# EFFECTS OF POSTURE ON
# RENAL SODIUM EXCRETION IN ORTHOSTATIC HYPOTENSION

by

Daniel M. Bachman

A THESIS

Presented to the Department of Physiology
and the Graduate Division of the University of Oregon Medical School
in partial fulfillment
of the requirements for the degree of
Master of Science

May 1952

APPROVED:

[redacted]

.....
(Professor in Charge of Thesis)

[redacted]

.....
(Chairman, Graduate Council)

Dedicated to

LISE

ACKNOWLEDGMENTS

I wish to express my appreciation to Dr. W. B. Youmans for his patient guidance and many helpful suggestions throughout the course of this work, to Miss Shirley Gullixson and Miss Betty Dornbusch for laboratory assistance, to Mrs. Kay Bittick for artistic preparation of the graphs, and to Mrs. Margaret Wolff for an excellent typing and final assembling of the manuscript.

D. M. B.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

# INTRODUCTION

While clinicians, in recent years, have become increasingly impressed with the importance of sodium ion in disturbances of fluid and electrolyte balance in a variety of disease states,(1-8) renal physiologists have been focusing their attention upon the underlying renal mechanisms influencing sodium* excretion.

These mechanisms may be understood best in the light of the current hypothesis explaining urine formation by the mammalian kidney: 1) An ultrafiltrate of plasma is formed in Bowman's Capsule by filtration of water and non-protein solutes of the blood through the semi-permeable glomerular membrane. The concentration of any substance in this filtrate is almost the same as its concentration in the plasma.** 2) As the plasma filtrate flows from Bowman's Capsule through the renal tubules, water and individual solutes are selectively reabsorbed into the peritubular capillaries by both simple diffusion and by cellular work. 3) Some substances, in addition, are actively secreted into the urine by the cells of the renal tubules. This hypothesis of urine formation rests fundamentally upon the experimental work of Richards, Walker, and their associates, who, by means of micropipette punctures of the renal tubules in amphibia and lower mammalia, withdrew samples of tubular urine and subjected these to chemical analysis.(10-12) It has been assumed that the human kidney functions similarly.

* Hereafter, the term "sodium" is used to mean "sodium ion".

** The Donnan Equilibrium is thought to account for the concentration differences.(9)

In terms of this hypothesis, investigations of the control of sodium excretion by the mammalian kidney have proceeded with a view to determining the relative importance of glomerular filtration and tubular reabsorption.

Numerous experimental procedures have been devised to alter the renal sodium excretion rate for the purpose of simultaneously studying changes in glomerular filtration and tubular reabsorption rates. In the dog the following procedures have been found to produce definite changes in the rate of renal sodium excretion: clamping the renal artery;(14-17) clamping the renal vein;(18-21) hemorrhage;(22) splanchnic nerve resection;(23-25) salt loading;(26-32) osmotic loading;(33,34) administration of mercurial diuretics;(35) administration of hormones;(36-38) and emotional stress.(39) In normal man changes in renal sodium excretion rate have been produced by: salt depletion;(40,41) salt loading;(40-43) osmotic loading;(44,45) quiet standing;(46-48) exercise;(47) hemorrhage;(49) tipping on a tilt-table;(50) administration of mercurial diuretics;(51) administration of hormones;(52-54) and inflation of blood pressure cuffs around the thighs.(55) In addition some of these procedures have been carried out upon man in certain disease states.(7,56-61) As a result of these experiments some students of renal physiology have favored glomerular filtration rate as the more important factor in the control of sodium excretion by the kidney, while others have favored tubular reabsorption. These viewpoints will be discussed in the "Review of the Literature".

In the present study it is demonstrated that in patients with orthostatic hypotension,(62-74) a disease characterized by a marked fall of

arterial blood pressure when the patient is in the upright position, large changes in the renal sodium excretion rate result from changes in body posture. It has been possible to interpret these changes in terms of alterations in the glomerular filtration and the tubular reabsorption of sodium.

# REVIEW OF THE LITERATURE

## I. The Relation of Glomerular Filtration and Tubular Reabsorption to Sodium Excretion

A review of the attempts to elucidate the mechanisms by which the kidney regulates sodium excretion is considered necessary to an understanding of the interpretation placed upon the data reported in this thesis.

Two major schools of thought have arisen with respect to the control of sodium excretion by the kidney: 1) the concept of glomerular-tubular imbalance, according to which, changes in tubular reabsorption are considered to be secondary to changes in the rate of glomerular filtration, and 2) the concept that altered tubular reabsorption occurs independently of changes in glomerular filtration rate.

### A. Glomerular-tubular Imbalance

The glomerular-tubular imbalance hypothesis had its origin, in part, from clinical studies of patients with chronic congestive heart failure. In such patients Mokotoff, Ross and Leiter observed decreased sodium excretion in the presence of subnormal mannitol clearance.(59) These workers stated that the decreased sodium excretion was caused by the decreased glomerular filtration rate (GFR) in the presence of normal tubular reabsorption. Merrill observed similar results in his patients; and, while admitting the possibility of other causal mechanisms, favored the concept that the decreased glomerular filtration of sodium allowed for more complete tubular reabsorption.(50) Subjecting patients with chronic congestive heart failure to mild exercise Merrill and Cargill observed marked reduction in sodium excretion accompanying decreases

in GFR.(75) As a result of similar experiments Sinclair-Smith and associates, although emphasizing the role of tubular reabsorption, stated that in the advanced stages of cardiac decompensation, decreased GFR contributes to the decreased sodium excretion "owing to a diminution in the total amount of sodium which is filtered through the glomeruli".(57)

Studying normal human subjects during quiet standing Epstein et al found decreases in GFR, sodium excretion, and in the fraction of filtered sodium excreted.(46) When these subjects received, during quiet standing, intravenous infusions of hypertonic saline, sodium excretion increased in three subjects whose glomerular filtration rates either remained the same or increased. Since serum sodium increased in all cases, the increased sodium excretion in each of these three subjects was accompanied by an increased filtered sodium load. In four subjects, in whom GFR decreased during the infusions of hypertonic saline, sodium excretion also decreased. These results are in accord with the glomerular-tubular imbalance hypothesis.

Additional support for this point of view has arisen from experimental procedures performed upon dogs. Shannon was among the first to suggest glomerular-tubular imbalance as an explanation for the increased sodium excretion he observed in dogs with diabetes insipidus allowed to drink hypotonic saline solution ad lib:(36) "After several of these episodes glomerular filtration is increased to such an extent that the filtration of sodium considerably exceeds the reabsorptive capacity of the proximal segment, and the sodium concentration of the urine attains that of the ingested fluid".

Ladd and Raisz included large quantities of salt (4 gm./kg.) in the diets of normal dogs and observed marked increases in glomerular filtration rate accompanying the increased sodium excretion.(27)

Selkurt and Post found simultaneous increases in glomerular filtration rate and sodium excretion during intravenous sodium loading of normal dogs. They postulated that the greatly increased sodium excretion occurring early in the experiment was due to a spillage of the excess filtered sodium into the urine, tubular reabsorption remaining unchanged.(30) In a similar type of experiment Baldwin, Kahana, and Clarke also found increased sodium excretion occurring with simultaneous increases in GFR.(31) Although these workers preferred to emphasize the correlation between the increased serum sodium and decreased percentage of filtered load reabsorbed, since filtered sodium loads increased simultaneously with sodium excretion, their results also are consistent with the glomerular-tubular imbalance hypothesis.

Alterations in renal arterial and venous pressure in dogs have been studied by several workers. Selkurt, Hall, and Spencer obtained marked ipsilateral decreases in creatinine clearance and sodium excretion by clamping the aorta above the left (and below the right) renal artery.(18) They stated that despite almost complete tubular reabsorption, decreases in GFR produced further decreases in sodium excretion. Pitts and Duggan clamped the aorta above both renal arteries and found simultaneous decreases in GFR and sodium excretion.(16) It was postulated that the decreased velocity of flow of glomerular filtrate along the renal tubule allowed for more complete tubular reabsorption. In an acute experiment, Hall and Selkurt obtained elevations of renal

venous pressure by clamping the renal vein.(21) Simultaneous decreases in GFR and sodium excretion occurred. With chronic elevation of renal venous pressure produced by inferior vena caval ligation Hwang and associates observed with one exception that the changes in sodium excretion tended to parallel the changes in GFR.(20)

From the experiments described above it is apparent that in a wide variety of circumstances, both in man and in the dog, changes in sodium excretion are found to be accompanied by somewhat parallel changes in glomerular filtration rate. Many have interpreted the changes in sodium excretion as being due simply to an imbalance between the amount of sodium filtered at the glomerulus and the amount reabsorbed by the tubules. This point of view regards the change in glomerular filtration rate as the primary cause of the change in sodium excretion, with tubular reabsorption remaining unchanged.

B. Altered Tubular Reabsorption

Most proponents of this second point of view imply that independent changes in tubular reabsorption occur due to changes in the activity of the tubular transport mechanism for sodium. A few workers imply that the changes in tubular reabsorption are due to changes in other intrarenal mechanisms.(25,78)

Using a single set of experimental measurements Berliner has clearly demonstrated that depending on whether one chooses to mean by "tubular reabsorption" the absolute amount of sodium reabsorbed, the amount reabsorbed per 100 ml. glomerular filtrate, or the per cent of filtered load reabsorbed, "tubular reabsorption" may be interpreted as increased, unchanged, or decreased, respectively.(13) This source of confusion was first circumvented by Wesson et al, who compared sodium

excretion at identical filtered sodium loads. They state, "So far as we are aware, this is the first direct demonstration that in reproducible experiments in a normal animal in which no identifiable variables are altered other than the volume of extracellular fluid (and plasma), that at a constant filtered load, the tubular reabsorption of sodium can undergo marked alteration".(32) Smith later emphasized that only when different rates of sodium excretion occur at the same glomerular filtration rate and at the same filtered load can changes in tubular reabsorption rate be presumed to have occurred.(9) For the sake of completeness it may be added that changes in tubular reabsorption are also apparent when filtered sodium load and sodium excretion are changing in opposite directions.

Some experimenters who claim to have demonstrated tubular reabsorption varying independently of GFR have not measured filtered sodium loads; hence, their work is not subject to strict interpretation. Others who have measured filtered sodium loads may be regarded as having obtained adequate proof of alterations in tubular reabsorption.

Claims for altered tubular reabsorption of sodium have been obtained from similar types of experimental studies as were employed by those favoring the glomerular-tubular imbalance hypothesis. Farnsworth observed, in patients with congestive heart failure, that the average ratio of sodium clearance to chloride clearance was reduced with respect to the control average ratio for normal individuals; therefore he concluded that increased tubular reabsorption of sodium must have occurred in the patients with cardiac disease.(60) Filtered sodium loads were not measured. Briggs et al found in patients with congestive heart failure

a correlation of restoration of compensation with increased sodium chloride excretion, increased GFR, and increased venous oxygen content. Omitting measurements of filtered sodium loads they concluded that in cardiac decompensation lowered blood oxygen content is responsible for increased tubular reabsorption of sodium.(7) Bradley and Blake, while admitting that the decreased GFR occurring in congestive heart failure may play some part in sodium retention, believe that the major factor is augmented sodium reabsorption.(61) Four patients convalescing from severe congestive heart failure were found by Futcher and Schroeder to have impaired ability to excrete sodium and chloride when the serum concentrations of both were elevated by intravenous infusions.(58) They concluded that the impaired sodium excretion was due to increased tubular reabsorption, possibly on the basis of anoxemia or on the basis of an endocrine disturbance. Sinclair-Smith subjected patients with congestive heart failure to mild exercise and, in at least one instance (Experiment 10), found a significant fall in sodium excretion with a constant glomerular filtration rate.(57)

Green et al, studying sodium excretion in patients with essential hypertension, glomerulonephritis, arteriosclerotic heart disease, and toxemia of pregnancy, under conditions of mannitol diuresis, observed that ten-fold to fifty-fold variations in sodium output occurred at nearly identical rates of glomerular filtration.(56) Since the experimental conditions included wide variations in sodium intake and the employment of an osmotic diuretic; and since no measurement of filtered sodium loads was obtained, no strict interpretation of the results is possible.

