OSMOLARITY DISORDERS OF THE BODY FLUIDS

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The development of rapid and precise methods for the measurement of the concentration of several important electrolytes has done much to elucidate the nature of body fluid disorders and to improve their treatment. Much of this work, as far as clinical problems is concerned, stems from the development about 15 years ago of the flame photometer as an instrument suitable for routine use.², ⁸, ¹⁹

There is, at the present time, an impressive list of new biochemical techniques which promise to extend even further the potential usefulness of the clinical laboratory in water and electrolyte problems. I need mention only a few of these, for example, apparatus designed to be automatic or semi-automatic, new electrode systems to measure sodium, pH and respiratory blood gas tensions with an ease and precision better than before, and atomic absorption spectroscopy with its promise of greatly extending the range of elements of clinical importance which can be readily measured by spectral analysis. Together with this flowering of biochemical techniques there are also impressive recent advances of a physiological, biochemical, pharmacological and clinical nature which concern the general subject of water and electrolyte balance. The discovery by Simpson and Tait¹¹ of aldosterone, the work designed to elucidate this hormone’s control,⁶, ²⁰, ³ the discovery of new diuretics and a whole host of useful synthetic steroids, the development of new methods for treating renal failure, hepatic failure, and the metabolic problems in surgery, are a few examples.

This rapid progress of clinical science poses the question of how to ensure the widest possible dissemination of new knowledge. Doctors can often expect to be confronted with a problem in water and electrolyte balance, albeit as a segment of a wider clinical entity, for example, heart failure, renal disease, or an endocrine disorder. It is by familiarity with general principles, rather than by preoccupation with minutiae or the use of rule-of-thumb methods, that the general physician can best be expected to keep abreast of modern developments and to obtain most benefit from therapeutic advances derived from laboratory work.

A problem which often confronts the clinician is the correct interpretation of laboratory reports. In the case of the electrolytes, plasma estimations are mostly concerned with sodium, potassium, chloride, and bicarbonate levels, although calcium, and now magnesium, are achieving increasing prominence. A great deal can now be said about the significance of changes of the level of each of these electrolytes, but I shall confine my attention in this paper, exclusively to the significance of the plasma sodium level.

The ‘Normal’ Plasma Sodium

In the sense that ‘normal’ implies ‘healthy’, it cannot be said that there is such a thing as a ‘normal’ plasma sodium for a hospital population, however, much care is taken to exclude patients suffering from diseases with known effects upon electrolytes. The failure to appreciate this point reduces the value of several reports upon normal values. Fawcett and I analysed the plasma of 25 healthy young men and 25 healthy young women. We used a laboratory built flame photometer, burning coal-gas and air, and employing light filters and an external standard. With this instrument the coefficient of variation (due to analytical error) was 0.5 per cent., and for duplicate analyses which were employed in the study, 0.4 per cent. We obtained the following results for the ‘normal’ plasma sodium.

| Table 1.—Plasma Sodium Concentrations (MEQ/l) in 25 Healthy Young Men and 25 Healthy Young Women |
|---------------------------------------------------------------|----------------|----------------|
| Mean... | 141.7 | 140.5 |
| Standard deviation (σ) | 1.0 | 1.7 |
| 95% range (m ± 2σ) | 139.7—143.7 | 137.1—143.7 |
| Value of t for sex difference | 3.1 | |
| Probability level for sex differences | 0.001; P < 0.01 |
We concluded that, in healthy young people mostly medical students and laboratory staff), the normal range for plasma sodium was narrow—about 137 to 144 mEq l. and that there was a statistically significant sex difference, women being, on the average, 1.2 mEq l. less sodium than men. This normal range is considerably less than that reported by other workers. We found a tendency for plasma sodium to be lower (by about 2 mEq l.) during the week before menstruation compared with two weeks after the onset of the flow. In individuals, repeated estimations of the plasma sodium level during the course of the day showed remarkably little variation (less than between individuals) and meals, moderate exertion, and posture seemed to be without noticeable effect on this (Table 2). On the other hand, repeated estimations in individuals over a period of six months gave a slightly greater scatter of results which we interpreted as most likely due to systematic analytical errors (Table 3).

