THE VOLUME CONTROL OF BODY-FLUIDS

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Some 60% of the human body consists of water, and the narrow limits between which, in health, body-weight fluctuates indicate the constancy of this fluid component. Osmotic pressures within the body-fluid compartments are predominantly determined by electrolytes. Since cations are fewer in number and more easily measured than anions (some of which are organic and highly labile) this review is to a large extent concerned with the metabolism of sodium (Na) and potassium (K), the predominant cations in extracellular and intracellular fluid respectively.

1. Intracellular Fluid

Calculation of intracellular osmolarity from known cation concentrations arrives at a figure some 40% higher than that of extracellular fluid (ECF). Even so, osmotic equilibrium between the two fluids has been generally assumed, and to explain the apparent discrepancy it has been suggested that a portion of intracellular cation exists in non-ionic form, or alternatively, that a large proportion of intracellular anions are polyvalent. Recently several workers have challenged this assumption. Opie (1956) has observed that kidney and liver slices swell in saline media unless the concentration is at least one-and-a-half times that of physiological saline. Robinson (1950) found that tissues in isotonic media do not swell as long as they respire normally, but that swelling develops when metabolism is inhibited by cold, cyanide, or oxygen lack. These workers believe that the cell normally maintains hypertonicity by the continual active extrusion of water.

However, Mudge (1951) and Leaf (1956) have demonstrated that the fluid entering the cells under these circumstances is not water alone but is isotonic with the medium. Leaf has pointed out that the swelling caused by metabolic inhibition can be explained by breakdown in the active extrusion of Na: intracellular colloid osmotic pressure then causes an entry of isotonic fluid from the medium and it is not necessary to postulate intracellular hyper-osmolarity.

Direct measurement of intracellular osmolarity has yielded conflicting results, apparently because any interference with cell metabolism causes a rapid increase in osmolarity from the breakdown of cell constituents. Perhaps, because of this difficulty, it is wisest to accept the lowest figures, those of Conway & McCormack (1953) who find cell osmolarity identical with that of ECF. Certainly in many circumstances the intracellular space as a whole behaves as if it were in osmotic equilibrium:

i. Potassium deficiency is accompanied by shrinking of the intracellular space (Black & Milne, 1952).

ii. Intravenous hypertonic saline causes a shift of water from the intracellular to the extracellular space (Hetherington, 1931).

iii. A large water load is evenly distributed over both spaces (Leaf, Chatillon, Wrong & Tuttle, 1954; Wynn, 1955).

2. Extracellular Fluid

The control of extracellular volume has recently received much attention, and the subject has been reviewed by Black (1954); Bull (1954); Robinson (1954); and Selkurt (1954).

Relative distribution of fluid between the intravascular and interstitial compartments is determined by the balance between, on the one hand, intracapillary hydrostatic and interstitial oncotic pressures tending to force fluid into the tissue spaces, and, on the other hand, plasma oncotic and interstitial hydrostatic pressures tending to force fluid into the capillaries. This hypothesis was first put forward by Starling (1896) sixty years ago and has recently been experimentally confirmed by Pappenheimer (1951). As interstitial hydrostatic and oncotic pressures are small and fairly constant, the relative amounts of intravascular and interstitial fluid depend on intercapillary pressures over the body and the total circulating plasma protein. The latter is in equilibrium with the general body-protein and returns to normal within a few days when either

TUBULAR SECRETION OF POTASSIUM

Continued from page 9

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depleted by plasmapheresis or increased by plasma infusion (Whipple, 1956), but there is little information on how this constancy is brought about.

Extracellular osmotic pressure is carefully controlled by two delicate mechanisms: thirst, and the osmoreceptor-posterior pituitary mechanism described by Verney (1954). The "drinking centre" of Andersson & McCann (1955) and Verney's osmoreceptor are both situated in the hypothalamus but seem to be anatomically distinct. Increase in ECF tonicity stimulates thirst and the secretion of antidiuretic hormone, decreased tonicity abolishes these effects. Both mechanisms work rapidly and without the overswing of many biological adjustments; the water diuresis following ingestion of water, for example, is usually complete within two hours.

