Clinical Physiology

EDITED BY

E.J. Moran Campbell C.J Dickinson
J.D.H. Slater C.R.W. Edwards
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Preface to the Fifth Edition

For the first time this book has five editors. The two new ones are Professor C.R.W. Edwards and Dr K. Sikora, who have also revised, respectively, the chapters on the pituitary gland and that on blood.

One of the problems in preparing another edition of an established textbook is to avoid the stagnation inevitable when the same author is given the task of revising his previous accounts. To prevent this we have brought in a large number of new contributors; but we should like at the same time to thank all those who have contributed to the four previous editions.

We welcome many new contributors to this edition. Dr J. Hamer has helped revise the account of heart and circulation. Dr C.S. Willcox has taken over and revised the renal chapter, and Dr G.J.R. McHardy the account of hydrogen ion and acid-base regulation. Immunology has been comprehensively rewritten by Dr J. Bienenstock and Dr Denburg, and Dr Kelton has helped to update the chapter on haemostasis and thrombosis. Dr Papapoulos has jointly revised the chapter on bone and calcium metabolism, and Dr Lecky the previous account of skeletal muscle. Dr A. McComas has revised the chapter on the nervous system in the control of movement. Dr Mee has brought up-to-date the account of gut, and Dr G.D. Sweeney has rewritten the chapter on the liver. Dr Hardisty has jointly revised the chapter on the thyroid and its disorders, and Dr Winter has taken over and revised the account of genetics.

We are very grateful to our previous contributors who have undertaken very extensive revisions of their previous contributions—Professor R.D. Cohen, Dr J.F. Cade, Dr J. Hirsh, Dr J.L.H. O'Riordan, Dr J.A. Morgan Hughes, Dr C.J. Toews and Professor H.S. Jacobs.

This edition has fewer pages, but a larger format, than the last, and it has been more difficult than ever to be selective enough in all these rapidly expanding fields to avoid the book reaching an unwieldy size. As in all previous editions we have tried to select and emphasize those aspects of normal structure and function which are relevant to clinical practice, and all the contributors are, as they have always been, clinicians as well as physiologists. The style remains as didactic as before, and we have continued to resist the temptation to fill up the book with references, preferring to provide a few key references for further study at the end of each chapter. The book makes no pretentions to provide the last word on any subject. Where subjects are controversial we have tried to indicate this, but some readers may nevertheless feel that we have been at times too dogmatic. However, an account in which every statement is hedged around with escape clauses makes for dull reading.

As before, this book covers no special syllabus. It was originally written to give medical students more background to their studies than textbooks of medicine or of 'pure' physiology commonly provide. We hope that it will continue to furnish such a background. In addition, the bridge it provides between basic sciences and clinical medicine makes it suitable for postgraduates training for the various specialties as well as for practising physicians wishing to review the scientific basis of their practice.

MORAN CAMPBELL
JOHN DICKINSON
WILLIAM SLATER
CHRIS EDWARDS
KAROL SIKORA

Preface to the First Edition

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 neuro-physiology 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.

The Middlesex Hospital
February, 1960

MORAN CAMPBELL
JOHN DICKINSON

Acknowledgements

We are grateful to our contributors, new and old, for their co-operation in this fifth edition. We also thank Mrs D. Blake for preparing the index, and Oxford Illustrators for preparing most of the figures. We acknowledge with thanks the permission of authors and publishers to reproduce those illustrations whose sources are cited in the text. As editors we are again indebted to Mr Per Saugman and the staff of Blackwell Scientific Publications for their help and forbearance.

Contents

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Body Fluids

Normal physiology

WATER

Water is the major constituent of living cells and it is therefore important to consider the special properties that suit it for this role. These properties confer on living organisms an element of temperature stability which is essential if the rates of biochemical reactions are to be controlled, and allow substances of importance in these reactions to be held in solution.

The special features of water are due to the shape of the water molecule, which allows links between the hydrogen atoms of one water molecule and the oxygen atoms of neighbouring ones (so-called 'hydrogen bonding'). One consequence of these links is that, compared with other liquids, an unusually large amount of heat energy has to be absorbed in order to raise the temperature by a given amount. This means that water itself acts as a buffer against temperature changes. Similarly, an unusually large amount of heat has to be used to convert a unit weight of water into vapour. Thus, a given amount of cooling of the animal by evaporation of surface water (e.g. sweat) involves the loss from the body of only a relatively small amount of fluid. The same properties of the water molecule which give rise to hydrogen bonding also confer on the molecule electrical polarity, i.e. the molecule has a positive and negative end. Such substances have a high dielectric constant, which means that they are capable of reducing the electrical attraction between parts of molecules of other substances, e.g. Na^+ and Cl^- in crystals of sodium chloride—water is thus a good solvent for salts. It also dissolves other 'polar' substances (e.g. compounds with hydroxyl or carboxyl groups) by forming hydrogen bonds with them, but does not dissolve 'non-polar' compounds or groups, such as hydrocarbon chains. This principle has particular importance in determining the structure and permeability of cell membranes.