The conclusions are that the plasma sodium concentration in healthy individuals falls within a narrow range, that variations within the day in an individual are even less than the variations between individuals, but day to day variations may be somewhat greater than the diurnal variations, most probably due to the effect of analytical error. The only consistent influence on the normal plasma sodium we could detect was a small change which occurred during the menstrual cycle. These conclusions are based upon duplicate analysis and precise work. In routine clinical chemical laboratories duplicates are rarely practical, while the assurance of work may easily impair precision. Under the best conditions, however, repeated plasma sodium estimations performed routinely on hospital patients should not differ by more than 3 to 4 mEq l. in an individual, due to analytical error and random variations alone.

The Plasma Sodium in Hospital Patients

Apart from the effect of analytical error upon the results it is general experience that the usual plasma sodium level in patients is, on the average, lower than in healthy, and nearer 135 than 140 mEq l. The reason for this is not known. Variations of the plasma sodium level about the individual patient's mean value, however, are not noticeably greater than in healthy people, unless the patient is suffering from a disorder involving water and electrolyte balance. In many illnesses there is a tendency for the plasma sodium level to be distinctly low and levels below 130 mEq l occur commonly. If such values persist it is nearly always a mark of serious illness, and the lower the plasma sodium level, generally the worse is the outlook for the patient.

Misleading Plasma Sodium Values

Before discussing the interpretation of the plasma sodium level it is necessary to discuss briefly four possible sources of confusion. The first is frank analytical error. This is difficult to guard against but if the four electrolytes, sodium, potassium, chloride and bicarbonate are determined, it may be possible to detect a gross error in the sodium value by finding an obvious imbalance between the milli-equivalents of cations and anions. The second is contamination of the blood sample. If the sodium salt of heparin is used as an anticoagulant excess of this elevates the plasma sodium level. The third possibility for confusion arises when the plasma solids form a much greater proportion of the whole plasma than is usual (the sodium of course is confined to the water of the plasma). This arises in hyperlipaemic plasma and when plasma protein values are greatly increased. Fig. 1 is an informative demonstration of this problem and shows how much lower the plasma sodium level is in whole, lipaemic plasma compared with the normal values obtained from the analysis of the plasma water of the corresponding sample. Finally, hyperglycaemia causes the plasma sodium to be lower than in normal plasma.

<table>
<thead>
<tr>
<th>Subject</th>
<th>J.F.</th>
<th>V.W.</th>
<th>B.H.</th>
<th>F.O.</th>
<th>T.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of samples</td>
<td>6</td>
<td>10</td>
<td>7</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Mean value</td>
<td>142.5</td>
<td>139.9</td>
<td>142.2</td>
<td>139.8</td>
<td>139.9</td>
</tr>
<tr>
<td>J.F., V.W., and B.H. were ambulatory. F.O. and T.I. were confined to bed. Normal meals were consumed.</td>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subject</th>
<th>K.K.</th>
<th>G.M.</th>
<th>J.F.</th>
<th>V.W.</th>
<th>P.B.</th>
<th>E.L.</th>
<th>E.W.</th>
<th>M.M.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>142.7</td>
<td>141.6</td>
<td>142.7</td>
<td>141.5</td>
<td>141.9</td>
<td>140.5</td>
<td>140.5</td>
<td>141.3</td>
</tr>
<tr>
<td>Range</td>
<td>2.6</td>
<td>1.7</td>
<td>1.7</td>
<td>0.8</td>
<td>1.6</td>
<td>1.0</td>
<td>1.7</td>
<td>1.3</td>
</tr>
<tr>
<td>K.K., G.H., J.F., and V.W. were men, and the remainder of the subjects women.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Some solutes are shared equally between the body fluids for example, urea and creatinine. They therefore exert no influence upon the distribution of body water between compartments and therefore, in this sense, are said to be not osmotically active. The osmotically-active solutes in body water are the electrolytes named above.