These osmo-regulatory mechanisms are unsuited to compensate for isotonic changes in ECF volume. The relative constancy of ECF volume indicates that the total amount of extracellular solute, and hence of Na, is closely regulated. As Na intake varies widely and extrarenal losses are small, this regulation is brought about by control of urinary Na excretion.

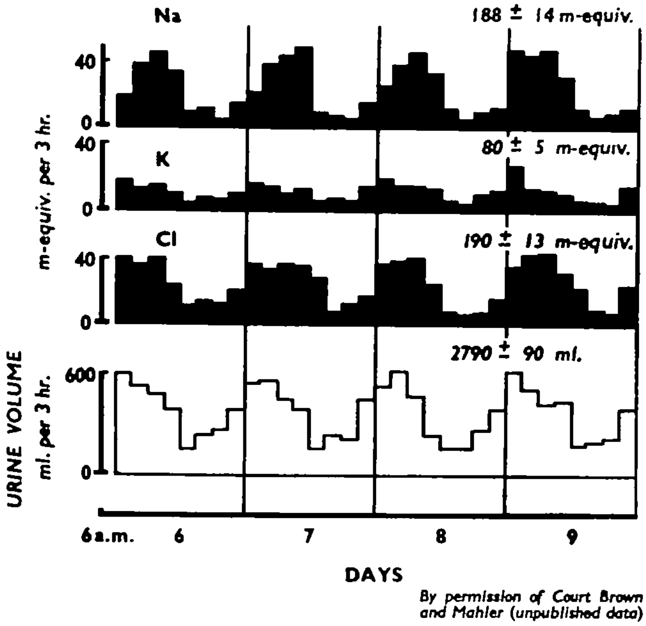
a. Renal Handling of Sodium

Measurements of the rate of Na excretion in the normal individual reveal large, apparently random, variations. Even on a diet of constant Na content Black (1953) has found daily variations in Na balance of the equivalent of as much as a litre of ECF. Important variables affecting excretion are exertion, emotion and posture, and when these are as vigorously controlled as possible a fairly constant pattern of Na excretion emerges after a few days. The results of such an unvarying regime, from unpublished data of Court Brown and Mahler, are shown in fig. 1. The chart shows not only a very constant Na excretion (the day-to-day fluctuations are only one-quarter of those encountered by Black) but also a wide diurnal rhythm in the excretion of the main electrolytes and water. The precise cause of this rhythm is still unknown.

A further difficulty which arises in the study of Na metabolism is the sluggishness of the renal response to sudden changes in intake. Borst (1954) has made use of carefully controlled observations such as those in fig. 1 to examine the effects of intravenous infusions of up to two litres of an artificial "extracellular fluid" (NaCl, 115 m-equiv./l.; $NaHCO_3$, 25 m-equiv./l.). The resulting Na diuresis developed slowly and took up to 48 hours for completion. In the opposite experiment—a very low Na intake—about 48 hours again elapsed before maximal reduction in Na excretion (Black, Platt & Stanbury, 1950; Rosenheim, 1951). But there is great individual variation in the rapidity with which Na balance can be attained, and Gamble (1951) reports one individual who took two weeks to reach equilibrium after an increase in intake of only 5 g. of NaCl daily.

Sodium is excreted by a process of glomerular filtration and tubular reabsorption. Approximately 600 g. of Na are filtered daily, but over 95% of this is reabsorbed in the renal tubules. Consequently an enormous range in Na excretion (over one thousandfold in the case of the healthy kidney) can be brought about by variations of under 5% in filtered or reabsorbed Na. Unfortunately renal clearance techniques are not sufficiently accurate to determine whether normal variations in Na excretion are caused by alterations in filtration or in tubular absorption. In the past, changes in filtration rate were thought to be the more important, but this view was based largely upon experiments on dogs, a species with a very labile filtration rate. In man the filtration rate is fairly constant and is not increased during the Na diuresis which follows isotonic saline infusions (Crawford & Ludemann, 1951; Green, Bridges, Johnson, Lehman, Gray & Field, 1950). Reduced tubular reabsorption must explain the Na diuresis under these circumstances. Black *et al.* (1950) have shown that an increase in tubular Na reabsorption takes place after a few days on a low-salt diet.

