SIGNIFICANCE OF THE

BODY FLUIDS IN CLINICAL MEDICINE

SECOND EDITION

ALEXANDER LEAF, M.D.
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(*Second Edition*)

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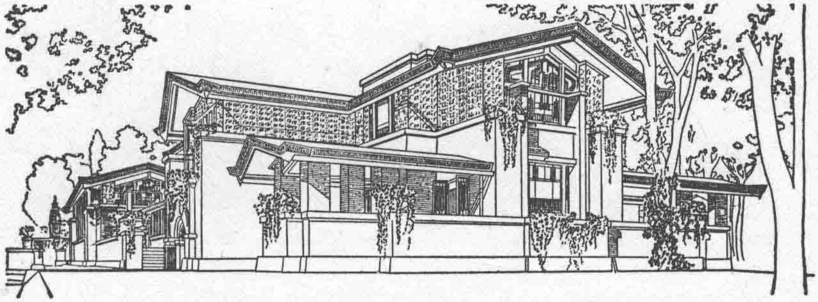

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FOREWORD

MUCH OF THE material presented in the First Edition was delivered at Portland, Oregon in the summer of 1946 as the *Ernest A. Sommer Memorial Lecture* by one of us (L.H.N.). Dr. Sommer hoped that the speakers would select as their topic, some advance in physiology or pathology that could be applied in the practice of medicine. The author tried to comply with Dr. Sommer's purpose by first describing the characteristics of extracellular fluid, and then by showing how this knowledge would increase the understanding of diseases and would be a useful basis for many therapeutic endeavors.

Since a portion of the extracellular fluid is contained in the plasma, it is easily accessible for examination, whereas information about the intracellular fluid is obtainable only by indirect approaches. Accordingly knowledge about the extracellular fluid, especially in its clinical aspects, became rather extensive, while information about changes in cell fluid that occur in disease was still meager. Recently, however, some far reaching data concerning disturbances in the cell fluid of great clinical significance have been obtained. This information is included in the present lectures.

Claude Bernard seems to have been the first person to sense the physiological importance of the extracellular fluid. He predicted that subsequent investigators would find that the composition of this fluid was kept in a nearly constant state in health, and that this constancy of composition was essential for normal cellular function. Subsequently, Lawrence J. Henderson substantiated Bernard's surmise and showed that this fixed composition was maintained largely by the activity of the kidneys. D. D. Van Slyke and his associates studied the details of the mechanism whereby the respiratory apparatus, by altering the rate at which carbon dioxide is exhaled, can avoid large shifts in the reaction of the plasma.

These investigations had been conducted by chemists, and their findings were published in a language that was foreign for most clinicians. However, James L. Gamble, the Harvard pediatrician, appreciated the significance of this new chemical physiology and realized that the data obtained by analysis of the plasma would elucidate many obscure clinical states and point to rational therapeutic procedures. We clinicians owe Gamble* a debt for his demonstration that acquaintance with the features of the extracellular fluid is of very great value to both the surgeon and the internist in the management of his patient. D. C. Darrow deserves our thanks for showing how changes in cell fluid composition can be measured and evaluated.

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* Gamble, J. L.: Chemical Anatomy, Physiology, and Pathology of Extracellular Fluid. Cambridge, Harvard Univ. Press, 1947.

CONTENTS

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Body Fluids
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Clinical Medicine

PHYSIOLOGY

CLOSE to 60 per cent of the human body consists of a dilute watery solution of inorganic ions and organic compounds. In the adult this amounts to about 50 liters, of which 35 liters are within the cells and the other 15 liters are in spaces outside of the cells. This Extra-cellular Fluid consists of about 12 liters of interstitial fluid and 3 liters of blood plasma.

Functional Units

In order to appreciate the physiological significance of the components of a body fluid, it is necessary to think about the chemical entities in terms of their activities. The weight of a substance tells us nothing about its conduct in a living organism. However, there is a functional vocabulary whose employment increases one's conception of what is going on so greatly that I appeal to those of you who are not familiar with it to listen to the following rules.

