Introduction to PHYSIOLOGY

VOLUME 1
BASIC MECHANISMS
PART 1

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PREFACE

We can think of two ways of composing an Introduction to Physiology. First we may take a large standard text and sieve the material contained in it to free it of as much experimental material, argument and other "extraneous matter" to reduce its bulk to about one third of the original. Alternatively one may compose something entirely new, expounding as simply as feasible the basic scientific principles governing the functioning of the animal. The former method has, we think, been employed before, and the result has been a *synopsis* of, rather than an *introduction* to, physiology. By memorizing it almost word-for-word the medical student probably passes muster at an undiscriminating examination, and completes his medical education with a very poor understanding of the basic principles of medicine.

Pursuing the latter method we found that the first draft was embarrassingly large, and in reviewing what had been written with a view to shortening the book, it became clear that any serious surgery would destroy its character since it was, in effect, rather more than an Introduction containing—to use a musical term—a great deal of "development" too. Rather than abandon the project of producing an Introduction that was both short and adequate, we carried out a different kind of surgery, namely the division into several volumes. Volumes 1 and 2, which we now present, are an introduction to the basic mechanisms whereby the animal absorbs, distributes and transforms its energy-giving materials; and whereby the energy thus made available is utilized in such fundamental activities as muscular contraction, the transmission of messages by both nerves and hormones, the defence mechanisms and in reproduction.

The difficulties in understanding physiology arise in the fundamental principles governing the activities of the animal's parts, such as the flow of fluids, the conduction of the nervous impulse, the elimination of secretions from a cell or epithelium and so on. If the student has a firm grasp of these principles, the way is clear for the understanding of the rest of physiology, which consists in the analysis of control mechanisms. The remaining volumes are designed to enable the student to take up where the first two left off; thus Volume 3 is devoted to visceral control mechanisms and may be regarded as the "development" of the themes introduced mainly in Volume 1. Very arbitrarily the control of somatic motor activity and of reproduction have been put together to make Volume 4; this is only because their inclusion in Volume 3 would have made it too large for convenience. Volume 5 deals with sensory mechanisms and higher integrative processes, involving the cerebral cortex.

A few words on the way the volumes have been written. The present two volumes, being concerned largely with fundamentals, require little or no documentation, so that we have contented ourselves mostly with general references to reviews and texts at the end of each volume. This does not mean that the information has been culled only from these sources, and it is rare if we have quoted work that we have not read in the original. In the remaining volumes the subject matter has been treated in greater experimental depth, so that a more elaborate documentation, comparable with that found in Starling's *Principles of Human Physiology*, has been employed.

To conclude, we think that a study of the completed work will provide the student of physiology, taking this as part of a larger course, such as in medicine or dentistry, with knowledge of the subject sufficient for his requirements; for the student intending to make physiology his career the book will, we trust, be a proper "Introduction".

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October 1974

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CHAPTER 1

Structure and Function

Introduction

Gross Anatomy

Physiology is the science of the functioning of living organisms; in order to discover how these living organisms work, i.e. the physical and chemical laws governing their behaviour, we must ultimately dissect them so as to reveal the relations of their parts.

With the naked eye to observe, and the scalpel to dissect, we can discover a great deal, and this "gross anatomical" approach has been followed exhaustively in man and other large animals, so that the subject of gross anatomy is essentially a completed story. In this way we have discovered the way in which blood is distributed to the body, the manner in which the bones are articulated and their muscles attached, and so on. Thus with only this gross anatomical knowledge the physiologist, by virtue of the ingenious design of his experiments on the living animal, has been able to attempt explanations for a great many of the phenomena of life in higher organisms, e.g. the mechanism of breathing, the intimate connection of breathing with the supply of blood to the lungs and the rest of the body, the mode of intake and digestion of food, the mechanics of the contraction of muscle and the relation of energy consumption to this process, and many features of the control mechanisms exerted through the nervous system.

Microscopy

The study of anatomy on a microscopical level—called *histology* and *cytology*—is necessary if the physiologist is to be permitted to interpret and design his experiments with more meaning; thus, with only a knowledge of gross anatomy we can derive an enormous amount of information regarding the circulation of the blood, its changes with exercise, with climbing to high altitudes and so on. However, the manner in which the circulation fulfils its functions (namely, absorbing oxygen from the air and delivering it to the tissues of the body; carrying absorbed materials from the intestine to the liver and depositing these materials in the organs) can only be more fully elucidated by a knowledge of the structure of the smallest blood vessels—the capillaries, which are fine tubes in the region of 10 μm diameter or less that form the connecting links between the arterial and venous systems. These tubes are too small to be seen with the unaided eye, and it required the development of the microscope and its application to the tissues of living organisms to demonstrate the structures of these vessels which, besides representing the connecting links between the arterial and venous systems postulated by Harvey, represent the locus in the blood vascular system at which materials are able to escape from, or enter, the blood. The microscope can reveal many details in the structure of these small vessels, and their relation to the tissues with which they come into contact. With this histological and cytological information the physiologist may carry out functional experiments designed both to show how materials can escape from these fine tubes and to elucidate the mechanisms of control of these transport phenomena.

