METABOLISM
in Health and Disease

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'He shoots higher that threatens the moon, than he that aims at a tree.' (HERBERT)

PREFACE

This monograph was written in competition for the Rogers Prize of the University of London; the closing date for entry was April, 1951. It is essentially therefore a critical review of work on sodium metabolism published up to the end of 1950. Research in this field is very active, and the more significant contributions which have since been published are referred to in a number of footnotes. The essay itself has been left as originally presented, since even a scientific monograph may aspire to some degree of unity of composition, which would be impaired by piece-meal reconstruction.

I shall not indulge myself in that species of casuistry which attempts to persuade the reader that a review of some particular field is of permanent value; for the tide of increasing knowledge makes nonsense of such pretensions. My more modest hope is that workers in this field may be directed to original publications which they may have overlooked in the maze of scientific writing; and that others of more general interests may be glad to have a review of a subject which is related to such diverse medical disciplines as biochemistry and practical therapeutics.

My interest in sodium metabolism was first aroused by reading R.A. McCance's Goulstonian Lectures. I have since had the privilege of working with him for a time, and of discussing problems with him on occasion. I take this opportunity of expressing my appreciation of his unique contribution to our knowledge of sodium metabolism.

I am greatly indebted to my chief, Professor Robert Platt, for having allowed me every facility both in the preparation of this monograph, and in research over the past few years. I have had the advantage of many fruitful discussions with him and with other members of this unit.

I am grateful to Professors J. L. Gamble and H. W. Smith for permission to reproduce diagrams; and to Dr. R. W. Ollerenshaw and Mr. J. Kilshaw of the Department of Medical Photography, Manchester Royal Infirmary, for their help in this and other publications.

Finally, I am grateful to the University of London for awarding me the Rogers Prize, and for permitting publication of this review.

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THE fiscal behaviour of governments is not commonly distorted by scientific prejudice; and so the prevalence of a salt tax in non-maritime countries demonstrates that the claims made for the importance of sodium in the human economy do not stem merely from the preoccupation of specialists with their own subject-matter. There is moreover a mass of more direct scientific evidence that an adequate intake of sodium is an essential of animal and human nutrition. Admittedly, simple dietary deficiency of sodium is so well compensated by diminished urinary excretion of sodium that adverse effects may be long delayed; but prolonged animal experiments have shown that a diet containing only traces of sodium is ultimately fatal (Orent-Keiles, Robinson, and McCollum, 1937). When active steps are taken to deplete the body sodium by sweating or forced vomiting, a characteristic syndrome of salt depletion quickly appears.

Any enquiry into the biological importance of sodium must be highly speculative, in view of our ignorance of intracellular metabolism, and the variations which certainly occur in the permeability of living membranes to electrolytes. On the gross chemical level, what we know of the distribution of sodium within the body enables us to assign it a prominent place in the maintenance of the volume, osmotic pressure, and acid-base composition of extracellular fluid. This type of biochemical function could be undertaken by any cation of similar valency and reactivity which did not easily penetrate into tissue cells. A rather facile explanation of the fact that it is sodium which subserves these particular functions is that of Macallum (1926), who suggested that the extracellular fluid of mammals represents a well-preserved specimen of the Palaeozoic ocean from which their ancestors emerged. This internal milieu protects the tissue cells from the constant variation implicit in a terrestrial as opposed to a marine environment. From this point of view, the regulation of plasma sodium can be equated with the regulation of the osmotic pressure of body fluid, and it is this aspect of sodium metabolism which has been most extensively studied, and is probably of most biological importance. There are clear indications, however, that sodium does not function merely as an osmotically active cation; if that were so, it should be replaceable by potassium, which is similar to it in chemical activity, and even in atomic structure, since there are seven electrons in the outer active ring of both elements (Findlay, 1942). It is well known since Ringer's classical studies in 1883 that potassium cannot replace sodium in perfusion fluid, and that a strict balance between these two ions has to be maintained. Similar effects on cardiac action and neuromuscular irritability can be observed in the intact animal when potassium is added in excess to the bloodstream. Reactions of this type cannot be explained on an osmotic basis, and it is probable that sodium and potassium are essentially different in their relation to the electrical phenomena of polarisation at membranes. This difference could only be formulated in the language of physical chemistry, and neither the basic data nor their valid treatment are within the compass of this essay. This applies also to the possible influence of sodium in stabilising the colloidal state of body proteins, and to the effects of sodium on action potentials in the giant axon of the squid, demonstrated by Hodgkin and Katz (1949).

