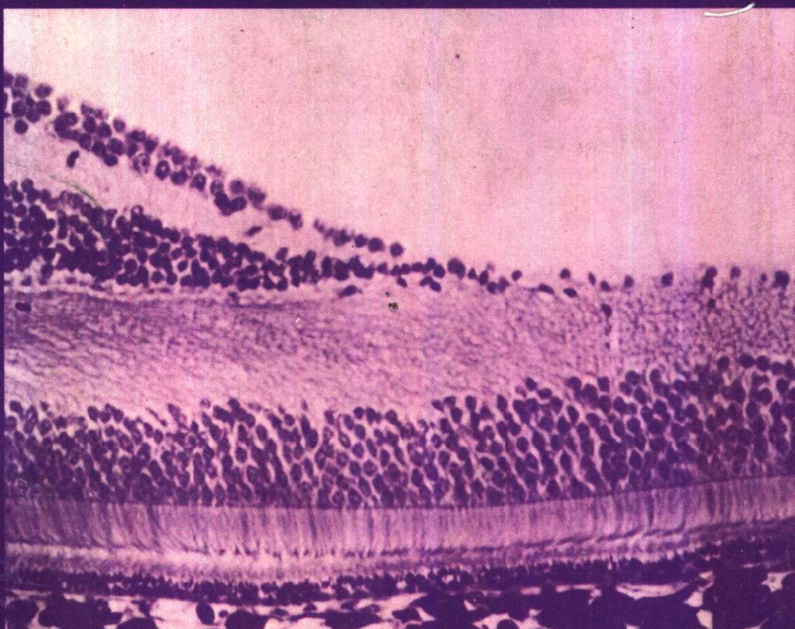
Physiological Principles in Medicine Series

Neurophysiology

R. H. S. Carpenter



Neurophysiology

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Physiological Principles in Medicine

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General preface to series

Student textbooks of medicine seek to present the subject of human diseases and their treatment in a manner that is not only informative, but interesting and readily assimilable. It is also important, in a field where knowledge advances rapidly, that the principles are emphasized rather than details, so that information remains valid for as long as possible.

These factors all favour an approach which concentrates on each disease as a disturbance of normal structure and function. Therapy, in principle, follows logically from a knowledge of the disturbance, though it is in this field that the most rapid changes in information occur.

A disturbance of normal structure without any disturbance of function is not important to the patient except for cosmetic or psychological considerations. Therefore, it is the disturbance in function which should be stressed. Preclinical students must get a firm grasp of physiology in a way that shows them how it is related to disease, while clinical students must be presented with descriptions of disease which stress the basic disturbance of function that is responsible for symptoms and signs. This approach should increase interest, reduce the burden on the student's memory and remain valid despite alterations in the details of treatment, so long as the fundamental physiological concepts remain unchallenged.

In the present Series, the major physiological systems are each covered by a pair of books, one preclinical and one clinical, in which the authors have attempted to meet the requirements discussed above. A particular feature is the provision of cross-references between the two members of a pair of books to facilitate the blending of basic science and clinical expertise that is the goal of this Series.

RNH
MH
KBS

Dark mysteries are here—old pathways, secret places
Under the tangled cortex, grown snugly thick now—
Intricately synapsed: electrode-proof.

Preface

The supervision system practised at Cambridge and elsewhere brings many benefits both to teacher and taught: not least, that lecturers are brought face to face with the results of deficiencies in their own teaching in a peculiarly immediate and painful way. What has seemed to many supervisors a most worrying trend over the last ten years or so is the extent to which a student may come away from a series of lectures on (let us say) the circulation, with an impressive amount of detailed information, including perhaps the minutiae of experiments published only a month or two previously, yet with little sense of what might be called *function*: of what the circulation really does, of how it responds to actual examples of changed external conditions, and how it relates to other major systems. And in the case of the central nervous system things seem even worse: a student may acquire an immensely detailed knowledge of the anatomical intricacies of the motor system, yet not be able to tell you even in the broadest terms what the cerebellum actually does, or have the slightest feel for what kinds of processes must be involved in such an act as throwing a cricket ball. The result is much knowledge, but little understanding, and very little sense of ignorance.

I believe this to be the result of two factors. The first is, paradoxically, that over the last decade or so, Universities and Teaching Hospitals have quite rightly begun to take teaching much more seriously than once was the case, and consequently a perfectly laudable sense of competition has developed amongst lecturers to gain the approval of their audiences. But students—at least in the short term—tend to form judgements rather on the basis of the number of 'facts' that they have succeeded in copying down in the course of a lecture: the more recent these facts are, the better they are pleased. Lecturers naturally respond to this by filling their lectures with increasing amounts of detail, at the expense of fundamental principles. The students' notebooks swell with quantities of undigested information, but they are bewildered—even resentful—when asked simple but basic questions like 'how does a man stand upright?'. This change in emphasis has made physiology less enjoyable either to study or teach than it used to be, as well as less educational in the broadest sense: there is no time and little motivation to ask questions of oneself, and all is reduced, in the end, to rote-learning.

