Regulation of Water and Electrolytes

By J. Russell Elkinton, M.D.

To include a discussion of the regulation of total body water and electrolytes in such a symposium on the cardiovascular system at first glance may require some justification. It should be quickly apparent, however, that the total body fluids and the circulatory system are so intimately interrelated that consideration of one without the other would be quite incomplete. Part of the body fluids, the cellular fluids of erythrocytes and the plasma, are distributed within the vascular system and constitute the medium, so to speak, upon which the circulatory system operates. Being that which is circulated, these fluid phases are an integral part of the circulatory system. Likewise the circulatory system is essential to the integrity of the fluids of the body. The circulation provides the mixing apparatus that maintains the homogeneity of multiple and widely separated portions of the body fluids and the circulation is the link of the organs of exchange with the external environment. It would seem proper, therefore, to include water and electrolytes in this discussion of regulation of the cardiovascular system.

The concept of regulation as already defined by our moderator can be applied to the body fluids as well as to the rest of the cardiovascular system. In the consideration that follows, I shall attempt to show not only that physiologic servomechanisms are operative but that a great deal remains to be learned of their modus operandi. The emphasis will be on the holes in, rather than the substance of, our knowledge.

Evidence That the Total Body Fluids are Regulated

Let us begin simply by considering the 2 major dimensions of any fluid, including body fluids, namely, concentration and volume. It has been known for many years that the total concentration of solutes, or osmolality, of plasma and extracellular fluid is maintained within rather narrow and constant limits. This constancy of osmolality or toneity was one of the features of the milieu interieur of Claude Bernard. It holds in amphibians, birds, and mammals and has been the subject of much investigation in the field of comparative physiology. On the other hand, constancy of volume of the body fluids has received relatively little attention until recent years. In 1916 that very shrewd observer of natural phenomena, L. J. Henderson, presented before the National Academy of Science a short note on the importance of volume in biology in which he pointed out that at a given level of development the maintenance of a constant volume is one of the basic properties of living organisms. Evidence for this phenomenon in our own bodies is to be found in the constancy of our body weights. Since body water constitutes such a large proportion of body weight, rapid fluctuations in the latter must approximate changes in the former. This is true, of course, only if concomitant changes in body fat are not being induced by neurogenic or iatrogenic dietary manipulations, or by the more natural processes of growth or senescence.

On one occasion I measured my own basal body weight daily for 56 days; the 2 standard deviation variations about the mean did not exceed ±1 per cent. This observation suggests that my total body water content was being regulated. In figure 1 are shown, again in myself, the oscillations in weight that occurred within one recent 24-hour period. On this Saturday away from the hospital, intake of food and fluid at breakfast was followed by considerable loss of body water and salt during the heavy exercise of cutting grass. At lunch a large thirst as well as hunger led to a copious intake; this was followed by a less
rapid loss of body water during an expedition with my young son to the zoo. A mid-afternoon oscillation (dotted line) occurred due to ingestion of peanuts and root beer but was unmeasured. Intake at dinner was succeeded by a slower rate of loss during the evening and sleep. At the end of the 24-hour period my body weight had changed by only a plus 0.2 Kg. while the total weight flux was 5.6 Kg. (2.9 in, 2.7 out). These oscillations approximate the fluctuations of total body fluid and delineate very nicely the operation of intake and output servomechanisms that regulate diurnally the volume of my total body water.

These servomechanisms are the main subject of my contribution to this symposium. It is a subject of concern to the physician as well as to the physiologist and biologist. In disease, servomechanisms go wrong; the result is a sick patient requiring diagnosis and treatment. The primary pathogenic factor may be a lesion of the heart, the kidney, the adrenal cortex, the brain, or other organ; the result may be one or more disturbances in volume or osmolar concentration that we label congestive heart failure or edema, or dehydration, or hypernatremia or hyponatremia, and so on. But proper therapy needs an understanding of the servomechanisms involved in the patient’s disturbed homeostasis. Let us as physicians consider these mechanisms of regulation.

