# SODIUM METABOLISM IN DISEASE

SWALES

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J. D. SWALES
M.D., M.R.C.P.
*Professor of Medicine, University of Leicester*



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*But incessant bowls of milk soup gave her no relief because my grandmother sprinkled them liberally with salt (the toxic effects of which were as yet, Widal not having made his discoveries, unknown). For medicine, being a compendium of the successive and contradictory mistakes of medical practitioners, when we summon the wisest of them to our aid, the chances are that we may be relying on a scientific truth, the error of which will be recognised in a few years time. So that to believe in medicine would be the height of folly, if not to believe in it were not greater folly still, for in this mass of errors, there have emerged in the course of time many truths.*

MARCEL PROUST: *Remembrance of Things Past*

# INTRODUCTION

THIS work deals with abnormalities of sodium metabolism that may occur in clinical medicine. It aims to outline our knowledge of how sodium metabolism may be altered by disease. It does not shrink from indicating the large areas of ignorance in the field. This is a subject in which physiology and pathophysiology are intimately linked, and each, therefore, throws light upon the other. Thus, for instance, the modifications of sodium handling produced by standing have much in common with the abnormalities observed in nephrotic syndrome. It is, in the opinion of the author, an archaic practice to include the first-named in a separate chapter upon normal renal physiology. Reference to normal physiological processes occurs, therefore, throughout the work where it is felt to be most appropriate. This involves cross-referral, of course, but if a reasonable analysis of disease processes is to be put forward, complex interactions cannot be neglected. The work represents the author's predilections and prejudices and does not, therefore, attempt to be comprehensive. It includes enough references for the reader to follow up statements made and the evidence upon which they are based. It ought to go without saying that no single volume work could ever record anything but the tiniest fraction of the published work upon any topic. No doubt a different author would have made a radically different selection of publications.

It is hoped that the phenomena described here will be of wide interest. The physiologist may be surprised at the new light that is thrown by pathological disorders upon normal physiological processes. The general physician, too, requires to deal with many problems which require an understanding of sodium metabolism. Much of the material presented here is of relevance to clinical medicine, and there has been major progress in this field, of which the clinician should be aware. This is particularly true of hypertension and renal failure, where the role of the sodium ion is of some practical importance. The retrospective observer cannot help being impressed by the contribution of clinical studies upon dialysed and nephrectomised patients to our knowledge of the part played by the sodium ion in hypertension, and by the way in which such information has supplemented animal work. There can be few better examples of the contribution of clinical research to our knowledge of fundamental physiological processes.

Nevertheless, more long-standing knowledge has to be presented. The need for this is apparent. Every renal unit can witness to the crimes of ignorance which are still committed by otherwise competent clinicians in the management of sodium requirements. A physican who would

never dream of giving propranolol to an asthmatic patient will attempt to "correct" the hyponatraemia of an oedematous patient with an infusion of hypertonic saline: the fluid-overloaded patient with renal failure will be given sodium bicarbonate to treat his acidosis, whilst the saline-depleted patient will be unnecessarily dialysed because of a low glomerular filtration rate. The present work is designed to illustrate the error of such manoeuvres, and to provide a summary of the scientific background to the treatment of abnormalities of sodium metabolism.

*May* 1975 J. D. SWALES

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My wife undertook the daunting task of typing the text and my secretary, Miss Anne Taylor, typed the references. Both operations involved a formidable process of checking and correction. I am also indebted to Mr. Brian Burch of Leicester University Library and his assistants for checking references.

Whilst the opinions and views are my own they inevitably reflect discussions and disagreements over the years with many colleagues: in particular, I am grateful to my colleagues at Manchester and now Leicester, Drs. George Pohl and Herbert Thurston, for helping me through the territory where renal disease, hypertension and electrolyte metabolism meet.

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## CHAPTER I

# HISTORICAL

THE SCHOLAR who seeks evidence of early insight into sodium metabolism in ancient Western literature will be largely disappointed. A search through ancient Chinese writings proves more profitable, and much that anticipates modern knowledge can be found therein.*

In the *Huang Ti Nei Ching Su Wen* (2nd century B.C.) is a description of a balanced inter-relationship between the heart and the kidneys: kidney function according to this text controls and moderates the function of the heart to maintain health. Thus, decreased activity of the kidneys gives rise to overactivity of the heart, which in turn determines the circulation of the blood, and hence the pulse. Salt was classified as a taste associated with kidney function: too much affects the pulse through the mediation of the heart. Thus, in Chapter X, we read: "Therefore, if large amounts of salt are taken, the pulse will stiffen or harden, and his colour will change".

