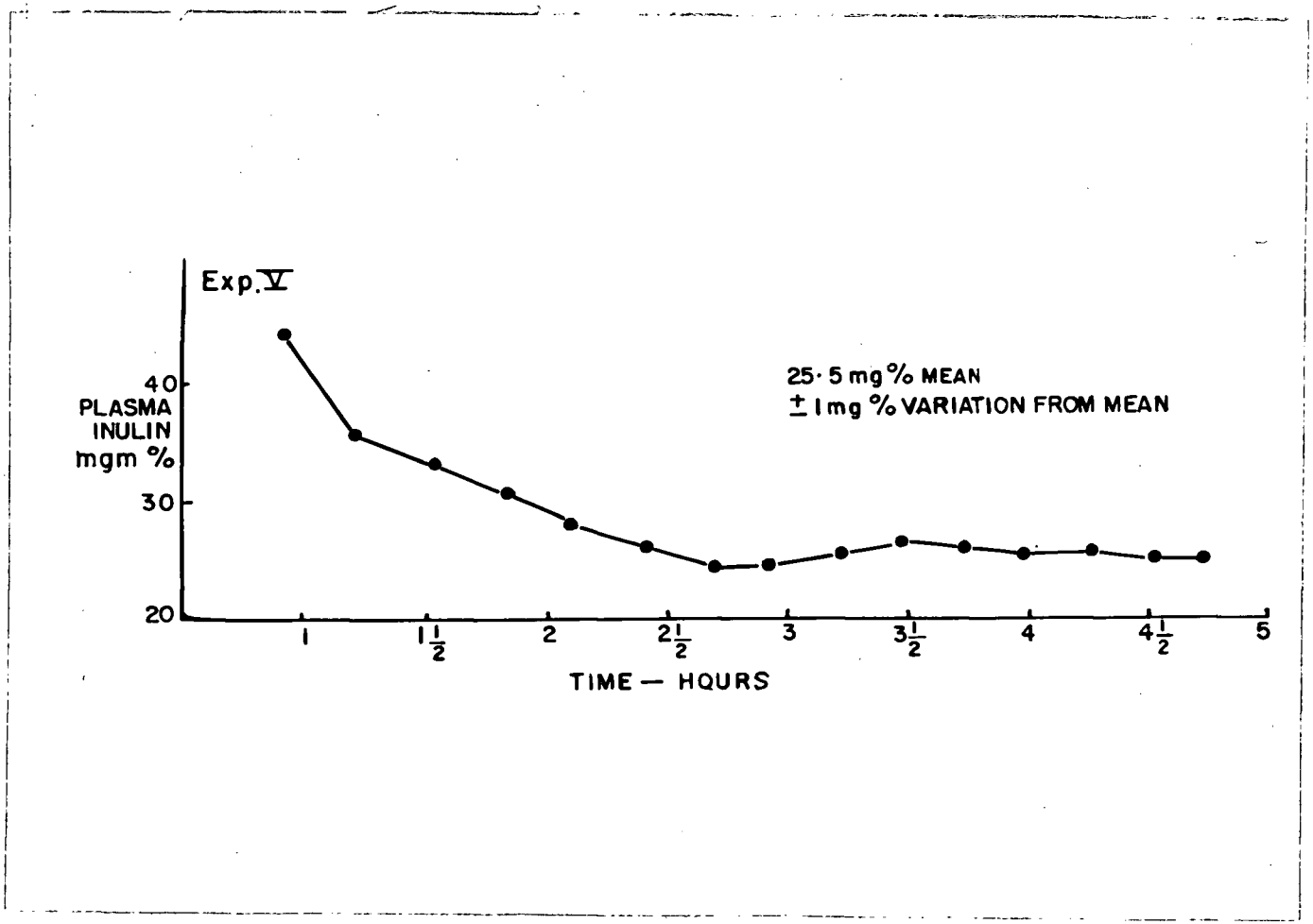
Exp. V
40
PLASMA
INULIN
mgm %
30
20
25·5 mg % MEAN
± 1 mg % VARIATION FROM MEAN
1
1½
2
2½
3
3½
4
4½
5
TIME — HOURS

Figure 2

TABLE III

EXPERIMENT VI — INULIN INFUSION — DOG D

| Sample | Time | In. mg% |
|---|---|---|
| | Start 10:30 | |
| 1 | 11:20 | 27.0 |
| 2 | 11:45 | 25.5 |
| 3 | 12:00 | 27.25 |
| 4 | 12:15 | 28.0 |
| 5 | 12:37 | 28.0 |
| 6 | 12:53 | 28.0 |
| 7 | 1:08 | 28.5 |
| 8 | 1:25 | 28.25 |
| 9 | 1:40 | 28.75 |
| 10 | 1:53 | 27.75 |
| 11 | 2:03 | 27.75 |
| 12 | 2:15 | 28.5 |
| 13 | 2:31 | 28.0 |
| 14 | 2:45 | 27.25 |
| 15 | 2:58 | 26.25 |

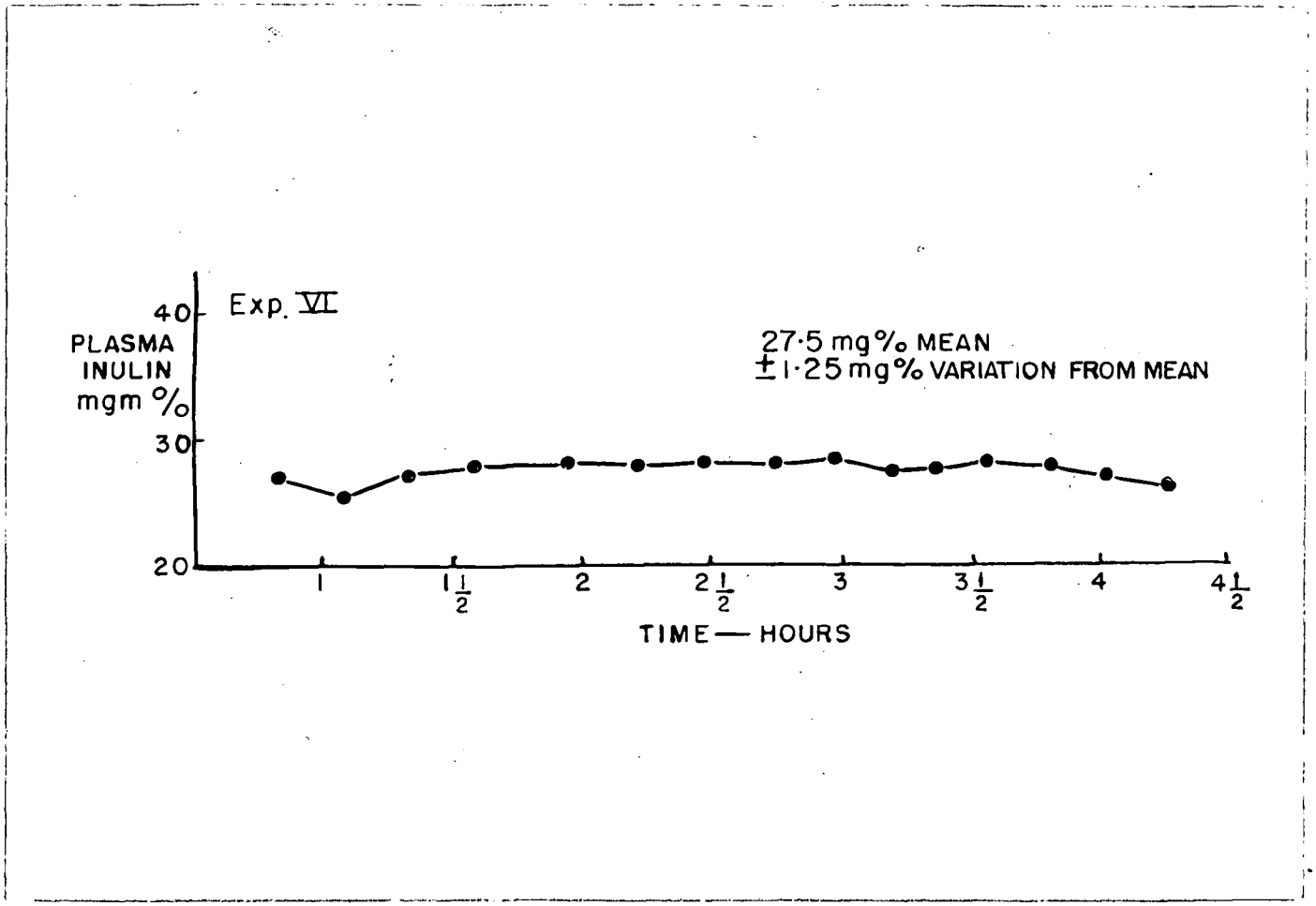
Exp. VI
40
30
20
PLASMA
INULIN
mgm %
27·5 mg% MEAN
±1·25 mg% VARIATION FROM MEAN
1
1 1/2
2
2 1/2
3
3 1/2
4
4 1/2
TIME — HOURS

