CLINICAL PHYSIOLOGY

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FOREWORD

THE fascination of the Medicine of my time, which has made it so exciting to have witnessed the last forty years, has been twofold: first, the rational understanding of the phenomena of disease in terms of physiology, and second, the therapeutic triumphs which although sometimes seeming to arise by chance were only possible on the new background of clinical science.

As a natural and essential accompaniment to these advances there has grown up a generation of younger physicians whose thinking and outlook on illness is essentially physiological. What is more, many of the men who might have been the pure physiologists of this generation went into medicine instead, feeling that the emphasis and interest was shifting from the crude procedures of experimental physiology to the more subtle experiments of nature as witnessed at the bedside, and in the pursuit of their clinical studies it is perhaps not going too far to say that they have in the last twenty years contributed as much or more to the study of physiology as have the physiologists to medicine.

This book is written by men of this generation. Instead of the physiologist picking out those aspects of his subject which he deems to be of interest to physicians, here is the clinician himself speaking mainly of his own contributions to physiology.

The book is long overdue, for the processes which have led up to it have been going on now for many years. It is high time that the fruits of this most fruitful period of clinical science were presented in readable form for the student, the postgraduate and, perhaps above all, for the established physician who realizes that the younger men have been getting ahead of him.

Here it is, and I wish it the success it deserves. I have in the past declined to write forewords and must therefore explain this lapse on my part. This was a venture in which I believed so much, I could not resist the temptation to be associated with it.

R. P.

PREFACE

ONE of the most striking changes in medicine in recent years has been the increasing use of physiology and biochemistry, not only to provide greater diagnostic accuracy, but also to guide treatment. In return, clinicians are making extensive use of their unique opportunities to observe disordered function in disease, and are thereby advancing basic physiological knowledge. For these and other reasons the contributors to this book believe that a good knowledge of physiology is becoming increasingly important in the practice of medicine. Applied physiology and functional pathology have, as yet, little place in teaching, and although there are many good textbooks of clinical biochemistry, there are few dealing with clinical physiology. This book, written by practising clinicians, is an attempt to fill the gap. We have not tried to cover the entire subject but have chosen rather to discuss those aspects which can profitably be presented from a more clinical standpoint than that of the academic physiologist, having in mind the interests of the senior student and postgraduate. Reluctantly, and only after much consultation, we decided not to include a chapter on neurology. This branch of medicine is, of course, firmly based on physiology, and neurophysiology is rapidly expanding in many directions. Unfortunately the time has not yet come when the newer knowledge can be encompassed in a short account designed for the general reader.

Each chapter is divided into four sections. The first and second sections deal with normal and disordered function. The third is an account of the physiological principles underlying tests and measurements used in modern practice. The fourth section, 'Practical Assessment', is essentially a summary of the three preceding sections, to show how the information can be used in diagnosis and assessment. We hope that this section will prove useful in clinical practice by showing how evidence can be built up starting with clinical information and then proceeding to generally available procedures and, if necessary, to special techniques. In some chapters the connection between physiology and practice is so clear that it has been possible to summarize 'Practical Assessment' in almost tabular form. Technical details of tests have not been included, because this book does not pretend to be a manual of 'function testing'. One of the happy results of increased physiological knowledge is that many symptoms, signs and tests

which were formerly empirical can now be rationally explained, thereby increasing the reliance that can be placed on clinical evidence and often decreasing the need for laboratory investigations.

References have not been included in the text. A selection of monographs, reviews and key papers is given at the end of each chapter. We share the belief that students should be encouraged to use the library and we realize also that some more experienced readers will be irritated not to have some statements supported by references in the text. It is unfortunately not practicable to document the text to a degree suitable for both the beginner and the expert. The beginner will find plenty of further reading in the references and the expert should have little difficulty in tracing the source of any point. The style of presentation of the references has been chosen to help both types of readers, the title and length of all works being stated.

Although each contributor has been responsible for the preliminary writing of the section dealing with his special interest, there has been extensive consultation between contributors and editors.