Orloff administered salt-poor albumin to three patients with the nephrotic syndrome and to one patient with toxemia of pregnancy. In each case increased urinary excretion of water and salt occurred without consistent changes in GFR.(3)

The data of Weston and associates, concerning a hypertensive human subject under the influence of Dibenamine, reveal a dissociation of sodium excretion from GFR.(2) At glomerular filtration rates of 51.3 and 55.7 cc./min. sodium excretion was 0.133 and 0.017 m-eq./min., respectively.

As a result of clearance studies of brief duration Kattus and associates claim that, in normal individuals standing quietly, a decrease in sodium excretion occurs without significant change in glomerular filtration rate. However, inspection of the data graphed reveals accompanying decreases in GFR of a magnitude which may have been significant.(47) In further experiments, in which normal individuals were subjected to mild exercise, again it is claimed that a decrease in sodium excretion occurred without significant change in GFR.(47) Inspection of these data also suggests that the decreases in glomerular filtration rate may have been significant, especially in view of the studies of normal individuals by White and Rolfe,(76) who demonstrated 8% decreases in inulin clearance during quiet standing and 50% decreases during moderately severe exercise. In spite of these criticisms, it appears that in one of the experiments (Experiment 8), the conclusion of Kattus et al appears justified.

In addition to the above data obtained from studies upon man evidence for independent changes in tubular reabsorption has been

obtained from experiments upon dogs. Blake, Wegria, Ward, and Frank clamped one renal artery and found reduced sodium excretion in the homolateral kidney without a corresponding decrease in glomerular filtration rate.(17) Since the base line of substances measured fell during the course of the experiment, all functions measured were expressed as the ratio to the corresponding functions of the contralateral kidney. Small errors in the measurement of the urinary substances, therefore, might result in large errors in the calculated ratios.

Blake, Wegria, Keating, and Ward elevated the renal venous pressure on one side to 300 mm. saline by clamping the renal vein and claimed to have found decreases in sodium excretion and urine flow without corresponding decreases in GFR.(19) Inspection of the results of the only experiment for which complete data are listed (Table I) reveals GFR decreasing with decreasing sodium excretion. The authors apparently do not consider the magnitude of the changes in GFR as significant, for they concluded that an increase in tubular reabsorption rate of sodium had occurred. They rejected hormonal and nervous mechanisms as the basis for the change and attributed the increased tubular reabsorption to an intrarenal mechanism. In one of Hwang's experiments on the effects of chronic venous pressure elevation accomplished by inferior vena caval ligation, a decrease of 40% in GFR occurred with only a slight decrease in sodium excretion.(20) These workers suggest that other mechanisms other than the change in glomerular filtration rate may be operative in the renal handling of sodium.

To normal human subjects, previously maintained on a low salt intake Leaf, Couter, and Newburgh administered sodium chloride and sodium

citrate. In some cases sodium excretion increased with no apparent change in glomerular filtration rate; however, filtered sodium loads were not measured.(42) In salt depletion and salt loading experiments on human subjects Wiggins et al found slight decreases and slight increases in glomerular filtration rate corresponding to proportionately larger decreases and increases, respectively, in sodium excretion.(40) They attributed the changes in sodium excretion to changes in tubular reabsorption. Since large changes in serum sodium occurred, the omission of sodium load calculations detracts from the strength of their conclusion.

In patients undergoing hypotonic saline and water diuresis while blood pressure cuffs were inflated to congestive levels about the thighs, Chalmers, Lewis and Pawan found approximately equal percentage decreases in glomerular filtration rate and sodium excretion (62% and 65% respectively).(55) When the blood pressure cuffs were deflated, glomerular filtration rate returned to within 90% of normal immediately, but sodium excretion did not return to normal levels for a much longer period of time.

Huckins, in this laboratory, produced decreases in glomerular filtration rate by subjecting dogs to rapid hemorrhage.(22) In some cases he was able to restore glomerular filtration rate to control levels by reinfusing the heparinized blood without obtaining restoration of sodium excretion to control levels. Observing large variations in sodium excretion, apparently independent of glomerular filtration rate, he concluded that there was no simple causal relationship between the two functions. Sodium filtered loads were not measured.

Following unilateral splanchnicotomy in dogs Kaplan and Rapoport observed greater sodium excretion by the kidney on the operated side, while glomerular filtration rate increased only minimally or not at all.(24,25) They concluded that the splanchnic nerve exerts an effect on the renal tubule favoring sodium chloride reabsorption.

Infusing dial-urethane-anesthetized dogs with saline solutions varying in concentration from 0.86% to 30%, Green and Farah(29) noted that the increased sodium excretion was not accompanied by consistent changes in glomerular filtration rate.

Duggan and Pitts have inferred that organic mercurical diuretics depress the distal tubular reabsorption of sodium.(35)

In adrenalectomized dogs maintained on a high sodium chloride intake, desoxycorticosterone (DOC), and adrenal cortical extract, Roemmelt, Sartorius, and Pitts withheld DOC for four days and then administered either DOC or adrenal cortical extract.(38) Both produced a delayed decrease in sodium excretion in the face of an increased glomerular filtration rate. Filtered sodium loads were not measured.

Blake has obtained evidence that emotional stress may produce decreased sodium excretion in the dog without associated change in glomerular filtration rate.(39)

Turning now to a consideration of the experiments in which filtered sodium loads have been measured one finds it apparent that very little such data exist, and none of the experiments have involved human subjects. It has been mentioned previously that Wesson et al were the first to demonstrate altered sodium excretion at identical filtered loads.(32)

Although not discussed by the authors the published data of Selkurt, Hall, and Spencer concerning their clamping of the aorta between the renal arteries also discloses sodium excretion varying independently of filtered sodium load: At filtered sodium loads of 4.83 and 4.89 millimols per minute sodium excretion was found to be 0.100 and 0.043 millimols per minute, respectively.(15) Fishman and associates observed that in early chronic experimental pericarditis with effusion in dogs sodium excretion decreased in the presence of an increased filtered sodium load, elevated venous pressure occurring as the only other associated finding.(77) Their conclusion that increased tubular reabsorption of sodium had occurred is well substantiated. Mudge, Foulks, and Gilman, employing urea diuresis in dogs, found that at identical filtered sodium loads, the presence of urea in the glomerular filtrate greatly decreased sodium reabsorption by the tubules.(78) Their discussion demonstrates that at least under conditions of severe osmotic diuresis with urea, it is unnecessary to postulate a hormonal or nervous basis for the change in tubular reabsorption.

It may be concluded that a review of the literature suggests that both glomerular-tubular imbalance and independent changes in tubular reabsorption are responsible for changes in renal sodium excretion.

II. Studies of Renal Function in Orthostatic Hypotension

Bradbury and Eggleston, the first in this country to report clinical investigation of patients with orthostatic hypotension,(68) observed that their patients excreted about three times more urine at night than during the day, which is a reversal of the normal night-to-

day ratio.(79-83 They attributed the nocturnal polyuria to improved kidney function at night caused by the increase in blood pressure in the recumbent position. The greater rate of urine flow in the recumbent position in patients with orthostatic hypotension has been confirmed by other workers.(68-74)

Results of the influence of postural change upon phenolsulfonphthalein excretion in patients with orthostatic hypotension have been conflicting: Bradbury and Eggleston found impairment of phenolsulfonphthalein excretion in the standing posture;(68) whereas, Ghrist and Brown,(69) and, independently, Alvarez and Roth,(70) found no impairment of phenolsulfonphthalein excretion in the erect posture.

Chew, Allen, and Barker found no significant change in uric acid clearance in one of their patients in the sitting posture as compared with the recumbent posture.(71)

Studies on glomerular filtration rate and renal plasma flow in patients with orthostatic hypotension have been done by the use of tilt-tables. Corcoran, Browning, and Page found marked decreases in the inulin and diodrast clearances of a patient with orthostatic hypotension tipped on a tilt-table to the 60° head-up position.(73) Merrill reports marked decreases in renal plasma flow and glomerular filtration rate in one patient with orthostatic hypotension and in one patient with a Smithwick sympathectomy, tipped to the 60° head-up position on tilt-tables. However, Merrill's report must be interpreted in the light of his statement that in neither subject was any simultaneous fall in blood pressure observed.

In summary, studies of renal function in patients with orthostatic hypotension have been confined to measurements of urine flow, phenolsulfonphthalein excretion, inulin clearance, diodrast clearance, and uric acid clearance. No study of sodium excretion in such patients has been found.

## METHODS

Studies of renal function were performed upon three patients with orthostatic hypotension and upon one hypertensive patient under the influence of Dibenamine. Changes in renal function were obtained simply by requesting the patient either to assume a position of recumbency in bed or to sit, stand quietly, or walk. In general, a period of erect posture was interposed between two periods of recumbency, or a period of recumbency was interposed between two periods of upright posture. Arterial blood pressures, pulse rates, fluid intake and output, and the general appearance of the patient were recorded. Diets were unrestricted except for that reported in Experiment 6, in which the patient was fasting, and Experiment 7, in which the patient was on a "salt-free" diet (about 1.5 grams sodium chloride per day). To assure an adequate urine output for urine volume measurements the patients drank varying quantities of water at the beginning of each study and throughout the course of the study. No intravenous infusions were employed. Urine samples were collected without catheterization, the patient standing or sitting to void. Blood samples were withdrawn from an antecubital vein either at the midpoint of the urine collection period or at the beginning and end of the urine collection period.

The endogenous creatinine clearance was employed as a measure of the changes in glomerular filtration rate. Although endogenous creatinine clearance is usually slightly less than inulin clearance, evidence is accumulating in the literature that this function is a reliable measure of glomerular filtration rate.(84-87)

Analytical Methods

A. Determination of Sodium and Potassium. Sodium and potassium ions were determined by means of a Barclay Flame Photometer with lithium ion employed as the internal standard.(88,89) The average deviation of the sodium determinations was higher than usually reported for such an instrument, averaging about 5%. Since the changes in sodium excretion were of the order of magnitude of 300% to 2000%, the accuracy of the sodium determinations was adequate for the purpose at hand. The error was reduced by averaging multiple determinations.

B. Determination of Chlorides. Chlorides were determined by the method of Volhard.(90)

C. Determination of Ammonia Nitrogen and Urea Nitrogen. Ammonia nitrogen and urea nitrogen in urine samples were determined by an aeration method described by West and Todd.(91)

D. Determination of Creatinine. Creatinine was determined in urine and plasma by a modification of the method of Hare and Hare.(87) This method allows for determination of "true creatinine" and not total "creatinine chromogen", as was determined by some of the older methods. The procedure is described in detail:

Urine samples were first tested with 20% trichloroacetic acid for the presence of interfering protein. None was found in any of the samples tested; had it been found, it would have had to be removed by filtration or centrifugation. The appropriate urine dilution for the creatinine determination was calculated from an empirical formula devised by the writer: The Dilution (1:D) equals U/15,000 T in which

U equals the total volume of the urine specimen, and T equals the duration of the urine collection period, expressed in hours. The urine was made up to approximately the calculated dilution in a volumetric flask.

Protein-free plasma or serum filtrates were prepared by adding two parts of 20% trichloroacetic acid solution to three parts of a 1:3 dilution of plasma or serum. The mixture was well mixed and then filtered.

Into 15.0 ml. centrifuge tubes were pipetted 5.00 ml. of each of the following: distilled water; diluted urine unknown; protein-free plasma or serum filtrate unknown; and creatinine standard solutions containing two, four, and eight micrograms of creatinine per ml., respectively. Duplicates were prepared of the unknowns. After adding 0.5 ml. of saturated aqueous oxalic acid solution and approximately 45 mg. of Lloyd's Reagent (hydrated silica) to each tube, the tubes were covered with Parafilm and shaken vigorously at intervals for a period of two minutes. The Parafilm was removed, and the tubes were centrifuged at 2000 RPM for from three to five minutes. The supernatant was decanted; the tubes were inverted over a paper towel to drain for five minutes. During the interim fresh alkaline picrate solution was prepared by adding one part of 10% sodium hydroxide to five parts of 0.04 M picric acid and diluting the mixture with twelve parts distilled water. Into each of the centrifuge tubes 10.0 ml. of this solution were pipetted. The tubes were covered with Parafilm and shaken vigorously to break up the impacted sediment. They were then allowed to stand in a rack for ten minutes with occasional shaking to

allow for full color development. The Parafilm was removed. Following five minutes of centrifugation at 2000 RPM the supernatant was poured into Corex cuvettes and the optical densities read at 500 millimicrons in a Beckman Model "B" Spectrophotometer.