Electron Microscopy

The ordinary light microscope does not permit the physiologist to see the complete details of the structures he is concerned with. To keep to our example, his physiological experiments tell him that the fine tubes or capillaries probably have holes in them that allow molecules of a certain size to pass through, whilst larger ones are retained either completely or partially, i.e. the experiments indicate that the tubes are behaving like sieves or filters, thereby exerting some control over the types of molecule that can pass into or out of the blood and the rates at which the permeating molecules pass to and fro. The holes, deduced theoretically, would have diameters of about 80 Ångstrom units (80 Å = 8 nm). Now the limit of resolution of the conventional light microscope is about 0·2 μm, and since 1 μm is 10^4 Ångstrom units, the resolution is some 2000 Ångstom units, so that it would not be possible to see the holes in the capillaries. Within the past twenty years, however, the sciences of anatomy and histology have been fortified by the development of the electron microscope, which has revealed details in structure that are quite unresolvable in the light microscope; its theoretical limit of resolving power is of the order of a few Ångstrom units, and as techniques of preparation of the specimens have improved, structural details of this order of magnitude have become visible. In the capillaries, the postulated holes have, indeed, been resolved, but of course the electron microscope is used to examine dried and chemically treated tissue, so that the holes revealed by this instrument may not be of the same size in the living material.

Structure and Function

The electron microscope has certainly revolutionized the anatomist's way of life, and has helped the physiologist to a great extent, often confirming deductions as to structure that were made entirely as a result of functional experiments, just as the light microscope confirmed Harvey's hypothesis of the connection between the arteries and veins. For example, the muscle of heart was recognized to have very special properties, in that the individual fibres of which it was composed were in some way connected with each other, in marked contrast to the muscles of the skeleton which behaved as though the fibres were quite separate. The resolution of the light microscope did not permit the anatomist to say categorically whether the cardiac muscle fibres were, indeed, connected or fused together, and it was not until the electron microscope was applied to the problem that the existence of localized regions of fusion between adjacent fibres was confirmed. This is an example of the usefulness of the anatomical studies in *confirming* a deduction from physiological experiments. It would be easy to cite other cases where, instead, the morphological discovery suggested a theory of function. Thus we may, once again, choose muscle.

Shortening of Muscle

The special feature of muscle is its ability to shorten, and thus perform mechanical work; this is illustrated in Fig. 1.1, where we see

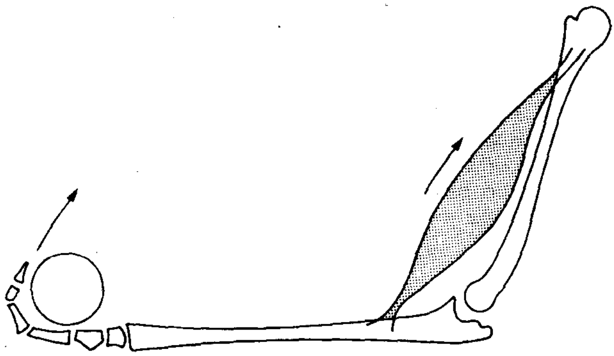

Fig. 1.1. A simple diagram of the arm showing the biceps muscle shortening to lift an object.

a muscle of the arm; it has its origin on the humerus and is inserted or attached to the bone of the forearm. By shortening, it causes the arm to bend, or flex, and mechanical work will be done if the bending of the arm causes a weight to be lifted.

Folding of Protein Chain. If we examine this muscle in the light microscope we see that it is composed of bundles of fibres running

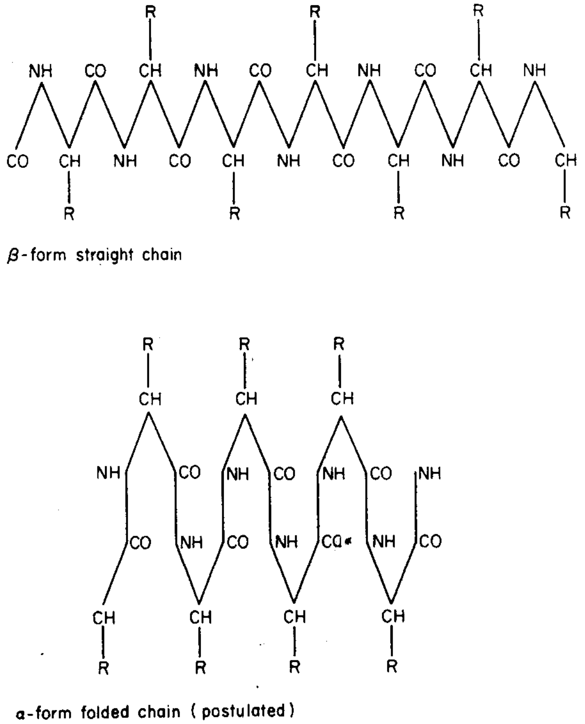

Fig. 1.2. Two forms in which fibrous proteins can exist—the β-form in which the molecule is stretched out and the α-form when the molecule is folded and much shorter. This folding of protein molecules was used to explain muscle contraction until the use of X-ray crystallography and the electron microscope on muscle sections suggested the sliding filament model. The folding illustrated here was that postulated in the nineteen-thirties by Astbury; later work, as we shall see, has shown that the α-chain is helical rather than linear.

