Clinical Physiology

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Foreword to the First Edition

BY SIR ROBERT (NOW LORD) PLATT

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 are 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 were 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 remptation to be associated with it.

Preface to the Fourth Edition

All chapters have been extensively revised and in most cases rewritten. Nine new contributors have joined the team, to maintain our policy of keeping this a book not only for but also by the younger generation.

Professor R. D. Cohen has written an account of body fluids. Dr J. Cade has collaborated with the rewriting of the chapter on respiration. Dr K. E. Britton has rewritten the chapter on the kidneys and Dr Jack Hirsh has contributed an entirely new chapter on haemostasis and thrombosis, a topic now distinct from haematology. Dr J. L. H. O'Riordan has rewritten the chapter on bone. The subject of skeletal muscle has been taken over by Dr J. A. Morgan-Hughes and the nervous system in the control of movement by Dr J. M. Newsom Davis, and both these authors have rewritten their chapters. Dr C. J. Toews has rewritten the previous chapter on energy sources and utilization and Dr A. D. Wright the previous chapter on the pituitary gland. The order of some of the later chapters has been changed and the final chapter on sex and reproduction has been taken over and rewritten by Dr H. S. Jacobs.

This edition has 192 more pages than the last but the basic design of the book has been preserved. As in the first edition, the emphasis throughout is on the physiological knowledge which we actually use in clinical practice. Although the style is didactic and the scientific pretensions are slight, we hope that the book will promote rational medicine by encouraging reference to the basic sciences and the acceptance of their critical approach. Despite the tendency to be dogmatic in order to be clear, we have tried to emphasize important areas of controversy, but we must stress again that this is not a textbook of physiology, it covers no specific syllabus and it deals with physiology as part of the practice of medicine rather than in the restricted sense of the science of normal function—an expansion of meaning not justified by usage.

Our experiment of including in the last edition a questionnaire was not a success because we obtained replies almost exclusively from librarians and failed to obtain a satisfactory sample of the readership. Once again, therefore, we remain dependent on our own judgement plus the comments and suggestions of a few friends, for which we are again very grateful.

We are also grateful to authors and editors of journals who have given permission for reproduction of figures, etc. in this book, acknowledgement of which is made in the text.

MORAN CAMPBELL
JOHN DICKINSON
WILLIAM SLATER

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 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.

The Middlesex Hospital
February, 1960

MORAN CAMPBELL
JOHN DICKINSON

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We are grateful to our contributors, both new and old, for their co-operation in this fourth edition. We also thank Mrs K. M. Suggate 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 Mr Robert Chaundy of Blackwell Scientific Publications for their help and forbearance.

Contents

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) involved 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 7 grams/100 ml, 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

There is substantial evidence that in man and vertebrates under equilibrium conditions the osmotic pressure is equal on either side of the cell membrane. It should not be assumed, however, that the two compartments are always isosmotic; under certain transient conditions there may be temporary inequalities and in man these produce clinical disturbances.

The relative solute composition of two body compartments separated by a membrane—be it a cell membrane or a more complex epithelial membrane—depends very much on the method of passage of the various solutes across the membrane.

(i) *Simple diffusion.* A number of substances of major importance distribute themselves between the intra- and extracellular spaces by simple diffusion, moving passively along concentration, or more precisely, activity gradients. Water has already been discussed in connection with osmosis; urea also diffuses rapidly across cell membranes. So do the respiratory gases, carbon dioxide and oxygen. Normally the gradients of these substances across cell membranes are very small, but under certain circumstances urea, for instance, may be removed faster from the extracellular space than it can be replaced by diffusion from the cells and concentration gradients of significant magnitude may occur.

(ii) *Distribution of electrolytes.* In addition to isosmolality a further important principle is that electroneutrality must be maintained on each side of the cell membrane, i.e. the number of positive charges due to cations must always equal the number of negative charges due to anions. The actual distribution of ions across the cell membrane