When the distilled water blank was set at zero absorbance, the optical densities of the creatinine standard solutions were found to vary linearly with concentration. The concentrations of the unknown creatinines were determined by proportion. Duplicate determinations usually agreed within 2% and did not exceed 5%.

# RESULTS

Protocols of the individual studies including tabular and graphic representation of results are presented below. A summary of the results appears on Page 38.

Data concerning fluid intake, urine output, and urine specific gravity are listed in Tables I to VII.

In Figures 1 to 7 the postural variations in urinary sodium excretion are depicted graphically with the simultaneous variations in either endogenous creatinine clearance* or in urinary creatinine excretion. In those cases in which serum sodium was measured the filtered sodium load, which is equal to the product of the endogenous creatinine clearance and the serum sodium,** is also shown.

In Figure 8 the simultaneous excretion rates of potassium, ammonia nitrogen, and urea nitrogen are graphed with the postural changes in the creatinine and sodium excretion rates.

Urinary chloride excretion rates were determined in all cases. Since the urinary excretion rate of chloride closely agreed in magnitude and direction of change with that of sodium in all instances, the data concerning chloride excretion are not presented.

* Endogenous creatinine clearances are uncorrected for body surface area.

** Correction for the Donnan Equilibrium and for plasma water content is not applied.

Protocols:

Experiment 1

H.B., a patient in the U.S. Veterans Hospital, Portland, Oregon, was diagnosed as having orthostatic hypotension. Detailed history is not available.

From 10:30 p.m., June 8, 1950 to 7:30 a.m., June 9, 1950 the patient was recumbent. Most of this time was spent in sleep. From 7:30 a.m. to 3:30 p.m., June 9, 1950 the patient was either in the sitting or standing postures. Some time was spent in walking.

Diet and fluid intake were not regulated.

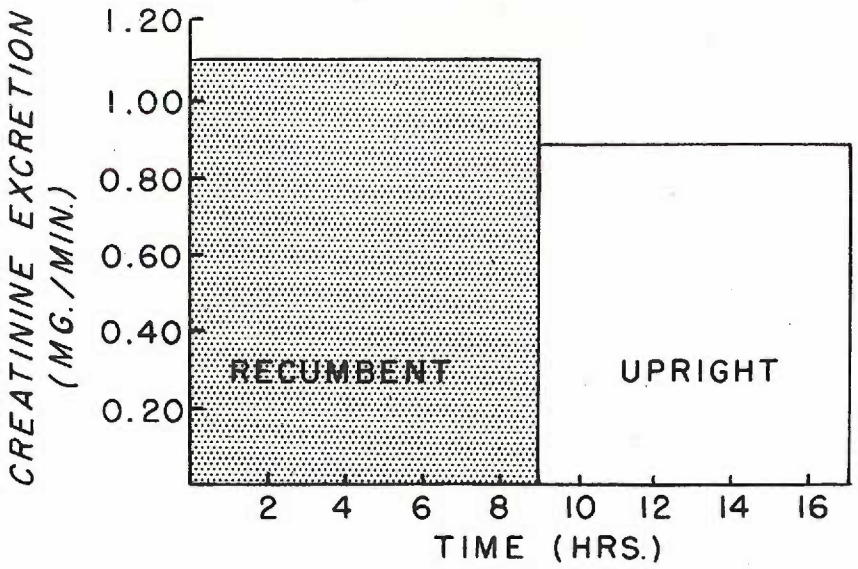
The data are included in Table I and in Figure 1.

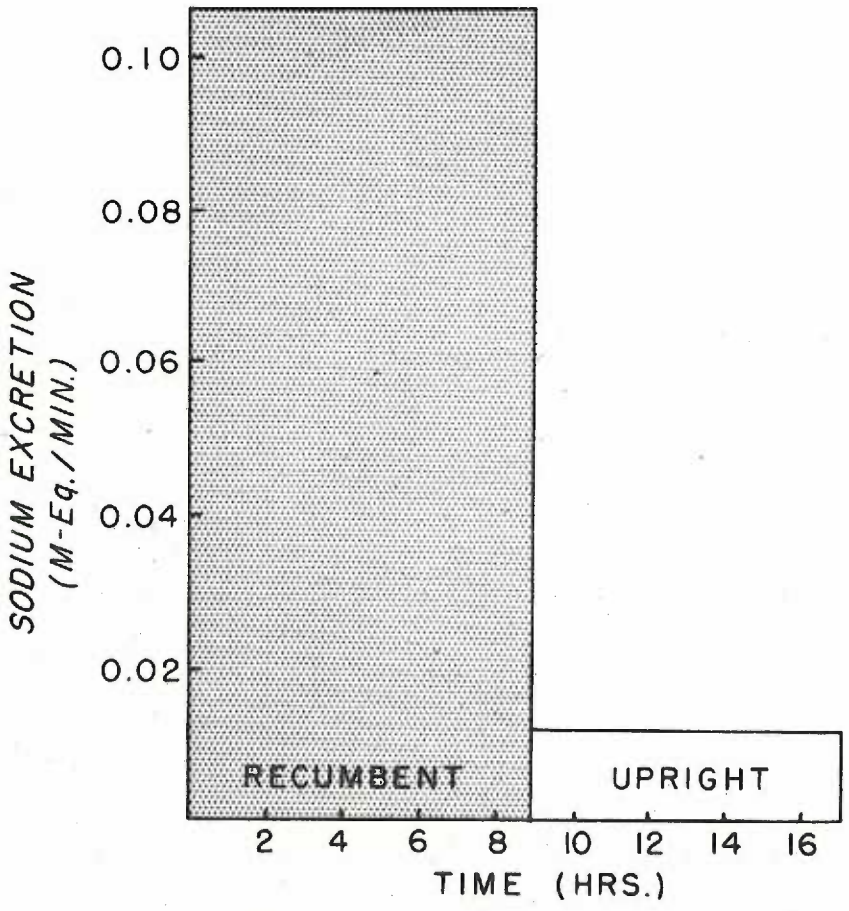
Table I

| TIME | POSITION | URINE OUTPUT | URINE SPECIFIC GRAVITY |
|---|---|---|---|
| 10:30 p.m. to 7:30 a.m. | Recumbent | 715 ml. | 1.015 |
| 7:30 a.m. to 3:30 p.m. | Upright | 163 ml. | 1.025 |

FIGURE 1

PATIENT H.B JUNE 8-9, 1950



## Experiment 2

F.B., a patient in the U.S. Veterans Hospital, Portland, Oregon, had idiopathic orthostatic hypotension. Detailed history and physical findings are presented in Appendix I.

The patient remained recumbent from 10:00 p.m., December 4, 1950 until 6:00 a.m., December 5, 1950. For the next sixteen hours the patient was in either the sitting or standing positions. Some walking was done.

Diet and fluid intake were unrestricted.

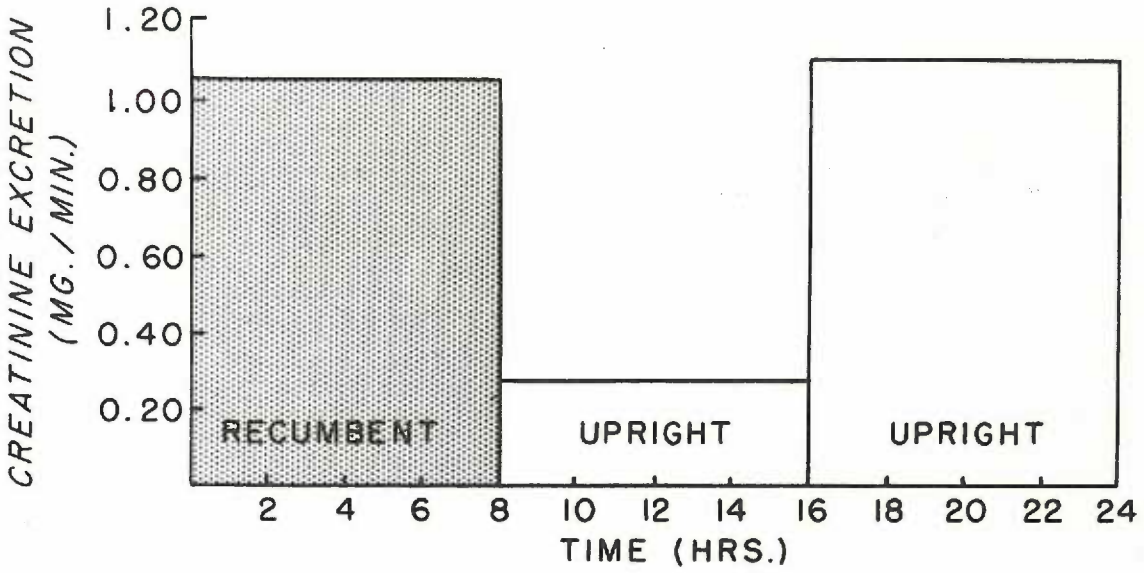
The data are presented in Table II and Figure 2.

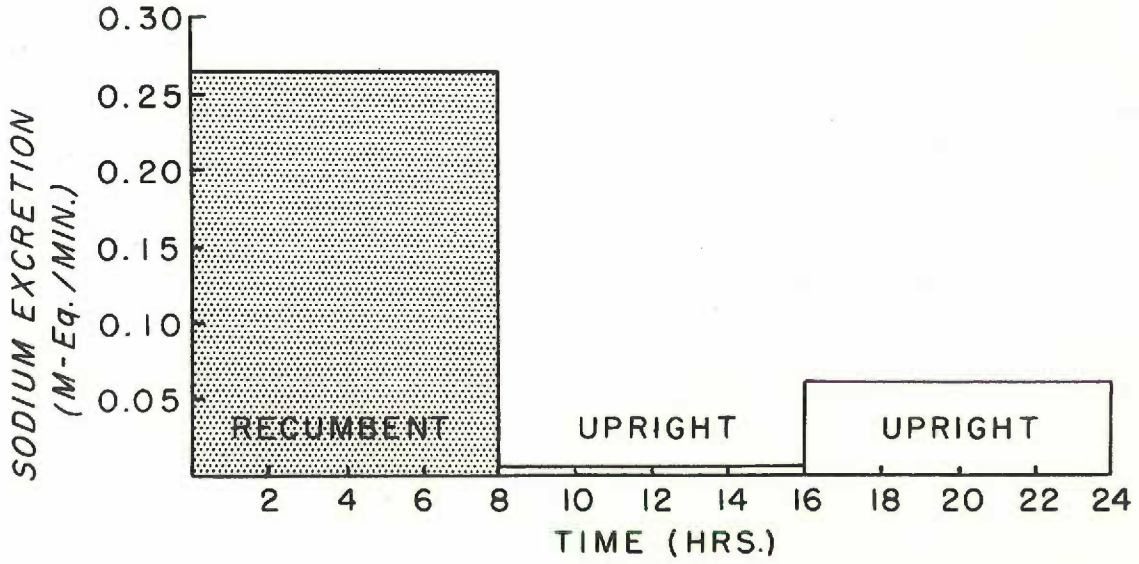
Table II

| TIME | POSITION | URINE OUTPUT | URINE SPECIFIC GRAVITY |
|---|---|---|---|
| 10:00 p.m. to 6:00 a.m. | Recumbent | 1510 ml. | 1.008 |
| 6:00 a.m. to 2:00 p.m. | Upright | 44 ml. | 1.028 |
| 2:00 p.m. to 10:00 p.m. | Upright | 302 ml. | 1.031 |