The exact reason why the composition of cell fluid and the E.C.F. are so strikingly different is not known. It seems to be a function of the metabolic processes within the cells. The ability to maintain a characteristic fluid pattern can easily be impaired, for example by anoxia, hypothermia, and enzyme poisons. Undoubtedly many disease processes have the same effect. However, so long as the cells function normally the cell membrane can be regarded as being effectively impermeable to electrolytes. Moreover, experiments, which I shall discuss later, show that the cells are freely and rapidly permeable to water. It follows therefore that the cell membrane may be regarded as being semi-permeable, and that the osmotic pressure (or chemical potential) of the body fluids will be determined by the total concentration of impermeable solutes, both unassociated molecules and ions. The total electrolyte concentration must therefore be an important factor in determining the distribution of water between cells and E.C.F., and the extent to which the cells behave as 'ideal' osmotic systems (in the sense of obeying the Boyle-van't Hoff Law) will determine the extent to which other factors need to be considered in this context.

*When a solution is separated from a quantity of pure solvent by a membrane which is permeable to solvent and not to the solute, then the solvent tends to be drawn through the membrane into the solution to dilute it. Movement of solvent can be prevented by applying a certain hydrostatic pressure to the solution. This pressure is called the osmotic pressure. Osmotic pressure is thus defined in terms of certain experimental conditions. It is an expression of a specific physical property of the solution but it comes into existence only when the defined conditions are fulfilled. The osmotic pressure of a solution is proportional to the sum of the individual concentrations of undissociated molecules and ions to which the membrane is impermeable. In the case of the body fluids these osmotically active particles are mostly electrolytes. The unit of osmotic pressure is the milliosmol. Chemical analysis of the solution will give the millimolar value for the solute and this is converted to milliosmos by multiplying by a factor called the osmotic coefficient. An error for incomplete dissociation of the salts and for any other factor causing the solution to depart from the behaviour of an ideal solution. It will be shown that in the case of the E.C.F., since the plasma electrolyte levels mirror closely changes in E.C.F. osmolarity, and since the sodium salts form about half of the osmotically-active solutes of the plasma, it is plasma sodium which reflects changes in the effective osmolarity of the E.C.F.
The Potential of Water in Mammalian Tissues

For more than half a century there has been interest in the problem of whether the osmotic activity of water inside and outside the living mammalian cell is the same, or whether osmotic gradients are maintained, and what influence disease plays in these processes. The problem is extremely complex one to solve by experiment, especially because of the unstable nature of some the intra-cellular solutes, and because pressure-volume changes cannot be directly measured in juice cells unless these are separable, as, for example, is the case with red blood cells, sea chin eggs and similar material. The main lines of investigation have been by direct chemical analysis of the tissues, especially after bathing in fluids of varying osmolarity, by using melting point freezing point depression as an index of the water potential of the tissues, compared with plasma, and by in-vivo methods which may best be described as measuring the osmotic volume of distribution of either water or solutes or both. The results of all these investigations tend to support the idea that the osmotic pressure of cells and extra-cellular fluid is the same. I will describe one of these latter experiments since they have close bearing upon clinical problems and the interpretation of electrolyte results.

Osmotic Volume of Distribution of Water

The effective osmotic pressure of the E.C.F. may be calculated by measuring the concentrations of the individual ions and applying the appropriate correction (osmotic co-efficient) to show for incomplete dissociation of the salts. Usually, in the case of the E.C.F., since mostlyivalent ions are involved, a close approximation of the effective osmolarity can be achieved by measuring only the cations, and multiplying the count by two. If water alone is added to the body fluids and there is no change in electrolyte balance the amount of other osmotically-active material, assuming free distribution of the added water throughout the already existing body water, the cation concentration of the E.C.F. should fall by the amount predicted by simple dilution. This experiment has been carried out in dogs and in dogs and man. The results confirm that added water is distributed equally over total body water, even when the degree of dilution is extreme and much below that which would normally be fatal without cardio-respiratory supportive measures. These experiments show that cell membranes are freely permeable to water, and support the idea of osmotic equality throughout the body fluid. They have helped to clarify the nature of certain

hypotonic and hypertonic states in man, especially syndrome of acute water intoxication.

