TEXTBOOK OF PHYSIOLOGY AND BIOCHEMISTRY

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With a foreword by
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FOREWORD

In all sciences, as the body of knowledge grows, specialization becomes inevitable. A point is reached, often suddenly, when the interests of the various workers in a science diverge. Then each worker pursues his own line of enquiry, dropping, as he goes, a curtain of new techniques and of new knowledge between himself and his former colleagues. In the past Physiology was peculiarly vulnerable to this process. At the present time the basic sciences, Physics and Chemistry, continually offer to the physiologist and biochemist new weapons to attack biological problems. These weapons demand in their use special training and skill. Thus disintegration advances knowledge.

Nevertheless, all workers in Biology are held together by the fact that the phenomena they study form part of a single whole, the living organism. However dissimilar the methods of approach, there is unity in the object attacked. An organism is an individual entity, a whole maintaining its integrity in a physical and chemical environment throughout a period of time. Thus the significance of the most recondite research cannot be fully appreciated without a knowledge of the entire living background which is the organism itself. Minor modification of a statement by Michael Foster gives a true picture of the position.

'We may speak of an organism as a complex structure, but we must strive to realize that what we mean by that is a complex whirl, an intricate dance, of which what we call biophysical activity, biochemical reactions, histological structure and gross configuration are, so to speak, the figures.'

Often an imperfect performance reveals the intricacy of a dance more clearly than the most polished execution. Not infrequently normal biological processes are first elucidated by a study of the abnormal. Some knowledge of Pathology is necessary for a full appreciation of Anatomy, of Physiology and of Biochemistry.

It is thus very obvious that a beginner, wherever his specialist studies may later lead him, must acquire and retain a knowledge of the fundamental integrated activities of the body as a whole. At the outset of his studies he must be provided with a basic text which will present in true perspective the multifarious activities of the living body.

Unfortunately, specialism has proceeded so far that it is doubtful if any one writer can to-day give a complete and balanced picture of even the elements of Physiology. Collaboration is essential. No happier combination could have been found that that of a physiologist, a biochemist and a clinician. Such successful collaboration ensures that balanced presentation of the knowledge which must be mastered by a beginner.

Because of its importance to Medicine, Physiology once received the title of 'Institutes of Medicine.' To-day, with her lusty bullying brood of offspring, she justifies that proud title more than ever before. This book is designed to lay a sure foundation for the medical undergraduate. The headlong advances in the Art of Medicine and in the Craft of Surgery in the past few decades are largely attributable to advances in Physiology, in Biochemistry and in the basic sciences. With every passing year Medicine is becoming more scientific. This is not to decry the importance of the sympathetic understanding which all good physicians have for their patients. Nevertheless the medical student neglects his study of Physiology and of Biochemistry at the peril of his future patients.

For those who mean to specialize in Physiology, in Biochemistry, in Pharmacy, or in Pharmacology, this book can be no more than an introduction. But it is an introduction which is essential if narrowness in thought and frustration in achievement are to be avoided.

R. C. GARRY.

PREFACE TO THE SIXTH EDITION

IN the four years that have elapsed since the fifth edition there has been a flood of new information in both physiology and biochemistry and explanations of many biological phenomena are now possible. The text has therefore had to be considerably revised. The biochemical chapters especially have been expanded and new ideas about chemical events in the cell are now dealt with in some detail. The names of enzymes have been changed to those officially recommended in 1961 by the Commission on Enzymes of the International Union of Biochemistry. We have added many pictures and diagrams. Wherever possible we have concentrated on human physiology partly because the lower animals are apt to differ from man in many ways but mainly because nowadays there is so much first hand information about human physiology. Much of the biochemical matter is, however, basic in the sense that it applies to both man and animals, and even to lower organisms.