Regulation of Water Relative to Solute

Osmolal regulation through the neurohypophyseal antidiuretic hormone (ADH) system is perhaps the best delineated servomechanism in the physiology of body fluid. The classic experiment in support of this mechanism was that of Verney,2 who demonstrated that hypertonic solutions of sodium salts or sucrose, but not urea, infused into the arterial blood supply of the hypothalamus of the dog would inhibit a pre-established water diuresis to the same degree as a known amount of pitressin (fig. 2). From his observation Verney postulated that there must be receptor cells, sensitive to osmolar changes in the extracellular fluid bathing them, that control the rate of release of antidiuretic hormone (ADH) from the posterior pituitary. These sensitive loci he designated “osmoreceptors,” and he presented evidence that they responded to changes in osmolar concentration of the order of 1 to 2 per cent.

It is now possible to characterize this servomechanism that regulates body water content relative to solute content (fig. 3). The stimulus on the afferent side of the arc is change in the total concentration in extracellular fluid or plasma of solutes that do not readily penetrate cells, (or, more precisely, change in the concentration of water). The effect of this stimulus on the receptor center is to alter the rate of release of an efferent humoral mediator,
antidiuretic hormone. This hormone, ADH, produces in the effector organ, the kidney, a change in rate of tubular reabsorption of water, and hence the rate of water output. The result is a modification of the original osmolar stimulus—in cybernetic terms, correction of an error by negative feedback.

It must be pointed out that a variety of other stimuli act on the neurohypophyseal system to produce changes in the rate of release of ADH. These stimuli, listed in table 1, strongly suggest that the hypothalamic center is subject to signals from areas of the central nervous system above the diencephalon. The experimental observation that changes in volume somewhere in the intravascular portion of the extracellular fluid also affect ADH release, is important and is discussed below.

So far we have discussed a servomechanism that regulates water content relative to solute only by regulation of water output, i.e., through adjustment of overflow through the kidney. The kidney, however, can never make up a deficit; equally important and essential to the maintenance of a steady state is the regulation of water intake. Although thirst, the effector system that leads to drinking, is a complex physiologic mechanism, there is no doubt that one of the principal stimuli is a rise in osmolar concentration. The receptor center for this stimulus again is in the hypothalamus adjacent to and, indeed, overlapping the area containing the osmoreceptors controlling ADH release. Figure 4 indicates that water regulation involves dual integrated servomechanisms operating on both intake and output of water. As in the case of ADH release, stimuli other than extracellular osmolar concentration stimulate thirst; these include habit patterns, conditioned reflexes, oral sensations, and changes in volume of extracellular fluid and perhaps of intracellular fluid as well. This dual mechanism for the regulation of body water relative to solute, however, is only part of the story. Unless the latter also be regulated, the body might swell to the point of bursting or shrink to the point of desiccation according to the fortuitous vagaries of solute content, the osmolar concentrations being maintained within constant limits. Regulation of solute content, therefore, is primary to regulation of the water or osmolar concentration if the volume of body fluids is to remain constant.
Table 1

Osmolal Regulation. Factors Affecting the Rate of Release of Antidiuretic Hormone

<table>
<thead>
<tr>
<th>Stimulation:</th>
<th>H2O reabsorption ↑</th>
<th>H2O reabsorption ↓</th>
<th>(H2O excretion ↓)</th>
<th>(H2O excretion ↑)</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ Osmolal concentration in extracellular fluid</td>
<td>↓</td>
<td>Volume: extracellular and intravascular fluid ↑</td>
<td>Emotion</td>
<td>Alcohol</td>
</tr>
<tr>
<td>Exercise</td>
<td></td>
<td></td>
<td>Sleep</td>
<td>Inhalation CO2</td>
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<tr>
<td>Sleep</td>
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<tr>
<td>Nicotine</td>
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</table>

Regulation of Solute Content, and Hence of Volume

The servomechanisms subserving this body fluid parameter are much less clearly understood than are those involved in osmolal concentration. And yet the reason for suspecting their existence is compelling, namely, the constancy of body weight to which I alluded at the start of this presentation. What is known of this servomechanism?