Observations upon Acute Osmolarity Changes in Disease

The same principle which underlies the experiment just described can be applied to the more usual clinical situation in which there is a change not only in water balance, but in electrolyte balance as well.

The following argument will show how to predict the changes in the plasma sodium concentration which would follow any given change in water and electrolyte balance.

Let \( A \) represent the total number of osmotically-active solutes in body water (milli-osmoles).

Let \( W \) represent the total body water (litres).

The symbol \([\ ]\) denotes osmolar concentration per litre.

The subscripts 1 and 2 refer to the values before and after a change in the quantity being considered.

Suppose the effective osmotic pressure of cells and E.C.F. is the same, and is represented by \([B]\) which denotes the total concentration of osmotically-active solute particles in milli-osmoles per litre of fluid.

Then at equilibrium

\[
\frac{A_1}{W_1} = \frac{[B_1]}{[B_1]W_1} = A_1
\]
Each point in the graph in fig. 3 represents the observed change in total cation level of the E.C.F. plotted as abscissa compared with the value predicted by means of the osmotic equation (ordinate). Each point represents an observation made in a patient at the end of 24 hours, during which time there has been a large change in the water and electrolyte balance, often involving extreme variations in plasma osmolarity.

It can be seen that the correlation between the observed change in the E.C.F. total cation level and the predicted change is very close and indistinguishable from unity. The metabolic data of these patients are recorded elsewhere.16, 17

after any change in A or W

\[ [\text{B}_2] = \frac{A_2}{W_2} \]

\[ \therefore [\text{B}_2]W_2 = A_2 \]

Now suppose that the change in A is represented by X milli-osmoles

\[ A_2 = A_1 + X = [\text{B}_2]W_2 \]

Substituting \([\text{B}_1]W_1\) for \(A_1\) we have finally

\[ [\text{B}_1]W_1 + X = [\text{B}_2]W_2 \]

It has already been said that the effective osmolarity of the E.C.F. may be taken as twice the plasma sodium concentration, as a close approximation, and therefore for \([\text{B}_1]\) and \([\text{B}_2]\) we may write \(2[\text{Na}_1]\) and \(2[\text{Na}_2]\). The osmotically-active solutes which may alter rapidly in the body (excluding glucose from this argument) are nearly all salts of sodium and potassium with mostly univalent anions. So as an approximate value for \(X\) we may take the algebraic sum of twice the external sodium and potassium balance.

\[ 2(\text{Na} + K) \]

Our osmotic formula may now be written as

\[ 2[\text{Na}_1]. W_1 + 2(\text{Na} + K) = 2[\text{Na}_2]. W_2 \]

and finally

\[ [\text{Na}_1]. W_1 + (\text{Na} + K) = [\text{Na}_2]. W_2 \]

All the measurements necessary to apply the osmotic formula can be made in man. This has been done in a wide variety of clinical situations involving large acute changes of water and electrolyte balance16, 17 and the results are shown in Fig. 3. It can be seen that the observed change in extra-cellular osmolarity (here measured as total cations) agree well with those predicted by a simple osmotic theory.