Shunyu I (who died in 147 B.C.) in his description of the case of a Queen Mother of the state of Chhi quotes the rules of the pulse as saying: "When in depth the pulse is full and hard, and when superficially it is full and tight, then the illness dominates the kidneys, and has its seat therein".

The complex relationship between salt, the kidneys and the circulation is still only partly understood. The undisputed priority for the recognition of such a relationship belongs to the Chinese; nothing comparable appears in the Western literature until the end of the nineteenth century with the work of Ambard and Beaujard.

Despite this, the clinical significance of the pulse was recognised in ancient times, although its connection with salt and water balance was not. Such recognition is seen, for instance, in the Smith papyrus, the original of which probably dates from the Old Kingdom of Ancient Egypt, where there is even a suggestion of an association between the pulse and the heart (Sarton, 1953). Strangely, the Hippocratic writings have little to say on the pulse, although this defect was remedied later at Alexandria with the writings of Herophilus. Perhaps a shadowy recognition of abnormalities of fluid balance can be found in the works of Erasistrasus, who described plethora of the organs from overfilling of the arteries. This perceptive observation was later nullified by Galen, who correctly observed the wide spectrum of pulse pressures in disease,

* I am indebted to Dr. Joseph Needham for providing me with a résumé and interpretation of the two Chinese texts quoted.

but incorrectly concluded that the plethoric pulse was therefore of no significance. Despite this, his demonstration that urine was formed in the kidneys and reached the bladder by way of the ureters represented a major advance (Galen, translated 1916). The early Christian fathers regarded human dissection as unacceptable; it was likewise prohibited by Mohammedan law and a dark age in medical history followed.

In the absence of techniques for measuring either sodium or blood pressure, even the interest in anatomy and physiology which developed with the Renaissance failed to achieve any significant knowledge of the role of sodium metabolism in disease. On a purely descriptive level, on the other hand, much had been achieved before technology could provide a basis for understanding. William of Salicet in the 13th century (Major, 1945), for instance, produced a classic description of renal oedema. In the 17th century, in addition to Harvey's description of the circulation of the blood, several classic anatomical studies were published, which laid the basis for subsequent insight. Of particular note is the work of Bellini upon the uriniferous tubules of the kidney and Malpighi upon the renal glomeruli. A more macabre, if equally fascinating study is the report of the autopsy upon the great Malpighi himself, performed by George Baglivi in 1694 (Wepfer, 1724). Malpighi had suffered for many years from renal calculi, bloody urine, palpitations and vomiting, and finally expired after the development of a hemiplegia. Baglivi records the presence of a large cerebral haemorrhage, but also notes that "the heart nearly normal was enlarged in its musculature, and especially the walls of the left ventricle, which equalled the thickness of two digits. . . . The left kidney was free from any blemish: the right on the contrary was observed to be almost one half as small as the left, the pelvis of the latter so greatly dilated that I could comfortably introduce in it two of my fingers". Malpighi clearly died of a stroke, probably secondary to hypertension of renal origin. The presence of a normal left kidney indicates that the hypertension was of renovascular rather than renoprival type (i.e. Chapter XIII rather than Chapter XII), and would not therefore be associated with gross sodium retention. By contrast, Henry Fielding suffered both from the extremes of sodium and fluid retention, and from the variety of remedy offered by his physicians. These do, however, serve to illustrate the deficiencies of pathophysiological knowledge: thus, of the cures tried, the two which were impeccably logical, rapid removal of ascitic fluid by tapping and by sweating, were both life-threatening, whilst the one remedy which gave subjective benefit, tar-water, was unquestionably ineffective, although probably safe; the fourth remedy "the milk diet" appears to enjoy neither a logical basis nor did it confer subjective benefit (Fielding, 1755).

Diabetes or an "abnormal flux of urine" was classified in exhaustive and unreadable detail by Erasmus Darwin (1801), who recognised

proteinuria as one of several possible associations with abnormalities of fluid retention and excretion.*