FIGURE 2

PATIENT F.B. DEC. 4-5, 1950



## Experiment 3

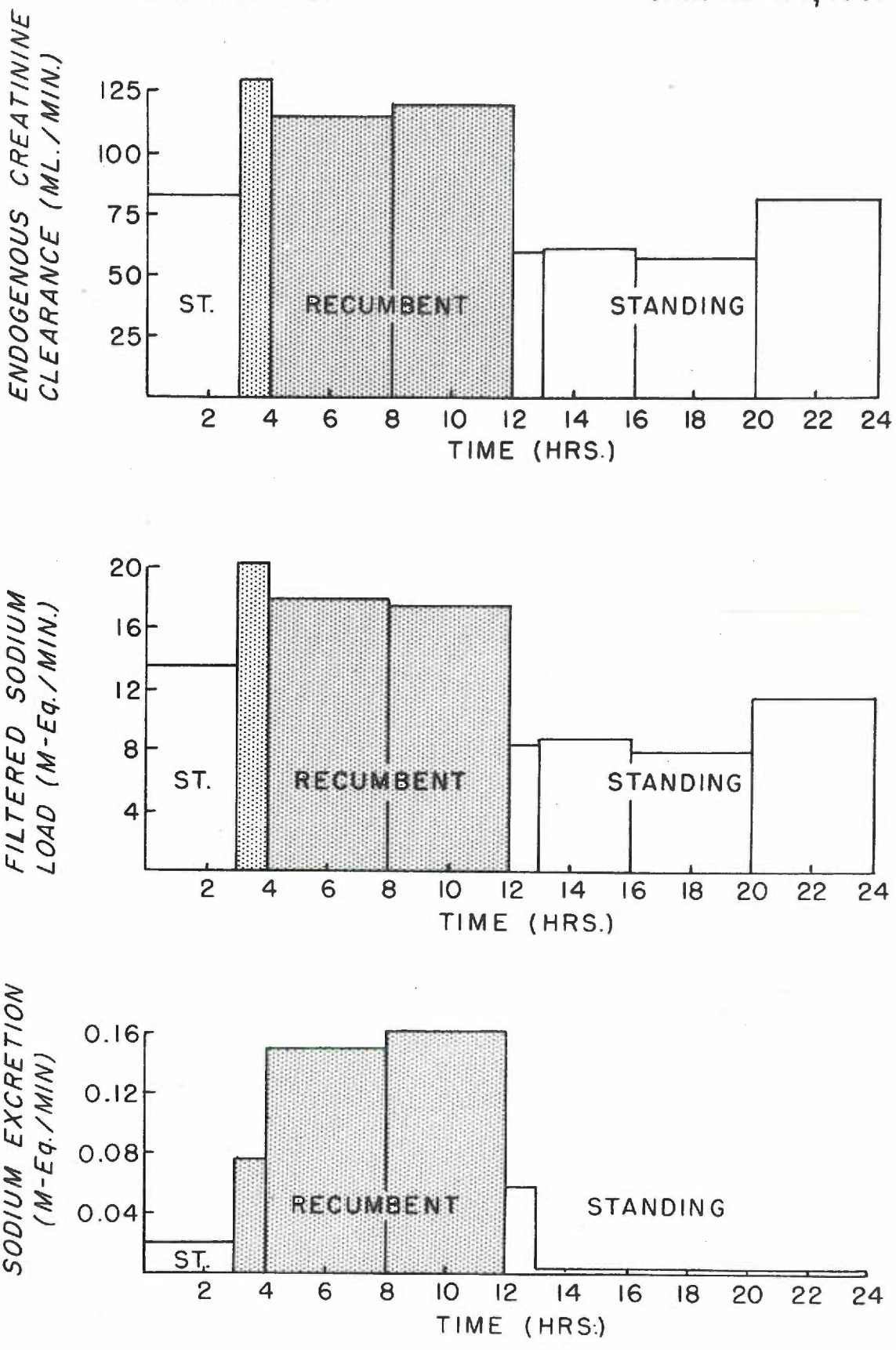
The patient, F.B., the same as in Experiment 2, was hospitalized at the Multnomah County Hospital, Portland, Oregon from January 23, 1951 to January 24, 1951 with a diagnosis of orthostatic hypotension. Details of history are presented in Appendix I. Average blood pressure when the patient was in the recumbent position was 130/80; pulse, 64. The patient's blood pressure while standing was 95/80; pulse, 90. The data are presented in Table I and in Figure 3.

Table III

| TIME | POSITION | WATER DRUNK | URINE OUTPUT | URINE SPECIFIC GRAVITY |
|---|---|---|---|---|
| 7:15 p.m. to 10:05 p.m. | Standing | 800 ml. | 175 ml. | 1.010 |
| 10:05 p.m. to 11:05 p.m. | Recumbent | | 385 ml. | 1.001 |
| 11:05 p.m. to 3:05 a.m. | Recumbent | | 1206 ml. | 1.003 |
| 3:05 a.m. to 7:05 a.m. | Recumbent | | 285 ml. | 1.013 |
| 7:05 a.m. to 8:05 a.m. | Standing | 500 ml. | 22 ml. | |
| 8:05 a.m. to 11:05 a.m. | Standing | | 25 ml. | |
| 11:05 a.m. to 3:17 p.m. | Standing | 500 ml. | 45 ml. | 1.025 |
| 3:17 p.m. to 7:00 p.m. | Standing | 800 ml. | 85 ml. | 1.027 |

FIGURE 3

PATIENT F.B. JAN. 23-24, 1951



## Experiment 4

This study of patient, F.B., about one year after Experiments 2 and 3, was done following a preliminary check of the patient's blood pressure, which was 110/70 in the recumbent position and 60/40 in the standing position, despite his wearing elastic stockings.

The patient was not hospitalized but was instructed carefully in the collection of urine samples at home.

Diet and fluid intake were unrestricted.

The patient remained recumbent from 7:45 p.m., December 15, 1951 to 6:30 a.m., December 16, 1951. He then arose and remained in the upright position, either sitting or standing, from 6:30 a.m. until 4:00 p.m., December 16, 1951.

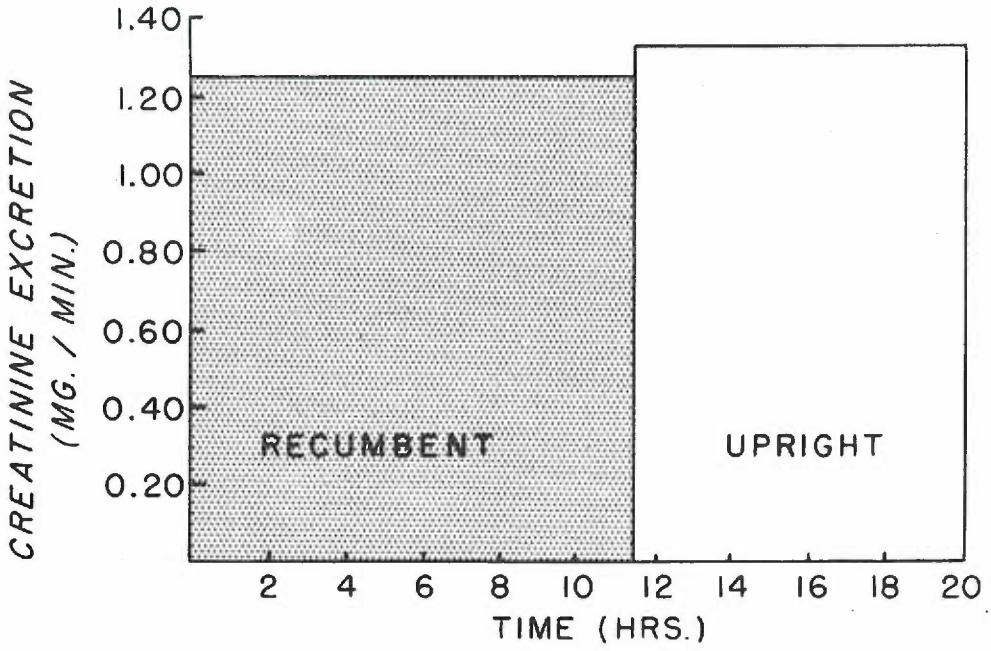
The data are presented in Table IV and in Figure 4.

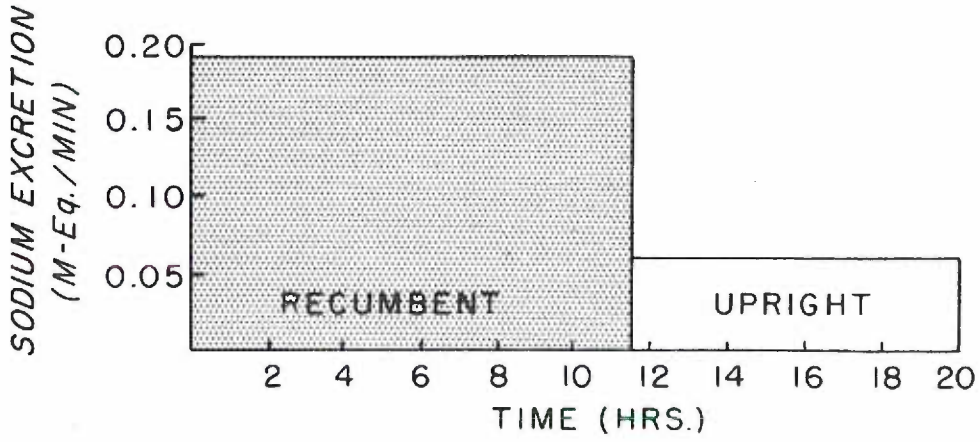
Table IV

| TIME | POSITION | URINE OUTPUT | URINE SPECIFIC GRAVITY |
|---|---|---|---|
| 7:45 p.m. to 6:30 a.m. | Recumbent | 1010 ml. | 1.015 |
| 7:46 a.m. to 4:00 p.m. | Upright | 310 ml. | 1.035 |

FIGURE 4

PATIENT F.B. DEC. 15 - 16, 1951



## Experiment 5

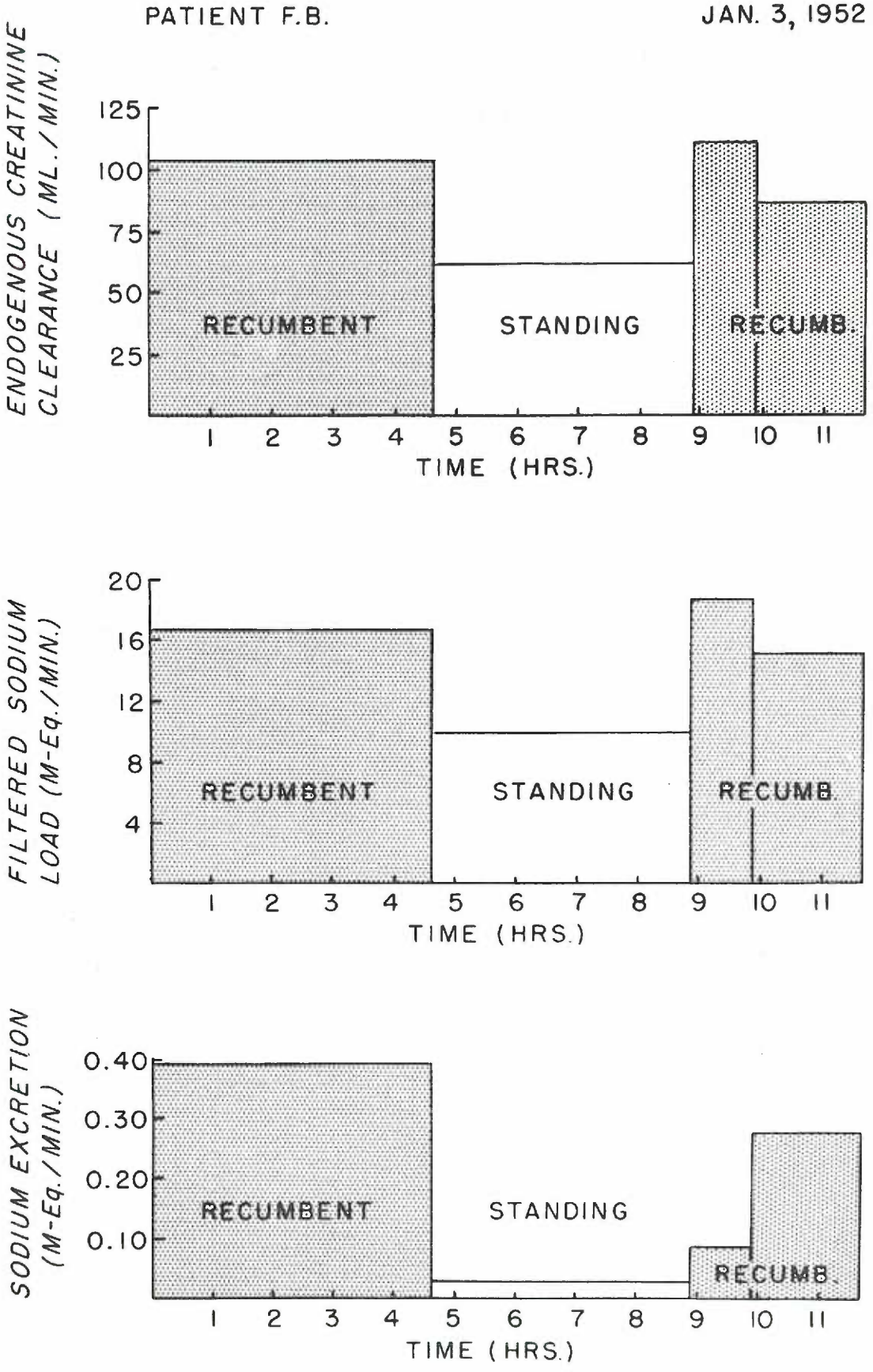
The subject of this experiment, F.B., the same as in Experiments 2 to 4, was studied in the Department of Physiology, University of Oregon Medical School on January 3, 1952. His average blood pressure in the recumbent position was 160/90; pulse, 64. At the standing position the patient's average blood pressure was 100/75; pulse, 80. The patient ate breakfast at home prior to coming to the laboratory. Lunch was eaten in the school cafeteria. Dinner was refused. The data are presented in Table 5 and in Figure 5.