FIG. 1. EXCRETION RATES OF ELECTROLYTES AND WATER IN A PHLEGMATIC YOUNG MAN, AT COMPLETE BED-REST, WITH CONSTANT THREE-HOURLY FEEDS OF MILK AND BISCUITS



Observations commenced on 6th day of regime. Figures on right are the means and standard deviations of the daily excretion rates.

Although the kidney has a rich nervous supply there is little evidence that tubular transport mechanisms are under direct nervous control. Renal denervation in the dog has, under some circumstances, led to an increase in Na excretion, but this is associated with a rise in filtration rate which is probably the result of altered vascular tone (Surtshin, Mueller & White, 1952). The most convincing evidence that the renal nerves do not play an important role in Na excretion comes from the experiments of Dempster & Joekes (1953) who showed that dogs in which the kidneys were transplanted (and therefore thoroughly denervated) maintained a normal ECF volume. However, there is considerable evidence that adrenal cortical activity profoundly affects tubular reabsorption of Na.

b. Adrenal Cortex

The adrenal cortex plays a role in the maintenance of ECF volume similar to that of the posterior pituitary in the control of ECF tonicity. Many of the manifestations of Addison's disease are due to shrinkage of the extracellular space following loss of Na in the urine. Sodium loss is not only to the exterior—there is in some cases an increase in intracellular Na which reverts to normal under the influence of cortisone (but not of deoxycorticosterone) (Wilson & Miller, 1953).

Aldosterone is much the most important mineralo-corticoid; it accounts for two-thirds of the Na-retaining activity of adrenal-venous blood and is about 20 times as active as deoxycorticosterone in this respect. Normal subjects secrete such minute amounts that it has not yet been possible to discover whether it is responsible for normal variations in Na excretion; advance in this direction requires even more sensitive methods of assay than those at present available. Intravenous aldosterone has an action which lasts eight hours or more (Thorn, Sheppard, Morse, Reddy, Beigelman & Renold, 1955; Muller, Mach & Naegeli, 1955), and for this reason it seems unlikely that variations in aldosterone production could explain sudden changes in Na excretion following, for example, change from a standing to a lying position. Conversely the slow Na diuresis following intravenous saline could well be explained by a reduction in aldosterone secretion; the well-known differences in the timing of a water and a saline diuresis might be due to the difference between the time needed to inactivate intravenous antidiuretic hormone (one hour) (Klisiecki, Pickford, Rothschild & Verney, 1932) and aldosterone (eight hours).

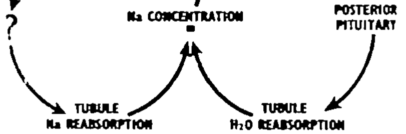
The stimulus for aldosterone secretion is still uncertain. The anterior pituitary does not appear to be necessary (Luetscher & Axelrad, 1954) and corticotrophin causes little or no increase in secretion (Cope & Garcia-Llaurado, 1954). Subjects on a low-salt diet (10 m-equiv. Na daily) excrete increased amounts (Luetscher & Johnson, 1954), but not unless K is provided (Laragh & Stoerk, 1955). Both Na and K would seem to be concerned in aldosterone regulation, but in the case of Na it does not seem to be the serum concentration that matters, rather the volume of some component of the ECF. Hyponatraemia is not necessarily present in sodium-depleted or oedematous subjects excreting increased amounts of aldosterone, and Farrell, Rosnagle & Rauschkolb (1956) have found that haemorrhage increases excretion without lowering the serum Na.

c. *Volume-Receptor Hypothesis*

Peters (1948) and Borst (1948) pointed out almost ten years ago that known mechanisms of body-fluid control could not explain the close regulation of ECF volume. They postulated the existence of a " volume receptor ", sensitive to changes in ECF volume or some closely related function, which regulates Na excretion by control of renal tubular activity. Such a mechanism would dovetail with that controlling extracellular tonicity in the manner shown in fig. 2 (from Bull, 1952).

Such a mechanism appears, to me, to be required to explain the constancy of ECF volume and the failure of changes in glomerular filtration to explain this constancy. There is strong evidence that the role of the question mark in fig. 2 is taken by the adrenal cortex. The chief problem remaining is the nature of the volume receptor itself.