The first condition to be defined is "Equivalence." Imagine these solutions: One gram molecule, that is, the weight in grams corresponding to the molecular weight, of NaOH, KOH and HCl, has each been dissolved in enough water to make 1 liter. The molecular weights are, for NaOH, Na$(=23)$ + OH$(=17) = 40$; for KOH, K$(=39)$ + OH$(=17) = 56$; for HCl, H$(=1)$ + Cl$(=36) = 37$. So the three solutions, each precisely one liter in volume, will contain, respectively, 40 grams of NaOH, 56 grams of KOH and 37 grams of HCl. Solutions containing 1 gram molecule of a substance are called molar solutions, and they contain one mole of the substance. When equal volumes, say 1 ml. of the alkaline

NaOH solution is mixed with 1 ml. of the acid HCl solution, they neutralize each other. The same result is obtained when 1 ml. of the alkaline KOH solution is mixed with 1 ml. of the HCl solution. The two alkaline solutions show the same combining power or the same activity for equal volumes. Each contains the same number of active particles per unit volume, but the weights of the substances per unit volume are not the same. Since 1 mole of NaOH exhibits the same combining power as 1 mole of KOH, they are "equivalent" mole for mole. Hence 1 equivalent of any of the three substances is 1 mole of the substance. It is evident that the comparison of the two alkalies in terms of their equivalence brings us much closer to what we want to know about their presence in living systems than does the comparison in terms of weight. Carrying this conception a step further, it is evident that 1 atom of Na is equivalent to 1 atom of K or H. That is, 1 equivalent of Na = 23 grams, of K = 39 grams, of H = 1 gram.

Substances react also on the basis of their valence. The chemicals mentioned thus far are all univalent. But Ca (atomic weight = 40) is bivalent, that is, 1 mole of Ca, which is 40 grams, possesses twice the combining power of 1 mole of Na. Hence 1 mole of Ca is 2 equivalents of Ca, or 40 grams of Ca is equivalent to 2 x 23 grams of Na, and 1 equivalent of Ca weighs 20 grams.

A second type of activity with which we must concern ourselves is entitled "Ionization." When poles of different electrical potential are immersed in a solution of sodium chloride, the particles of Na move through the solution to the relatively negative pole and the particles of Cl migrate to the positive pole. Such charged entities are called ions. Ions that migrate toward the negative pole are named cations. Na is a cation. Ions that migrate toward the positive pole are labeled anions. Cl is an anion. The + sign as a superscript means "cation."

The — sign indicates "anion." Some molecules become completely dissociated into their ions when they are dissolved. All the substance has then broken up into its ions. Thus NaCl, when dissolved, is dissociated completely to Na^+ and Cl^-. Other molecules, for example $H_2\ CO_3$, become only partly ionized, the remainder continuing to exist as the molecule. Molecules that dissociate are spoken of as electrolytes.

Water, itself, is ionized to a minute degree into H^+ and $(OH)^-$. These two ions are necessarily present in equal numbers in water. This state is called neutrality. An excess of hydrogen over hydroxyl ions in a solution produces the condition designated as acidity; the opposite relationship is called alkalinity. Measurement has shown that the concentration of hydrogen ions in pure water equals $\frac{1}{10{,}000{,}000}$ of an equivalent of hydrogen per liter.* (Necessarily the water also contains $\frac{1}{10{,}000{,}000}$ of an equivalent of (OH) per liter.) Expressed exponentially, this fraction is written, 10^{-7}. Furthermore, concentration is expressed in chemical shorthand by [ ]. Hence hydrogen ion concentration $= \frac{1}{10{,}000{,}000}$ of an equivalent becomes $[H^+] = 10^{-7}$. Finally further simplification results in the substitution of "p" for the complete logarithmic expression, that is, 10^{-7}, becomes merely 7. So hydrogen ion concentration $= 10^{-7}$, becomes pH $= 7$.