Table V

| TIME | POSITION | WATER DRUNK | URINE OUTPUT | URINE SPECIFIC GRAVITY |
|---|---|---|---|---|
| 8:15 a.m. to 12:53 p.m. | Recumbent | 500 ml. | 1860 ml. | 1.008 |
| 12:53 p.m. to 5:14 p.m. | Standing & walking | 1000 ml. | 94 ml. | 1.021 |
| 5:14 p.m. to 6:17 p.m. | Recumbent | 250 ml. | 192 ml. | 1.007 |
| 6:17 p.m. to 8:00 p.m. | Recumbent | none | 940 ml. | 1.003 |

FIGURE 5

PATIENT F.B. JAN. 3, 1952



## Experiment 6

V.L., a hypertensive, tuberculous patient, was studied at the University State Tuberculosis Hospital, Portland, Oregon on December 31, 1951, while under the influence of Dibenamine, administered as a diagnostic test for possible pheochromocytoma. Additional details are presented in Appendix I.

No food was allowed for twelve hours prior to the test and for the duration of the urine collection periods.

Renal function studies were performed with the patient in the recumbent position and in the partial sitting posture with the head, neck, and trunk elevated 30° to 45° from the horizontal by means of pillows. A more vertical sitting position was not employed due to the patient becoming nauseated. The foot of the bed was elevated on shock blocks for a brief period (Table VI, "Head-down 27 minutes").

The patient's blood pressure averaged 195/125 in the recumbent position; 160/110 in the partial sitting position.

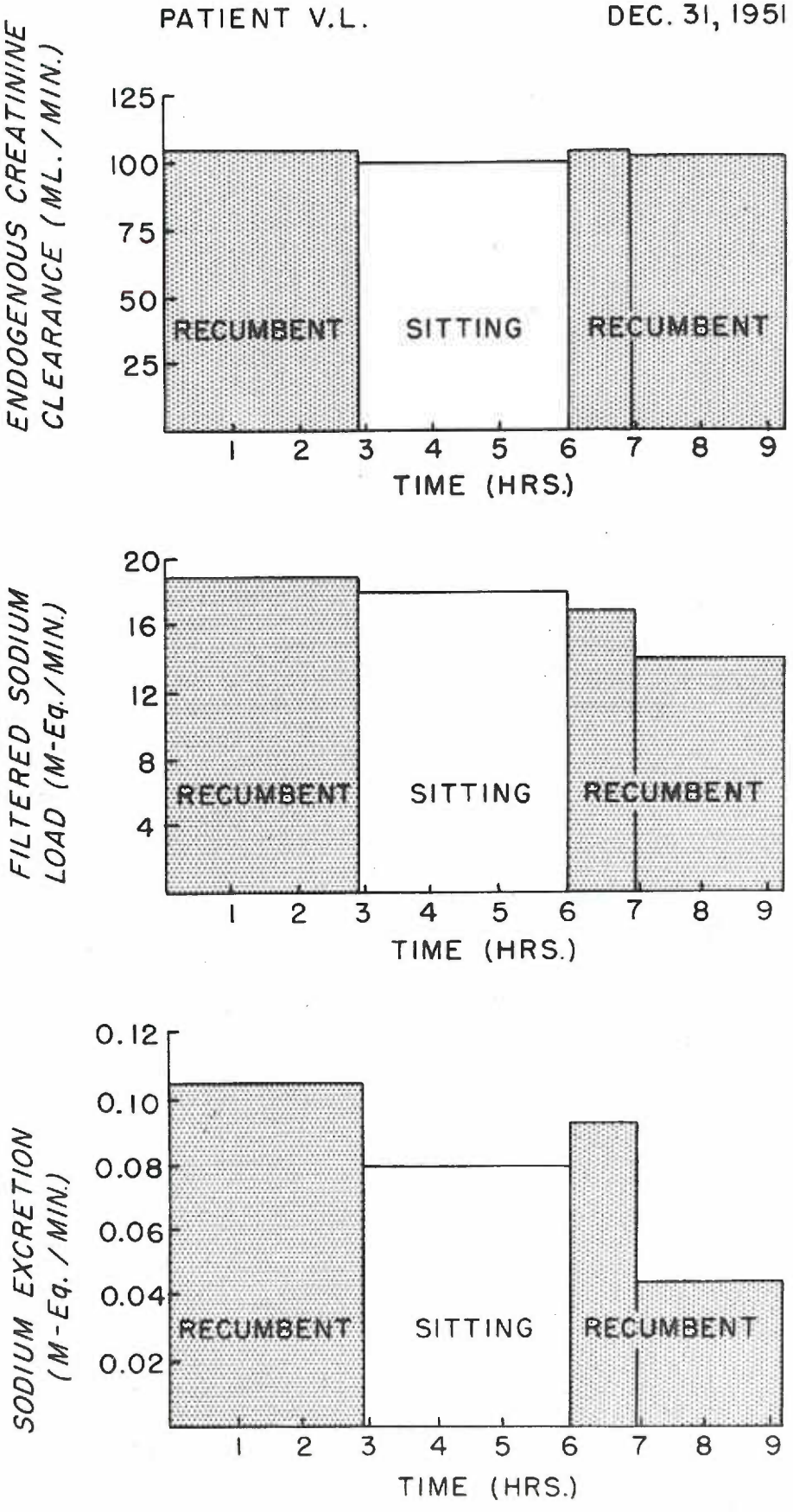
The data are included in Table VI and in Figure 6.

Table VI

| TIME | POSITION | WATER DRUNK | URINE OUTPUT | URINE SPECIFIC GRAVITY |
|---|---|---|---|---|
| 2:55 p.m. to 5:50 p.m. | Recumbent | 1040 ml. | 76 ml. | 1.035 |
| 5:50 p.m. to 8:55 p.m. | Sitting | 800 ml. | 167 ml. | 1.015 |
| 8:55 p.m. to 9:50 p.m. | Head-down 27 min. Recumbent 18 min. | 500 ml. | 277 ml. | 1.005 |
| 9:50 p.m. to 12:06 a.m. | Recumbent | 450 ml. | 632 ml. | 1.003 |

FIGURE 6

PATIENT V.L. DEC. 31, 1951



## Experiment 7

H.G. was hospitalized at the Multnomah County Hospital, Portland, Oregon with diagnoses of pernicious anemia and orthostatic hypotension. See Appendix for details.

The patient had been on a "salt-free" diet (1.5 gm. NaCl/day) for at least ten days prior to the renal function studies and was maintained on the same diet for the duration of the studies.

She drank 200 ml. of water at the beginning of the experiment and then 100 ml. of water hourly until its conclusion.

During the upright period the patient sat in a wheelchair most of the time. Two periods of ambulation, each of twenty minutes duration, were included in the upright period.

Blood pressure while the patient was recumbent averaged 100/70; pulse, 56. Blood pressure taken while the patient was in the sitting position was not audible--systolic impulse was palpated at the radial artery at 90 mm. of mercury; pulse, 72.

The data are presented in Table VII and in Figure 7.

Table VII

| TIME | POSITION | WATER INTAKE | URINE OUTPUT | URINE SPECIFIC GRAVITY |
|---|---|---|---|---|
| 8:35 a.m. to 11:29 a.m. | Recumbent | 400 ml. | 402 ml. | 1.002 |
| 11:29 a.m. to 2:30 p.m. | Sitting and Walking | 350 ml. | 160 ml. | 1.004 |
| 2:30 p.m. to 5:30 p.m. | Recumbent | 350 ml. | 440 ml. | 1.000 |

FIGURE 7

PATIENT H.G. APRIL 8, 1952

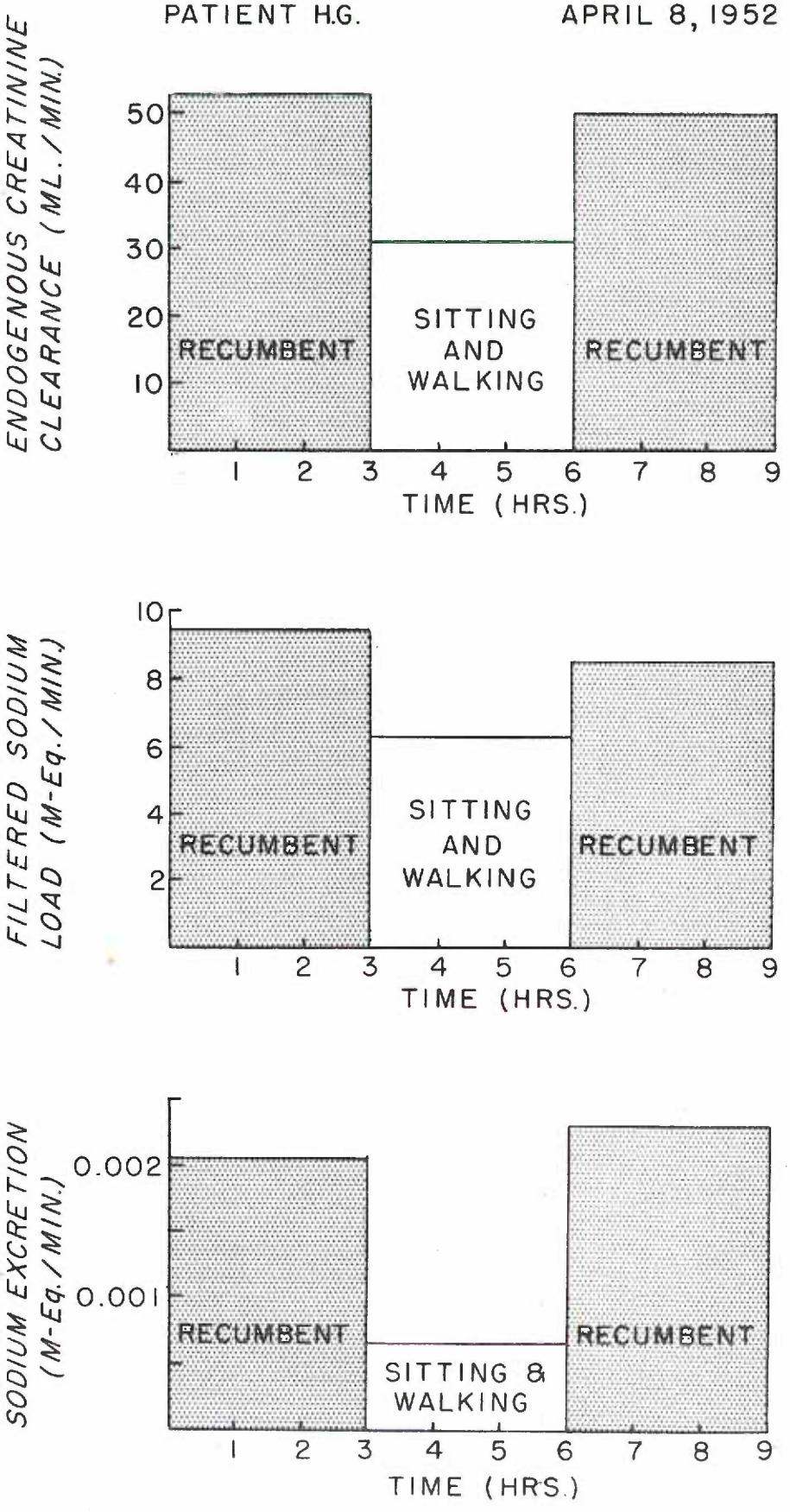


Figure 8

The data depicted in Figure 8 were obtained during the course of Experiment 3. The measurements were made simultaneously with those shown in Figure 3.

