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RENAL EXCRETION OF SODIUM AND THE CONCEPT OF A VOLUME RECEPTOR‡

The mechanisms by which a healthy individual maintains constant the volume of his plasma and extracellular fluid have interested and baffled physiologists for years. The problem is peculiar to multicellular, complex organisms; our unicellular ancestors, enclosed by a semipermeable membrane and swimming in a sea of constant composition, had only to maintain intact the effective osmotic concentration inside their cells for cellular volume to adjust itself automatically. When they became larger and moved on land, taking with them a bit of the primeval ocean in their extracellular fluid, it became important to preserve not only the composition, but also the volume of the fluids bathing their cells. Bodily regulations which serve these ends must necessarily be concerned with the intake and excretion of the chief inorganic constituent of extracellular fluid, namely, the sodium ion. It is for this reason that studies of the regulation of sodium excretion by the kidneys have attracted physiologists and clinicians primarily interested in such diverse states as dehydration, congestive heart failure, nutritional edema, anemia, hemorrhage, and hypertension.

It was recognized clearly by Ernest Starling,[87] though not by some later physiologists, that the balance of forces across the capillary membrane which he described explains only the localization of salt and water in edematous tissues, not their over-all retention by the body. It is tautologous to say that the kidney normally operates in such a way that the volume of extracellular fluid is maintained constant; to delineate clearly the mechanisms by which this is accomplished, it is necessary not only to describe the intrarenal factors affecting the excretion of sodium, but to examine the bodily processes through which the kidney is notified to retain or excrete this ion. Hence the search for a "volume receptor"—an afferent mechanism sensitive to some crucial function of the volume of body fluids.

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RENAL MECHANISMS FOR SODIUM EXCRETION

Of primary importance in any attack on the problem of the regulation of the volume of body fluids are the circulatory, hormonal, and neural factors directly influencing renal excretion of sodium.[3] All other things being equal, even small changes, immeasurable by present techniques, in the rate of glomerular filtration inescapably alter the rate of sodium excretion. Because glomerular filtration rate and renal blood flow so frequently are found to change in the same direction as sodium excretion in a variety of clinical and experimental situations, it has correctly been concluded that they are powerful determinants of the excretion or retention of sodium, but it is too often assumed that they are the only, or even the most important, determinants. Here physiologists specializing in the tractable dog are at some disadvantage when attempting to extrapolate to the human. Glomerular filtration rate in the dog is much more readily changed than in humans. The dog initially excretes a load of salt largely by increasing the rate at which glomerular fluid is filtered.[38] Intravenous saline loads in man, on the other hand, may produce no measurable increase in glomerular filtration rate, even when they provoke a huge sodium diuresis.[11] Renal retention of sodium in man during quiet standing can be demonstrated to occur even when a fall in the amount of filtered sodium is prevented by simultaneously infusing albumin or hypertonic saline.[17] The administration of digitalis to cardiacs in congestive failure is followed by a diuresis of sodium and water before any change is apparent in renal hemodynamics.[22] Cirrhotics with normal renal clearances of inulin and para-aminohippurate retain sodium with avidity even when it is given in hypertonic solution.[29] Opening an arteriovenous fistula is followed by a drop in sodium excretion, while closing it provokes an increase, all without measurable changes in renal blood flow or glomerular filtration rate.[19] Even the separately perfused kidney can apparently vary its excretion of sodium widely without altering its blood flow or filtration rate. Selkurt has shown that increasing or decreasing renal arterial perfusion pressure produces an increase or decrease in the excretion of sodium and water without parallel changes in the formation of glomerular fluid[58]; this suggests that intrarenal pressure changes may be reflected in alterations in tubular behavior.