AMOUNT AND DISTRIBUTION OF SODIUM IN THE BODY

THE total amount of sodium in the body of a man of average size, with body weight 70 kg., is about 2,800 mEq, or 65 g. The figure of 1 g. of sodium per kg. of body weight is thus a reasonable approximation; in obese people the body fluid and sodium content are proportionately less than in men of spare habit. The physiological importance of sodium, so far as is known, derives from its relationship to other electrolytes and its osmotic effects in aqueous solution; both these are more conveniently dealt with when the amount of sodium is expressed as milli-equivalents (mEq.), rather than as milligrams (mg.). Amounts and concentrations of sodium will therefore be expressed in terms of chemical equivalence (mEq. or mM) or osmotic activity (milliosmols), the litre (L.) being used as the unit of volume. In dilute solutions such as the body fluids, sodium is present in the ionised state, so that its concentration in mEq./L. also expresses the osmotic activity due to sodium in milliosmols/L.

It is illogical to discuss the distribution of sodium in the body on an anatomical basis; it is true that the amount of sodium in different organs varies considerably, but such differences are in the main reflections of the varying fluid content of the organs. With the exception of the bones, the location of body sodium is in compartments which bear little correspondence to gross topography, as they interpenetrate the whole body. The intracellular compartment has a firm histological basis, but the extracellular compartment, the main reservoir of body sodium, is only obvious in tissues in which it is distended by oedema. The evidence is conclusive, however, that throughout the tissues of the body there does exist a mass of fluid external both to blood-vessels and to cells, however little it may be apparent in normal tissues. In a few places, such as the lumbar theca or the anterior chamber of the eye, definite collections of this type of fluid are found; and in oedematous tissues the expanded extracellular spaces are readily seen. This extracellular fluid contains most of the sodium in the body.

EXTRACELLULAR FLUID COMPARTMENT

This includes the plasma, within the blood-vessels, and the interstitial fluid, lying between the tissue cells. The concentration of sodium in plasma is about 142 mEq./L., with a fairly narrow normal range of 5 mEq./L. on either side of the mean *. The sodium concentration in interstitial fluid is somewhat higher, about 145 mEq./L., (Darrow, 1945); this difference can be attributed to the greater 'fluidity' of interstitial fluid, which has 993 g. of water/litre, as opposed to 940 g of water/litre in plasma. For an assessment of the total amount of sodium contained in the extracellular fluid compartment, the total volume of fluid within the compartment must be determined. This problem, whose difficulties are obvious, has been approached by determining the volume of distribution within the body of various substances which were thought to be uniformly diffused through extracellular fluid, but not to enter cells. Mannitol, inulin, radio-active sodium and chloride, and sodium thiocyanate have all been used. Sodium and chloride are clearly unsuitable for absolute measurements of extracellular fluid volume, as both are known to enter cells, and sodium is also found in bone

* Sodium concentration in plasma from normal subjects has a normal distribution curve, with 80 % of values falling between 137 and 148 mEq./1., and 98 % of values between 133 and 152 mEq./1 (Wootton, King, Smith, and Haslam 1951, *Biochem. J.*, **48**, *lix*.)

in large amounts; changes in 'chloride space' are currently used in assessing gross changes in extracellular fluid volume. Thiocyanate is known to enter red blood cells, and a correction is applied for this; even so, the method gives results which are probably too high. Mannitol gives results which are sometimes much too high, and at present inulin is the substance whose volume of distribution seems to correspond most closely to extracellular fluid volume. Schwartz, Schachter, and Freinkel (1949) have studied this matter extensively; they found that the volume of distribution of inulin (inulin space) was consistently less than that of thiocyanate, radio-active sodium, or bromide, all of which are known to enter some cells. Accurate results demand a constant infusion technique, rather than a single injection of inulin, as time is needed for the inulin to diffuse uniformly through the extracellular fluid. Their results with this technique in man give an inulin space of 14 to 18 per cent of the bodyweight. This corresponds to a total of 1600 mEq. of sodium in the extracellular fluid of a 70 kg. man. Sodium is the predominant cation of extracellular fluid, amounting to about 93 % of the total base, the remainder being potassium, calcium and magnesium in amounts which are very small relative to sodium. This base is balanced by chloride, bicarbonate, sulphate, phosphate, organic acids, and by protein, as indicated in Fig. 1. The sodium in extracellular fluid seems to be present entirely as sodium ion; the loss of one electron from the sodium atom, giving it a more stable configuration, like that of the inert gas neon, may go some way towards explaining how it is that the fiery element which splutters when cast into water should become so apparently docile a constituent of our body-fluids.