It should be noted that, for example, $pH = 8 = \frac{1}{100{,}000{,}000}$, that is, the $[H^+]$ is now less than in pure water. Since $[OH^-]$ has increased proportionately there

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* Since the atomic weight of hydrogen is 1, pure water contains $\frac{1}{10{,}000{,}000}$ of a gram of hydrogen ions per liter.

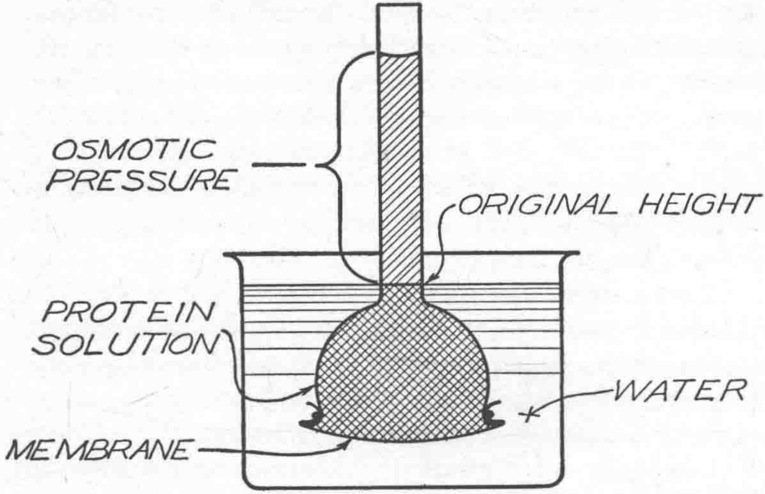

Figure 1. Osmotic Pressure. A sheet of collodion permeable to water but impermeable to protein is fastened over the mouth of a funnel. It is then placed stem up in a beaker containing water, and a solution of protein in water is poured down the stem until the two fluid levels coincide. Water flows from the outside of the funnel through the membrane into the protein solution, causing fluid to rise in the stem. When equilibrium is reached, the length of the column of liquid in the stem above the water level in the beaker is a measure of the osmotic pressure.

is an excess of $[OH^-]$ over$[H^+]$, and, therefore, the solution is alkaline.

We are equally concerned with an activity of a third kind, namely, "Osmotic Pressure." When pure water is separated from a solution by a membrane permeable to the water but impermeable to the particles in the solution, water moves across the membrane into the solution. The attractive force causing this flow, that is, the osmotic pressure, is proportional to the number of particles in solution. One equivalent of a univalent element, for example, 23 grams of sodium, exerts a pressure of one osmol. But in the case of a bivalent element, two equivalents are required to obtain one osmol. Forty grams of Calcium = 2 equivalents = 1 osmol.

Further, since the number of particles in solution per gram of the substance is inversely proportional to the molecular weight, it is evident that a gram of NaCl exerts a vastly greater pressure than a gram of protein. For example, if one compares a hypothetical protein of molecular weight = 300,000, with NaCl, $\frac{300,000}{59} = 5102$, it is found that per equal weights, the osmotic pressure of the NaCl is more than 10,000 (2 x 5102) times as great as that of the protein.

Since the biologist is concerned with relatively small amounts of chemical substances he finds it convenient to record the values in milliequivalents and milliosmols, that is, one thousandth of an equivalent or osmol.

Composition of Body Fluids

We are now ready to examine the Extra- and Intracellular Fluids by means of diagrams. The Extracellular Fluid constitutes the Blood Plasma and the Interstitial Fluid as shown in Figure 2. Each fluid is described in terms of a double column. On the left side are the cations, Na^+, K^+, Ca^{++}, and Mg^{++}, each assigned a length of column equal to its milliequivalence per liter. On the right, the anions are designated according to the same plan. You will notice that the only important chemical difference between the interstitial fluid and the plasma is the presence of 16 mEq. of protein in the latter. These two fluids are separated by the capillary wall which is permeable to all of the constituents of both fluids other than the plasma proteins. Hence the only effective (net) osmotic pressure between plasma and interstitial fluid is that exerted by the plasma proteins. The hydrostatic pressure in the arterial part of capillaries is greater than the osmotic pressure of the plasma protein and net movement of fluid out of the vascular compartment and into the interstitial spaces occurs. At the venous end of capillaries the hydrostatic pressure is low and the osmotic pressure of the plasma proteins acts unopposed to draw fluid from the interstitial spaces back into the vascular compartment. The presence of the serum proteins within the vascular compartment thus serves to maintain a continuous circulation and mixing of all of the extracellular fluids. The pumping action of the heart which circulates about 25 per cent of the extracellular fluid volume through the vascular compartment affords the energy for this continuous process of mixing and replenishing the fluid environment of the body cells.