Figure 3

TABLE IV

EXPERIMENT VII — INULIN INFUSION — DOG D

| Sample | Time | In. mg% |
|---|---|---|
| Start | 11:30 | |
| 1 | 12:10 | 24.5 |
| 2 | 12:27 | 22.5 |
| 3 | 12:40 | 22.5 |
| 4 | 12:43 | 23.0 |
| 5 | 12:46 | 22.25 |
| 6 | 12:49 | 23.0 |
| 7 | 12:52 | 22.25 |
| 8 | 12:55 | 23.0 |
| 9 | 1:10 | 23.0 |
| 10 | 1:25 | 23.75 |
| 11 | 1:40 | 23.75 |
| 12 | 1:43 | 21.25 |
| 13 | 1:46 | 21.25 |
| 14 | 1:49 | 20.75 |
| 15 | 1:52 | 21.25 |
| 16 | 1:55 | 21.5 |
| 17 | 2:12 | 21.5 |
| 18 | 2:25 | 21.5 |

URINE - Sample I collected 12:47-1:03 - 336 mg In. or 21 mg In./min.

Sample II collected 1:48-2:04 - 280 mg In. or 17.5 mg In./min.

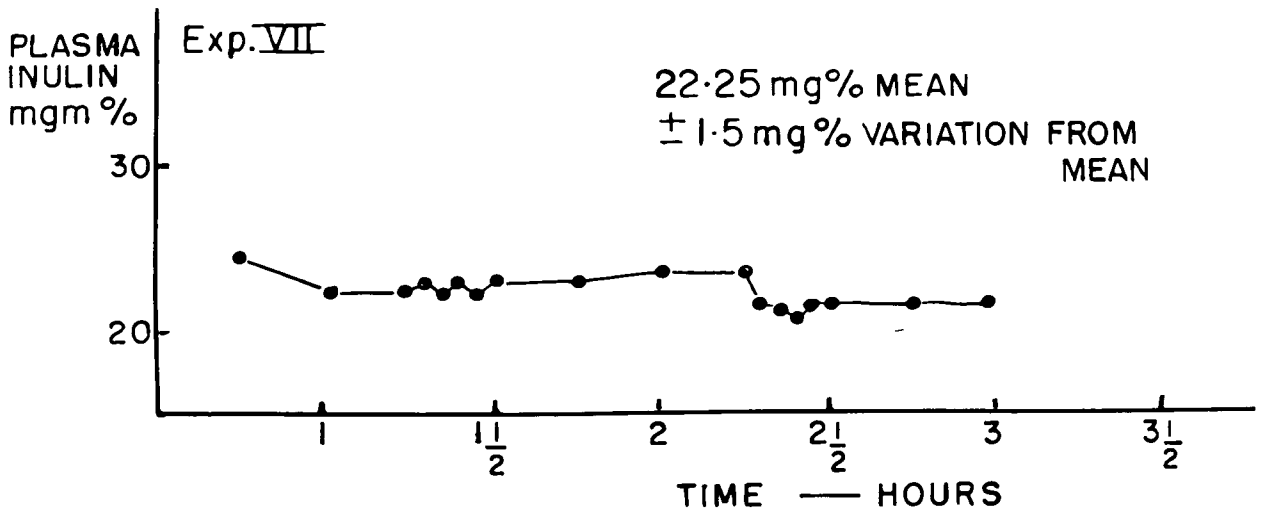
PLASMA
INULIN
mgm %
Exp. VII
22·25 mg% MEAN
± 1·5 mg % VARIATION FROM
MEAN
30
20
1
1 1/2
2
2 1/2
3
3 1/2
TIME — HOURS

Figure 4

THE EFFECTS OF NOREPINEPHRINE INJECTION

The effect of norepinephrine injection on water and cation shifts was tested in six experiments. Water movement was estimated by the method previously established.

In experiment VIII the priming dose of inulin, 1.0 grams was given at 11:20 A.M. The sustaining infusion was begun simultaneously and continued for three and one-half hours. Norepinephrine (0.4 µg/Kg) was given at 2:03 P.M. Blood samples were taken every three minutes for fifteen minutes following the norepinephrine injection and at fifteen minute intervals after this. Blood samples were taken as a control every three minutes for fifteen minutes and at fifteen minute intervals prior to norepinephrine injection. Results are presented in Table V and Figure V. Urinary inulin excretion in the fifteen minute interval before and after norepinephrine injection is presented in Table V. No consistent movement of plasma inulin concentration is seen following the injection of 0.4 µg/Kg norepinephrine.

In experiment IX the priming dose of inulin, 1.0 grams was given at 11:00 A.M. The sustaining infusion was begun simultaneously and continued for three and one-half hours. Norepinephrine (1.6 µg/Kg) was given at 1:58 P.M. Blood samples were taken as before. Urinary inulin excretion was measured as before. Results are shown in Table VI and Figure VI. No consistent movement of plasma inulin concentration is seen following the injection of 1.6 µg/Kg norepinephrine.

In experiment X the priming dose of inulin, 1.0 grams was given at 10:00 A.M. The sustaining infusion was begun simultaneously and continued for four hours. Norepinephrine (2.4 µg/Kg) was given at 1:14 P.M. Blood samples were taken as before. Urinary inulin

excretion was measured as before. Plasma sodium and potassium were measured in each sample. Results are presented in Table VII and Figure VII. No consistent movement of plasma sodium or plasma potassium is seen. The possibility of a slight fall of plasma inulin concentration thirty minutes after norepinephrine injection is suggested.

In experiment XI the priming dose of inulin, 1.0 grams was given at 11:15 A.M. The sustaining dose was begun simultaneously and continued for three and one-half hours. Norepinephrine (2.4 μg/Kg) was given at 2:12 P.M. Blood samples were taken as before. Urinary inulin excretion was measured as before. Plasma sodium and potassium were measured in each sample. Results are presented in Table VIII and Figure VIII. No consistent movement of plasma sodium or potassium is seen. The possibility of a slight fall of plasma inulin concentration thirty minutes after norepinephrine injection is suggested again.

In experiment XII the priming dose of inulin, 1.0 grams was given at 10:00 A.M. The sustaining dose of inulin was begun simultaneously and continued for four and one-quarter hours. Norepinephrine (3.2 μg/Kg) was given at 12:46 P.M. Blood samples were taken at fifteen minute intervals only. Plasma sodium and potassium were measured in each sample. Urinary inulin excretion was measured over intervals of an hour before and an hour after norepinephrine injection. Results are presented in Table IX and Figure IX. No consistent movement of plasma sodium or potassium is seen. The suggestion that plasma inulin concentration decreases thirty minutes after norepinephrine injection is not supported.