As in former prefaces we willingly express our indebtedness to many colleagues. The success of this book has been in no small way due to their help and advice, both spontaneous and requested. When acknowledgment has been made of the source of all diagrams, figures and plates, there remains much of other people's ideas the source of which it is not always possible to specify or even to identify. That does not mean to say that we are not grateful for it. In previous prefaces we named various colleagues who had given us the benefit of their advice. We are still grateful to them and they may still recognize their contributions in this edition. We wish to express our thanks to the following for their help with this new sixth edition: Dr. B. L. Andrew, Dr. G. S. Brindley, Professor W. Burns, Dr. C. Cameron, Dr. D. M. Cathro, Professor R. E. Coupland, Dr. M. G. Coyle, Dr. G. P. Crean, Mrs. R. S. Creed, Dr. G. Dawes, Dr. C. Forsyth, Professor A. C. Frazer, Dr. J. K. Grant, Dr. R. F. Jameson, Dr. H. M. Keir, Dr. R. D. Keynes, Professor J. Knowelden, Dr. N. Loveless, Dr. R. S. McNeil, Dr. H. G. Morgan, Professor H. N. Munro, Dr. W. W. Park, Dr. B. Schofield, Dr. R. M. S. Smellie, Mr. J. S. S. Stewart, Dr. J. Picton Thomas and Dr. W. Walker. Our special thanks are due to Dr. D. P. High for reading so carefully through the proofs, and to Dr. R. Y. Thomson for much help on many of the biochemical chapters.

We would like to express our gratitude for the help we have received from the library staffs of our universities and from Mr. Callender, who has prepared many of the illustrations. Mrs. M. I. Glenday has earned our thanks for preparing the index. With regard to our publishers we wish also to express our appreciation of Mr. Parker's patience and tolerance and of Mr. Macmillan's sympathetic encouragement.

G. H. B.
J. N. D.
H. S.

June, 1965.

PREFACE TO THE FIRST EDITION

THE desirability of collaboration in a book covering a wide field is quite obvious in these days of growing specialization when the many administrative responsibilities increasingly thrust upon teacher and research worker divert them from their proper duties. While no doubt it may be an advantage that the authors should bring experience from very different fields into the writing of one book, yet for any one of a team to satisfy the other members completely is well-nigh impossible and we are now convinced that the difficulties of writing a book increase as the power of the number of its authors.

Now that we see our ideas expressed in cold print we still have sufficient self-criticism left to wonder whether we have in this textbook fully realized our aims.

What then are the aims of this book ? The first is that it is intended to be an *introduction* to the study of physiology and biochemistry. Although it is intended primarily for medical students it should also serve the needs of those studying dentistry, veterinary science, or pharmacy, as well as students of pure science in the early stages of their study of physiology and biochemistry. We hope that we have included sufficient material of an applied or clinical nature to emphasize the importance of physiological knowledge in clinical medicine and we trust that the medical student will find it profitable to retain the book and consult it from time to time in his clinical years.

The custom of teaching the elementary stages of physiology and biochemistry in close association has more than mere convenience to commend it, since the subject matter is so inextricably interwoven. This intimate relationship is apt to be forgotten, however, by the more advanced student if he comes to rely on one textbook dealing with biochemistry alone and another confined mainly to physiology. Our aim has therefore been to treat the two subjects as one and to indicate wherever possible their relevance to clinical problems. The numerous cross-references in the text serve to demonstrate the many interrelations at all points of our subject and to underline the importance of considering man as a co-ordinated and integrated whole.

When he has passed the elementary stages and has gained some knowledge of the groundwork of the subject the student can then proceed to more advanced texts and monographs which deal with specialized aspects of physiology or biochemistry. To enable him to do so references are given at the end of each chapter. An additional way of entry into the literature is provided by the references in the legends to those figures which have been taken from original papers.

Because we have the medical student chiefly in mind we have tried to emphasize the human aspects of our subject but it is, of course, quite impossible to confine our attention exclusively to the physiology and biochemistry of man. Indeed any such attempt would leave the student without a sense of obligation to the pioneers of physiology and without any idea of the contribution of animal investigation to the progress of diagnosis and the treatment of human suffering. It is important to remember, however, that clinical investigators have added to physiological knowledge by developing new techniques applicable to man alone. Considerable advances in our knowledge of renal function and of the physiology of the heart and peripheral circulation have arisen in this direct way.

For the reader's convenience in finding figures, tables and plates we have adopted the slightly unconventional method of numbering these in sequence in the chapter to which they belong. Thus Fig. 50, 6, is the sixth illustration in Chapter 50. This system which is now coming into use has, we believe, much to recommend it. We have adopted the current anatomical terminology and the conventions of spelling and usage advised by the Physiological and Biochemical Societies.

G. H. B.
J. N. D.
H. S.

September, 1950.