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We are grateful to all those who read the manuscript and who advised us about the style and content of the book. On behalf of the contributors we also thank friends and colleagues for their help. Many people have helped in the preparation; among them we would particularly like to acknowledge the following: the staff of the photographic and medical art departments of the Middlesex Hospital who prepared many of the illustrations; Mr. T. F. Howarth who checked the references; Mr. L. T. Morton who compiled the index. We are grateful to the authors and publishers of illustrations reproduced and acknowledged in the text. As editors, we thank Mr. Per Saugman of Blackwell Scientific Publications for his help in many ways during the publication, and the contributors for tolerating so much editorial interference.

Sir Robert Platt has always been an inspiration to clinical scientists in this country, and we are very grateful to him for writing a foreword to introduce this book.

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Adrenal glands; blood sugar regulation

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CHAPTER ONE

THE BODY FLUIDS

Normal Function

Normal Composition and Distribution

Water is the largest single component of the human body: the average man contains about 45 l. The amount of water in an individual is more closely related to height than to weight, because weight depends greatly on the amount of fat.

The body consists of three components: lean tissue mass, water and fat. Of these, the first two are constant both in relation to one another and in relation to the height of the individual, and only the fat is independently variable. Of the fat, a small amount represents an essential constituent of the body substance, but the major portion is not essential and varies greatly from person to person. As a result a fat person contains by weight proportionately less water than a thin one. In a normal adult male some 60% by weight of the body substance consists of water, but in obese individuals the figure falls to 40%. In general, females contain more fat than males, and accordingly the water content of women is relatively less than that of men. The water content of the body is highest in infancy, falling to adult levels in late childhood, with the sex difference becoming apparent at puberty.

The body water is divided into two main portions, the intracellular fluid and the extracellular fluid. There is a constant exchange of water between these two compartments, and isotopically labelled water is evenly distributed throughout the body water within half an hour of administration. Of these two compartments the intracellular is by far the larger, constituting about 70% of the total body water, and in an average 70 kg. adult measures about 30–35 l., representing some 45–50% of the body weight. The extracellular fluid constitutes only about 30% of the total body water, measuring about 12 l. in the

average subject, and representing only 12–15% of the body weight. This extracellular fluid is further divided into two portions—the extravascular or interstitial fluid which lies outside the blood-vessels in the interstices between the cells, and the intravascular fluid or plasma water. Of the 12 l. of extracellular fluid some 9 l. are in the interstitial space and only 3 l. in the vascular space.

The plasma volume is, of course, much smaller than the total blood volume, which consists of the plasma plus the volume of the erythrocytes, leucocytes and platelets. Under normal circumstances the blood volume is constant, any alterations in red cell volume being compensated for by changes in the plasma volume. Like the total amount of water in the body, the blood volume is related to height, and its proportion in relation to weight varies according to the obesity of the subject. Despite this the blood volume is usually expressed in relation to weight. In a person of average build it is usually about 70 ml./kg. body weight and the plasma volume about 45 ml./kg. body weight, giving absolute figures for the blood and plasma volumes of 5.0 l. and 3.0 l. respectively.

The body fluids differ greatly in their composition (Fig. 1). Intracellular fluid is an integral part of protoplasm and as such contains protein: its main cation is potassium, and its main anions HPO_4^{--} and SO_4^{--}. By contrast, extracellular fluid contains little potassium, its main cation is sodium, and its main anions chloride and bicarbonate. Within the extracellular space, the composition of the interstitial and intravascular fluids is almost identical save in respect of their protein content. Whereas interstitial fluid contains only a trace, the intravascular fluid contains protein in a concentration of 6–8 g./100 ml. (albumin 5 g./100 ml.; globulin 3 g./100 ml.), these plasma proteins playing an important part in the distribution of fluid within the extracellular space.