Some biologically important properties of solutions

Most biochemical reactions take place in solution and the speed of such reactions is related to the concentration of the reactants in solution. The relation to concentration is not a straightforward one because particles of a substance in solution, particularly if they are ions, interact electrostatically with each other, usually so as to reduce the

effective concentration. The factor by which the actual concentration has to be multiplied to obtain the effective concentration is known as the activity coefficient, and the effective concentration is known as the activity of the solute. 'Activity' is an apt term because it is closely related to the amount of 'drive' ('chemical potential') that a solute has for taking part in chemical and physical processes. The most important determinant of the activity coefficient in a solution of ions in water is the ionic strength (which is calculated from the concentrations and the valencies of the individual ions), but other factors are involved.

When in clinical practice we measure the amount of a constituent in, for example, plasma, in some instances we obtain actual concentrations and in others activities. Thus, when plasma sodium is measured by flame photometry, the actual concentration is measured. On the other hand, when pH is measured, using the potential generated at a glass electrode, it is the actual 'driving force' or activity of the hydrogen ion that is responsible for the reading obtained.

An important consequence of the concept of activity is the mechanism of osmotic pressure. When, for instance, sodium chloride is dissolved in water, not only is the activity of sodium and chloride ions lowered but so is that of the water itself, and the greater the concentration of sodium chloride the greater the lowering of the activity of water. Thus, if two sodium chloride solutions of different concentrations are separated by a membrane which impedes the movement of the sodium and chloride ion but not that of water, water will flow from the solution of higher water activity into that of lower activity, i.e. from the less concentrated solution into the more concentrated—unless the movement is opposed by a mechanical force equal to the difference in 'osmotic pressure' between the two solutions. These phenomena are fundamental in determining the passage of water across biological membranes.

For most solutes in biological fluids, the solute itself takes up a negligible volume of the solution. This is not so, however, for proteins. In plasma, for instance, the plasma proteins, which are present at a concentration of approximately 70 g/litre, occupy about 5 per cent of the volume of the plasma; thus, a concentration of sodium of 140 mmol/l plasma represents a concentration of 147·3 mmol/l plasma water. This becomes of clinical importance in conditions when plasma protein concentrations are grossly altered, as for example in myeloma or hyperlipoproteinaemia. In these conditions the plasma sodium may appear markedly lowered, with the plasma water sodium remaining normal.

BODY COMPARTMENTS

As the higher animals evolved from unicellular organisms, control of the physical and chemical composition of the cells' external environment became essential. This was not only because of the narrow limits of conditions under which life would be sustained, but also a consequence of cell differentiation. Thus, as organs of different functions within the animal developed it became essential for them to be able to communicate

and interact with each other. Thus, the extracellular compartment evolved, comprising both a circulation and an interstitial space—that portion of the extracellular compartment which lies outside the circulation and lies functionally and anatomically between the circulation and the cells. The approximate water content of the intra- and extracellular compartments in a man weighing 70 kg are shown in Table 1.1.

Table 1.1. Average sizes of body compartments in an adult man

	% of body weight	Litres
Total body water	60	42
Intracellular water	40	28
Total extracellular water	20	14
Interstitial water	16	11·2
Plasma water	4	2·8

Not included in this table is a small amount of water that has been transferred across epithelial membranes into specialized spaces, such as the cerebrospinal fluid space, the lumen of the gut and the space between the osteoblast membrane and the surface of the bony trabeculum. The compositions of all of these transepithelial fluids are modified in varying degrees from ordinary extracellular fluid.

The intracellular compartment is delineated by the cell membranes, but because of the diversity of intracellular organelles is heterogeneous in composition. The volume and composition of each of the body compartments is normally maintained within narrow limits both by passage of water and solutes between the compartments and by interaction with the outside environment of the organism, mainly via the gut, kidneys, lungs and skin.

Factors affecting the relative composition of intra- and extracellular compartments

When the concentrations of substances in cells and in the extracellular compartment are unchanging this might be due to impermeability of cell membranes to the solute concerned. Thus no interchange between the two compartments would be possible, other than by specialized exo- and endocytotic mechanisms involving vesicle formation, which are not considered here. However, when the membrane is not impermeable to a particular solute, constancy of extra and intracellular concentrations must be due to one of two thermodynamically distinct types of distribution—these are known as 'equilibrium' and 'steady state' distributions.