In experiment XIII the priming dose of inulin, 1.0 grams was given at 11:00 A.M. The sustaining dose of inulin was begun simultaneously and continued for four hours. Norepinephrine (4.8 µg/Kg) was given at 1:46 P.M.. Blood samples were taken at fifteen minute intervals only. Plasma sodium and potassium were measured with each sample. Urinary excretion of inulin was measured over intervals of forty minutes before and fifty minutes after norepinephrine injection. Results are presented in Table X and Figure X. No consistent movement of plasma sodium or potassium is seen. A decrease of plasma inulin at thirty minutes is not observed.

Increasing doses of norepinephrine were used in these experiments. In each case the test interval was preceded by a similar control interval. Experiments 8, 9, 10, 11 show no consistent pattern of inulin movement in the fifteen minute interval following norepinephrine injection. Experiments 10 and 11 suggested the possibility of a slight fall in plasma inulin concentration at thirty minutes but Experiments 12 and 13 offer this no support. Experiments 10, 11 and 12 and 13 examine the effect of norepinephrine in large doses on the cations both in the fifteen minute interval and over ninety minutes. No significant cation movement is observed.

The blood pressure was not recorded in these experiments. With doses of 1.6 µg/Kg norepinephrine and over, the animal reacted violently and abruptly. She began to pant, groan and whine, an abrupt tachycardia ensued, followed closely by a more prolonged bradycardia which lasted five to ten minutes.

TABLE V

EXPERIMENT VIII INULIN INFUSION WITH NOREPINEPHRINE INJECTION DOG D

| Sample | Time | In. mg% |
|---|---|---|
| | Start 11:20 | |
| 1 | 12:30 | 30.0 |
| 2 | 12:50 | 29.5 |
| 3 | 1:10 | 30.75 |
| 4 | 1:13 | 33.0 |
| 5 | 1:16 | 34.0 |
| 6 | 1:19 | 34.25 |
| 7 | 1:22 | 31.5 |
| 8 | 1:25 | 33.5 |
| 9 | 1:28 | 32.5 |
| 10 | 1:31 | 32.25 |
| 11 | 1:50 | 33.5 |
| | 2:03 | - 0.4 μg/Kg · norepinephrine I.V. |
| 12 | 2.05 | 35.5 |
| 13 | 2:08 | 34.25 |
| 14 | 2:11 | 33.5 |
| 15 | 2:14 | 34.25 |
| 16 | 2:17 | 33.5 |
| 17 | 2:20 | 32.75 |
| 18 | 2:23 | 33.5 |
| 19 | 2:26 | 33.5 |
| 20 | 2:40 | 34.25 |
| 21 | 2:50 | 35.25 |

URINE - Sample I collected 1:17-1:33 - 352 mg In. or 23.5 mg/In./min

Sample II collected 2:11-2:28 - 350 mg In. or 20.6 mg/In./min

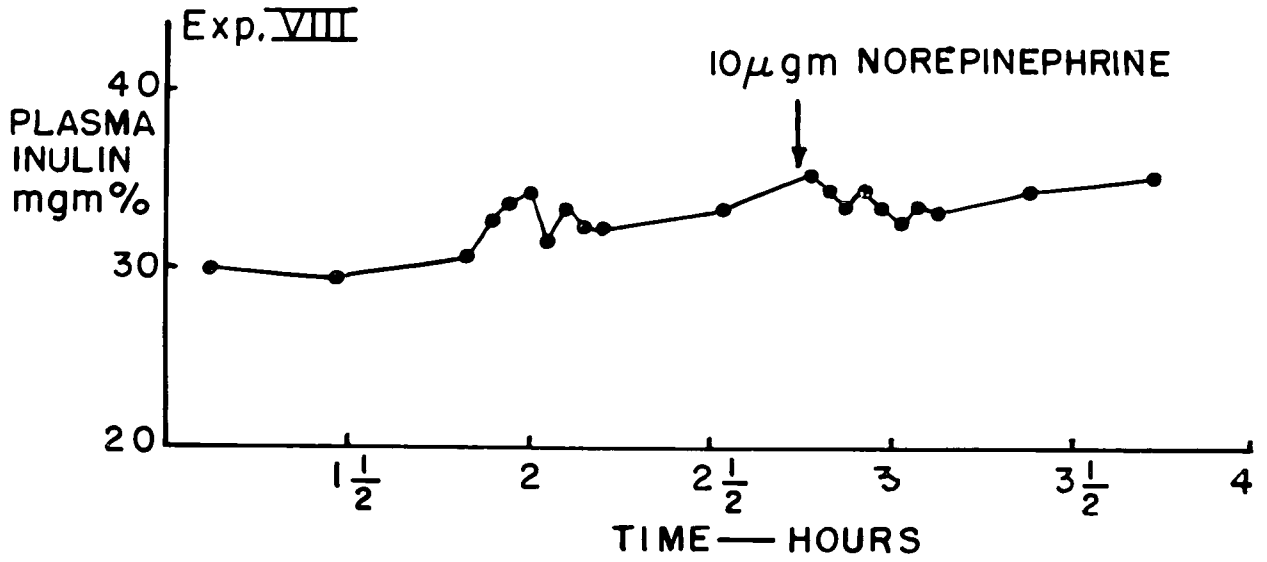
Exp. VIII
10μgm NOREPINEPHRINE
40
PLASMA
INULIN
mgm%
30
20
1 1/2
2
2 1/2
3
3 1/2
4
TIME — HOURS

Figure 5

TABLE VI

EXPERIMENT IX INULIN INFUSION WITH NOREPINEPHRINE INJECTION DOG M

| Sample | Time | In. mg% |
|---|---|---|
| | Start 11:00 | |
| 1 | 12:45 | 26.75 |
| 2 | 1:00 | 26.25 |
| 3 | 1:15 | 27.0 |
| 4 | 1:18 | 26.75 |
| 5 | 1:21 | 26.25 |
| 6 | 1:24 | 26.25 |
| 7 | - spoiled - | |
| 8 | 1:30 | 27.0 |
| 9 | 1:45 | 25.5 |
| | 1:58 - 1.6 µg/Kg. | norepinephrine I.V. |
| 10 | 2:00 | 24.0 |
| 11 | 2:03 | 24.25 |
| 12 | 2:06 | 25.5 |
| 13 | 2:09 | 24.25 |
| 14 | 2:12 | 23.5 |
| 15 | 2:15 | 24.25 |
| 16 | 2:18 | 25.0 |
| 17 | 2:30 | 25.0 |

URINE - Sample I collected 1:20-1:36 - 502 mg In. or 31.2 mg In./min.

Sample II collected 2:05-2:21 - 355 mg In. or 22.2 mg In./min.

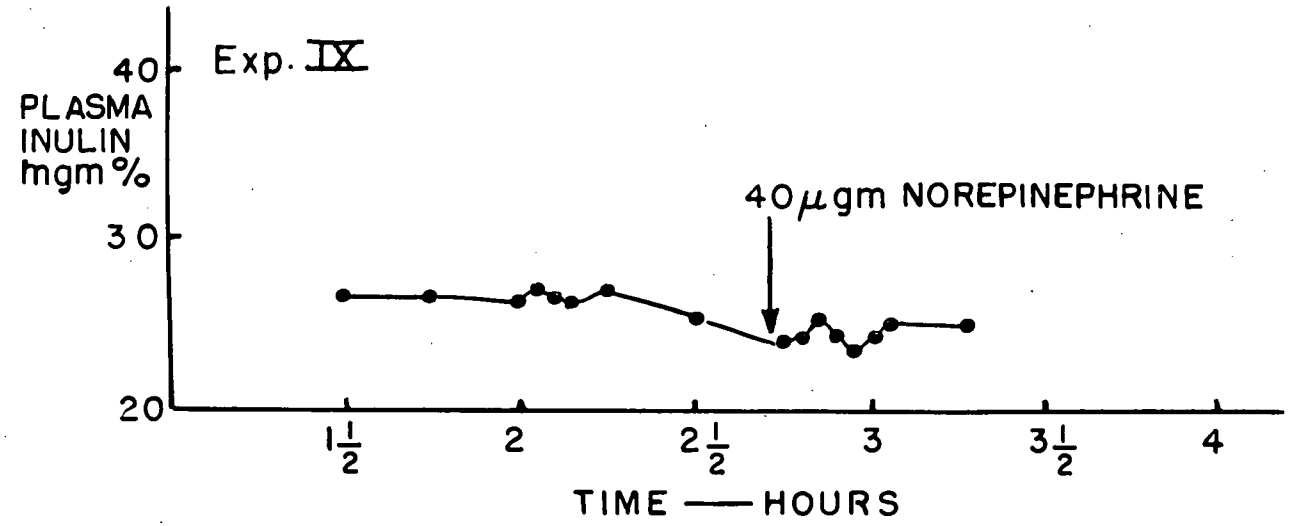
Exp. IX
40
PLASMA
INULIN
mgm %
30
20
40μgm NOREPINEPHRINE
1½
2
2½
3
3½
4
TIME — HOURS