The possibility that changes in the intrarenal distribution of blood among nonhomogeneous nephrons may alter sodium excretion has been recently reopened by the experiments of Pappenheimer which suggest that cortical nephrons are perfused by blood having a different hematocrit from nephrons in the medulla.[46] If certain nephrons handle a disproportionate share of glomerular filtrate in a different way from their fellows, it would not be

hard to visualize readjustments occasioned by changes in renal arterial perfusion pressure which might, for example, result in a greater proportion of fluid being filtered through the glomeruli of long, sodium-retaining nephrons and a smaller proportion through short nephrons unable to reabsorb as much sodium. This kind of readjustment would not be detected by the usual (Fick) clearance techniques which measure only the total flow of blood to an organ. If indeed there is considerable nonhomogeneity of blood flow to nephrons within the kidney, traditional concepts of the division of responsibility for sodium retention between alterations in "glomerular filtration" and active changes in "tubular reabsorption" in a variety of states may have to be revised. Subject to the above considerations it appears that in man hormonal and possibly nervous influences on tubular reabsorption of sodium play a major rôle, in addition to changes in glomerular filtration rate, in determining whether sodium is to be retained or excreted.

NEURAL INFLUENCES ON SODIUM EXCRETION

The regulatory rôle of the autonomic nerves to the kidney has been assigned variously to the renal vasculature alone[59] or to the control of tubular function, including the active reabsorption of sodium in the proximal tubules as well.[56] Because of the relatively inexact techniques available for measuring small changes in tubular handling of a substance so largely reabsorbed from glomerular fluid as sodium, it has been difficult to amass data proving that renal tubules are in fact responsive to renal denervation or to stimulation of the renal nerves, apart from the changes in renal hemodynamics which frequently accompany such maneuvers. Renal denervation in an animal under anesthesia usually results in an increase in sodium excretion, glomerular filtration rate and blood flow in the denervated kidney, while experiments in unanesthetized dogs have generally been unsuccessful in detecting differences between denervated and innervated kidneys.[58] It seems reasonable to conclude that "denervation diuresis" may be a consequence of the release of enhanced vasoconstrictor activity under anesthesia, especially since small changes in glomerular filtration occurring acutely are known to produce large percentual changes in sodium excretion. Sympathectomized patients, in whom nervous connections to the kidneys have presumably been interrupted, usually retain or excrete sodium in normal fashion so that plasma and extracellular fluid volumes are maintained intact; furthermore, they develop sodium retention and edema when congestive heart failure supervenes. Moreover, as will be seen below, they promptly retain sodium when blood is acutely sequestered in the limbs by congesting cuffs even though glomeru-

lar filtration and renal blood flow are not measurably depressed by this maneuver. Complete renal denervation fails to prevent the fall in glomerular filtration rate and sodium excretion caused by primary reduction of the cardiac output[6] and high spinal anesthesia does not restore the diminished renal blood flow and filtration rate or increase the rate of urine excretion in patients with congestive heart failure.[48] Autonomic blockade with hexamethonium or unilateral renal denervation does not prevent the reduced excretion of water, sodium, and chloride which is induced by hemorrhage, even though the arterial blood pressure is well maintained and there is no significant change in filtered sodium and renal plasma flow.[37] It would appear that renal innervation is not essential in men or dogs to the decreased excretion of sodium which follows reduction in "effective blood volume."

HORMONAL INFLUENCES ON SODIUM EXCRETION

There is considerable evidence that in almost every clinical state characterized by the formation of edema the renal tubules are influenced by salt-retaining hormones manufactured by the adrenal cortex and secreted in supernormal amounts. Increased quantities of aldosterone have been detected in the urine of patients with congestive heart failure,[1] cirrhosis with ascites,[1] toxemia of pregnancy,[21] and nephrosis.[42] In patients with these disorders the output of aldosterone appears to fluctuate in parallel fashion with the intensity of the circulatory stimulus to salt retention.[41] For example, patients with cirrhosis and ascites demonstrate a greatly increased excretion of aldosterone immediately after paracentesis, when the rate of transudation of fluid from the blood stream is greatest.[3] In addition, blood loss,[28] sodium restriction,[40] and dehydration of the *extracellular*[3] fluid call forth an increased output of sodium-retaining hormone. On the other hand, selective dehydration of the *intracellular* fluid compartment induced by the infusion of hypertonic saline is not accompanied by an increased titer of salt-retaining substances in the urine.[3]