These observations support the idea that the osmolarity inside the cells is the same as that in the E.C.F. Further studies, the data of which cannot be given here16 show also that acute changes of E.C.F. osmolarity are followed by movements...
ter to equalize the changes and that shifts of
electrolytes play little part in acute osmotic ad-
justments. Movement of electrolytes, however,
y play a part in stabilizing the osmolarity of
body fluids in chronic disorders.
These observations have practical application.
It is not necessary to measure total body water
rectly because knowledge of normal physiology
and clinical judgement will usually suffice to give a
reasonable estimate. Acute changes in total body water
may be assessed from weight changes or from the
urinary balance record if this is accurately known.
Uteral electrolyte balance is readily determined
by measuring the differences between input and output. From
these data one can proceed to elucidate disorders of
osmolarity of the body fluids and prescribe
correctively for their correction. 16
It is worth stressing at this point that the osmotic
characteristics of the plasma sodium gives the same osmotic value to potassium
as to sodium. The loss of large amounts of
potassium from cells causes their osmolarity to
decrease. This may be countered by inward
movement of sodium from the E.C.F., or by an
outward movement of water. In either case the
plasma sodium would fall, but the distribution of
body water would be different in the two eventu-
ties described. The osmotic formula indicates
that hyponatraemia may be the result of excessive
sodium retention, loss of sodium, loss of potassium,
any combination of these disorders. Hyper-
atraemia, on the other hand, results from the
opposite changes, namely, water depletion, sodium
or potassium gain, or any combination of these
changes.
The normal stability of the plasma sodium level
is already been discussed. When acute changes
are observed they have as their explanation some
change in the three parameters which control the
osmolarity and distribution of the body fluids,
ely, the water balance and the sodium and
potassium balance (but see paragraph on mislead-
ence plasma sodium values).

Observations upon Chronic Osmolarity
Changes in Disease
While acute changes in water and electrolyte
balance are quite common, the more usual clinical
situation is a chronic change occurring in a long-
drawn-out illness. The interpretation of these
published osmolarity disorders, and the quanti-
itive relationships between body composition and
concentration of plasma sodium has been
published recently. 4
Edelman and co-workers 4 measured effective
plasma osmolarity, plasma sodium concentration,
body water, and total exchangeable sodium
and potassium in a heterogeneous group of
chronically ill patients. Ninety-eight patients
whose illnesses varied widely, were studied.
Their ages ranged from 27 years to 90 years.
The plasma sodium level was between 108 and 196
mEq/l. These workers’ results are very informa-
tive. They found a close relationship
between the plasma sodium level and the effective
osmolarity of the plasma, as has been already
widely accepted. The correlation coefficient of this relationship was 0.97.
They found a high degree of correlation between
plasma sodium and the fraction
\[
\text{Total body water} = \text{total body sodium} + \text{potassium}
\]
The correlation coefficient of this relationship,
corrected for attenuation, * was 0.92.
These results suggest that total body sodium and
potassium, and total body water are the primary
determinants of the plasma sodium concentration.
This relation seems to hold for the full range of
clinical osmolarity disorders and without regard to
the seriousness of illness. The results support the
idea of a uniform osmolarity throughout body
water and provide no evidence for the occurrence
of ‘shifts’ that of electrolytes, ion-binding, osmoti-
inactivation or activation and similar devices
which have often been invoked to explain these
changes seen in the plasma sodium concentration
in disease.

Conclusion
Observations in animals and in patients now
make it possible to give an integrated account of
concomitant alterations in plasma sodium concen-
tration and body composition. There is a
quantitative relationship between the plasma
sodium level and the total amount of water,
sodium, and potassium in the body. Variations in
plasma sodium can be explained in terms of the
alteration of these three parameters of the body fluids, taking into consideration a few exceptional
situations which would be misleading if over-
looked. These results, if applied to clinical
problems, can do much not only to elucidate the
nature of disturbances in the osmolarity of the
body fluids, but also to suggest ways of preventing
these or treating them if they occur.

REFERENCES
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3. DENTON, D. A., GODING, J. R., and WRIGHT, R. I.

References continued on page 119.

*That is, corrected for errors of measurement.
†That is, in the sense of shifting into an osmotically
inert area. Movements of ions between cells and
E.C.F are not precluded.