The second factor that has debased the intellectual quality of much of our teaching is the increasing emphasis that is put on mechanism instead of function. More time is often spent in talking about the detailed physics of nerve conduction than in discussing exactly what information is being carried by nerves, how it is coded, and how the nervous system is actually used. Again, lecturers' fear of instant student opinion is perhaps partly the cause: most students get immediate and easy satisfaction (of a limited kind) by seeing the detailed steps that cause a particular phenomenon; and if all can be reduced to a series of biochemical reactions, then so much the better. To understand whole systems and their interactions requires rather more effort of thought, and one can never be sure one is right. But in the long run, and most particularly for medical students, it is precisely the large-scale functioning of physiological systems that is important. A doctor needs to have a feel for what is likely to be the consequence of chronic heart failure in terms of problems of fluid balance, or for what may happen if his asthmatic patient decides on a holiday in the Andes. Whether the cardiac action potential is due mainly to calcium or to sodium, and whether or not the substantia nigra projects to the red nucleus, are for him matters of singularly little interest or significance.

This book is an attempt to go counter to this trend by starting from the premise that a more satisfactory way to teach physiology is to build a scaffold of general principles on which factual details may later be hung as the need arises, and to prefer to consider *what* systems do rather than *how* they do it. However, this is largely a matter of emphasis and organization rather than of content, and the reader will find details of mechanism if they are required. Above all, the aim has been to recreate something of the intellectual excitement of the study of physiology that has been lost sight of in recent years, and to encourage the student to think and to question. If it is at all successful in this, the thanks should go not to me but rather to those past and present students of mine for whose intellectual stimulation I am—as all teachers must surely be—deeply indebted.

Cambridge, 1984 R. H. S. Carpenter

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Contents

1

Studying the brain

This book is about trying to understand the brain; we might begin by asking whether such an aim is not in fact hopelessly ambitious.

The human brain is a machine whose complexity far exceeds anything made by Man. It is made up of units called *neurones* that provide both the pathways by which information is transmitted within it and also the computing machinery with which its decisions are made. There are quite a lot of these neurones: about thirty times as many as the total number of men, women and children on this planet. Each neurone communicates with a large number of its neighbours, perhaps several thousand of them, and it is the pattern of these connections that determines what the brain does. Studying the brain is thus like studying human society: for a society can only be fully understood in terms of the interactions that each of its individuals makes with the circle of people with whom he is in contact. Consequently the understanding of the brain is a task as daunting as trying to comprehend the behaviour of the entire human race, its politics, its economics, and all other aspects of what it does; in fact, about thirty times more difficult. For this reason, the study of the brain has in some respects a closer affinity with 'arts' subjects like history than it does with much conventional science, and this for many people is part of its attraction. Our brains *need* to be complex: part of what they do is to embody a kind of working model of the outside world, that enables us to imagine in advance what would be the result of different courses of action. It follows that the brain must be at least as complicated as the world we experience. How has such complexity come about? The evolutionary history of the brain is not well understood, but was probably something like the account that follows.

The history of the brain

The co-ordination of a single-celled organism such as an amoeba is essentially chemical: its brain is its nucleus, acting in conjunction with its other organelles. But the proper co-operation of the cells of a multicellular organism clearly demands some kind of communication between them, particularly when, as in Hydra, there is specialization of cells into different functions: secretion, movement, nutrition, defence and so on. In small and slow creatures, such communication may still be chemical; but as an organism gets bigger, it takes a disproportionately longer time for a chemical signal released at one end of it to reach the other, because the time taken for diffusion is proportional to the square of the distance travelled. If speed of response is not particularly important, and if in addition there is some kind of fluid circulation that will increase the rate of dispersion of chemical transmitters, this kind of communication may still be satisfactory even in very large organisms. Our own hormonal control systems are of course precisely of this kind. But such systems are not only slow, they are also imprecise. When a sudden fright leads to release of adrenaline into our blood, it acts indiscriminately on the whole body. For fast and localized action, we need an arrangement that will release chemical transmitter as rapidly as possible at the site where it is required, and nowhere else (Fig. 1.1). Without spatial selectivity of this kind, we would need as many different transmitter substances as target organs: in fact, as we shall see, all the thousands of millions of skeletal muscle cells in our bodies are controlled by just one chemical transmitter: acetylcholine.