It is not altogether clear to what degree the action of the adrenocortical steroids on renal salt excretion is "permissive"[34] and to what extent they directly mediate the degree and duration of sodium retention following withdrawal of blood from the "effective" central circulation. It seems at least possible that the rôle of the mineralcorticoid aldosterone is a direct one; its endogenous excretion rises promptly after hemorrhage[28] or sodium restriction,[40] and its effects upon the excretion of sodium and potassium vary in proportion to the amount injected.[56] Although it has been suggested that altered tubular reabsorptive behavior resulting from increased mineral-

corticoid secretion represents a *chronic* adjustment to circulatory states requiring sodium retention, whereas *acute* changes in sodium excretion are accomplished by intrarenal hemodynamic adjustments,[44] there seems no reason why hormonal adjustments might not also be almost as rapid and immediately responsive to bodily needs as are changes in blood flow. The body manufactures many hormones whose action is immediate and may be short lived; pitressin, epinephrine, and insulin are examples. Huffman, Wilson, Clark, and Smyth have recently accumulated data which show that within 15 minutes after an infusion of 9α-fluorohydrocortisone sodium excretion diminishes markedly;[32,33] this suggests the possibility of direct adrenal participation in a number of acute renal adjustments, such as the antinatriuresis of quiet standing, of limb congestion, or of hemorrhage.

INTERRELATIONSHIP BETWEEN HORMONES AND HEMODYNAMIC FACTORS IN SODIUM RETENTION AND EDEMA FORMATION

It is difficult in most clinical situations to place the entire responsibility for salt and water retention upon the salt-retaining adrenal hormones. The proper hemodynamic background appears to be essential for the prolonged retention of sodium which results in edema formation—the edema "has to have some place to go." Primary hypersecretion of aldosterone is usually characterized not by edema but by depletion of body potassium.[10] Administration of excessive amounts of desoxycorticosterone to normal dogs produces not edema or ascites but a condition resembling diabetes insipidus.[50]

The interplay between hemodynamic and hormonal factors necessary for edema formation is nowhere better illustrated than in the painstaking experiments of Davis, Howell, and Southworth.[12] Constriction of the inferior vena cava in the thorax produces massive ascites in normal dogs allowed access to salt. Adrenalectomy results in complete loss of the ascites, through progressive renal excretion of salt and water, after which the signs of adrenal insufficiency supervene. Administration of a normal maintenance dose of DOCA halts the renal losses of sodium and will *maintain* ascites, but despite an appropriate hemodynamic background ascites does not *develop* and increase in severity until DOCA is given in twenty to fifty times the normal maintenance dose. Progressive sodium retention and the development of ascites in this species apparently require that the proper circulatory background be coupled with excessive adrenal secretion. On the other hand, Blackett has reported a case of congestive heart failure with edema occurring in an untreated Addisonian;[8] there may, however, have been some residual adrenal secretory activity in this patient.

The rôle of hydrocortisone and of cortisone with respect to sodium excretion appears to be "permissive"; that is, their presence enhances but does not necessarily mediate stimuli to the excretion or retention of sodium. Administration of cortisone restores the normal diurnal excretory pattern of electrolytes in subjects with Addison's disease and improves their ability to retain sodium in the seated posture and to excrete it when supine.[52] Figure 1 shows the results of applying congesting cuffs to the thighs of a patient who had a bilateral total adrenalectomy and was maintained on 2 mg. of DOCA and 50 mg. of cortisone per day. Despite a presumably constant level of circulating adrenal steroids, salt and water excretion fell promptly when the cuffs were applied and rose toward normal when the sequestered blood was allowed to return to the central circulation. Inulin clearance fell slightly during the period of congestion but returned to control levels after the cuffs were released at a time when sodium excretion was still depressed.

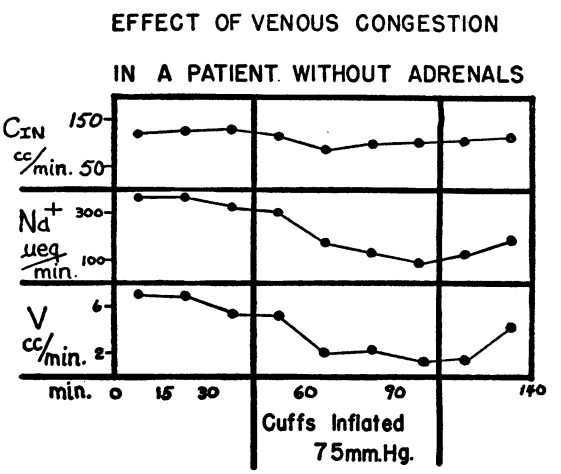

FIG. 1. Trapping blood in the legs of a patient without adrenal glands but maintained on DOCA and cortisone produced a fall in sodium excretion associated with a slight decline in GFR.