Figure 6

TABLE VII

EXPERIMENT X INULIN INFUSION WITH NOREPINEPHRINE INJECTION DOG M

| Sample | Time | In.mg% | K.mEq/L | Na.mEq/L |
|---|---|---|---|---|
| Start | 10:00 | | | |
| 1 | 12:00 | 20.75 | 3.49 | 156.88 |
| 2 | 12:15 | 22.0 | 3.34 | 153.29 |
| 3 | 12:30 | 23.0 | 3.34 | 152.57 |
| 4 | 12.45 | 24.0 | 3.80 | 150.06 |
| 5 | 12.48 | 23.5 | 3.70 | 156.16 |
| 6 | 12:51 | 25.0 | 3.60 | 152.57 |
| 7 | 12.54 | 23.5 | 3.62 | 152.57 |
| 8 | 12:57 | 24.0 | 3.71 | 153.29 |
| 9 | 1:00 | 25.0 | -Spoiled- | 153.65 |
| | 1:14 - 2.4µg/Kg norepinephrine I.V. | | | |
| 10 | 1:15 | 25.25 | 3.68 | 152.57 |
| 11 | 1:18 | 25.25 | 3.46 | 153.29 |
| 12 | 1:21 | 25.25 | 3.35 | 152.57 |
| 13 | 1:24 | 24.25 | 3.33 | 153.29 |
| 14 | 1:27 | 24.75 | 3.22 | 150.06 |
| 15 | 1:30 | 25.5 | 3.38 | 150.06 |
| 16 | 1:45 | 25.5 | 3.48 | 152.57 |
| 17 | 2:00 | 24.25 | 3.72 | 152.57 |

URINE - Sample I collected 12:51 - 1:07 - 527mg In. or 33 mg In/min.

Sample II collected 1:21 - 1:37 - 637 mg In. or 39. mg In/min.

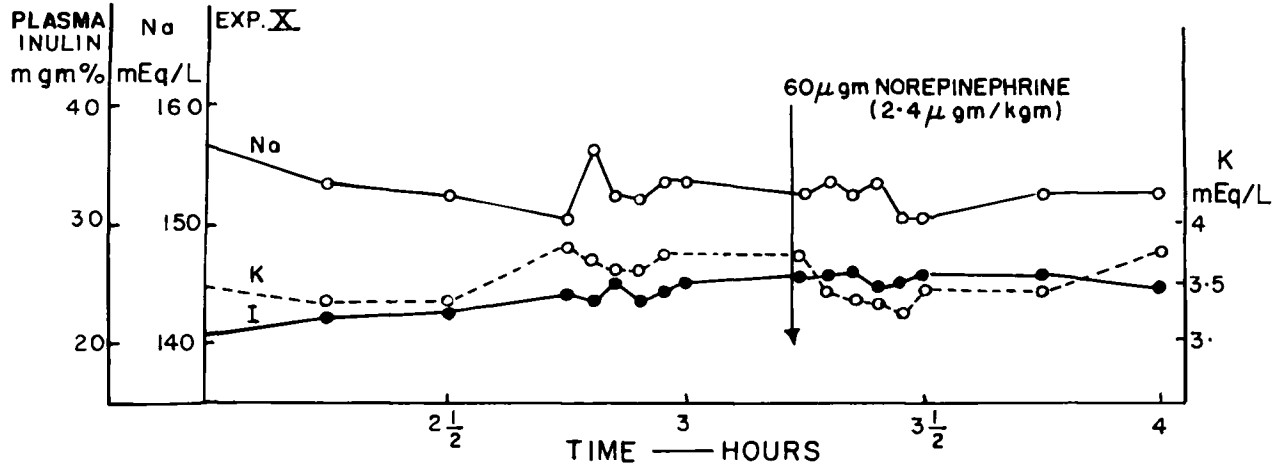
PLASMA INULIN
m gm%
Na
mEq/L
EXP. X
40
30
20
160
150
140
Na
K
I
60μ gm NOREPINEPHRINE
(2·4μ gm/kgm)
K
mEq/L
4
3·5
3·
2 1/2
3
3 1/2
4
TIME — HOURS

Figure 7

TABLE VIII

EXPERIMENT XI INULIN INFUSION WITH NOREPINEPHRINE INJECTION DOG D

| Sample | Time | In.mg% | K.mEq/L | Na.mEq/L |
|---|---|---|---|---|
| | Start 11:15 | | | |
| 1 | 1:15 | 36.5 | 3.1 | 151.49 |
| 2 | 1:30 | 37.0 | 3.3 | 151.49 |
| 3 | 1:33 | 38.0 | 3.35 | 147.19 |
| 4 | 1:36 | 39.5 | 3.3 | 150.75 |
| 5 | 1:39 | 39.5 | 3.35 | 147.90 |
| 6 | 1:42 | 39.5 | 3.3 | 148.98 |
| 7 | 1:45 | 36.75 | 3.0 | 145.39 |
| 8 | 2:00 | 38.0 | 3.2 | 147.19 |
| | 2:12 - 2.4 µg/Kg norepinephrine I.V. | | | |
| 9 | 2:15 | 39.0 | 3.1 | 152.57 |
| 10 | 2.18 | 39.75 | 3.2 | 148.98 |
| 11 | 2:21 | 40.75 | 3.3 | 147.90 |
| 12 | 2:24 | 40.5 | 3.1 | 148.98 |
| 13 | 2:27 | 39.5 | 3.4 | 145.39 |
| 14 | 2:30 | 39.35 | 3.3 | 147.90 |
| 15 | 2:40 | 38.25 | 3.1 | 145.39 |
| 16 | 2:50 | 38.75 | 3.2 | 145.39 |

URINE - Sample I collected 1:36 - 1:52 - 900 mg In. or 56.2 mg In/Min.

Sample II collected 2:19 - 2:37 - 892 mg In. or 49.5 mg In/min.