However, whilst the empirical practice of medicine was proceeding at times falteringly (if lucratively), the basis for a more scientific analysis of sodium and fluid metabolism was being laid. Knowledge progressed slowly at first. Harvey's work was followed a century later by Hales's classic animal experiments in which blood pressure was measured objectively for the first time (Hales, 1733). Another century passed before Poiseuille described his mercury haemodynamometer (Poiseuille, 1828), and it became possible to measure human blood pressure in health and disease. Richard Bright's (1836) classical observations upon the clinical and pathological findings in glomerulonephritis include not only a description of renal oedema, but also demonstrate the association between the granular contracted kidney and cardiac enlargement. He did not consider the two mechanisms for the production of renal hypertension that are currently accepted, i.e. fluid retention and the secretion of a pressor substance by the kidney. Rather, he postulated that blood reaching the heart was abnormal, or that greater action by the heart was required to force blood through the diseased vascular tree. Both of these mechanisms, i.e. anaemia and hypertensive vascular disease are still held to play a role, albeit a minor one, in the cardiovascular abnormalities of renal disease. Allbutt (1896) was the first to distinguish clearly between essential and renal hypertension, and thereby added to the foundations of an understanding of the varying role of sodium retention in different types of hypertension.

Another epoch-making work in a different sphere of science which has contributed enormously to our knowledge of sodium metabolism was, of course, that of Claude Bernard (1878–79). Bernard demonstrated and analysed the stability of the "*milieu intérieur*" and drew attention to the independence from environmental change conferred upon higher organisms by this stability. This work was developed by Macallum (1926), who drew an analogy between the electrolyte concentration of sea water of the remote past and that of the mammalian serum, and suggested that the external environment had been preserved as the internal environment of higher organisms. This imaginative hypothesis is not, however, supported by what is known of the composition of sea water at the time of the evolution of terrestrial life (Conway, 1932). The fundamentals of electrolyte distribution and control had already been worked out before the advent of the flame photometer; particularly noteworthy in this respect are the classical studies of Gamble (1942) on the composition of the body fluids.

The turn of the century witnessed two other major advances in know-

* Darwin's complexities have proved too much for one recent distinguished group who, misinterpreting his use of the term diabetes, find in his work the first description of nephrotic syndrome due to diabetes mellitus (Gellman *et al.*, 1959).

ledge which are of relevance to the present work. That of J. Rose Bradford upon experimental renal failure is discussed elsewhere (Chapter XII); the second study, that of Ambard and Beaujard (1904), was the first to relate salt retention and hypertension. These investigators took a group of hypertensive patients, some of whom probably had primary, and some of whom had renal, hypertension. Blood pressure was correlated with chloride balance during treatment with a low-salt diet. A negative chloride balance was associated with a fall in arterial pressure and loss of oedema. They concluded that chloride retention was a cause of hypertension. This illustrates the pitfalls imposed by the limitations of laboratory technique. The chloride ion could readily be measured by chemical methods and it was therefore tempting to select chloride as the relevant electrolyte, rather than sodium which was not at the time susceptible to laboratory analysis. Much subsequent work has been confused by the similar methodological error of believing that the measurable factor was the relevant one.

It was forty years before Ambard and Beaujard's work was applied on any significant scale with the development of the Kempner rice-fruit diet (Chapter XIII). Study of the role of salt in hypertension meanwhile underwent eclipse. The description of a consistently reproducible technique for the production of hypertension in the dog by Goldblatt *et al.* (1934) led to a revival of interest in the renal pressor substance, renin, which had been extracted by Tigerstedt and Bergman (1898). There was, therefore, little interest in the role of an ion which could only be monitored with extreme difficulty by a lengthy chemical technique. The sodium ion came into its own in the post-war years with the development of the flame photometer. Therapy advanced hand in hand with investigation as progressively more effective diuretics were produced. Animal experiments confirmed conclusions from clinical experience with the Kempner diet, that sodium was involved in some forms of hypertension. Then, long-term dialysis and renal transplantation made it possible for the first time to make prolonged observations upon anephric patients and patients with advanced renal disease. The mass of animal experimentation, whilst illuminating in many respects had failed signally to predict in detail the behaviour of blood pressure in such patients. The past fifteen years have, therefore, yielded fascinating and invaluable studies on man. Initially confusion reigned, due partly to insufficient control of sodium intake in patients on dialysis; latterly a firm place has been found for the sodium ion in the pathogenesis of some forms of hypertension and a beginning has been made in unravelling the complex relationship between the renin-angiotensin system and sodium metabolism. Whilst new clinical and experimental techniques have provided some answers, they have created new and intriguing problems.

Flame photometry and measurement of exchangeable body sodium

by isotope dilution are now firmly established laboratory techniques. Continuous monitoring of sodium concentration by means of a glass electrode and measurement of total body sodium by neutron activation analysis are both experimental techniques that are in research, but not clinical, use at the moment. Great progress has been made in physiological knowledge of the cellular handling of sodium and clinical knowledge of disorders of sodium handling by organs. It is to be hoped that the relatively few bridges between these two approaches will be multiplied in the next decades.