VENOUS CONGESTION DURING MANNITOL DIURESIS

Some of the above information is especially pertinent when considering the sequence of events which occurs when blood is trapped in the limbs of normal and sympathectomized subjects during mannitol diuresis. Because venous congestion of the legs is always accompanied by antidiuresis in normal subjects, the calculated renal clearances of inulin and para-aminohippurate as well as other substances are especially susceptible to artifactual depression during this maneuver. In order to overcome this difficulty, a moderate osmotic diuresis can be induced with mannitol which will prevent any great depression of urine flow. When congesting cuffs are applied to the legs of a normal subject under these circumstances, there is an abrupt and progressive decline in the urinary sodium

concentration and sodium excretion associated with a less dramatic fall in glomerular filtration rate and renal plasma flow. This is illustrated in Figure 2. When the same procedure is carried out on a patient who has had a lumbodorsal sympathectomy (Fig. 3), glomerular filtration rate and renal plasma flow do not change, suggesting that effectual renal denervation has indeed been accomplished. Nevertheless, the concentration of sodium in the urine and the renal excretion of sodium promptly decrease, continue to decline during the period of cuff congestion, and start

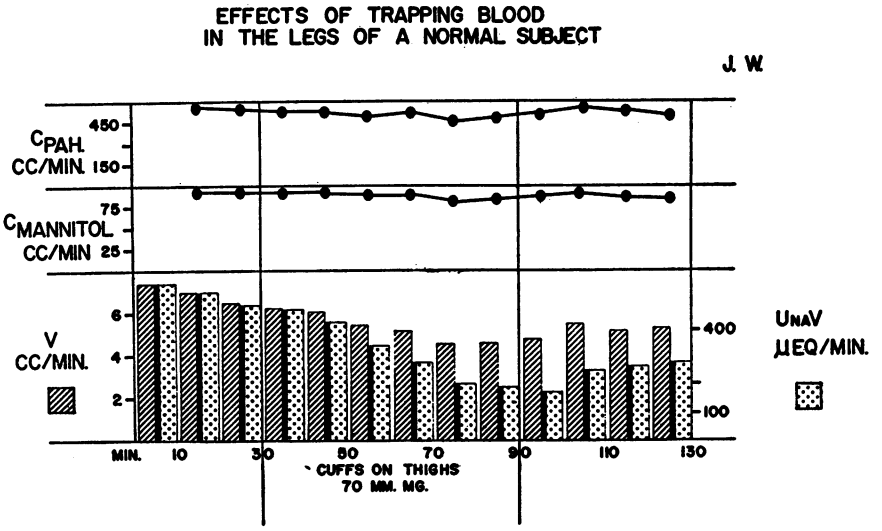

FIG. 2. Venous congestion of the legs of a normal subject *during mannitol diuresis* provokes a greater fall in the excretion of sodium than in the excretion of water. There is a slight drop in GFR and RPF. Mean arterial pressure (not shown) usually does not change during this maneuver.

to return towards normal only when the cuffs are released.[18] In these experiments, as in analogous ones in dogs by Goodyer and Jaeger,[27] possible explanations for the observed retention of sodium might be: (a) intrarenal redistribution of blood flow and filtration rate; and/or (b) the action of rapidly acting and quickly dissipated humoral agents upon the renal tubules.