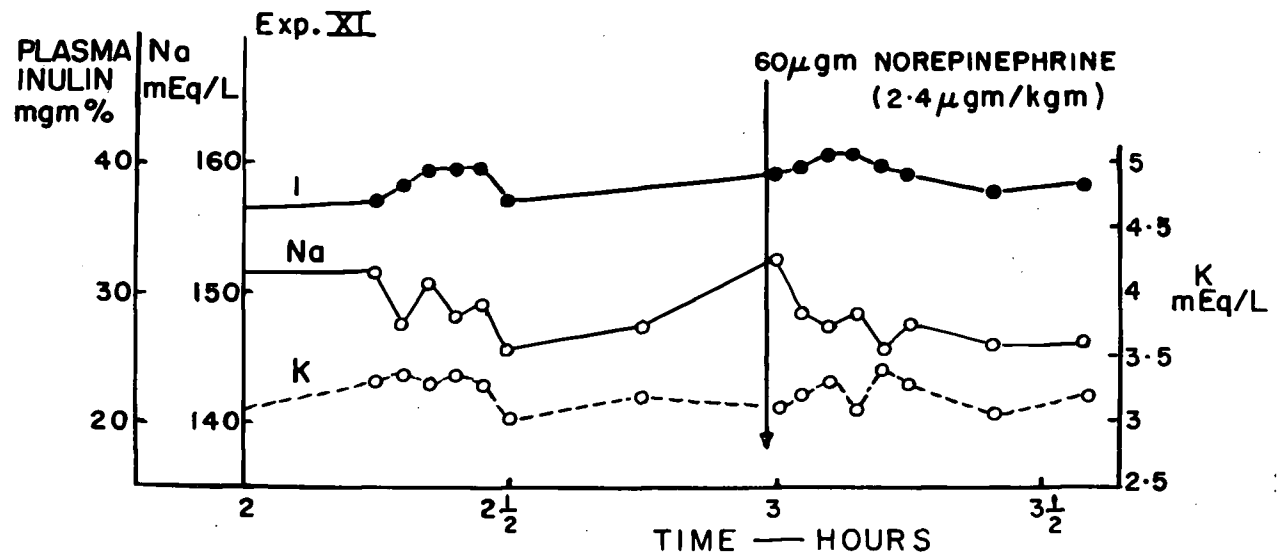
Exp. XI
PLASMA INULIN mgm%
Na mEq/L
60μgm NOREPINEPHRINE
(2·4μgm/kgm)
40
30
20
160
150
140
I
Na
K
5
4·5
4
3·5
3
2·5
K mEq/L
2
2½
3
3½
TIME — HOURS

Figure 8

TABLE IX

EXPERIMENT XII INULIN INFUSION WITH NOREPINEPHRINE INJECTION DOG M

| Sample | Time | In.mg% | K.mEq/L | Na.mEq/L |
|---|---|---|---|---|
| Start | 10:00 | | | |
| 1 | 12:00 | 26.25 | 3.40 | 155.08 |
| 2 | 12:10 | 26.75 | 3.30 | 156.16 |
| 3 | 12:30 | - Spoiled - | | |
| 4 | 12:45 | 26.5 | 3.12 | 152.57 |
| | 12:46 | - 3.2 µg/Kg. norepinephrine I.V. | | |
| 5 | 1:00 | 27.0 | 3.10 | 148.26 |
| 6 | 1:15 | 27.25 | 3.12 | 155.80 |
| 7 | 1:30 | 28.75 | 3.15 | 151.85 |
| 8 | 1:45 | 28.5 | 3.35 | 152.57 |
| 9 | 2:00 | 27.0 | 3.12 | 154.72 |
| 10 | 2:15 | 27.25 | 3.02 | 145.03 |

URINE - Sample I collected 12:00 - 1:05 - 1401.75 mg In. or 21.6 mg In/min.

Sample II collected 1:05 - 2:05 - 1336.6 mg In. or 22.6 mg In/min.

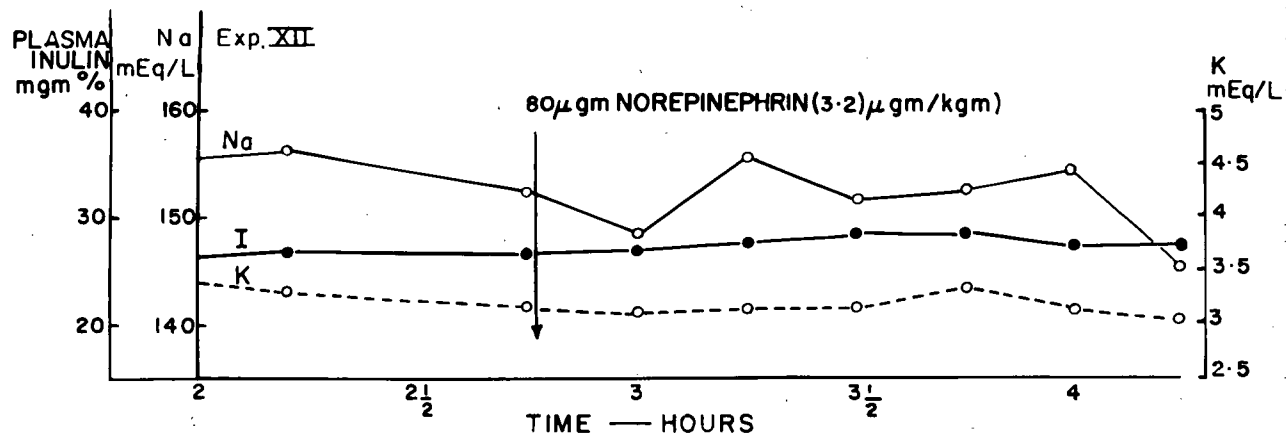
PLASMA INULIN mgm %
Na mEq/L
Exp. XII
80μgm NOREPINEPHRIN (3·2)μgm/kgm)
K mEq/L
40
30
20
160
150
140
5
4·5
4
3·5
3
2·5
Na
I
K
2
2½
3
3½
4
TIME — HOURS

Figure 9

TABLE X

EXPERIMENT XIII INULIN INFUSION WITH NOREPINEPHRINE INJECTION DOG M

| Sample | Time | In.mg% | K.mEq/L | Na.mEq/L |
|---|---|---|---|---|
| Start | 11:00 | | | |
| 1 | 1:00 | 26.75 | 3.05 | 151.85 |
| 2 | 1:15 | 27.0 | 3.08 | 151.13 |
| 3 | 1:30 | 27.5 | 3.02 | 152.93 |
| 4 | 1:45 | 25.0 | 2.90 | 150.78 |
| | 1:46 - 4.8 µg/Kg. norepinephrine I.V. | | | |
| 5 | 2:00 | 24.75 | 3.00 | 153.65 |
| 6 | 2:15 | 26.0 | 3.02 | 151.85 |
| 7 | 2:30 | 25.0 | 3.03 | 151.45 |
| 8 | 2:45 | 25.25 | 3.01 | 159.75 |
| 9 | 3:00 | 25.25 | 3.91 | 151.85 |

Urine not measured for Volume but:

Sample I collected 1:10 - 1:50 - 36.5 mg In/cc*

Sample II collected 1:50 - 2:40 - 36.75 mg In/cc*

* including washout.

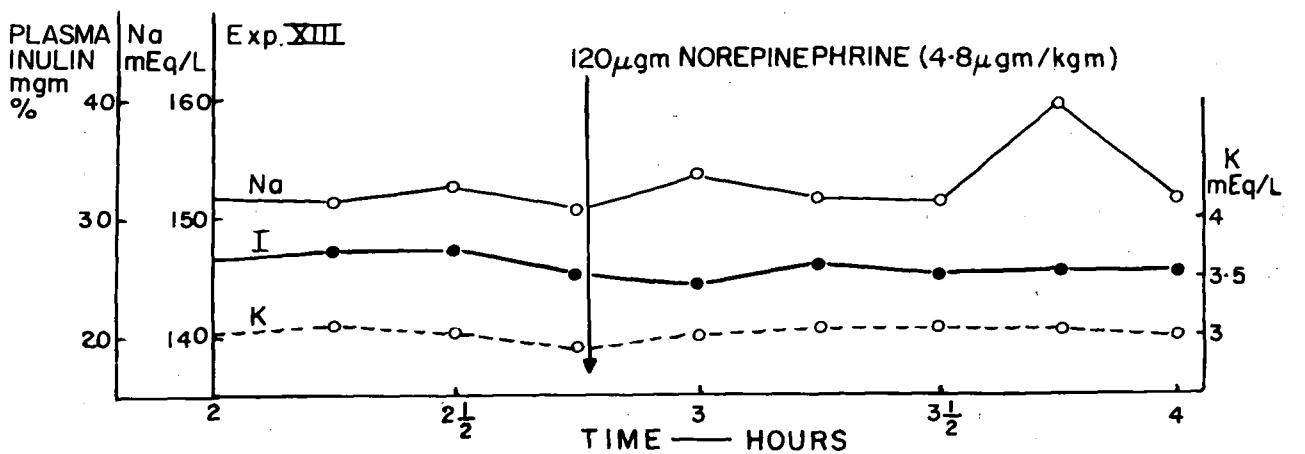
PLASMA INULIN mgm %
Na mEq/L
Exp. XIII
120μgm NOREPINEPHRINE (4·8μgm/kgm)
40
30
20
160
150
140
Na
I
K
K mEq/L
4
3·5
3
2
2½
3
3½
4
TIME — HOURS

Figure 10

THE EFFECTS OF PITRESSIN INJECTION

The effects of pitressin injection on water and cation shifts were tested in three experiments. Water movement was estimated by the method previously established.