The excretion rates of various substances are arranged in Figure 8 according to the manner in which they are excreted by the kidney.

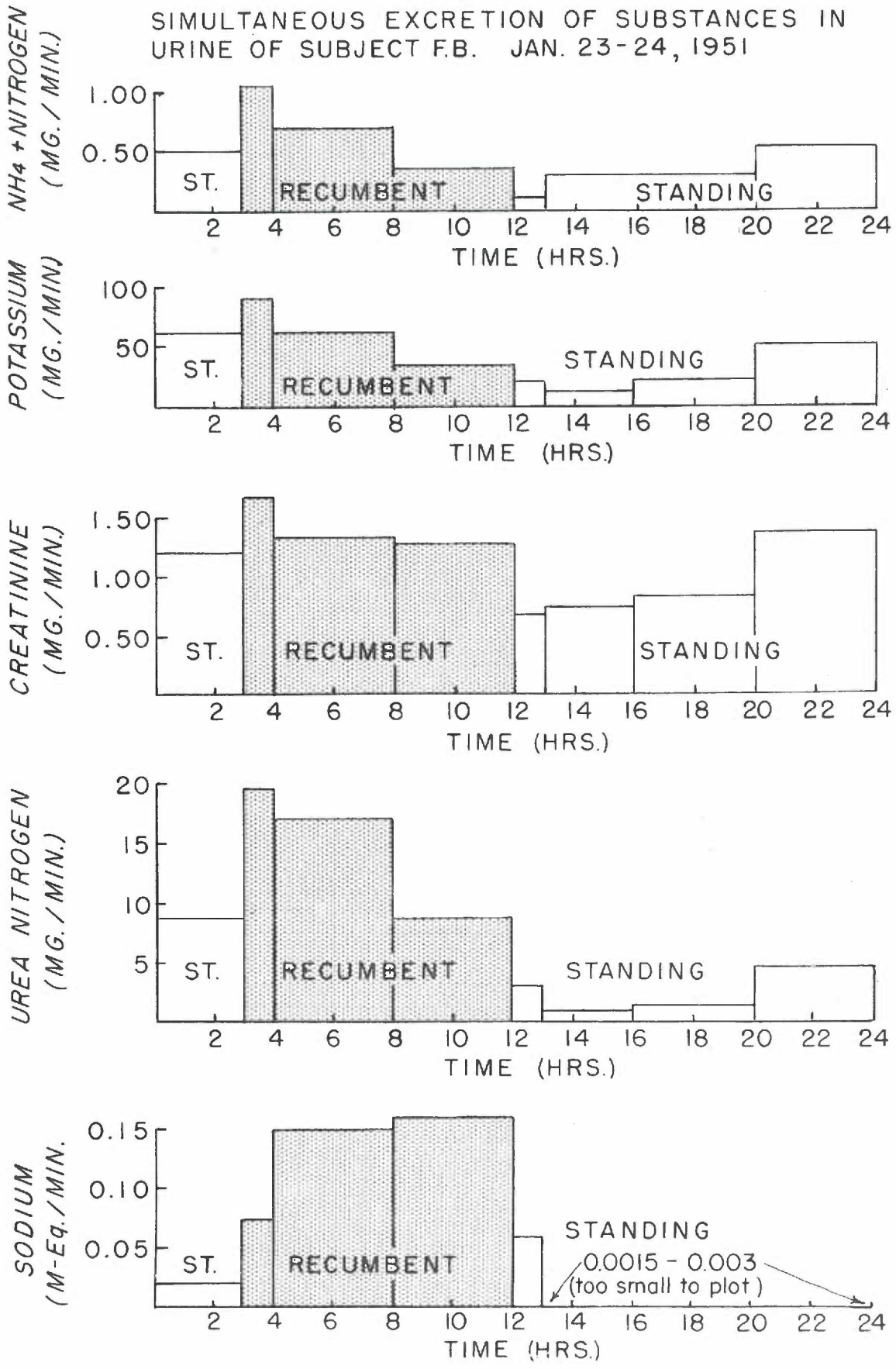
From top to bottom of Figure 8 are presented: ammonia nitrogen,* a substance which enters the urine mainly by tubular secretion; potassium, a substance which enters the urine both by tubular secretion and by glomerular filtration; creatinine, a substance which enters the urine solely by glomerular filtration; urea nitrogen,* a substance which enters the urine only by filtration, but which also back-diffuses into the peritubular capillaries at a rate dependent on the rate of urine flow; and lastly, sodium, a substance, which in addition to entering the urine solely by filtration and in addition to back-diffusing, is also reabsorbed actively by a tubular transport mechanism.

The relative effect of the decreased glomerular filtration rate (about 50%), occurring during the final standing period, upon the excretion of these different substances is readily apparent: ammonia nitrogen excretion is affected least; sodium, most of all.

*Ammonia nitrogen is used to represent ammonium salts; urea nitrogen, to represent urea.

FIGURE 8

SIMULTANEOUS EXCRETION OF SUBSTANCES IN URINE OF SUBJECT F.B. JAN. 23-24, 1951



Summary of Results. The renal excretion of sodium was found to decrease strikingly in all of the patients with orthostatic hypotension when they assumed the upright posture after a period during which they were recumbent. A marked percentage of decrease in sodium excretion while the patient was in the upright posture occurred even in Experiment 7, in which the patient was on a "salt-free" diet and excreting only minute quantities of sodium during the control period. In all subjects, with the exception of the hypertensive patient under the influence of Ditenamine, the sodium excretion of the patient in the upright posture fell to less than 50% of the rate during recumbency.

Decreases in glomerular filtration rate and filtered sodium load were observed to accompany the decreased sodium excretion rate induced by the upright posture. Relatively small percentage decreases in glomerular filtration rate or filtered sodium load were accompanied by relatively large decreases in sodium excretion rate.

In three experiments, 3, 5, and 6, filtered sodium load and urinary sodium excretion were found to change simultaneously in opposite directions. A similar result is suggested by Experiment 4, in which urinary sodium excretion decreased while urinary creatinine excretion increased.

In Experiment 5 restoration of the glomerular filtration rate and filtered sodium load to the levels obtained while the patient was in the recumbent position occurred without restoration of urinary sodium excretion. A similar result is suggested by Experiment 2, in which urinary creatinine excretion returned to the value obtained during the period of recumbency, while urinary sodium excretion remained depressed.

On the other hand, in Experiment 7, urinary sodium excretion returned to the value obtained while the patient was recumbent in spite of the failure of the filtered sodium load to return to the level observed during recumbency.

In Experiment 3, Figure 3, during hour 12, a decrease in sodium excretion is seen to accompany a decrease in the endogenous creatinine clearance. During hour 13 a further decrease in sodium excretion occurs in the face of an unchanged glomerular filtration rate and filtered sodium load. While it is possible that the urine sample of hour 12 may have been contaminated with sodium from the urine of hours 8 to 12, inspection of Figure 8, concerning the same experiment, reveals no corresponding trend in the excretion of ammonia nitrogen or potassium.

## DISCUSSION

In patients with orthostatic hypotension renal sodium excretion decreases markedly when the subject assumes the standing posture. The decreased sodium excretion in the upright posture is accompanied by large decreases in glomerular filtration rate and filtered sodium load. This is in contrast to the situation in the normal individual in the upright posture, in whom, at most, only minor decreases in sodium excretion and glomerular filtration of sodium may occur.(47)

That glomerular-tubular imbalance plays a role in the decreased sodium excretion is indicated by the results of Experiment 3 shown in Figures 3 and 8. Ammonia nitrogen and potassium, substances excreted by tubular secretion, are little affected by the decrease in glomerular filtration rate occurring during the second standing period. Creatinine, a substance which is excreted only by glomerular filtration, is decreased proportionately to the filtration rate. In the case of urea, a substance not reabsorbed by an active process, the greater percentage decrease in urea excretion as compared with the percentage decrease in glomerular filtration rate constitutes evidence for glomerular-tubular imbalance. Sodium, like urea, is also a freely-diffusible substance. Therefore, glomerular-tubular imbalance may also account, in part, for the greater percentage decrease in sodium excretion as compared with the percentage decrease in filtered sodium load. The finding of a greater percentage decrease in the excretion of sodium as compared with urea may be explained by the supposition that the active cellular transport mechanism for sodium is also contributing to the glomerular-tubular imbalance.

In the present study it is demonstrated that, in man, alterations in the tubular reabsorption of sodium may occur independently of changes in filtered sodium load. In Experiment 3, Figure 3, during the recumbent period, sodium excretion is seen to increase while filtered sodium load is decreasing. During the early part of the second period of standing, a marked decrease in sodium excretion occurs in the face of an unchanged filtered sodium load. During the last period of standing, sodium load tends to be restored towards control values without an accompanying increase in sodium excretion. In Experiment 6, Figure 6, during hour 6, sodium excretion increased in spite of a decreasing filtered sodium load. In Experiment 7, Figure 7, filtered sodium load remains below the level observed during the last recumbent period, while sodium excretion returns to above the control level.

The results suggest that changes in sodium excretion which are due to glomerular-tubular imbalance occur rapidly, whereas the adjustments in tubular reabsorption occurring independently of changes in filtered sodium load occur more slowly. During the recumbent period in Experiment 3, Figure 3, an immediate rise in filtered sodium load is accompanied by a gradual increase in sodium excretion. In the same experiment a sudden decrease in filtered sodium load is accompanied by a simultaneous decrease in sodium excretion; however, a further decrease in sodium excretion occurs with the passage of time, in spite of no further change in filtered sodium load.

The mechanism for the changes in tubular reabsorption occurring independently of changes in glomerular filtration rate and filtered sodium load remains unknown. Possible mechanisms would include

nervous and hormonal influences, and, possibly in addition, changes in intrarenal pressure relationships. The pressure gradient between the glomerulus and the peritubular capillary bed, as affected particularly by alterations in the tonus of the efferent arteriole, may be anticipated to be of importance. This idea is in agreement with the conclusions of Kaplan, Pomon, and Rapoport.(25)

The present work suggests that in normal man a sudden large decrease in glomerular filtration rate and filtered sodium load from any cause may result in greatly decreased sodium excretion. Later adjustments in tubular reabsorption, occurring independently of glomerular filtration rate and filtered sodium load, may tend either to restore or to decrease sodium excretion further depending upon variables not yet clearly identified.

## SUMMARY

The relative importance of the glomerular filtration and the tubular reabsorption of sodium upon sodium excretion by the kidney recently has been the subject of many investigations in both man and experimental animals. Some workers have demonstrated that changes in renal sodium excretion are frequently accompanied by somewhat parallel changes in glomerular filtration rate. Others have reported changes in sodium excretion occurring independently of changes in glomerular filtration rate. Two schools of thought concerning the mechanism by which the kidney regulates sodium excretion have developed: 1) the concept of glomerular-tubular imbalance, according to which changes in the tubular reabsorption of sodium are considered secondary to changes in glomerular filtration rate, and 2) the concept of tubular reabsorption varying independently of glomerular filtration rate.

To prove the occurrence of changes in the tubular reabsorption of sodium it is necessary to demonstrate different rates of sodium excretion at the same filtered sodium load or to show that sodium excretion and filtered sodium load are changing in opposite directions. Most investigators claiming to have demonstrated altered tubular reabsorption of sodium have not measured filtered sodium load.

No prior studies of sodium excretion in orthostatic hypotension have been reported. In the present study the effect of posture upon renal sodium excretion in orthostatic hypotension has been observed, filtered sodium loads have been measured, and the changes in sodium excretion have been interpreted in terms of alterations in the glomerular filtration and tubular reabsorption of sodium.