John P. Peters in 1935⁵ pointed out that the excretion of sodium, the principal extracellular electrolyte, must somehow be responsive to changes in volume of the extracellular fluid, most probably to some intravascular portion of that fluid phase. Subsequently Borst⁶ in 1948 suggested that the renal secretion of sodium is related to cardiac output. Since then a host of investigators have provided evidence that changes in intravascular fluid volume and hemodynamics induced in the head, the thorax, the abdominal cavity, or the extremities will lead to changes in rate of excretion of sodium and water; some of these factors as experimentally demonstrated are listed in table 2 (modified from Robinson⁷). Although it is apparent that considerable uncertainty obtains in both the afferent and efferent portions of this regulatory circuit, it is possible to construct a tentative schema to outline the servomechanisms that must be involved, (fig. 5). The stimulus must be a change in volume at one or more loci in the circulatory system. Changes in pressure in the left atrium have been shown to lead to changes in the rate of water excretion.⁸ This reflex appears to be dependent on continuous pulsatile stretch of the atrial walls and the afferent nerve fibers are carried in the vagus.¹⁰ In contrast, changes in excretion rate of sodium rather than of water are produced by alterations in pressure in, and stretch of, the right atrium and great veins, apparently through the mediation of aldosterone.¹¹ In view of the variety of conditions that lead to changes in sodium excretion it is most probable that the degrees of filling of the vascular tree in both the venous and the arterial sides are stimuli in multiple receptor sites. From these receptor sites afferent neural pathways must lead to an integrating center in the central nervous system, again location unknown.

The efferent arc has been the subject of considerable recent investigative activity; the effector organ is the kidney but is the mediator humoral or neural or both? Changes in rate of aldosterone secretion have been shown to be affected by experimental alterations in extracellular fluid, and especially in plasma volume.¹² Cross-circulation experiments to normal dogs from dogs with constricted inferior vena cavae (an experimental preparation known to lead to increased secretion of al-
Table 2

<table>
<thead>
<tr>
<th>Stimulation</th>
<th>Inhibition</th>
</tr>
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<tbody>
<tr>
<td>Na reabsorption ↑</td>
<td>Na reabsorption ↓</td>
</tr>
<tr>
<td>(Na excretion ↓)</td>
<td>(Na excretion ↑)</td>
</tr>
<tr>
<td>↓ Volume: extracellular and</td>
<td></td>
</tr>
<tr>
<td>intravascular fluid ↑</td>
<td></td>
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</tbody>
</table>

Experimental

Hemorrhage, shock Intravenous hypotonic saline in water loaded subject

Upright posture Intravenous isotonic saline

Cuff on proximal portion of limbs Supine posture

Abdominal compression Compression neck

Balloon in inferior vena cava Lowering central venous pressure in congestive heart failure with digoxin

Constriction inferior vena cava

Intravenous hyperoncotic albumin solution Compression of legs by elastic bandages

Table 2

Volume Regulation. Factors Affecting the Rate of Sodium Excretion

dosterone have demonstrated that the trigger to increased aldosterone production in the second dog is a humoral agent. It is not ACTH and, as far as I know, it has not been identified biochemically. Hence in figure 6 it is labeled X hormone, although some workers have called it glomerulotropin. These experiments, of course, suggest that 2 humoral mediators (one from the adrenal cortex) are involved in the efferent arc of this regulatory circuit. On the other hand, there are some further observations that cast doubt on the role of an adrenocortical steroid as the sole efferent mediator. Some of the experimental manipulations of fluid volumes, such as production of intracranial congestion or rapid infusion of hypotonic saline solutions, have been shown to be equally natriuretic in patients or animals with diseased or absent adrenal glands. Such observations have led to the postulation by Dr. Homer Smith of an antinatriuretic hormone ("ANH") that perhaps is elaborated in the neurohypophysis and acts directly on the renal tubule. These findings also have raised again the possibility of a direct neural efferent pathway to the kidney. Only 2 experimental studies in support of such neural pathway will be cited. One is the finding that a completely denervated kid-

Figure 5

Regulation of sodium content and extracellular fluid volume by sodium output.

ney, as transplanted from an identical twin donor, does not respond in a normal way to some of the experimental volume manipulations listed in table 2. The other is the demonstration in the dog with experimental congestive heart failure that injection into one renal artery of an epinephrine-norepinephrine antagonist will lead to unilateral changes in sodium excretion by that kidney, thereby suggesting interference with the action of an abnormal sympathetic tone. In view of the variety, if not the contradictory nature, of a plethora of experimental evidence, we must conclude that much remains to be learned of the servomechanisms involved in the regulation of sodium content and volume of extracellular fluid.