In experiment XIV the priming dose of inulin, 1.0 grams was given at 9:45 A.M. The sustaining infusion was begun simultaneously and continued for three hours and twenty minutes. Pitressin (200 mU/Kg) was given at 12:29 P.M. Blood samples were taken every three minutes for fifteen minutes following the pitressin injection and at ten minute intervals after this. Blood samples were taken as a control every three minutes for fifteen minutes and at fifteen minute intervals prior to the pitressin injection. Plasma sodium and plasma potassium were measured in each sample. Urinary inulin excretion was measured as before. Results are presented in Table XI and Figure XI. With the administration of 200 mU/Kg of pitressin the plasma inulin concentration rose from 32.75 mgm % to 39 mgm % in six minutes. The plasma sodium concentration fell from 153.4 mEq/L to 144.67 mEq/L in three minutes. The plasma potassium concentration rose from 3.26 mEq/L to 3.42 mEq/L over a fifteen minute interval.

In experiment XV the priming dose of inulin, 1.0 grams was given at 10:15 A.M. The sustaining infusion was begun simultaneously and continued for four hours. Pitressin (40 mU/Kg) was given at 1:44 P.M. Blood samples were taken as before. Urinary inulin excretion was measured as before. Results are presented in Table XII and Figure XII. With the administration of 40 mU/Kg of pitressin the plasma inulin concentration rose from 34.5 mgm % to 36.25 mgm % in three minutes. The plasma sodium

concentration fell from 159.3 mEq/L to 154.01 mEq/L in six minutes. The plasma potassium concentration rose from 3.80 mEq/L to 4.09 mEq/L in an interval of 12 minutes.

In experiment XVI the priming dose of inulin, 1.0 grams was given at 10:20 A.M. The sustaining infusion was begun simultaneously and continued for four and one-half hours. Pitressin (40 mU/Kg) was given at 1:32 and again at 2:11. Blood samples were taken as before. Urinary inulin excretion was measured as before. The results are shown in Table XIII and Figure XIII. With the first injection of 40 mU/Kg of pitressin, plasma inulin concentration rose from 25.0 mgm % to 26.75 mgm % in thirteen minutes. Plasma sodium concentration fell from 150.06 mEq/L to 147.19 mEq/L in seven minutes. Plasma potassium concentration rose from 3.4 mEq/L to 4.08 mEq/L in thirteen minutes. With the second pitressin injection of 40 mU/Kg the plasma inulin concentration rose from 23.75 mgm % to 25.0 mgm % in eleven minutes. The plasma sodium concentration fell from 152.6 mEq/L to 148.6 mEq/L in five minutes. The plasma potassium concentration rose from 3.77 mEq/L to 3.96 mEq/L in eleven minutes. A blood pressure tracing was taken with the administration of the second dose of pitressin. The result is shown in Figure XIV.

In experiment 14 the administration of a large dose of pitressin (200 mU/Kg ) was followed by a sudden and distinct rise of 6.25 mg % plasma inulin. The rise in plasma inulin concentration reached its peak in six minutes and remained elevated for fifteen minutes. Plasma sodium concentration behaved as a mirror image of plasma inulin. Plasma sodium concentration fell 9 mEq/L in three minutes and then rose coincidentally with the fall of the plasma inulin concentration. Plasma potassium

concentration rose 0.16 mEq/L reaching its peak at fifteen minutes. Similar changes were noted with 40 mU/Kg doses of pitressin in three occasions in experiments 15 and 16. These changes were of less magnitude than in experiment 14. Though the direction of shift is similar in all experiments there is variation in the magnitude of movement of cations relative to water and of sodium relative to potassium.

The blood pressure response was observed in experiment 16. This is shown in Figure 14. Our findings correspond with those of Kolls and Geiling (14). A rise of diastolic pressure of 30-40 mm/Hg is recorded. The systolic pressure rose less, so the pulse pressure diminished. The bradycardia observed developed over a thirty second period. The clinical description of the reaction corresponded closely with the description given by Kolls and Geiling.

TABLE XI

EXPERIMENT XIV INULIN INFUSION WITH PITRESSIN INJECTION DOG D

| Sample | Time | In.mg% | K.mEq/L | Na.mEq/L |
|---|---|---|---|---|
| Start | 9:45 | | | |
| 1 | 11:45 | 32.5 | 3.58 | 154.37 |
| 2 | 12:00 | 31.5 | 3.18 | 153.65 |
| 3 | 12:03 | 31.5 | 3.30 | 153.65 |
| 4 | 12:06 | 33.0 | 3.50 | 150.78 |
| 5 | 12:09 | 32.0 | 3.36 | 153.29 |
| 6 | 12:12 | 31.25 | 3.06 | 147.19 |
| 7 | 12:15 | 32.5 | 3.18 | 148.98 |
| | 12:29 - 200 mU/Kg. pitressin I.V. | | | |
| 8 | 12:30 | 32.75 | 3.26 | 153.39 |
| 9 | 12:33 | 34.75 | 3.24 | 144.67 |
| 10 | 12:36 | 39 | 3.41 | 150.78 |
| 11 | 12:39 | 34.75 | 3.38 | 147.19 |
| 12 | 12:42 | 34.0 | 3.36 | 147.90 |
| 13 | 12:45 | 33.5 | 3.42 | 148.62 |
| 14 | 1:00 | 29.75 | 3.40 | 153.29 |
| 15 | 1:10 | 29.25 | 3.40 | 153.29 |
| 16 | 1:20 | 28.75 | 3.27 | 150.06 |
| 17 | 1:25 | 29.25 | 3.52 | 148.98 |
| 18 | 1:35 | 29.25 | 3.50 | 148.62 |