Three patients with orthostatic hypotension and one hypertensive patient under the influence of Dibenamine assumed the recumbent and upright postures for varying periods of time. No intravenous infusions were employed, but the patients were given moderate quantities of water to drink. The total urine output for each period was collected and saved separately. Venous blood samples were withdrawn either at the middle of each urine collection period or at the beginning and end of each period. Urine samples were analyzed for sodium, chloride, and creatinine. In one experiment the urine was also analyzed for potassium, urea nitrogen, and ammonia nitrogen. Serum or plasma samples were analyzed for sodium and creatinine. Sodium and potassium were determined by means of a Barclay flame photometer with lithium ion serving as the internal standard. "True creatinine" was determined by the method of Hare and Hare.(87) Chlorides were determined by the method of Volhard.(90) Urea nitrogen and ammonia nitrogen were determined by the aeration method of West and Todd.(91) The endogenous creatinine clearance was used as a measure of the glomerular filtration rate. Filtered sodium loads were calculated as the product of the glomerular filtration rate and the serum sodium concentration.

Large decreases in the rates of urinary sodium excretion and in glomerular filtration occurred when patients with orthostatic hypotension were in the upright posture. When they returned to the recumbent posture, sodium excretion was not restored immediately in spite of the immediate increases in filtered sodium load. Other examples of sodium excretion varying independently of filtered sodium load were observed. Thus, proof

was obtained of altered tubular reabsorption of sodium occurring in man.

It was concluded that the decreased sodium excretion found to occur in patients with orthostatic hypotension when in the upright posture is partly due to the decreased load of sodium filtered and partly due to changes in tubular reabsorption that are independent of filtered sodium load.

# APPENDIX

## Case Histories

### F.B.

F.B. was a 65-year old white male meat-cutter of German descent who, during the years of 1946 to 1948, noticed occasional episodes of "light-headedness" and a feeling as though he were going to faint. In June 1948 and in May 1950 he experienced episodes of syncope while in the standing position. The symptoms usually occurred in the morning at about 10:00 a.m. He was hospitalized in the U.S. Veterans Hospital from October 18, 1950 to December 23, 1950 where the diagnosis of orthostatic hypotension was made. Treatment consisted of supplying the patient with a tightly fitting elastic abdominal binder and elastic stockings. Since wearing these his symptoms were relieved entirely. He was admitted to Multnomah County Hospital on January 23, 1951 for renal function studies. Review of systems disclosed that the patient tired easily at work and had nocturia three to five times per night. Past history, family history and social history were all non-contributory. Physical examination: Temperature 97.0° F.; Blood pressure 140/90, recumbent; 100/80 standing; Respiration 16; pulse 64 reg. General appearance: 65-year old, well-nourished, well-developed, white, male, appearing younger than his age; right pupil 3 mm. in diameter; left, 2 mm. Slight increase in tortuosity of retinal arterioles. Pale conjunctivae and oral mucous membranes. Truchterbrust. Fine and medium resonant rales in left base. Prostate slightly enlarged but of normal shape and consistency. Varicose veins on lower extremities. The remainder of the complete examination was normal. A survey chest film was reported negative.

V.L.

V.L. was a 42-year old, white male truck driver, who entered the University State Tuberculosis Hospital for the second time on December 10, 1951 with a diagnosis of far-advanced bilateral pulmonary tuberculosis with bilateral therapeutic pneumothorax. Past history included four prior hospitalizations for pulmonary tuberculosis. On physical examination, admission blood pressure was found to be 180/130. Subsequent blood pressure readings taken at different times during the day for a period of one week ranged from 160/116 to 210/150. A blood pressure reading during his first admission had been 150/100. Dilution and concentration test, performed December 14, 1951, disclosed dilution to 1.001 and concentration to 1.031. Intravenous pyelograms revealed no abnormality. EKG was normal. A Dibenamine test for detection of pheochromocytoma was performed on January 4, 1952. There was no fall of blood pressure while the patient remained in the supine position. Clinical diagnosis was essential hypertension. On February 16, 1952, in addition to a decortication of the right lung with resection of the apical and posterior segments, the patient had an ipsilateral sympathectomy from the second thoracic to first lumbar ganglia. The sympathetic chain and splanchnic nerves were removed. Blood pressure on May 13, 1952, three months postoperatively, averaged 160/105.

H.G.

H.G. was a 73-year old, white female of Swedish descent, who in spite of treatment of her pernicious anemia with Vitamin $B_{12}$, complainted of severe dizziness in the standing position. In the outpatient clinic on March 12, 1952, her blood pressure when she was standing was found to be 60/40; recumbent blood pressure was 110/70. She was admitted to Multnomah County Hospital on March 25, 1952. She related a history of repeated episodes of "light-headedness" followed by syncope since she was 24 years of age. The syncope always occurred while she was in the standing position and could be prevented by sitting down. In 1945, the character of the episodes changed. She would not lose consciousness, but everything would look "woozy", she would get a weak feeling in her legs and would fall to the ground. Since treatment with Vitamin $B_{12}$, the symptoms seemed to have decreased somewhat. Past history included hospitalization in May 1951 for acute chest pain, rapid pulse, hypotension, pulmonary edema, and rapid sedimentation rate. EKG was non-contributory at the time but one month later revealed a non-specific abnormal tracing suggestive of old posterior wall infarction. Physical examination: undernourished, alert 73-year old female. Blood pressure 116/62 recumbent; 108/62 standing. Pulse 60, reg. Resp. 20, Temp. 97.8°F. Rt. pupil 4 mm. in diameter; left, 6 mm. Bilateral cataracts. Tongue more smooth than normal. Left heart border at mid-clavicular line. Soft systolic apical blowing murmur. Sharp, slightly tender liver edge palpated 7 cm. below right costal margin. Romberg test was positive. Loss of vibratory sense on right to iliac crest, and also much reduced on left. Position sense impaired. Laboratory: 13.3 gm. hemoglobin. RBC 4.7 million, WBC 7,700, 34% granulocytes, 45% lymphocytes, 13% monocytes, 4% eosinophils. Sedimentation rate 2/11.

Chest X-ray revealed heart to be of normal size. EKG suggested incomplete A-V block, borderline.

# BIBLIOGRAPHY

1. Borst, J. G. G. The maintenance of adequate cardiac output by the regulation of urinary excretion of water and sodium chloride: an essential factor in the genesis of oedema. Acta Med. Scandinavica, Supplement CCVII (207), pp. 1-71, 1948.

2. Weston, R. E., L. Hellman, D. J. W. Escher, I. S. Edelman, J. Grossman, and L. Leiter. Studies on the influence of the low sodium cardiac diet and the Kempner regimen on renal hemodynamics. J. Clin. Invest., vol. 29, 639-650, 1950.

3. Orloff, J., L. G. Welt and L. Stowe. The effects of concentrated salt-poor albumin on the metabolism and excretion of water and electrolytes in nephrosis and toxemia of pregnancy. J. Clin. Invest., vol. 29, pp. 770-780, 1950.

4. Randall, H. T., D. V. Habif, and J. S. Lockwood. Sodium deficiency in surgical patients and the failure of urine chloride as a guide to parenteral therapy. Surgery, vol. 28, pp. 182-208, 1950.

5. Coller, F. A., K. N. Campbell, H. H. Vaughan, L. V. Iob, and C. A. Moyer. Postoperative salt intolerance. Ann. Surg., vol. 119, pp. 533-542, 1944.

6. Coller, F. A., L. V. Iob, H. H. Vaughan, N. B. Kalder and C. A. Moyer. Translocation of fluid produced by the intravenous administration of isotonic salt solutions in man postoperatively. Ann. Surg., vol. 122, pp. 663-667, 1945.

7. Briggs, A. P., D. M. Powell, W. F. Hamilton, H. C. Wheeler and J. A. Winslow. Renal and circulatory factors in the edema formation of congestive heart failure. J. Clin. Invest., vol. 27, pp. 810-817, 1948.

8. Stead, E. A., Jr. Edema of heart failure. Bull. N. Y. Acad. Med., vol. 24, pp. 607-614, 1948.

9. Smith, H. W. The Kidney. Structure and Function in Health and Disease. Oxford University Press, New York, 1951.

10. Richards, A. N. The Croonian Lecture: Processes of urine formation. Proc. Roy. Soc. London, Series B., vol. 126, pp. 398-431, 1938.

11. Walker, A. M. and J. Oliver. Methods for the collection of fluid from single glomeruli and tubules of the mammalian kidney. Am. J. Physiol., vol. 134, pp. 562-579, 1941.

12. Walker, A. M., P. A. Bott, J. Oliver, M. C. Macdowell. The collection and analysis of fluid from single nephrons of the mammalian kidney. Am. J. Physiol., vol. 134, pp. 580-595, 1941.

13. Berliner, R. W. Renal excretion of water, sodium chloride, potassium, calcium, and magnesium. Seminars on Renal Physiology, Am. J. Med., pp. 68-86, New York, 1950.

14. Selkurt, E. E., P. W. Hall, and M. P. Spencer. Graded arterial pressure decrement and renal clearance of para-amino-hippurate, creatinine, and sodium. Federation Proc., vol. 8, p. 143, 1949.

15. Selkurt, E. E., P. W. Hall, and M. P. Spencer. Influence of graded arterial pressure decrement on renal clearance of creatinine, p-aminohippurate and sodium. Am. J. Physiol., vol. 159, pp. 369-378, 1949.

16. Pitts, R. F., and J. J. Duggan. Studies on diuretics. II. The relationship between glomerular filtration rate, proximal tubular absorption of sodium and diuretic efficacy of mercurials. J. Clin. Invest., vol. 29, pp. 372-379, 1950.

17. Blake, W. D., R. Wegria, H. P. Ward and C. W. Frank. Effect of renal arterial constriction on excretion of sodium and water. Am. J. Physiol., vol. 163, pp. 422-429, 1950.

18. Selkurt, E. E., P. W. Hall, and M. P. Spencer. Response of renal blood flow and clearance to graded partial obstruction of the renal vein. Am. J. Physiol., vol. 157, pp. 40-46, 1949.

19. Blake, W. D., R. Wegria, R. P. Keating and H. P. Ward. Effect of increased renal venous pressure on renal function. Am. J. Physiol., vol. 157, pp. 1-13, 1949.

20. Hwang, W., L. C. Ackman, A. J. Miller, N. Silber, J. Stamler and L. N. Katz. Effects of sustained elevation of renal venous pressure on sodium excretion in the unanesthetized dog. Am. J. Physiol., vol. 162, pp. 649-654, 1950.

21. Hall, P. W., III. and E. E. Selkurt. Effects of partial graded venous obstruction on electrolyte clearance by the dog's kidney. Am. J. Physiol., vol. 164, pp. 143-154, 1951.

22. Huckins, A. R. The relationship between glomerular filtration and sodium excretion. Unpublished thesis, University of Oregon Medical School, June, 1950.

23. Kriss, J. P., P. H. Futcher and M. L. Goldman. Unilateral adrenalectomy, unilateral splanchnic nerve resection and homolateral renal function. Am. J. Physiol., vol. 154, pp. 229-240, 1948.

24. Kaplan, S. A. and S. Rapoport. Urinary excretion of sodium and chloride after splanchnicectomy, effect of the proximal tubule. Am. J. Physiol., vol. 164, pp. 175-181, 1951.

25. Kaplan, S. A., J. J. Fomon, and S. Rapoport. Effect of splanchnic nerve division on urinary excretion of electrolytes during mannitol loading in the hydropenic dog. Am. J. Physiol., vol. 166, pp. 641-648, 1951.

26. Wesson, L. G. and W. P. Anslow, Jr. Excretion of sodium and water during osmotic diuresis in the dog. Am. J. Physiol., vol. 153, pp. 465-474, 1948.

27. Ladd, M. and L. G. Raisz. Responses of the normal dog to dietary sodium chloride. Am. J. Physiol., vol. 159, pp. 149-152, 1949.

28. Wesson, L. G., Jr., W. P. Anslow, Jr. and H. W. Smith. The excretion of strong electrolytes. Bull. N. Y. Acad. Med., vol. 24, pp. 586-606, 1948.

29. Green, D. M. and A. Farah. Influence of sodium load on sodium excretion. Am. J. Physiol., vol. 158, pp. 444-456, 1949.

30. Selkurt, E. E. and R. S. Post. Renal clearance of sodium in the dog: effect of increasing sodium load on reabsorptive mechanism. Am. J. Physiol., vol. 162, pp. 639-648, 1950.

31. Baldwin, D., E. M. Kahana, and R. W. Clarke. Renal excretion of sodium and potassium in the dog. Am. J. Physiol., vol. 162, pp. 655-664, 1950.