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CHAPTER 1

INTRODUCTION

IN the subjects of Physiology and Biochemistry we are concerned with living matter at two different levels. The biochemist studies biological systems at the level of molecules and atoms, while the physiologist is more concerned with the intact organ, or the whole organism. Physiologists and biochemists are concerned essentially with changes in the organism as it reacts to changes in its environment. In other words, they try to take a cinematographic view of living material; however they frequently find it necessary to stop the cine-film from time to time to make a detailed examination of a single frame. For example, the chemical analysis of a tissue is a statement referring to one particular instant and a series of such analyses may indicate a progressive change from which the biochemist is able to build up a dynamic picture of the chemical activities of the tissue. Similarly the microscopic examination of a single stained section of a tissue is of value in showing its minute anatomy, but it may give little information as to its function. Such a section indeed represents only a momentary glimpse of what may be a continuously changing process. One must recognize too that disturbances of function occur that seem to have no structural basis. For example, interference with an enzyme system may produce disease, and changes in the arrangement of molecular layers may alter significantly the properties of cells and tissues.

In this book the terms 'physiology' and 'biochemistry' are used in a relatively narrow sense. We shall deal, so far as we can, with human physiology, supplementing it by descriptions of experiments on other mammals and by occasional but important references to the frog. Anyone actively engaged in the study of physiological problems is soon made painfully aware of distinct differences of function between different species and is reluctant to assume that what holds good for an animal applies without modification to man. There are, however, obvious limitations to experiments on man and it will always be necessary in a text-book such as this to fill in some gaps by reference to lower animals.

STRUCTURE AND FUNCTION

The single cell is the functional unit of the body and each tissue is made up of vast numbers of cells. We must not imagine, however, that a single cell is a simple uncomplicated structure. Although the ordinary light microscope may reveal little difference between one part of its cytoplasm and another, the electronmicroscope and modern biochemical techniques have revealed an amazing complexity. For this reason it is not yet possible to describe the subtle difference between a living cell and a mere aggregation of molecules.

In the case of the more complex animals such as birds and mammals, the first characteristics of life that come to mind are warmth and movement. If an animal is still and cold it is assumed to be dead. By taking in food and oxidizing it an animal obtains energy which is used to produce heat or movement. The energy is obtained by oxidation of body constituents by a process known as *catabolism.* The energy obtained by these catabolic processes may also be used for *anabolic* or synthetic processes such as are necessary for growth. Since both processes occur side by side it is convenient to use the word *metabolism* when referring to the total chemical changes occurring in the cell or in the body. So long as metabolic processes continue, however slowly, the cell is alive; their arrest is death. Since these chemical processes are under the control of enzymes the cells can move or grow only within certain limits of temperature. If the temperature is too high the enzymes are destroyed, while at low temperatures enzymatic reactions are retarded and finally cease.

Living material is *organized,* that is, it has a definite structure. Moreover, particular functions, such as movement or secretion or conduction, are carried out by cells or organs whose structure is peculiarly fitted to these purposes. For a cell to survive there must be *integration* of function within it. In multi-cellular organisms there must be *co-ordination* of the activities of various cells, either by chemical messengers (*hormones*) or by a system of *nerves.*

Growth is a characteristic feature of living material. Growth of a single cell however cannot go on indefinitely because, as the cell increases in volume, its surface through which oxygen and food materials are admitted becomes so far removed from its centre that the supply of essential material to the latter is endangered. Before this stage is reached the cell divides into two daughter cells, a process known as *reproduction.*

Because a cell does not live in isolation, and is dependent on obtaining its food from outside, it must be capable of *reacting* to changes in its environment. Such changes are called *stimuli.* If a stimulus increases the rate of chemical changes in the cell it is said to *excite*; if it decreases the metabolic rate it is said to *depress*, or to be an *inhibitory* stimulus.

Living organisms possess two properties which at first sight seem to conflict. These are best described under the headings of *adaptation* and *homeostasis.* Simple forms of life can survive over a wide range of temperature and can adapt themselves to changes in their environment and to the foodstuffs available. Indeed, if they could not do so they would soon die. The study of adaptation forms a large part of the subject of physiology, for the cells of the body can adjust themselves to a wide variety of changes. On the other hand, many physiological reactions are directed towards preserving the *status quo.* Practically all the cells in the body except those on the surface are provided with a fluid environment of relatively constant temperature, hydrogen ion concentration and osmotic pressure. This permits many bodily activities, the functioning of nerve cells and the working of enzymes for example, to be carried out under optimum conditions. As Claude Bernard put it: 'La fixité du milieu intérieur est la condition de la vie libre, indépendante.' Small changes in the *milieu intérieur*, produce reactions which quickly restore the internal environment to its original state. Many of the adjustments of the activity of the cells and organs of the body are examples of the working of this principle, which Cannon called homeostasis.