URINE - Volume not recorded

Sample I collected 12:02 - 12:18 - 40 mg In/cc

Sample II collected 12:30 - 12:47 - 37 mg In/cc

Sample III collected 1:09 - 1:26 - 34 mg In/cc

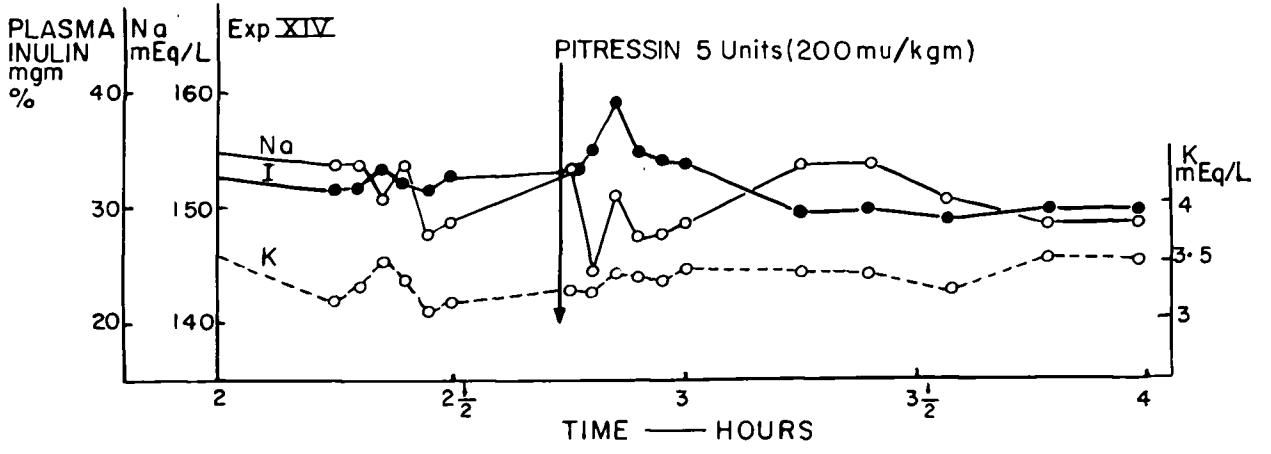
PLASMA
INULIN
mgm
%
Na
mEq/L
Exp XIV
PITRESSIN 5 Units(200mu/kgm)
40
30
20
160
150
140
Na
I
K
K
mEq/L
4
3·5
3
2
2½
3
3½
4
TIME —— HOURS

Figure 11

TABLE XII

EXPERIMENT XV INULIN INFUSION WITH PITRESSIN INJECTION DOG D

| Sample | Time | In.mg% | K.mEq/L | Na.mEq/L |
|---|---|---|---|---|
| Start | 10:15 | | | |
| 1 | 12:15 | 34.5 | 3.91 | 160.83 |
| 2 | 12:30 | 35.25 | 4.12 | 156.52 |
| 3 | 12:45 | 37.0 | 4.0 | 152.93 |
| 4 | 1:00 | 37.25 | 4.02 | 155.80 |
| 5 | 1:03 | 36.0 | 3.89 | 156.52 |
| 6 | 1:06 | 34.25 | 3.65 | 151.49 |
| 7 | 1:09 | 32.5 | 3.74 | 155.80 |
| 8 | 1:12 | - Spoiled - | | |
| 9 | 1:15 | 33.0 | 3.75 | 160.47 |
| 10 | 1:30 | 34.75 | 3.90 | 163.26 |
| | 1:44 - 40 mU/Kg pitressin I.V. | | | |
| 11 | 1:45 | 34.5 | 3.80 | 159.03 |
| 12 | 1:48 | 36.25 | 4.01 | 157.96 |
| 13 | 1:51 | 34.0 | 3.75 | 154.01 |
| 14 | 1:54 | 34.0 | 3.99 | 157.24 |
| 15 | 1:57 | 34.5 | 4.09 | 157.24 |
| 16 | 2:00 | 33.25 | 3.89 | 157.24 |
| 17 | 2:10 | 32.5 | 4.18 | 150.06 |
| 18 | 2:20 | 31.75 | 4.01 | 147.54 |

URINE - Sample I collected 1:05 - 1:16 - 390 mg In. or 35.5 mg In/min.

Sample II collected 1:48 - 2:04 - 890 mg In. or 55 mg In/min.

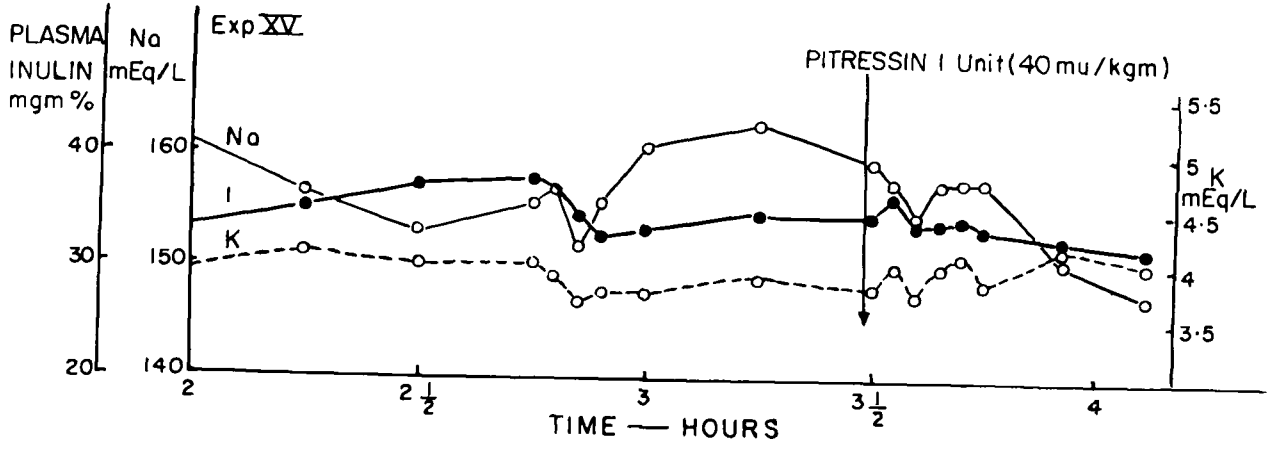
PLASMA INULIN mgm %
Na mEq/L
Exp XV
PITRESSIN 1 Unit (40 mu/kgm)
Na
I
K
40
30
20
160
150
140
5·5
5
4·5
4
3·5
K mEq/L
2
2 1/2
3
3 1/2
4
TIME — HOURS

Figure 12

TABLE XIII

EXPERIMENT XVI INULIN INFUSION WITH PITRESSIN INJECTION DOG M

| Sample | Time | In.mg% | KmEq/L | Na.mEq/L |
|---|---|---|---|---|
| Start | 10:20 | | | |
| 1 | 12:25 | 26.0 | 3.5 | 150.06 |
| 2 | 12:45 | 26.0 | 3.25 | 147.90 |
| 3 | 12:55 | 25.75 | 3.55 | 144.32 |
| 4 | 1:00 | 26.0 | 3.5 | 150.78 |
| 5 | 1:10 | 26.0 | 3.47 | 148.63 |
| 6. | 1:30 | 25.0 | 3.4 | 150.06 |
| | 1:32 - 40 mU/Kg. pitressin I.V. | | | |
| 7 | 1:33 | - spoiled - | 3.35 | 148.63 |
| 8 | 1:36 | 25.5 | 3.7 | 147.90 |
| 9 | 1:39 | 25.5 | 3.7 | 147.19 |
| 10 | 1:42 | 25.75 | 3.92 | 148.63 |
| 11 | 1:45 | 26.75 | 4.08 | 152.93 |
| 12 | 1:48 | 23.0 | 3.4 | 152.57 |
| 13 | 2:00 | 23.75 | 3.92 | 153.29 |
| 14 | 2:10 | 23.75 | 3.77 | 152.57 |
| | 2:11 - 40 mU/Kg. pitressin I.V. | | | |
| 15 | 2:13 | 24.75 | 3.6 | 153.29 |
| 16 | 2:16 | 24.75 | 3.65 | 148.63 |
| 17 | 2:19 | 24.25 | 3.72 | 148.63 |
| 18 | 2:22 | 25.0 | 3.96 | 152.57 |
| 19 | 2:36 | 24.25 | 3.85 | 150.06 |
| 20 | 2:45 | 24.25 | 3.85 | 145.04 |

URINE - Sample I collected 12:39 - 12:58 - 499.5 mg In. or 26.75 mg In/min.
Sample II collected 2:13 - 2:25 - 410 mg In. or 31.5 mg In/min.

Blood pressure was recorded from 2:11 to 2:16 and shown in Figure 14.