THE NATURE OF THE "VOLUME RECEPTOR"

Whether sodium retention is accomplished by hormones acting upon renal tubules, by nervous impulses to renal vasculature or renal parenchyma, or by intrarenal adjustments of pressure and flow, the nature and sites of action of *afferent* stimuli to renal excretion or retention of

sodium constitute one of the more important unanswered problems about fluid metabolism today. It is obvious from the very existence of clinical states characterized by edema that the kidneys are not sensitive to the total amount of extracellular fluid. It would seem more likely, perhaps, that they respond to some fraction of the extracellular fluid volume—

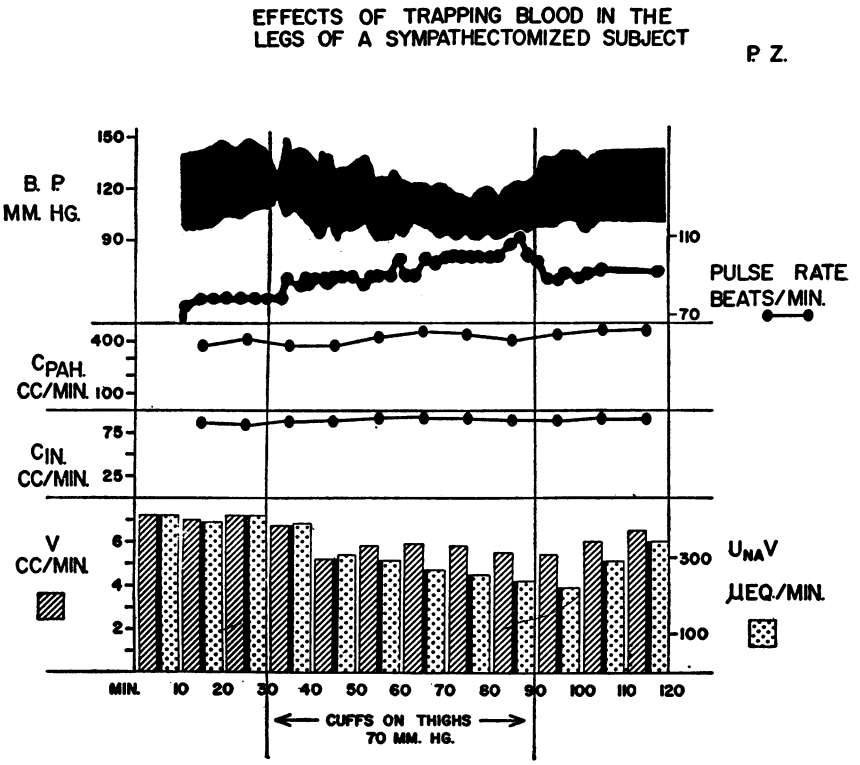

FIG. 3. When blood is trapped in the legs of a sympathectomized subject undergoing mannitol diuresis, sodium excretion falls (in association with a drop in mean arterial pressure) although renal blood flow and glomerular filtration rate are not diminished.

that portion possibly whose function it is to stir and mix the body fluids and to be distributed to all parts of the body. As Peters suggested in 1935,[47] the kidneys behave in many situations as though they were peculiarly sensitive to some function of the volume of circulating blood. It is apparent also from purely clinical considerations that the total volume of blood is not as important to the kidneys as the way it is distributed inside the vascular system. Congestive heart failure is a clinical case in point. Although earlier measurements of plasma volume, using dyes bound to albumin, probably

overestimated the volume of circulating blood in congestive heart failure,[48] it is clear from studies employing tagged red cells that heart failure may be characterized by avid renal retention of sodium at a time when blood volume may be normal or high.[14] The same is true in patients with hepatic cirrhosis and portal hypertension[15] and in patients or animals with large arteriovenous fistulas.[19, 21]

A normal standing subject is in many ways the paradigm of these clinical states of sodium retention. When a man stands erect, venous and capillary pressures in the legs rise, transudation from the blood stream increases, plasma volume falls, blood pools in the large veins and there is compensatory vasoconstriction of arterioles and venules. There is a fall in pressure in the great veins of the thorax, cardiac output usually declines, and arterial pulse pressure diminishes, though mean arterial blood pressure may not decrease. Renal retention of sodium can be demonstrated within the first 20 minutes after the erect posture is assumed. This occurs even when contraction of total blood volume (though not its redistribution) is prevented by simultaneously infusing albumin.[17] Exactly the same sequence can be demonstrated in subjects in the supine position by trapping blood in the limbs with congesting cuffs. Normal persons promptly excrete a load of saline solution given intravenously when they are in a supine position; seated or standing subjects do not, nor do patients in congestive failure. In attempting to fit these and other facts to a single hypothesis, the cranial cavity, the "cephalad portion of the body," the great veins and cardiac atria, and the arterial pressoreceptors have all been proposed as possible sites for the initiation of afferent impulses designed to modify renal excretion of salt or water.