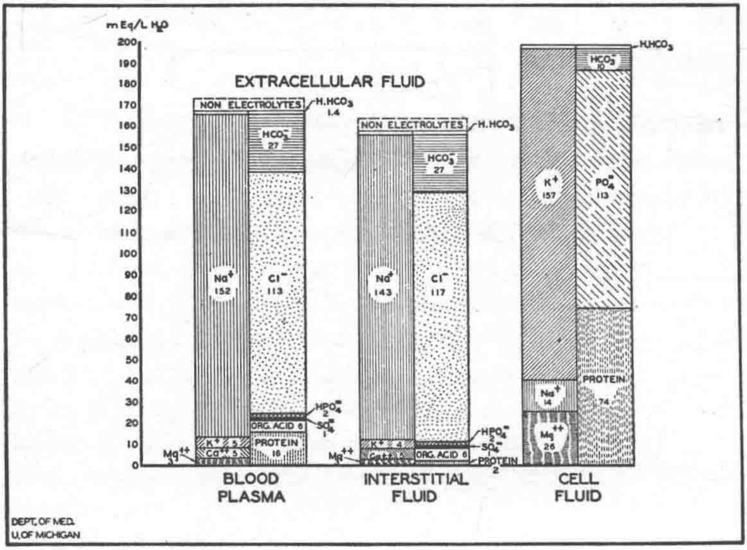

Figure 2. Composition of Body Fluids.

Figure 2 shows that the plasma is somewhat more concentrated than the interstitial fluid, and that the cell fluid is more concentrated than the plasma. This is due to the presence of protein on one side of a membrane impermeable to it. Donnan has presented equations which permit one to calculate the concentrations of the ions on each side of the membrane when a state of equilibrium has been attained. This is the so-called "Donnan Equilibrium." It may be visualized as follows: A rigid box whose walls are made of impermeable materials is separated into equal compartments by a membrane impermeable to protein but permeable to Na^+, Cl^- and H_2O. The volume of each compartment is 1. Compartment (a) is filled with a solution of Na proteinate and compartment (b) is filled with a solution of NaCl. A tight lid is then applied. Since protein does not cross the membrane, an equivalent amount of Na^+ will continue to be present in compartment (a). However, since no Cl^- is present in (a) at the beginning, some of it will diffuse into (a) from (b) and this will be accompanied by an equivalent transfer of Na^+ from (b) to (a). When equilibrium has been established, compartment (a) will contain some Cl^- and an amount of Na^+ that equals the sum of the equivalences of the protein and the Cl^-.

The fundamental equation of equilibrium is:

$$[Na^+]a[Cl^-]a = [Na^+]b[Cl^-]b \qquad (1)$$

This is solved as follows: let original concentration of Na proteinate = P; let original concentration of NaCl in compartment (b) = M. When equilibrium has been established, an amount, F, of NaCl has diffused from (b) to (a);

then

$$\begin{aligned}[Na^+]a &= P + F\\ [Cl^-]a &= F\\ [Na^+]b &= M - F\\ [Cl^-]b &= M - F\end{aligned}$$

Substituting in equation (1):

$$\begin{gathered}(P + F)\ F = (M - F)^2\\ PF + F^2 = M^2 - 2MF + F^2\\ F(P + 2M) - M^2 = 0\end{gathered}$$