FIG. 2. POSSIBLE MECHANISM FOR THE CONTROL OF EXTRACELLULAR FLUID VOLUME



Bull (1952) by permission of J. & A. Churchill

The circulating plasma is the most vital part of the ECF and the one most extensively investigated in this respect. Robinson (1954) has summarized the procedures which affect both the circulation and Na excretion. Generally speaking, Na excretion is increased by manoeuvres which increase the blood pressure or central circulatory volume: infusion of isotonic or hypotonic saline, lying down, compression of the legs by elastic bandages, or the closure of an established arterio-venous fistula (Epstein, Post & McDowell, 1953). Sodium excretion is decreased by procedures which diminish blood volume or cause pooling in the extremities: haemorrhage, passive standing, and obstruction of venous return from the limbs. Some of these last procedures—for example haemorrhage (Rydin & Verney, 1938)—also cause antidiuresis, probably through stimulation of the posterior pituitary.

Peters, Welt, Sims, Orloff & Needham (1950) and Cort (1954) have described a salt-losing state in certain forms of intracranial disease. This suggests that the volume receptor might lie within the skull. Experimentally, Viar, Oliver, Eisenberg, Lombardo, Willis & Harrison (1951) have found evidence for this: they inflated venous-occluding cuffs around the necks of seated subjects and found an increase in Na excretion. These results have not been confirmed by Bull (1954). Barbour & Bull (1954) have also reduced the cerebrospinal pressure by lumbar puncture without change in Na excretion.

The thorax has also received attention as the possible site of a volume receptor. Sims, Welt, Orloff & Needham (1950) have described a group of " pulmonary salt-wasters "—patients with various pulmonary lesions and symptomless hyponatraemia. Drury, Henry & Goodman (1947) and Sieker, Gauer & Henry (1954) used breathing under positive and negative pressure in a search for a receptor on the low-pressure side of the pulmonary circulation. No changes in Na excretion were observed, but breathing against a low pressure caused a water diuresis, and breathing against raised pressure, an antidiuresis. Henry, Gauer & Reeves (1956) have shown, in dogs, that this water diuresis is probably mediated by stretch receptors in the left atrium.

Bull (1954) has explored the possibility that the volume receptor is a chemo-receptor sensitive to changes in partial pressures of the respiratory gases. If this were so, breathing 10% oxygen or 5% carbon dioxide might be expected to reduce Na excretion. In neither case did this happen, but during CO_2 inhalation there was a moderate water diuresis.

The search for a volume receptor, or receptors, continues. It is worth noting that, if the efferent pathway of volume regulation is through the adrenal cortex, some of these experiments may have been too short in duration to influence Na excretion.

d. *Volume Regulation versus Osmo-Regulation*

The method of volume control envisaged in fig. 2 suggests that extracellular Na concentration and Na excretion do not necessarily proceed in the same direction. There are at least two interesting circumstances where they proceed in opposite directions, and, in a sense, volume regulation overrides osmo-regulation:

i. Black, McCance & Young (1944) found that individuals deprived of water retained Na even though the serum Na rose as a result of haemoconcentration. Elkinton & Taffel (1942) studied more severe dehydration in dogs and found that Na and Cl disappeared from the urine although the serum Na rose by as much as 40 m-equiv./l. Large amounts of intracellular electrolyte (K and phosphate) appeared in the urine. The authors called this the " dehydration reaction " and interpreted it as an attempt to preserve ECF volume at the expense of intracellular water. More recent work of Bartter (1956) has shown that, in man, dehydration is accompanied by an increase in aldosterone excretion, which probably explains the urinary Na and K changes.

ii. Leaf, Bartter, Santos & Wrong (1953) investigated the effects of water retention induced by antidiuretic hormone (pitressin) in man. Water retention caused serum dilution, and falls in serum Na concentration to as low as 116 m-equiv./l.; at the same time there was a marked Na diuresis. Pitressin administration without water retention had no effect on Na excretion. These workers interpreted the sodium diuresis as a response to overexpansion of the body-fluid volume. It is probably mediated through the adrenal cortex; Muller, Riondel & Mach (1956) demonstrated a concomitant decrease in aldosterone excretion, and I found (Wrong, 1956) the expected delay of about eight hours between hydration and maximal Na diuresis.