32. Wesson, L. G., Jr., W. P. Anslow, Jr., L. G. Raisz, A. A. Bolomey, and M. Ladd. Effect of sustained expansion of extracellular fluid volume upon filtration rate, renal plasma flow and electrolyte and water excretion in the dog. Am. J. Physiol., vol. 162, pp. 677-686, 1950.

33. Rapoport, S. and C. D. West. Excretion of sodium and potassium during osmotic diuresis in the hydropenic dog. Am. J. Physiol., vol. 163, pp. 175-180, 1950.

34. West, C. D. and S. Rapoport. Urine flow and solute excretion of hydropenic dog under resting conditions and during osmotic diuresis. Am. J. Physiol., vol. 163, pp. 159-174, 1950.

35. Duggan, J. J. and R. F. Pitts. Studies on diuretics. I. The site or action of mercurial diuretics. J. Clin. Invest., vol. 29, pp. 365-371, 1950.

36. Shannon, J. A. The control of the renal excretion of water. I. The effect of variations in the state of hydration on water excretion in dogs with diabetes insipidus. J. Exper. Med., vol. 76, pp. 371-386, 1942.

37. Shannon, J. A. The control of the renal excretion of water. II. The rate of liberation of the posterior pituitary antidiuretic hormone in the dog. J. Exper. Med., vol. 76, pp. 387-399, 1942.

38. Roemmelt, J. C., O. W. Sartorius, and R. F. Pitts. Excretion and reabsorption of sodium and water in the adrenalectomized dog. Am. J. Physiol., vol. 159, pp. 124-136, 1949.

39. Blake, W. D. Effect of exercise and emotional stress on renal hemodynamics, water and sodium excretion in the dog. Am. J. Physiol., vol. 165, pp. 149-157, 1951.

40. Wiggins, W. S., C. H. Manry, R. H. Lyons, and R. F. Pitts. The effect of salt loading and salt depletion on renal function and electrolyte excretion in man. Circulation, vol. 3, pp. 275-281, 1951.

41. Leaf, A. and W. T. Couter. Evidence that renal sodium excretion by normal human subjects is regulated by adrenal cortical activity. J. Clin. Investigation, vol. 28, pp. 1067-1081, 1949.

42. Leaf, A., W. T. Couter, and L. H. Newburgh. Some effects of variation in sodium intake and of different sodium salts in normal subjects. J. Clin. Invest., vol. 28, pp. 1082-1090, 1949.

43. Stewart, J. D. and M. G. Rourke. The effects of large intravenous infusions on body fluid. J. Clin. Invest., vol. 21, pp. 197-205, 1942.

44. Rapoport, S., C. D. West, and W. A. Brodsky. Excretion of solutes and osmotic work during osmotic diuresis of hydropenic man. The ideal and the proximal and distal tubular work; the biological maximum of work. Am. J. Physiol., vol. 157, pp. 363-368, 1949.

45. Rapoport, S., W. A. Brodsky, C. D. West, and B. Mackler. Urinary flow and excretion of solutes during osmotic diuresis in hydropenic man. Am. J. Physiol., vol. 156, pp. 433-442, 1949.

46. Epstein, F. H., A. V. N. Goodyer, F. D. Lawrason, and A. S. Relman. Studies of the antidiuresis of quiet standing: The importance of changes in plasma volume and glomerular filtration rate. J. Clin. Invest., vol. 30, pp. 63-72, 1951.

47. Kattus, A. A., B. Sinclair-Smith, J. Genst, and E. V. Newman. The effect of exercise on the renal mechanism of electrolyte excretion in normal subjects. Bull. Johns Hopkins Hosp., vol. 84, pp. 344-368, 1949.

48. White, H. L., I. T. Rosen, S. S. Fischer, and G. H. Wood. The influence of posture on renal activity. Am. J. Physiol., vol. 78, pp. 185-200, 1926.

49. Lombardo, T. A., E. Seymour, B. B. Oliver, W. W. Viar, E. E. Eddleman, and T. R. Harrison. Effects of bleeding on electrolyte excretion and on glomerular filtration. Circulation, vol. 3, pp. 260-270, 1951.

50. Merrill, A. J. Mechanisms of salt and water retention in heart failure. Am. J. Med., vol. 6, pp. 357-367, 1949.

51. Pitts, R. F. and Duggan, J. J. Studies on diuretics. II. The relationship between GFR, proximal tubular absorption of sodium and diuretic efficacy of mercurials. J. Clin. Invest., vol. 29, pp. 372-279, 1950.

52. Ingbar, S. H., A. S. Relman, B. A. Burrow, E. H. Kass, J. H. Sisson, and C. H. Burnett. Changes in normal renal function resulting from ACTH and cortisone. J. Clin. Invest., vol. 29, p. 824, 1950.

53. Thorn, G. W. and E. Kendall, Jr. The role of gonadal and adrenal cortical hormones in the production of edema. Ann. Int. Med., vol. 14, pp. 757-769, 1940.

54. Chalmers, T. M., A. A. G. Lewis, and G. L. S. Pawan. The effect of posterior pituitary extracts on the renal excretion of sodium and chloride in man. J. Physiol., vol. 112, pp. 238-242, 1951.

55. Chalmers, T. M., A. A. G. Lewis, and G. L. S. Pawan. Relation between glomerular filtration rate and sodium excretion in man. J. Physiol., vol. 115, pp. 17P-18P, 1951.

56. Green, D. M., W. C. Bridges, A. D. Johnson, J. H. Lehman, R. Gray, and L. Field. Relation of glomerular filtration rate and tubular rejection fraction to renal sodium excretion. Am. J. Physiol., vol. 160, pp. 306-310, 1950.

57. Sinclair-Smith, B., A. A. Kattus, J. Genest, and E. V. Newman. The renal mechanism of electrolyte excretion and the metabolic balances of electrolytes and nitrogen in congestive heart failure; the effects of exercise, rest, and aminophyllin. Bull. Johns Hopkins Hosp., vol. 84, pp. 369-394, 1949.

58. Futcher, P. H. and H. A. Schroeder. Studies on congestive heart failure. II. Impaired renal excretion of sodium chloride. Am. J. Med. Sc., vol. 204, pp. 52-62, 1942.

59. Mokotoff, R., G. Ross, and L. Leiter. Renal plasma flow sodium reabsorption and excretion in congestive heart failure. J. Clin. Invest., vol. 27, pp. 1-9, 1948.

60. Farnsworth, E. B. Electrolyte partition in patients with edema of various origins. Am. J. Med., vol. 4, pp. 338-342, 1948.

61. Bradley, S. E. and W. D. Blake. Pathogenesis of renal dysfunction during congestive heart failure. Am. J. Med., vol. 6, pp. 470-480, 1949.

62. Yuskis, A. S. and G. C. Griffith. Orthostatic hypotension and orthostatic tachycardia. Calif. Med., vol. 69, pp. 255-261, 1948.

63. MacLean, A. R., E. V. Allen, and T. B. Magath. Orthostatic tachycardia and orthostatic hypotension: defects in return of venous blood to the heart. Am. Heart J., vol. 27, pp. 145-163, 1944.

64. Young, R. H. Association of postural hypotension with sympathetic nervous system dysfunction; case report with review or neurologic features associated with postural hypofunction. Ann. Int. Med., vol. 15, pp. 910-916, 1941.

65. Ellis, L. B. and F. W. Haynes. Postural hypotension with reference to its occurrence in disease of the central nervous system. Arch. Int. Med., vol. 58, pp. 773-398, 1936.

66. Gregory, R. The treatment of orthostatic hypotension with particular reference to the use of desoxycorticosterone. Am. Heart J., vol. 29, pp. 246-252, 1945.

67. Korns, H. M. and W. L. Randall. Benzedrine and paredrine in the treatment of orthostatic hypotension with supplementary case report. Ann. Int. Med., vol. 12, pp. 253-255, 1938.

68. Bradbury, S. and C. Eggleston. Postural hypotension. A report of three cases. Am. Heart J., vol. 1, pp. 73-86, 1925.

69. Ghrist, D. G. and Brown, G. E. Postural hypotension with syncope; its successful treatment with ephedrine. Am. J. Med. Sc., vol. 175, pp. 336-349, 1928.

70. Alvarez, W. C. and G. Roth. Orthostatic hypotension; report of a case with some unusual features. Proc. Staff Meet. Mayo Clinic, vol. 10, pp. 483-489, 1935.

71. Chew, E. M., E. V. Allen, and N. W. Barker. Orthostatic hypotension; report of six cases and review of the literature. Northwest Med., vol. 35, pp. 297-303, 1936.

72. Baker, T. W. Recognition of orthostatic hypotension. Report of a case. Proc. Staff Meet. Mayo Clinic., vol. 13, pp. 169-174, 1938.

73. Corcoran, A. C., J. S. Browning, and I. H. Page. Renal hemodynamics in orthostatic hypotension: effects of angiotonin and head-up bed. J.A.M.A., vol. 119, pp. 793-794, 1942.

74. Merrill, A. J. Mechanisms of salt and water retention in heart failure. Am. J. Med., vol. 6, pp. 357-367, 1949.

75. Merrill, A. J. and W. H. Cargill. The effect of exercise on the renal plasma flow and filtration rate of normal and cardiac subjects. J. Clin. Invest., vol. 27, 272-277, 1948.

76. White, H. S. and D. Rolfe. Effects of exercise and of some other influences on the renal circulation in man. Am. J. Physiol., vol. 152, pp. 505-516, 1948.

77. Fishman, A. P., J. Stamler, L. N. Katz, A. J. Miller, E. N. Silber, and L. Rubenstein. Mechanisms of edema formation in chronic experimental pericarditis with effusion. J. Clin. Invest., vol. 29, pp. 521-533, 1950.

78. Mudge, G. H., J. Foulks, and A. Gilman. Effect of urea on renal excretion of electrolytes. Am. J. Physiol., vol. 158, pp. 218-230, 1949.

79. Mills, J. N. and Stangury, S. W. Intrinsic diurnal rhythm in urinary electrolyte output. J. Physiol., vol. 115, pp. 18P-19P, 1951.

80. Sirota, J. H., D. S. Baldwin, and H. Villarreal. Diurnal variations of renal function in man. J. Clin. Invest., vol. 29, pp. 187-192, 1950.

81. Manchester, R. C. The diurnal rhythm in water and mineral exchange. J. Clin. Invest., vol. 12, pp. 995-1008, 1933.

82. Norn, M. Untersuchungen uber das Verhalten des Kaliums im Organismus. II. Über Schwankungen der Kalium-, Natrium-, und Chloridausscheidung durch die Niere im Laufe des Tages. Skandin. Arch. f. Physiol., vol. 55, pp. 184-210, 1929.

83. Simpson, G. E. Diurnal variations in the rate of urine excretion for two hour intervals: some associated factors. J. Biol. Chem., vol. 59, pp. 107-122, 1924.

84. Steinitz, K. and H. Turkand. The determination of the glomerular filtration by the endogenous creatinine clearance. J. Clin. Invest., vol. 19, pp. 285-298, 1940.

85. Brod, J. and J. H. Sirota. The renal clearance of endogenous "Creatinine" in man. J. Clin. Invest., vol. 27, pp. 645-654, 1948.

86. Hare, K., H. Goldstein, H. L. Barnett, H. McNamara, and R. S. Hare. Renal excretion of creatinine in man. Federation Proc., vol. 8, p. 67, 1949.

87. Hare, R. S. Endogenous creatinine in serum and urine. Proc. Soc. Exper. Biol. and Med., vol. 74, pp. 148-151, 1950.

88. Hald, P. M. The flame photometer for the measurement of sodium in biological materials. J. Biol. Chem., vol. 167, pp. 499-510, 1947.

89. Barnes, R. B., D. Richardson, J. W. Berry, and R. I. Hood. Flame photometry. Ind. Eng. Chem., Anal. Ed., vol. 17, pp. 605-611, 1945.

90. Hawk, P. B., B. L. Oser, and W. H. Summerson. Practical Physiological Chemistry, 12th Edition, pp. 893-894, The Blakiston Company, Philadelphia, 1947.

91. West, E. S. and W. R. Todd. Laboratory Outline of Biochemistry for Medical Students, Department of Biochemistry, University of Oregon Medical School, September, 1948.