CHAPTER II

# SODIUM CONTENT AND DISTRIBUTION

## The Sodium Ion

The average human body contains about 115 grams of sodium, although the range is wide. Since the atomic weight of sodium is 23 and the valency 1, the equivalent weight of sodium is 23 and one millimole equals one milliequivalent. A value of 115 grams of sodium is thus equal to 5000 millimoles (or milliequivalents). These latter two units of measurement have great advantages over simple weights in discussing handling of sodium by the body and will be used throughout this work. Thus, molality has biological as well as chemical significance. One millimole of an element (say sodium) will combine with one millimole of another univalent element (say chloride), since one millimole of any substance contains an equal number of atoms or molecules. For the same reason, one millimole of potassium moving into the cellular mass will exchange with one millimole of sodium moving out (simplifying the situation by assuming that these two elements are the only ones involved).

Most of the metabolically active sodium in the body is present in solution. The unique properties of water profoundly modify the physical state of sodium when a sodium salt is dissolved. Under these circumstances, water molecules act as a powerful "insulation", reducing the electrostatic forces which bind the atoms together so that positively charged cations (sodium) and negatively charged anions (say chloride or sulphate) are formed. In solution, therefore, sodium is present as a cation surrounded by a "hydration shell" of water molecules orientated round this nucleus. The size of this shell and the presence of the positive charge probably play a role in determining the permeability of biological membranes to sodium; thus pore size and charge may limit the movement of sodium through a membrane.

As we shall see, a fraction of body sodium is bound by a wide variety of body tissues. Even excluding this, however, there are gross inequalities between the sodium content of different body fluids which cannot be explained in terms of simple passive distribution of the sodium ion.

## Sodium Distribution

The distribution of sodium within the body can only be meaningfully considered in relation to the distribution of water. Thus, the fundamental division of body fluid into intracellular and extracellular spaces approximately, but not precisely, coincides with an equally fundamental

division between sodium-poor and sodium-rich fluid (Fig. 1). The high concentration of sodium in the extracellular fluid is largely responsible for maintaining the osmotic pressure of this fluid, performing a similar role to that played by potassium in the intracellular fluid; in addition, the extracellular sodium prevents disastrous cell swelling resulting from the colloid osmotic pressure exerted by intracellular protein which is present in higher concentration than in extracellular fluid. Any change in extracellular fluid sodium concentration, therefore, produces important changes in intra- and extracellular fluid volumes. It is at the inter-

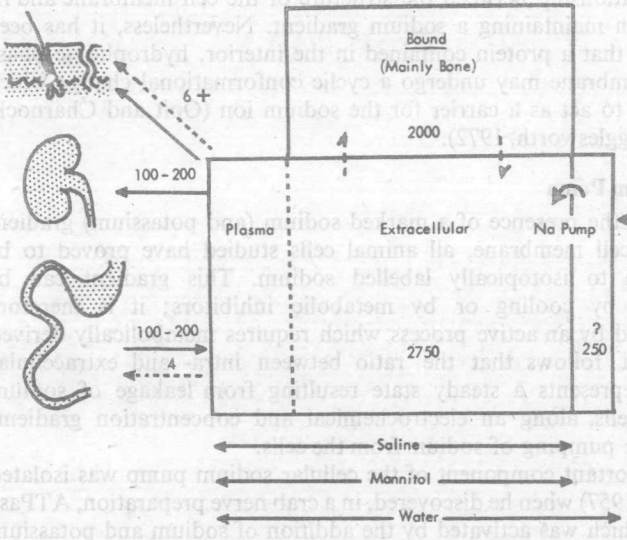


FIG. 1.—Schematic view of partition of sodium in the body. Figures (mmol) refer to total quantities of sodium in body compartments and total sodium movements in a 24-hour period. Approximate volumes of distribution of infused isotonic saline, mannitol and water are illustrated.

face between the two, the cell membrane, that this vitally important electrolyte gradient occurs. It is the activity of this cell component which preserves the fluid compartments of the body from distortion by osmotically induced water movements.