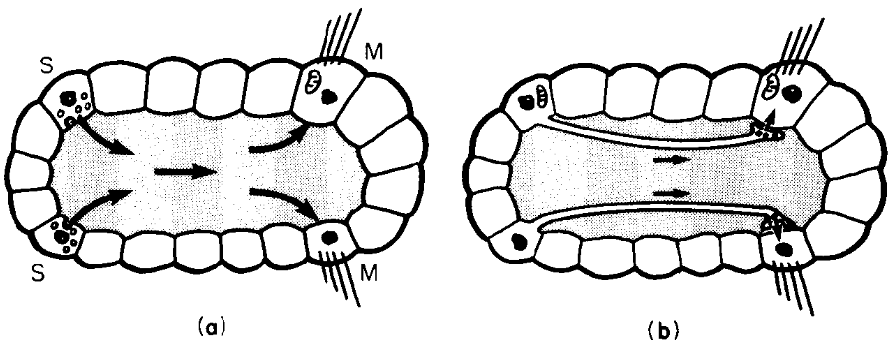
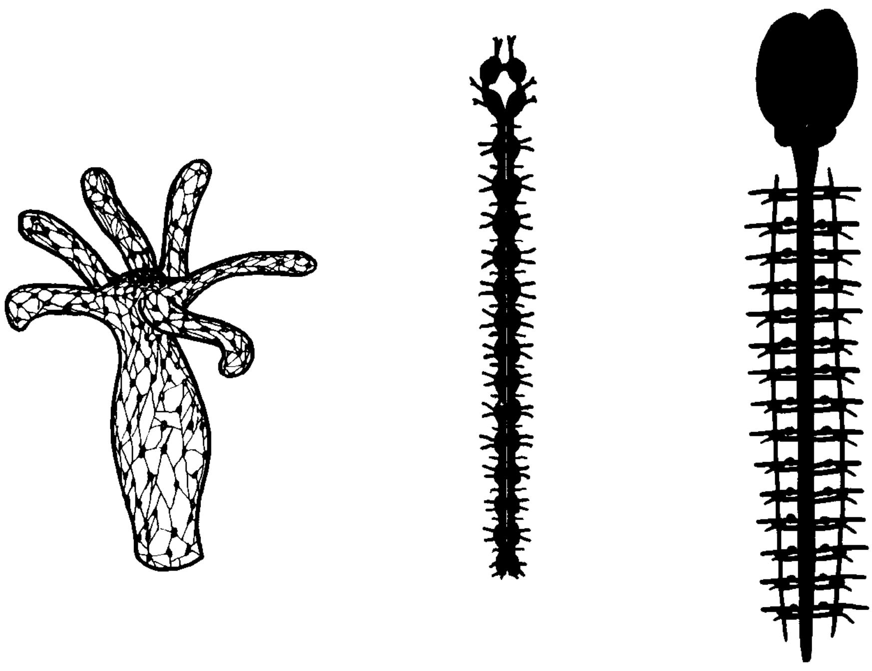


Fig. 1.1 (a) A hypothetical multicellular organism with sensory cells (S) that control motor cells (M) by releasing a chemical transmitter or hormone into the common fluid space. (b) Direct connections between sensory and motor cells by means of nerve axons, providing communication that is both quicker and more specific. Their ultimate action on the motor cells is still chemical.

This function of localized secretion is carried out by the nerve cells or *neurones*. Neurones are of ectodermal origin, and some remain in epithelia as *sensory receptors* that are sensitive to mechanical or chemical stimuli, to temperature or to electromagnetic radiation. Others have migrated inward, and have become specialized as *interneurones*, responding only to the chemicals released locally by sensory neurones or other interneurones, and in turn releasing transmitter at their *terminals* which form junctions called *synapses* either with interneurones or with effectors such as muscles or secretory cells. They thus provide the communication channels by which information is passed rapidly from one part of the central nervous system to another, through mechanisms that form the subject of Chapters 2 and 3. In Hydra, for example, we find a network of such intercommunicating neurones, making contact on the one hand with sensory cells on its surface that respond to touch and chemical stimuli, and on the other with muscle cells and secretory glands. Hydra's brain is thus spread more-or-less uniformly throughout its body, with only a slight increase in density in the region of its mouth: yet even such a relatively undifferentiated structure is capable of well co-ordinated, even 'purposeful' behaviour.