longitudinally, and when it contracts these fibres shorten and become fatter. An attractive theory of the structural basis of contraction was based on the assumption that the muscle fibres consisted essentially of bundles of very thin long molecules of a fibrous type of protein called myosin, and these long molecules were thought to exist in two forms, a fully stretched, or β-state and a more folded or α-state, as illustrated schematically in Fig. 1.2. Such stretched and partially folded states had been recognized to occur in other protein molecules, such as the protein of the wool fibre, keratin, the structures being recognized by the use of X-ray diffraction, the only method of deducing structure on a very small scale before the advent of the electron microscope. The protein, myosin, a prominent constituent of muscle, was shown to be able to undergo this transformation under certain experimental conditions. However, examination of the muscle by X-rays gave no evidence of this sort of change during contraction, and the true nature of the contractile process was revealed by a combination of morphological studies, involving the light and electron microscopes, and the use of X-ray diffraction.

Sliding Filaments. The studies indicated that the fibrils did not fold up but retained their original lengths; instead of folding, one type of fibre slid alongside its neighbours of another type, and as a result

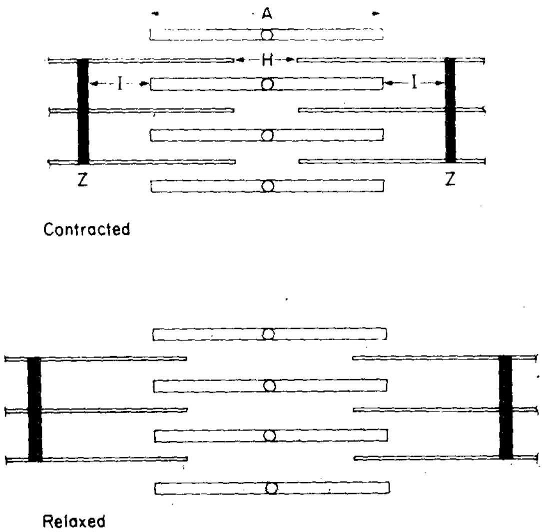

Fig. 1.3. The sliding filament model of muscle contraction. The thin filaments are muscle protein actin and are attached to the Z line. The thicker filaments are myosin, and shortening follows from a sliding action leading to increasing overlap.

the bundle as a whole shortened (Fig. 1.3). Thus the problem left for the physiologist, after this deduction from structure, was: "What makes the filaments slide?" Here, then, is an example of how morphological study has suggested a physiological mechanism, although of course, in general, the two approaches are made together so that it is never easy to say whether the structure has suggested the mechanism or the physiological phenomenon has suggested or demanded a structure.

THE FUNCTIONAL UNITS OF STRUCTURE AND BEHAVIOUR

The Cell

The structural analysis of muscle has shown us different orders of magnitude, based primarily on the limits of resolving power of the unaided eye, of the microscope and the electron microscope and X-ray diffraction. With the naked eye we may discern the fibrillar nature of many muscles, and in the light microscope we can see that the basis for this is the grouping together of long thin muscle fibres to form bundles. Now these muscle fibres are more than their name implies; they are functional units endowed with many more properties than the obvious one of shortening when treated in a certain way. The muscle fibre is a *cell*, and is one of many different types of functional unit that, working together, form the basis of the structure and function of the organism. It was Schwann who proposed what was then called the "cell theory" of structure; according to this the various tissues of the body could be resolved into units, or *cells*, of characteristic types, the behaviour of the tissue being determined by the characters of these units of structure and behaviour.

Muscle Fibre

Thus the unit of the skeletal muscle we have just been discussing is the muscle cell or fibre, so that the basic structure of a given skeletal muscle consists of bundles of these cells running side by side. These cells vary in size and shape from one muscle to another, but they have sufficient features in common to enable a clear differentiation from these and the cells of smooth muscle, which forms the basis for the contraction of the gut, the blood vessels and some other tissues.

Neurone

Another type of cell is the neurone, or nerve cell; like the skeletal muscle cell it is fibrous in type and arranged in groups, so that the bundles of fibrous extensions of these nerve cells make up what is visible to the naked eye, namely the nerve of the gross anatomist.