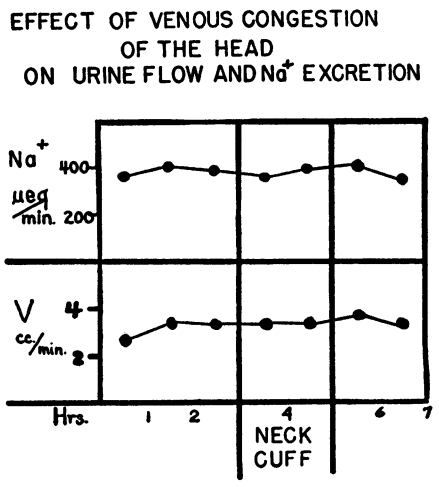

FIG. 4. Inflation of a cuff about the neck to 25 mm. Hg for one hour had no effect on sodium excretion or urine flow.

The idea of a cranial "volume receptor" is a simple and attractive one. It is consonant with the facts that the erect posture is associated with the retention of salt and water and recumbency with diuresis, though not necessarily with the observation that sodium retention occurs with obstruction of the superior vena cava[21] as well as in congestive heart failure, two con-

ditions characterized by the elevation of cerebral venous pressures. Harrison and his collaborators produced an increase in the excretion of salt when congesting cuffs were inflated about the necks of normal semirecumbent subjects.[62] These findings were not confirmed by others[45] or ourselves. Figures 4 and 5 demonstrate that over a period of 30 to 60 minutes sodium excretion is not altered by venous congestion of the head produced either by a pneumatic cuff or by head-down tilting. Moreover, the sodium retention which normally accompanies quiet standing or venous congestion of the legs is not prevented by simultaneous elevation of cerebral venous pressure (Fig. 6). Alterations in cerebrospinal fluid pressure, cerebral venous pressure, or cerebral venous distention within the physiological range were not noted by Fishman to influence renal excretion of sodium in anesthetized dogs.[24] Changes in venous pressure in the head therefore do not appear to play a major rôle in regulating sodium excretion under usual circumstances.

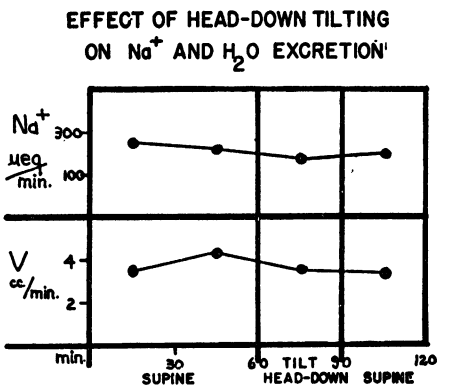

FIG. 5. Tilting head downward at an angle of 45° for 30 minutes had no effect on sodium excretion or urine flow.

The fact that sodium retention regularly accompanies the peripheral dislocation of blood into congested veins has led to speculation that neural impulses from the distended segments of veins might provoke the kidneys to reabsorb salt. Judson, Hatcher, Halperin, and Wilkins showed that the renal effects of venous congestion in a supine subject were secondary to the withdrawal of blood from the general circulation.[35] Sodium was not retained when a volume of blood equal to that being trapped in the limbs was infused simultaneously.

That cardiac output might be directly related in some way to renal sodium excretion was suggested by Borst,[9] primarily because it seemed to be so related in patients with gastrointestinal hemorrhage and congestive heart failure. It is difficult to visualize how the kidneys could be accurately apprised of the minute volume of cardiac output per se, unless it were reflected in the renal blood flow. Cardiac output is *inversely* related to salt excretion in normal persons performing muscular exercise in the standing position,[37] in patients and dogs with arteriovenous fistulas[19, 31] and in all types of "high-output" cardiac failure.