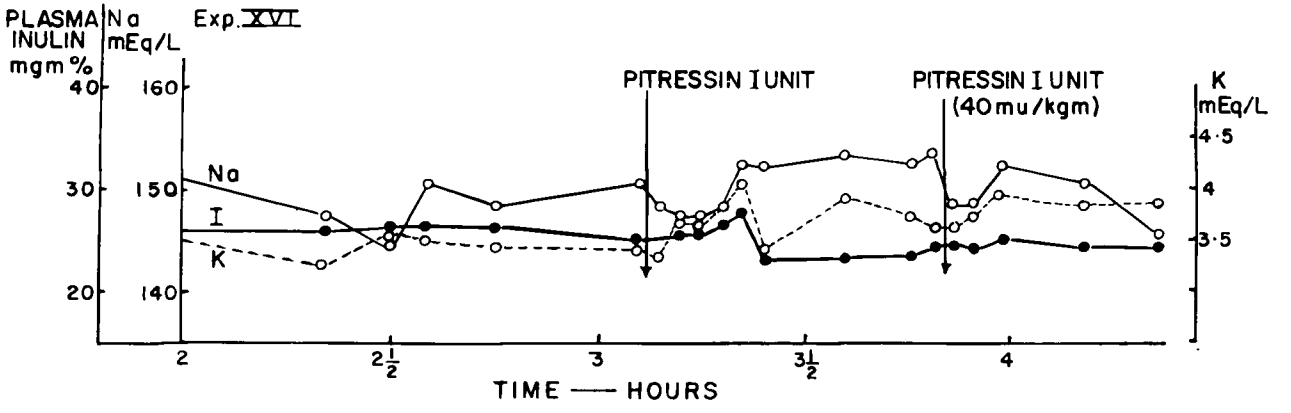
PLASMA INULIN mgm %
Na mEq/L
Exp. XVI
40
30
20
160
150
140
Na
I
K
PITRESSIN I UNIT
PITRESSIN I UNIT
(40 mu/kgm)
K
mEq/L
4·5
4
3·5
2
2½
3
3½
4
TIME — HOURS

Figure 13

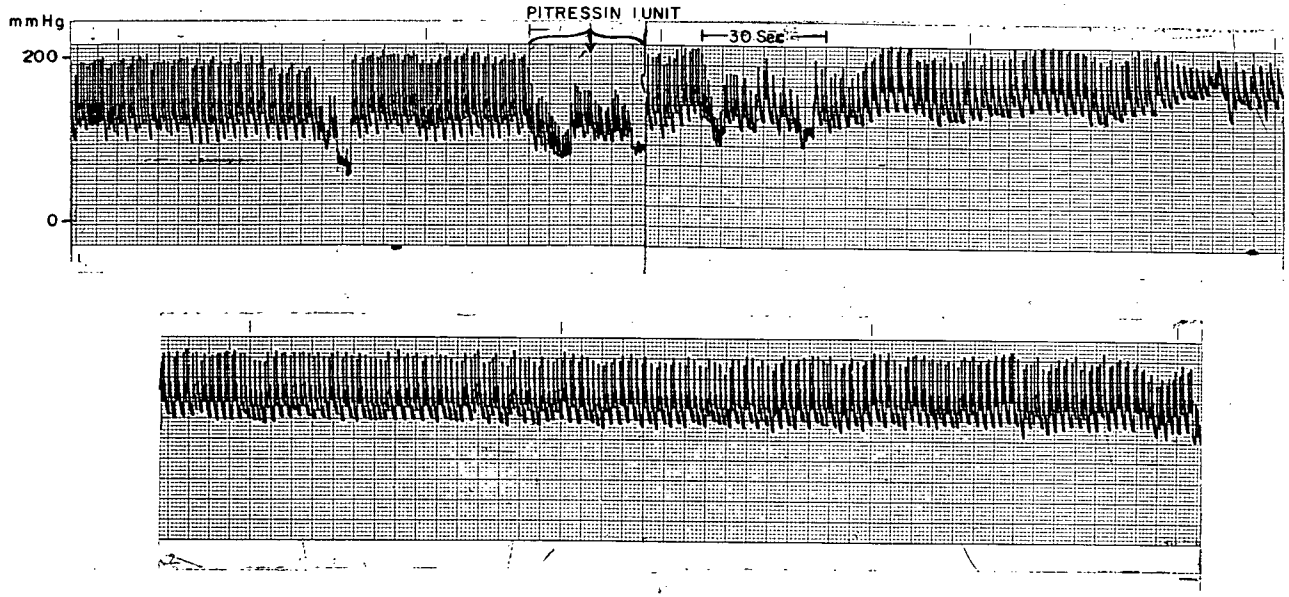


Figure 14

DISCUSSION

The reliability of the inulin infusion technique was tested. A fairly constant level of extracellular inulin can be maintained for up to three hours by this technique. The greatest variation from the mean was 1.5 mg% of plasma inulin. The plasma inulin concentration measured over three minute intervals showed no more variation than it did in fifteen minute intervals. Enough control of the plasma inulin concentration was thus achieved to justify the use of the technique to indicate the direction of extracellular water shift.

In addition to providing constant extracellular inulin levels the inulin infusion technique has the advantage of simplicity. No critical intake and output methods are necessary. The technique simply involves the administration of an approximate concentration of inulin solution at a constant rate.

Norepinephrine and pitressin show different effects on cation and water movement in the conscious dog. Six experiments with norepinephrine injection were performed and our results do not conflict with those results recorded in the literature for the anaesthetized animal. We observed no change in the plasma sodium concentration with the doses of norepinephrine we administered. Friedman et al (8) observed no change in the plasma sodium concentration in anaesthetized dogs with comparable doses of norepinephrine. Muirhead et al (15) noted a significant decrease in the extracellular sodium concentration with a norepinephrine infusion but the doses in his experiments were twenty times the doses used in our work. Similar comment can be made in respect to the work of Robertson and Peyser (19).

Muirhead et al (15) observed no change in the radiosulfate space with a norepinephrine infusion. In our experiments the inulin space did not change in response to a norepinephrine injection. Both of these observations are at variance with the results of Friedman et al (8) who observed a distinct depression of the inulin space in response to a norepinephrine infusion in the dog. In order to observe this depression in the rat Friedman found it necessary to induce a hypotensive state, such is the rapidity of the change in the extracellular space. Undoubtably the infusion of norepinephrine provides a measurable interval not provided by a single injection. It is also conceivable that the conscious dog may have an adaptive capacity not present in the anaesthetized dog. In view of the fact, however, that the space does change with a pitressin injection the latter possibility is unlikely. We observed no change in the plasma potassium concentration in response to the norepinephrine injection. Plasma potassium concentration did not change in response to norepinephrine infusion in the work of Friedman et al (8). Muirhead et al (15) observed a slight rise in the plasma potassium concentration but with very large doses of norepinephrine.

Three experiments were performed with pitressin injections. These three experiments suggest a definite pattern of water and cation movement associated with the pressor response. No inference can, however, be drawn as to which comes first. Following a pitressin injection water moves out of the extracellular space as is shown by the sudden increase in the plasma inulin concentration. The renal excretion of inulin did not diminish during the testing intervals. In association with the water movement plasma sodium concentration dropped markedly while plasma

potassium concentration rose slowly.

These responses to a pitressin injection are similar to those responses obtained by Friedman et al (8) on anaesthetized dogs with comparable pitressin doses. It can be seen in Friedman's work and ours that the magnitude of the change varies with the magnitude of the dose. Tobian and Fox (21) noted the individual variation of cationic changes in dogs and this may explain the relative differences observed by us since experiments 14 and 15 were performed with dog D and experiment 16 with dog M. As stressed by Friedman et al, the shift of water and cations is less rapid with pitressin than with norepinephrine, as is the pressor effect. Consequently pitressin changes are more easily measured.

## CONCLUSIONS

1. An index of extracellular fluid shift has been developed.

2. Norepinephrine has not been shown to affect water or cationic movement in the extracellular compartment.

3. Pitressin has been shown to affect water and cationic movement in the extracellular compartment. This has been interpreted to indicate a movement of water and sodium into cells and potassium out of cells in association with the pressor response.

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