The term 'equilibrium state' as applied to the cells and their environment means that the flux of a substance (e.g. an ion) into the cell is equal to the flux of that substance out of the cell *and that no input of energy is needed to maintain this situation.* The term 'steady state' distribution means that concentrations of a substance on either side of a membrane remain constant, *but are not in thermodynamic equilibrium.* The

difference is well illustrated by reference to sodium, which is characterized by a far higher concentration in extracellular than intracellular fluid, in spite of the fact that both the concentration gradient and the direction of the potential across the cell membrane favour sodium entry into the cell. Since by and large the concentrations of sodium remain constant the fluxes of sodium into and out of cells must be equal. Nevertheless this does *not* represent an equilibrium state because the situation is maintained by the well-known 'sodium pump' in cell membranes, which continually extrudes sodium which has leaked in. In order to do so the pump needs extraneous energy, supplied in the form of adenosine triphosphate (ATP) by cell metabolism. This distribution is therefore a 'steady-state' as defined above. Interference with the sodium pump by treatment with ouabain or curtailing the supply of ATP will cause the intracellular sodium to rise at the expense of extracellular sodium until a new and lower concentration gradient is reached which is a little closer to a true equilibrium. Another type of steady-state is where cell metabolism is producing a metabolite which is lost from the cell, but to which the cell membrane is not very highly permeable. Thus in the case of the muscle cell producing lactate ions during exercise the intracellular lactate may rise to a level which drives sufficient lactate through the cell membrane to match the metabolic production rate of lactate. The cell lactate concentration then remains steady. Removal of the source of lactate production immediately results in a fall of intracellular lactate. In the case of carbon dioxide produced by tissue respiration the permeability of the cell membrane for CO_2 is so high that, even though CO_2 is being continually produced, under most conditions the cell partial pressure of CO_2 is probably not detectably different from its equilibrium value, which is in the case of CO_2 the same as that in the extracellular space. Of course, the cell PCO_2 must be *slightly* higher than the extracellular value, since otherwise there would be no net escape of CO_2 from the cell.

Appreciation of the contrast between equilibrium states and steady states is crucial to the understanding of the distribution of different substances across cell membranes. These distributions depend on the mechanisms by which those substances cross the membrane.

Distribution of water

As has been discussed water moves across cell membrane under the influence of the osmotic gradient. There is substantial evidence under normal conditions in man and vertebrates that equilibrium is attained with the cells being isosmotic with the extracellular space. The two compartments are not always necessarily isosmotic. Under certain transient conditions there may be temporary inequalities, and in man these produce clinical disturbances. Furthermore, quite apart from such transients, situations are seen not infrequently in clinical practice in which movement of water between the intra- and extracellular compartments may not be predictable on the basis of the cells behaving like perfect osmometers, i.e. with no change in the solute content of the cell

under any conditions. Under some circumstances there are substantial movements of solute into and out of the cell. In other circumstances, osmotically active particles appear to be generated within the cell itself. Alternatively, cell solute may become less osmotically active. Because of the need to state general principles, the subsequent discussion of clinical states in this chapter takes no account of this type of event except in the case of brain cells, but its occurrence should nevertheless be borne in mind.

Distribution by simple diffusion

A number of substances of major importance distribute themselves between the intra- and extracellular compartments by simple diffusion, moving passively along concentration, or, more precisely, activity gradients. Urea diffuses rapidly across cell membranes; so do the respiratory gases, carbon dioxide and oxygen. The equilibrium condition for all these substances is that of equal activities (usually represented as concentrations or partial pressures) on either side of the membrane. For CO_2 and urea at least these conditions are usually present, but under certain circumstances urea may be removed faster from the extracellular space than it can be replaced by diffusion from the cells, and concentration gradients of clinically significant magnitude may occur.

Distribution of electrolytes

Since electrolytes are charged the membrane potential plays a major part in their distribution across cell membranes. If equilibrium is reached the membrane potential E (positive on the outside) is related to the external and internal concentrations (more properly, activities) $[X^+]_e$ and $[X^+]_i$ of an ion X^+ by the equation

$$E \text{ (volts)} = \frac{RT}{nF} \log_e \frac{[X^+]_e}{[X^+]_i} = 0{\cdot}061 \log_{10} \frac{[X^+]_e}{[X^+]_i} \text{ (at } 37^\circ \text{ C)} \qquad (1)$$

where T is the absolute temperature, R the gas constant, F the charge (faraday) and n the valency of the ion. This relationship is a fundamental one and is known as the Nernst equation. In many tissues this relationship is obeyed for the chloride ion and in skeletal muscle it is nearly obeyed for the potassium ion. In other words if for either of these ions one measures separately the membrane potential and the distribution ratio they are found to be related by the Nernst equation. It follows that in skeletal muscle

$$\frac{[K^+]_i}{[K^+]_e} \simeq \frac{[Cl^-]_e}{[Cl^-]_i} \qquad (2)$$

This type of distribution is known as the Gibbs-Donnan equilibrium. Note that since the chloride ion is negatively charged the ratio of intra/extracellular concentration is inverted with respect to that for potassium. Thus for a membrane potential of 90 mV in skeletal muscle, if extracellular chloride has its normal value of about 100 mmol/l, intracellular chloride is just over 3 mmol/l. On similar reasoning, with $[K^+]_i$ about 150