Integration of Volume and Osmolal Regulation

Nevertheless, from what has been presented we may feel sure of the existence of servomechanisms for regulation of these functions or dimensions of the body fluids. That the primary mechanism for regulation of sodium content and volume of extracellular fluid must be closely coordinated with the secondary mechanism of osmolal concentration, or water relative to solute, hardly needs to be said. In figure 6 the relationship is presented schematically of these double regulatory circuits. On the left is shown that which concerns sodium content and fluid volume; a possible but undemonstrated circuit involving
appetite and sodium intake is indicated by a broken line. Nothing has been said previously about a servomechanism for regulating intake of sodium because essentially little is known about such a mechanism; the kidney may operate only on overflow of an entirely fortuitous intake of this solute. In any case, the output regulatory circuit operates through the kidney as effector organ with an effferent mediator that is either neural or humoral (as shown) or both. The secondary regulation of the amount of water relative to the amount of solute, or osmolal concentration, is presented on the right in figure 6. The principal stimulus, change in osmolal concentration, acting on a single or on several closely integrated hypothalamic receptor centers, effects a change in water intake through thirst and in water output by mediation of the antidiuretic hormone acting on the kidney. In addition, the receptors in these 2 circuits are directly stimulated by changes in volume of some portion of the extracellular fluid;\(^3,4,18,19\) other stimuli from higher levels in the central nervous system must play only an occasional and intermittent role in this regulation. This schema as presented is deceptively oversimplified but represents in broad outline the general plan and relationships of these 2 dual integrated servomechanisms that are responsible for the regulation of water and solute content of the extracellular fluid of the body.

Some of the Things That We Do Not Know

These are many, and their appraisal is conducive to humility. Such appraisal perhaps is best conducted within the frame of reference of the concepts of cybernetics or information theory as outlined by our moderator in his introduction to this symposium.
Figure 7
Possible transfer functions of the osmoreceptor.

Let us first consider the mechanism of osmolar regulation, since of the 2 servomechanisms that we have been discussing this is the more clearly delineated. Is the hypothalamic osmoreceptor one cell or a large number of cells in an area? Is the response to an osmolar stimulus a graded response per cell or is it an all-or-none response that produces a graded total efferent signal according to the number of cells responding? Does the stimulus act on synapses or on neurones? What are the transfer functions in the osmoreceptor? A possible schema for such is shown in figure 7. Here it is suggested that a change in extracellular osmolar concentration produces (via an osmotic shift of water) a change in receptor cell volume; the volume change at least transiently alters pressure, which in turn results in stretch of the cellular membrane. The stretch is then converted into an information signal, presumably electrical in nature. This sequence, of course, is almost entirely speculative, for there is very little direct experimental evidence in its support; it is quite possible that the change in osmolar concentration produces a signal in some other way. Some of my colleagues, however, have established that neurones growing in tissue culture undergo changes in volume when the osmolar concentration of the surrounding medium is altered; currently they are investigating the possibility that differential volume changes between dendrites and axon hillock may lead to alterations in electrical potential of the cell. Almost everything remains to be learned of the conversion of a change in osmolar concentration into a signal of information.

And given such an information signal, it must then be compared, if a self-correcting servomechanism is operative, with an ideal or "normal set" value in order to quantitate the error that needs to be corrected. In the case of body fluid osmolar concentration the normal set value is a phylogenetic inheritance that is much the same throughout most vertebrate species. How it functions in the osmoreceptor is quite unknown. If change in volume due to osmotic shift of water is the critical transfer function, then the normal value must be set by the amount of osmotically active solute present inside the receptor cell. Some years ago we hypothesized that an alteration in this factor must be responsible for the abnormal set of the osmoreceptor-ADH system in certain patients with persistent hyponatremia or hypo-osmolality of their body fluids. But we are totally ignorant of the factors in health or disease that condition the quantity of osmotically active intracellular solute in these particular receptor cells.

In any case, the error having been measured, an efferent information symbol (y' in figure 7) must then be further integrated with the signals from other efferent stimuli from volume receptors and from the cerebral cortex. The resultant modified information (y") is then sent out on the efferent areas of both the intake and output-regulating circuits. No attempt is made to list here the many questions concerning the efferent mechanism of thirst or concerning the mode of action of the antidiuretic hormone in the renal tubule.