It is generally appreciated that the body regulates its internal environment with some accuracy. For example we are apt to say it keeps its hydrogen-ion concentration remarkably constant. But to leave it at that is simply to admire it from a distance without going to the trouble of making enquiries about the working of the regulatory mechanisms. The first requirement of such a mechanism is a detector of deviation from the standard conditions; the appropriate regulator must then be 'instructed' to reduce the deviation. The new state of affairs is continuously assessed by the detector and the regulator is given fresh instructions. In other words the activity of the regulating device is constantly modified on the basis of information fed to it from the detector; such systems in modern jargon are termed 'feed-back' mechanisms. Sensory receptors in muscles and joints send information to the central nervous system about length of muscles and angle of joints and movement and posture are regulated: cells sensitive to osmotic changes in the blood regulate the loss of water from the body: receptors in blood vessels detect changes in blood pressure and so the output of the heart and the calibre of the blood vessels are altered to regain the *status quo*. In many cases, however, the detecting mechanism is still to be discovered—for example we do not yet know how the level of blood volume, or the level of blood sugar, are detected. Both, however, are regulated within quite narrow limits.

Although the regulation of the internal environment reaches its highest development in man he has gone still further by attempting to control his external enviromnent. At first this involved the wearing of clothing, the building of shelters and houses, and the use of artificial heating, lighting and ventilation. These have not all proved to be unmixed blessings. Artificial lighting, for example, while it makes life more pleasant in the darkness of winter, introduces new problems of eyestrain, fatigue and extended hours of work. Later, with the advent of the industrial era, unfavourable environments were created in which men had to labour, but the dangers of many of these were mitigated by the design of machinery which could be easily and safely worked. More recently man has attempted to conquer the air, an adventure which has resulted in a vast number of new biological problems. The description and investigation of such problems falls properly under the heading of applied physiology, but there is no definite boundary between pure and applied in this or any other science.

Although our knowledge of the properties and functions of living cells is incomplete, we know that the laws of conservation of matter and energy apply to the animal body just as certainly as they apply to non-living material. Investigation of living matter is largely a question of observation supplemented by the methods of physics and chemistry. Thus we may measure pressures and potentials, make chemical analyses, or trace the pathways of chemical substances through the body. The results of these observations are correlated, interpreted in the light of previous knowledge, and used as evidence for or against a particular hypothesis. Thus physiology and biochemistry imply much more than a mere catalogue of the functions of the various parts of the body. However, neither has yet become a highly organized body of knowledge comparable to the exact sciences of physics or mathematics and many of the phenomena to be discussed can be given as yet only an incomplete explanation. Nevertheless their description must not be regarded as irrelevant since empirical findings may have immediate practical importance in the diagnosis and treatment of disease.

At one time the organic basis for a patient's symptoms could be established only at post-mortem examination. The trend in modern medicine and surgery, however, is to study the living patient more and more intensely in order to understand not only his symptoms but the way in which normal physiological and biochemical processes have broken down, for disease is increasingly thought of as a disordered physiology in which the homeostatic mechanisms have been overstrained or are inadequate. The cure and prevention of numerous diseases is due to rapid advances in our knowledge of bacteriology and immunology: to many the methods of experimental physiology are being successfully applied. Biochemical methods have been used for many years for the examination of the body fluids, to provide important diagnostic information and to control treatment. Thus, for example, much of our recent knowledge of cardiac diseases, cardiac failure and the surgical treatment of congenital cardiac malformations is based upon physiological studies made in the laboratory or in the clinic, while the modern treatment of diabetes mellitus depends almost entirely on material and methods originally developed in the laboratory.

The bodily activities are so closely dependent on one another that the workings of one part of the system cannot be comprehended without an understanding of the functioning of the whole. For example, in describing the activities of the heart we have to discuss the influence of the peripheral blood vessels, of the central nervous system, of respiration and of the chemical changes occurring in cardiac muscle. Our subject may, therefore, be likened to a circle in which all the parts are connected together, no one portion being more important than another. It is difficult, therefore, to know where to enter the circle to begin our study, for it is only when we have completed the circle that we can fully understand our subject. For this reason it is necessary to consider briefly the subject as a whole before beginning a more detailed description of its various parts.