There is a great difference between the distribution of potassium and sodium in the body. The potassium content of the average-sized person amounts to some 3400 mEq. (133 g.) of which over 95% is in the intracellular fluid at a concentration of 100–110 mEq./l., whilst the remainder is in the extracellular fluid at a concentration of about 4.5 mEq./l. The body sodium content amounts to some 4000 mEq. (90 g.). Nearly half of this is in the bones. Most of the sodium in bone (60%) is not available to the body for day-to-day exchanges, and can be neglected in considering acute changes in sodium metabolism. Of the remainder, some 400 mEq. are in the intracellular fluid at a concentration of about 15 mEq./l., whilst the extracellular fluid contains about

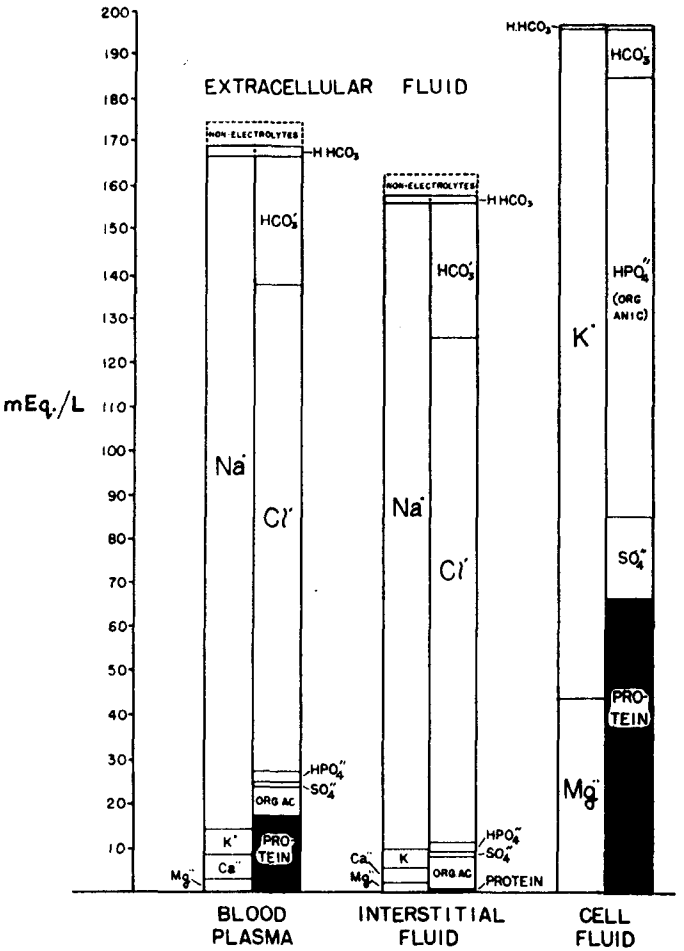

FIG. 1.—*The composition of plasma, interstitial fluid and cell fluid.* Note (*a*) the predominantly extracellular position of sodium; (*b*) the predominantly intracellular position of potassium; and (*c*) the relatively large amount of protein in the plasma compared to very small amount in the interstitial fluid (From Gamble, 1954.)

1600 mEq., at a concentration of 136–148 mEq./l. Ignoring the bone sodium, it is thus true to say that potassium is essentially intracellular in distribution and sodium essentially extracellular.

According to the classical theory of the distribution of water and electrolytes in the body, the location of potassium and sodium respectively within and without the cells is an inherent property of the organism. The cell membrane, whilst freely permeable to water, is relatively impermeable to both potassium and sodium ions, particularly the latter. From this it follows that the distribution of water depends upon the osmotic force set up on either side of the cell membrane. Any change in electrolyte concentration in either the intra- or extracellular fluid leads to a compensatory shift in water from one compartment to the other. It is now clear that this theory is not adequate to account for the known facts. Neither potassium nor sodium is as exclusively intra- or extracellular in distribution as was previously thought. Further, though it may well be that differential membrane permeability plays some part in the intra- and extracellular distribution of potassium and sodium, and that osmotic forces are responsible for many acute changes in the distribution of water within the body, it is also clear that forces other than simple physico-chemical ones are involved in maintaining the normal distribution of water and electrolytes between the two main fluid compartments.

It has been shown by isotopic labelling of sodium and potassium that there is a constant exchange of these ions across the cell membrane, and there is considerable and accumulating evidence that the maintenance of the essentially extracellular position of sodium depends upon a constant, active process of extrusion of this ion from within the cell (the so-called 'sodium pump'). It seems likely that a similar mechanism may be responsible, at least in part, for the intracellular position of potassium, but further investigation is required.