Conflict between the interests of volume regulation and osmo-regulation was even better seen in the classic salt-depletion experiments of McCance (1936). Here progressive Na loss was at first accompanied by proportionate water loss, and ECF osmolarity was maintained at the expense of volume. When a Na deficit of about 350 m-equiv. was reached, water loss became less and further Na depletion caused hyponatraemia; volume was being preserved at the expense of tonicity. At this stage subjects lost their ability to have a water diuresis. Leaf & Mamby (1952) observed a similar failure of water diuresis in Na-depleted dogs, and demonstrated an increase in serum antidiuretic activity, probably of posterior pituitary origin. From these observations it seems that gross reduction of ECF volume stimulates the posterior pituitary, even in the presence of hypo-osmolarity, the usual inhibitor of the posterior pituitary.

3. Some Clinical Implications

a. Dehydration

Marriott (1947) pointed out that the clinical syndrome of dehydration, with subcutaneous desiccation, inelasticity of the skin, cold extremities and hypotension, indicates shrinkage of the extracellular space and hence loss of Na.

Paradoxically a pure water deficit does not, unless very severe, result in the clinical picture of dehydration: thirst, oliguria, and raised serum concentrations of Na and Cl are earlier signs. The thirst and posterior pituitary mechanisms are so efficient that, in temperate climates, a severe water deficit can develop only when one or both are damaged by disease:

i. In untreated diabetes insipidus, even when access to water is free, a considerable water deficit may develop with serum Na concentrations as high as 165 m-equiv./l.

ii. In any patient unconscious for a long period from any cause there is a danger of a water deficit. These patients cannot experience thirst, their attendants may have difficulty ensuring an adequate fluid intake, and water loss may be increased by fever or a complicating diabetes insipidus. The syndrome is not uncommon and cases have been reported by Allott (1939) and Higgins, Lewin, O'Brien & Taylor (1951). Unfortunately it is seldom recognized for what it is. Higgins *et al.* were impressed by the combination of hyperchloraemia and low urinary Cl—the dehydration reaction of Elkinton and Taffel—and interpreted the metabolic abnormality as a disturbance of Cl excretion.

b. Oedema

Most of the symptoms of congestive heart failure are due to retention of Na and expansion of the extracellular space. Although this may lead to further circulatory embarrassment it is probably mediated by the over-action of physiological mechanisms which normally maintain ECF volume, and is in the nature of a compensation for a failing circulation. The exact feature of circulatory failure which leads (by the hypothetical volume receptor) to Na retention is still unknown. In nephrotic and cirrhotic oedema, Na retention may arise by a similar mechanism, but here it is excessive loss of intravascular fluid into the tissues which stimulates Na retention. In all three forms of oedema there is a marked increase in aldosterone excretion (Luetscher & Johnson, 1954), and in nephrotic oedema this returns to normal if corticotrophin treatment results in a Na diuresis (Luetscher, Deming & Johnson, 1952). But excessive secretion of aldosterone alone cannot explain oedema in these diseases for, of the patients with proved aldosterone-secreting tumours, none has shown oedema, though they excrete even more aldosterone; moreover all have presented with K deficiency (Conn & Louis, 1956).

When depleted of Na, oedematous patients behave as normal subjects do. At first water is lost pari passu with Na; at a later stage water loss may not keep pace with Na loss, and hyponatraemia develops (the usual form of " low-salt syndrome "). These subjects lose their ability to have a water diuresis, and their serum contains increased amounts of an antidiuretic substance, probably of posterior pituitary origin (Leaf & Mamby, 1952). Laragh (1954) and Cort & Matthews (1954) have shown that some of these patients are K-depleted, with an increase in intracellular Na. The metabolic disturbance is complex; one of the possible causes of K deficiency is the increased secretion of aldosterone, the " secondary aldosteronism " of Conn & Louis (1956).

4. Summary

The delicate equilibrium between the body-fluid compartments poses many unanswered problems for the physiologist. It is clear, however, that the amounts of Na and K in the body, on which extracellular and intracellular fluid volumes largely depend, are closely regulated by the kidney. At present aldosterone is attracting much attention, for it has a greater effect on the urinary excretion of Na and K than any other known physiological variable. The exact stimuli for aldosterone secretion are still uncertain; their discovery will greatly help to solve the challenging problem of oedema.

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