The source of all the energy required by the body for carrying out muscular activity, for respiration, for the beating of the heart, is the food. This consists mainly of proteins, fats and carbohydrates which are oxidized (burnt) in the tissues. In addition to sources of energy the food must contain inorganic substances which are necessary to make good the loss of salts in the excreta and to provide material for formation of blood and bone. The food must also supply certain substances which the body cannot synthesize, such as vitamins and essential amino acids. Since there is continuous loss of fluid, by way of the kidneys as well as by the skin and lungs, water must be drunk to make good this loss. When food is swallowed it reaches the stomach and small intestine, where it is broken down by enzymes into substances of relatively simple chemical constitution which are absorbed through the lining of the small intestine into the blood stream and distributed throughout the body. In the case of fats, however, absorption may occur with very little modification of the original chemical structure.

The oxygen required for combustion of the foodstuffs reaches the blood through the lungs. During breathing the chest expands and air flows into the lungs which are spongy organs richly supplied with blood vessels. Oxygen diffuses readily through the very thin walls of the capillary vessels of the lung tissue, becoming attached to the hæmoglobin contained in the red cells in which it is distributed throughout the body by the circulation. The carbon dioxide produced in combustion in the tissues is taken up by the blood and carried to the lungs where it escapes from the blood and is exhaled. By-products of oxidation not needed by the body reach the kidneys in the blood and are excreted into the urine.

The heart is a two-sided muscular pump which drives the blood along the blood vessels. The left side pumps blood to the heart muscle itself, to the brain, skeletal muscles, kidneys and intestine. The blood from these parts returns to the right heart which sends the blood to the lungs where oxygen is taken up and carbon dioxide is eliminated. The oxygenated blood then returns to the left side of the heart and is pumped out to the tissues. The blood is conveyed away from the heart at a fairly high pressure in thick-walled tubes, the arteries. These vessels branch repeatedly and become smaller in diameter, with thinner and thinner walls. In the tissues the smallest blood vessels, the capillaries, are bounded by a single layer of cells through gases, fluid, or chemical substances of small molecular size move easily. The blood is drained away from the tissues at low pressure in wide vessels (the veins) with relatively thin walls.

The skeletal muscles are the main effector tissues. By their contractions the position of the bones is altered and respiration and speech are made possible. The highly complex movements of the limbs in walking, and of the tongue in speech, are co-ordinated by the central nervous system, consisting of the brain and spinal cord. Nerves called *efferent* or *motor* nerves leave this system and pass to all the structures of the body and control muscular movement as well as the secretion of the glands, the heart beat and the calibre of the blood vessels. Central control is, however, of no value unless the centre has full information about events in the body and around it. This information is conveyed to the central nervous system by the *sensory* or *afferent* nerves which carry impuless from the eye, the ear, the skin, the muscles and joints, and the heart and intestines. The sensory nerves are actually much more numerous than the motor nerves. Although many of the activities occurring in the central nervous system are exceedingly complex, relatively few rise to consciousness. We are quite unaware, for example, of the muscular adjustments needed to maintain balance or to move our eyes so that images of the external world are kept fixed on the retinæ. These adjustments are called *reflex* and the pathways involved, namely sensory nerves, central nervous system and motor nerves, are called *reflex arcs*. The lowest part of the brain, the medulla oblongata, is responsible for the muscular movements of respiration, for the control of the heart rate and the regulation of the blood vessels, and is concerned in the maintenance of posture. The cerebellum, which lies above the medulla, is concerned with co-ordination of muscular movements. The fore-part of the brain, the cerebrum, has a layer of grey matter (nerve cells) on its surface and also masses of grey matter within. The grey matter is interconnected by innumerable nerve fibres which together make up the white matter. The cerebrum is concerned in all the higher mental activities and with reading, writing and speaking, as well as in so-called voluntary movements, the perception of touch and temperature and in the special senses of vision and hearing.

In addition to the rapidly acting co-ordinating and integrating mechanism of the nervous system there is a chemical (*humoral*) system which operates more slowly. For example, during the digestion of food in the duodenum a chemical substance (*hormone*) called secretin is produced in the mucous membrane, absorbed into the blood and carried to the pancreas which responds by pouring out its digestive juices. The thyroid gland in the neck produces a chemical substance which is absorbed directly from the gland into the blood stream and influences the rate of metabolic activity of the tissues.

Finally, under the heading of reproduction, we shall have to consider the processes necessary for the maintenance of the species. The male cells, the *spermatozoa*, are produced in the testis, and when deposited in the female