Although no longer thought to be correct, the classical theory remains of importance as a guide in the clinical management of acute disturbances of water and electrolyte balance, and it is of value in focusing attention upon the osmolarity of the body fluids. In normal health osmolarity is maintained constant within narrow limits, and the volume of water in the body may be regarded as being controlled by the amount of electrolytes. Of particular significance is the osmolarity of the extracellular fluid (ECF) which, constituting the *milieu intérieur* of Claude Bernard, bathes all the cells of the body. The

long-term maintenance of the constancy of extracellular fluid composition depends upon the intake and excretion of electrolytes and upon their distribution between the fluid compartments. But in acute disturbances ECF composition depends upon osmotic shifts of water between the intra- and extracellular compartments, the osmolarity of the extracellular space being maintained constant at the expense of its volume. Herein lies the great importance of sodium in the body economy. Constituting over 90% of the extracellular fluid cations, it is osmotically the predominant single ion in this space. Furthermore, whilst losses of the main anion (chloride) can be rapidly replaced by bicarbonate, no ion can replace sodium in the extracellular space. If the concentration of sodium in the extracellular space falls, osmolarity is restored to within normal limits in part by an increased renal output of water, and in part by an osmotic shift of water into the cells, both leading to a diminution in size of the extracellular space. Similarly, if the extracellular concentration of sodium becomes raised, there is an osmotic shift of water from the intra- to the extracellular compartment. Accordingly, except under unusual circumstances, variation in the sodium concentration in the extracellular fluid causes alterations in both the extra- and intracellular fluids.

Within the extracellular compartment, the distribution of fluid between the interstitial and intravascular fluids is dependent upon the plasma proteins. The capillary membrane is freely permeable to both water and electrolytes, so that the osmotic pressure of the electrolytes can play no part in the distribution of water on either side of this membrane. The membrane is, however, almost impermeable to the proteins, so that their osmotic pressure (2 milli-Osmols per litre), though constituting only a small fraction of the total osmotic force of the plasma, is yet of critical importance. At the arterial end of the capillary bed the hydrostatic pressure is sufficient to eject fluid out into the interstitial space. This loss of fluid increases the osmotic force of the plasma proteins which is then sufficient to counteract the lessened hydrostatic force at the venous end of the capillary and cause most of the ejected fluid to return to the vascular compartment. Albumin is of particular importance because its molecular weight (70,000) is much less than that of the globulins (200,000–500,000), and as a result its osmotic activity weight for weight is 3–7 times greater. If the plasma albumin content falls too low oedema may develop. The critical level at which this may occur is usually quoted as a plasma albumin concentration below 2.0 g./100 ml. The lack of strict correlation between the

plasma albumin concentration and the occurrence of oedema indicates that this explanation must be over-simplified, and there is as yet no general agreement on the mechanism of hypoproteinaemic oedema.

As suggested above, the capillary membrane is not completely impermeable to protein, and a small quantity does escape into the interstitial fluid. This, together with any excess of water and other plasma constituents, is returned to the circulation via the lymphatics. This is one of the most important functions of the lymphatics and its failure is another cause of oedema.

The total osmolarity of both the intracellular and intravascular fluid slightly exceeds that of the interstitial fluid (Fig. 1). The slight excess of intravascular electrolytes is due to the presence of the plasma proteins. The excess in the intracellular space is probably due to an active extrusion of water from the cells, for there is evidence that under conditions of oxygen deprivation water accumulates in and distends the cells.

Normal Intake and Output

The body fluids are not static, but are in a state of dynamic equilibrium, large internal and external exchanges taking place continuously. Internally there is a constant interchange of fluid between the various body compartments, and it has been calculated that three-quarters of the plasma water exchanges with the interstitial fluid every minute. Further there is a large and continuous turn-over of fluid in the kidneys and alimentary tract. Every day some 170 l. of glomerular filtrate is formed, and the digestive glands secrete into the alimentary tract about 8 l. of fluid—yet of all this normally only 1–2 l. are lost from the body each day, the remainder being reabsorbed in the renal tubules and intestine respectively.