Most of the states in which renal retention of sodium is prominent are associated with either a diminution of total blood volume or a sequestration of blood in peripheral veins. There is one situation in which this is not the case. Infusions of concentrated solutions of albumin into normal subjects raise cardiac filling pressure, increase cardiac output, and expand blood volume at the expense of interstitial fluids. This is, paradoxically, accompanied by a *decrease* in the renal excretion of sodium.[28] These facts have suggested that the kidneys might be sensitive in some way to a contracted interstitial fluid even in the presence of a swollen vascular volume, or that there might be a receptor organ within the vascular tree responsive to alterations in oncotic pressure.[49, 68] Conceivably this "receptor" might be in the cranial cavity. Infusions of concentrated albumin solutions into the carotid artery of a dog do not, however, provoke renal retention of sodium (Table 1). Although an elevation in the level of serum albumin in blood perfusing the kidney might be expected to exert a direct effect in diminishing slightly glomerular filtration and/or increasing tubular reabsorption of water and salts, Goodyer and Glenn[26] observed this to occur only inconstantly when 25 per cent albumin was injected directly into the left renal artery. In many experiments of Goodyer and Glenn, however, renal excretion of sodium was already at a minimum before albumin was injected. For this and other reasons the possibility remains an important one that the sodium-retaining action of concentrated albumin in normals is a direct intrarenal effect.

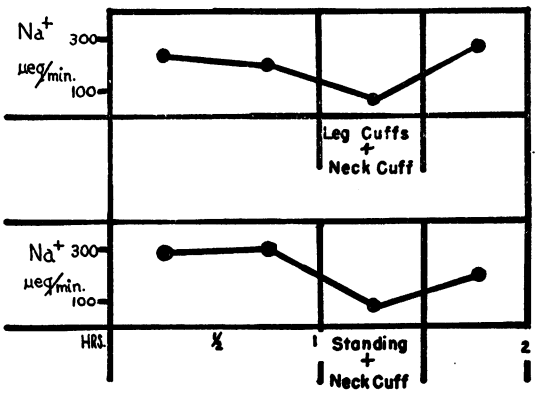

FIG. 6. Failure of head congestion to prevent retention of sodium. In two separate experiments on the same subject, inflating a cuff about the neck to 25 mm. Hg did not prevent the fall in sodium excretion which normally accompanies venous congestion of the legs or quiet standing. The subject was supine during the CONTROL and RECOVERY periods.

If the kidneys do respond to changes in volume (or pressure) in some portion of the vascular system, the question remains, which portion? Observing that immersion of the body in water always produced a diuresis, Bazett deduced that a shift of blood from peripheral venules in the skin to a more central location was responsible.[5] Pressures in the great veins of the

chest, including both atria, are easily altered by relatively small changes in blood volume induced by blood-letting or infusions. For this reason, Gauer, Henry, Sieker, and Wendt suggested that these structures might be the locus of stretch receptors which would initiate renal conservation or excretion of fluid.[25] Negative-pressure breathing distends the intrathoracic vasculature and provokes diuresis in men[55] and dogs.[25] This reaction is also obtained when the left atrium of the dog is distended with a balloon but not when the pulmonary veins are occluded.[30] Positive-pressure breathing causes a decreased excretion of both water and salt;[18] however, the increased urinary flow which sometimes follows negative-pressure breathing is not ac-

TABLE 1. EFFECT OF INFUSING 25 PER CENT ALBUMIN INTO THE CAROTID ARTERY OF AN UNANESTHETIZED DOG

Time min.	*Procedure*	$U_{Na}V$ *uEq./min.*
10	Control	264
22	"	285
33	"	297
43	Infuse 100 cc. 25 per cent	308
52	albumin into carotid artery	320
64	Recovery	330
79	"	332

companied by a diuresis of sodium. Nor does loss of water from the body normally provoke sodium excretion, or a positive balance of water, sodium retention; in fact, the exact reverse is true.[16, 39] For these reasons the importance of atrial receptors in the homeostatic defense of the volume of plasma and extracellular fluid is unclear. They would not explain why sodium and water are retained in congestive heart failure in association with increased distention of the atria and other "low-pressure" areas of the lesser circulation.