The physiological importance of extracellular fluid can scarcely be exaggerated. It is the immediate environment of the tissue cells, and so it constitutes that 'milieu interne' whose fixity Claude Bernard proclaimed to be a necessary condition for the health of body cells. Constancy of composition of extracellular fluid is

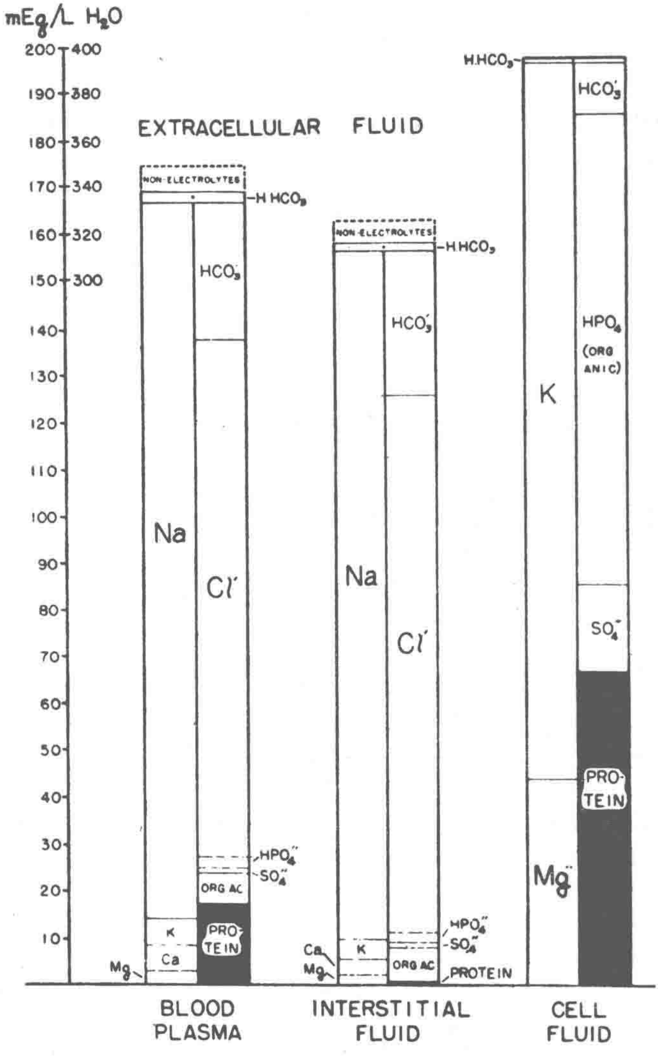

Fig. 1. Comparison of electrolyte composition of blood plasma, interstitial fluid, and cell fluid. (Gamble, 1947).

maintained at the expense of changes in volume, when necessary. For example, an injection of as much as 180 mEq. of sodium as 10 % sodium chloride within 20 minutes led to a change of only 2 mEq./L. in the plasma sodium concentration; the expected rise in plasma sodium from the addition of this amount of sodium to extracellular fluid, had no volume changes occurred, would be about 15 mEq./L. The speed with which this type of osmotic adjustment occurs in healthy people reflects the enormous size of the interfaces between plasma, interstitial fluid, and intracellular fluid. The short-term regulation of the sodium concentration of extracellular fluid is carried out mainly by a shift of water out of the cells when sodium concentration threatens to rise, and into the cells when sodium concentration is falling. Actual transfer of sodium itself into and out of the cells may also take place, but has not been demonstrated experimentally as part of the immediate reaction to threatened changes in plasma sodium concentration. The long-term regulation of extracellular fluid sodium concentration is mainly an intake-output regulation of total body sodium, but balance experiments show that shifts of sodium into and out of the cells also occur. The regulation of total body-sodium will be considered later, and the existence and availability of intracellular sodium will be the subject of the next section.

The main reason for the rather close regulation of the sodium concentration in extracellular fluid seems to be the provision of osmotic stability in body fluid. (This teleological phrasing may perhaps be excused on the plea that in health most physiological changes tend towards survival, and it would be tedious, and perhaps even unconvincing, to explain each time that no purpose lies behind such apparently purposive changes.) The contribution of non-electrolytes to the osmotic pressure of interstitial fluid, and even of plasma, is quite trivial by comparison with that of the electrolytes. Sodium, as we have seen, accounts for 93 % of the total base, so that changes in sodium concentration,