The size of the external exchanges of water and electrolytes varies from day to day. Governed largely by individual taste and habit, the daily intake of water and electrolytes usually exceeds that necessary to maintain equilibrium in the body fluids, the excess being excreted by the kidneys. To this extent it is impossible to define the normal intake. However, the essential metabolic processes necessitate certain losses from the body which must be replaced if the fluid content of the body is to be preserved. Consideration of these losses enables the essential intake of water and electrolytes to be calculated. These are far less than usually considered normal and desirable.

NORMAL WATER EXCHANGES

Water is normally lost from the body by four routes.

1. *The lungs*

Inspired air is relatively dry, whilst that in the lungs is saturated with water vapour, this saturation taking place largely in the upper air passages by a process of diffusion of water vapour from the lining membranes. The amount of water lost in this way varies according to the temperature and humidity of the inspired air and the pulmonary ventilation, but under normal circumstances in temperate climates amounts to about 400 ml. each 24 hours.

2. *The skin*

Water is lost from the skin in two ways, by the insensible permeation of water through the skin and by sweating. Both these processes are closely bound up with the heat-regulating mechanisms of the body, and the amount of water lost in these ways varies greatly according to the metabolic rate, body temperature, bodily activity, the amount of clothing and the temperature, humidity and circulation of the surrounding air. Under normal circumstances in a temperate climate the daily loss of water from the skin by permeation and sweating combined is 500–1000 ml. per 24 hours, though under other circumstances this figure may be far exceeded. Whilst the loss by insensible permeation is of pure water, sweat contains salt in a concentration about one-third to one-half that of extracellular fluid; but unless sweating is excessive (as in the tropics or during certain illnesses) this salt loss can usually be neglected.

In clinical work the water losses from the skin and lungs are usually considered in conjunction with each other. The maximum rate of loss from the two routes combined is 5% of the body weight per hour, representing in a 70 kg. man a loss of 3.5 l. in an hour. This far exceeds the usual rate of loss which under normal circumstances in a temperate climate amounts to 850–1500 ml. per 24 hours, the minimal loss being 800 ml. each 24 hours. Two facts about this combined loss from the skin and lungs require emphasis. First, neglecting the small salt content of the sweat, the loss is of pure water. Secondly, the loss is inevitable and is outside the control of the water-regulating mechanisms of the body: as such it can be regarded as having first demand on the water supplies available to the body.

3. *The faeces*

Normally some 200 ml. of water are lost from the body each day in the faeces. In normal subjects this loss can be neglected, but in conditions causing severe diarrhoea the loss of both water and electrolytes in the stools may easily reach serious proportions. It is of interest to note that the first observations on the dire effects of large losses of water and electrolyte were made on cholera patients, and that the first recorded use of intravenous saline infusions was also in the treatment of this disease.

4. *The urine*

It is by alterations in the water loss through the kidneys that the water content of the body is controlled. Water excretion is not the sole function of the kidneys, which are also responsible, *inter alia*, for the excretion of various end-products of metabolism, notably urea and excess electrolytes. The minimum volume of water required for these purposes by the kidneys depends on their concentrating power and on the amount of solutes requiring excretion. The maximal urinary concentration of which normal kidneys are capable is 1400 milli-Osmols/l., representing a specific gravity of 1.032–1.035; and by secreting urine at this concentration the kidneys can excrete the normal daily solute load in 500 ml. of urine. If the water intake is so low that the water available to the kidneys for excretion falls below this figure, metabolic end-products accumulate, causing notably a rise in the blood urea concentration. If for any reason the concentrating power of the kidneys is diminished, the minimal obligatory urine volume rises (see Fig. 2). Similarly, if the amount of electrolytes or nitrogenous waste products requiring excretion is increased an increased urine flow is necessary to allow of their excretion. This latter point is well illustrated in cases of severe bleeding into the alimentary tract, in which the sudden increase of absorption of nitrogenous substances is one of the factors causing a temporary rise in blood urea concentration.

Considering together the losses from all these four routes, it is apparent that the minimal daily water loss from the body amounts to about 1500 ml. (skin and lungs, 800 ml.; faeces, 200 ml.; urine, 500 ml.) and that accordingly if equilibrium is to be preserved the intake must be at least equal to this. If the intake is less than this the urine output will fall below the minimal obligatory volume and nitrogen retention will occur. Normally the intake is considerably greater than this figure and the excess is excreted as urine of a concentration well below the