Patients and animals with compressible arteriovenous fistulas afford a unique opportunity to study the reaction of the kidneys to abrupt dislocations in the circulation. As has been said of the patient with congestive heart failure,[4] the subject with an arteriovenous fistula is literally bleeding into his large veins. When the fistula is occluded, the arterial tree is emptied more slowly and less completely, and mean arterial pressure rises. Pressures in the great veins, the right atrium, and the pulmonary vessels tend to fall as these regions become less distended with blood. Cardiac output is decreased as the heart rate slows and stroke volume diminishes. At

the same time, there is an abrupt increase in the renal excretion of sodium without concomitant changes in glomerular filtration rate or renal blood flow.[19] When the fistula is opened, arteries become less distended and mean systemic arterial pressure falls, while the great veins become more swollen and pressures in the lesser circulation may increase. As this occurs, renal excretion of sodium diminishes markedly. These data suggest that changes in arterial filling or arterial pressure stimulate changes in the renal handling of sodium.[19,20] It may be pertinent in this connection to note that patients with arterial hypertension excrete saline loads much more rapidly than do normotensive subjects.[7,60]

It is interesting to list the circulatory states, chronic as well as acute, in which the kidneys tend to retain sodium. Anemia, hemorrhage, hypoproteinemia, and dehydration are characterized by a decreased total blood volume. During stationary standing, venous congestion of the limbs, partial occlusion of the superior or inferior vena cava, and portal hypertension, filtration from the capillaries is increased and in addition blood is pooled in the peripheral veins away from the general circulation. Constrictive pericarditis, constriction of the pulmonary artery, and congestive heart failure are characterized by distention of the central veins with blood which the heart is unable to pump efficiently into the aorta. In some of the above conditions the volume of blood in the central veins is reduced; in others these vessels are engorged. In all, however, there exists a tendency toward inadequate filling of the systemic arterial tree, either because of a diminished total blood volume or an altered distribution of blood within the vascular system. The latter may have its origin either in pooling or shunting of blood in the periphery or in failure of the heart as a pump. These facts are consistent with the hypothesis that renal excretion or retention of sodium is conditioned by the degree of filling of some portion of the arterial tree. In this view renal retention of salt and water would fall into the same category as a variety of vascular reactions (e.g., the carotid sinus and aortic reflexes) designed to maintain the integrity of the circulation.

The ingenious experiments of Goodyer and Jaeger[27] suggest that some vascular volume, rather than arterial pressure per se, is important in influencing sodium excretion. Arterial pressure was maintained constant in dogs at the level of an outside reservoir of blood to which the animals' arterial system was connected. When a ganglionic blocking agent was injected, blood entered the vascular system from the reservoir without changing arterial pressure; this was followed by an increase in the output of sodium from both innervated and denervated kidneys.

A corollary of the idea of a volume receptor located in the arterial tree is the concept that changes in intravascular volume need not follow passively

changes in intravascular pressure. (It may be worth while to point out that this is equally true of afferent arterial receptors for vascular reflexes; if the heart rate responds chiefly to the level of mean arterial pressure, why does it increase along with a rise in mean arterial pressure in the upright position?) The measurement of the distensibility of the great arterial reservoir *in vivo* presents almost insuperable difficulties. Nevertheless, Remington, Noback, Hamilton, and Gold[81] have adduced evidence, based on measurements of cardiac stroke volume by the Fick method compared with calculations of simultaneous stroke output from pulse pressure measurements, that the distensibility of the aorta may indeed be decreased in congestive heart failure, a condition in which blood is sequestered in the great veins without necessarily producing a fall in arterial blood pressure, while sodium is retained by the kidneys.

The concept of a volume receptor is perhaps too easily verbalized and visualized; its appeal is seductive. Undoubtedly there is danger in looking for simple and concrete answers to complex problems; it is difficult, as Wolf has remarked, to avoid casting one's lot with that of a neat idea. Yet the question of volume regulation is a real one; it cannot be begged by mere descriptions of the filtration and reabsorption of sodium and water by the kidneys. If the Hunt for the Volume Receptor is to proceed on a firmer footing than the Hunting of the Snark, it behooves the careful investigator[84] to observe more stringent standards than that of the Bellman in Lewis Carroll's poem:

> "Just the place for a Snark," the Bellman cried
> As he landed his crew with care,
> Supporting each man on the top of the tide
> With a finger entwined in his hair.
>
> "Just the place for a Snark! I have said it twice.
> That alone should encourage the crew.
> Just the place for a Snark! I have said it thrice:
> What I tell you three times is true."

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