## Cellular Sodium Handling

The cell membrane appears on electron microscopy as a translucent layer sandwiched between two dense layers (e.g. Yamamoto, 1963). Chemically, apart from a small amount of carbohydrate on the outer surface, the membrane consists of lipid and protein. The electron

microscopic appearance conforms with the hypothetical structure proposed by Davson and Danielli (1943) in which a lipid central layer is coated on both aspects by a surface film of protein bound by electrostatic and/or hydrophobic forces. Such a view is almost certainly oversimplified. One important postulated modification is represented by the suggestion that the basic structure is not one of leaflets, but of individual lipoprotein sub-units, possibly in a globular formation or in more than one configuration undergoing transition from one to the other (see Malhotra, 1970 and Wrigglesworth, 1972 for reviews). Little is known of the relationship between the structure of the cell membrane and its function in maintaining a sodium gradient. Nevertheless, it has been suggested that a protein contained in the interior, hydrophobic phase of the membrane may undergo a cyclic conformational change which enables it to act as a carrier for the sodium ion (Opit and Charnock, 1965; Wrigglesworth, 1972).

**The Sodium Pump**

Despite the presence of a marked sodium (and potassium) gradient over the cell membrane, all animal cells studied have proved to be permeable to isotopically labelled sodium. This gradient can be abolished by cooling or by metabolic inhibitors; it is therefore maintained by an active process which requires metabolically derived energy. It follows that the ratio between intra- and extracellular sodium represents a steady state resulting from leakage of sodium into the cells, along an electrochemical and concentration gradient, and active pumping of sodium from the cells.

An important component of the cellular sodium pump was isolated by Skou (1957) when he discovered, in a crab nerve preparation, ATPase activity which was activated by the addition of sodium and potassium to the assay medium. There is now overwhelming evidence that this Na-K-activated ATPase is a component of the cellular pump (Glynn, 1968). Thus, there is a close relationship between the presence of a cellular cation pump and the presence of the Na-K ATPase system in the cell membranes of different tissues from widely different sources. The addition of the cardiac glycoside, ouabain, has a similar inhibitory effect upon both this enzyme system and the sodium pump; intracellular sodium and extracellular potassium ions stimulate both. It appears that Na-K-linked ATPase is a phospholipid-protein complex located within the cell membrane (Bonting, 1970).

Some degree of functional heterogeneity is evident in the sodium pump. Thus, when red cells are exposed to maximally inhibitory concentrations of ouabain, further inhibition of sodium efflux can be obtained by the use of ethacrynic acid or frusemide. The ouabain inhibitable component has been termed "pump I" and the ethacrynic acid component "pump II" (Hoffman, 1966). Pump I has been further

subdivided into one component which is dependent on external potassium, but independent of external sodium, pump Ia, and a second component which is dependent on external sodium, but independent of external potassium (Hoffman, 1966); this may, however, be an artefact related to the composition of the medium in which flux is studied (Welt, 1969).

Apart from its role in maintaining the relationship between body fluid compartments, the sodium pump plays a fundamental role in the specialised function of nervous tissue, muscle, the retina and cochlea, and all the body tissues which are concerned with active fluid transport. In spite of the universal importance of the sodium pump to these vital activities, comparatively little is known of the relationship between abnormalities in, for instance, nervous or muscular function and abnormalities of the sodium pump. Disorders of sodium handling and distribution have acquired clinical importance mainly through the changes they cause in fluid distribution (Chapter 4). Nevertheless, Woodbury (1958) demonstrated an increase in brain cell sodium with a deficiency of adrenal steroids. This change was associated with an increased electroshock threshold, behavioural changes and fits. There is also evidence for increased neuronal permeability to sodium in experimental convulsive states (Colfer and Essex, 1947; Shanes, 1958). It is possible that such changes may be causal since injection of hypertonic saline into the brain ventricles provokes fits whilst injection of other hypertonic fluids does not (Glaser, 1964). Pleasure and Goldberg (1966) showed an association between hypernatraemia and muscle weakness, possibly indirectly through an effect upon muscle potassium content. Such studies are, however, exceptional.

**Total Body Sodium**

For obvious reasons, chemical analysis of the adult human body has been performed on comparatively few occasions. Values for an adult man, however, of about 80 mmol/kg of fat-free body tissue have been obtained (Forbes and Lewis, 1956; Widdowson and Dickerson, 1964). The water content of such bodies is about 700 g/kg fat-free weight. Calculated on a fresh body weight basis, the variation is, of course, much greater, but probably figures of 57·1–67·6 mmol/kg for the body sodium content are representative. These values are based on two patients, one of whom died following 5 days' unconsciousness due to a skull fracture, and the other following myocardial infarction with post-mortem evidence of heart failure (Forbes and Lewis, 1956). Other studies utilising subjects who died of renal failure and drowning have yielded higher figures for sodium content (Widdowson and Dickerson, 1964). The quoted values may also be subject to a technical error in that they were obtained by adding samples from component parts and there is, therefore, a possibility of cumulative error. Nevertheless, the values