Turning to the regulatory system for extracellular solute content and hence for volume we find an even greater number of unanswered questions. The uncertainties about the precise stimuli and the sites of reception of those stimuli have already been set forth. The transfer functions of such volume receptors are also a matter of conjecture. There is more direct experimental evidence than in the case of osmolar regulation to support a volume...
pressure \rightarrow stretch sequence fig. 8 in the volume receptors in the right atrium,\textsuperscript{11} the left atrium,\textsuperscript{8} and in other loci in the arterial system.\textsuperscript{7,22} Wherever and however initiated, information signals must be integrated with each other somewhere in the central nervous system, presumably the hypothalamus. Again that information must be compared with an ideal or normal set value in order to measure the error to be corrected (fig. 8). Of the mechanism for maintaining the normal "set" and making this comparison, I have not the faintest clue. But the error is determined and the resultant modified information is then sent out over an effenter arc of which we have only fragmentary knowledge of a humoral portion. Truly, we have much to learn.

There are ancillary areas of ignorance that should at least be mentioned. Throughout this discussion we have stressed the control of circulating hormone levels solely in terms of production of the humoral mediating agents. The rate of destruction of humoral agents also may be an important factor in regulation. At any given moment the amount of hormone present in the circulating blood stream is a function of both the rate of production and the simultaneous role of destruction. This concept complicates our inquiry and extends our uncertainties. Another puzzle that is related to our subject is the role of electrolytes, and especially of sodium, in the wall of arterial blood vessels. To what extent, and how, is arterial wall sodium related to the complicated regulations of total peripheral resistance and peripheral blood flow that have been detailed by previous speakers? These, too, are questions awaiting answers.

Table 3

<table>
<thead>
<tr>
<th>Extracellular</th>
<th>Intra-Cellular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma Volume</td>
<td>Volume integrity</td>
</tr>
<tr>
<td>Na</td>
<td>H\textsubscript{2}O</td>
</tr>
<tr>
<td>Integrity of Circulation Exchanges with Environment</td>
<td>Integrity of Cellular function</td>
</tr>
</tbody>
</table>

Conclusion

Regulation implies an ideal function or a homeostatic goal, as it were, on the part of the organism. This is not teleology but biologic fact, although Drabkin\textsuperscript{23} has pointed out how very imperfect most homeostatic mechanisms are. If we define the homeostatic goals of the organism in terms of maintenance of its integrity, we can attempt to fit the regulations that I have been discussing into the general homeostatic scheme (table 3). Regulation of extracellular solute content and volume supports the plasma volume, and this in turn is essential to the integrity of the circulation. On the circulation depends all the multifarious exchanges between the organism and the external environment. Regulation of water relative to extracellular solute, or osmolar concentration, on the other hand, directly affects the volume of fluid inside cells by means of the osmotic shift of water. The other factor that conditions the volume of intracellular fluid is the amount of osmotically active solute present inside the cells; but the regulation of this factor lies outside the purview of our symposium. In any case, regulation of cell volume must be essential to proper cellular function. So the 2 servomechanisms that we have been discussing contribute to the integrity of the organism by subserving both its cellular function and its exchanges with the external environment—an ample excuse for their inclusion in the present discussion.

Summario in Interlingua

Regulation presuppone un function ideal, un obiectivo homeostatic (a si dicir) del parte del organismo. Isto non es teleologia sed facio biologie,
ben que Drabkin ha signalate le extreme imperfection
del majoritate del mehismos homeostatique. Si nos
defini le objectivos homeostatique del organismo ab le
puncto de vista del mantenencia de su integritate,
nos pote interponder le tentativa de visualisar le
tie-discusitate typos de regulation—illo del agua e illo
del electrolytos—in un schema de homeostate general.

Le regulation del contento extracellular de soluto e
del volume del liquido extracellular supporta le
volume del plasma, e isto—de su parte—es essential
pro le integritate del circulation. Omne le multiple
formas de exambio inter le organismo e le ambiente
externe depende del circulation. Del altere latere, le
regulation de agua in relation al solutos extracellular,
o le concentration osmotal, affece directamente le
volume de liquido intra le cellulas per le agentia
del transition osmotic de agua. Le altere factor que
conditiona le volume de liquido intracellular es le
quantitate del osmoticamente active soluto que es
presente intra le cellulas (sed le regulation de iste
factor non es parte del thema formulete pro le
presente symposio). In omne caso, le regulation del
volume cellular debe esser essential al normal func-
tion cellular. Assi le duo servomehanismos discutite
in le presente analyse contribue al integritate del
organismo per le facto que illos es subserviente al
function cellular e al exambio del organismo con
le ambiente externe, e isto es plus que adequate como
justification de includer los in le presente symposio.

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