The next step in the evolution of the nervous system comes with the increasing specialization of sensory organs, particularly of *teloreceptors* such as eyes and olfactory receptors. For an animal that normally moves in one particular direction, such organs tend to develop at the front end, and the result of the consequent extra flux of sensory information to a localized region is an increased proliferation of interneurones in the head. In Planaria we have the first true brain of this kind, a dense concentration of neurones close to the eyes and sensory lobes of the head, giving rise to a pair of nerve cords that run down the body and send off side branches connecting with other neurones and effector cells. In segmented animals like the earthworm, the nerve cords show a series of swellings or *ganglia*, one to each segment; each of them can be thought of as a kind of sub-brain, and a decapitated earthworm is still capable of many kinds of segmental and intersegmental co-ordination. Though our bodies are not of course segmented, our nerve cord, the *spinal cord*, still shows some segmental properties, particularly in the organization of the incoming and outgoing fibres, and in the existence of corresponding chains of ganglia along each side (Fig. 1.2). We shall see later, in Chapter 10, that our spinal



(a) (b) (c)

Fig. 1.2 Schematic representations of *Hydra* nerve-net (a), and central nervous systems of earthworm (b) and Man (c). (Partly after Buchsbaum, 1971).

cord is also capable of a limited degree of brain-like activity. The primitive nerve net has not been altogether superseded, but survives as an adjunct to the central nervous system in the diffuse networks near the viscera that control gut movement and some other visceral functions.

The subsequent development of the brain is rather more complex, and not well understood. By looking at its evolutionary history in conjunction with the sequence of its growth in fetal development, one can postulate a framework that may help to relate the primitive nervous system to the more intricate structure of the adult human brain.

The central nervous system is derived from a narrow strip of ectoderm, the *neural plate*, which runs down the middle of the vertebrate embryo's back. The

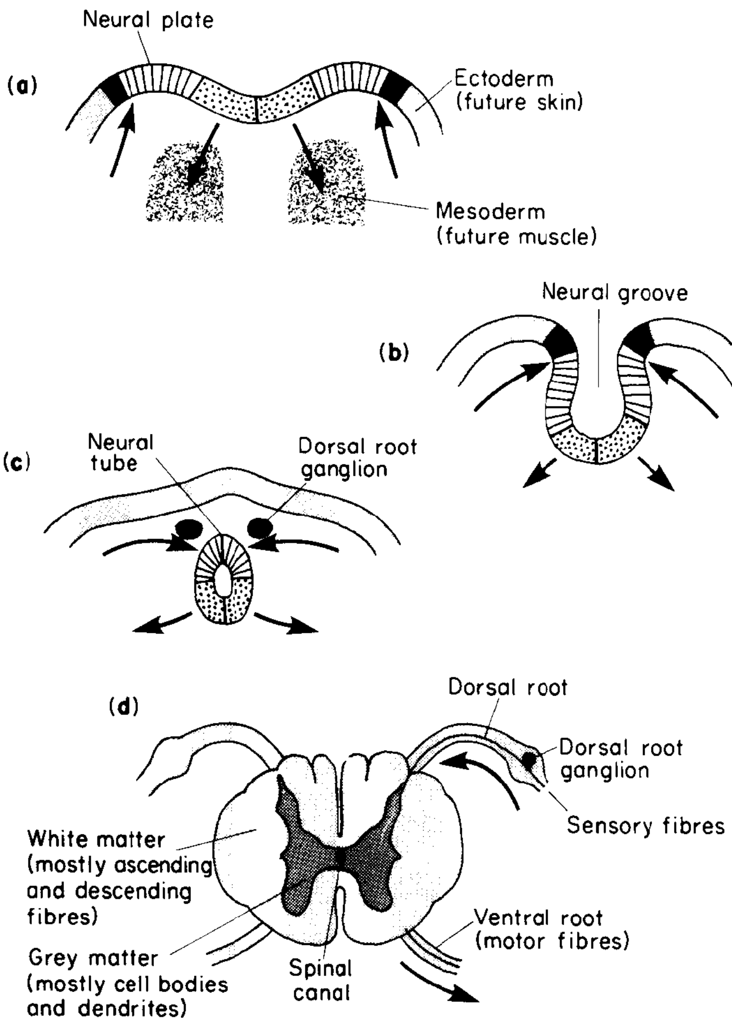


Fig. 1.3 (a)–(c) Highly schematic representation of development of neural tube from neural plate, showing relative positions of sensory (striped) and motor (stippled) regions. (d) Cross-section of adult human spinal cord, at the level of the second thoracic vertebra

centre of this strip becomes depressed into a trough or groove, and eventually its edges come to meet in the middle to form a closed structure, the *neural tube* (Fig. 1.3). It is natural for sensory fibres from the skin to enter at the margins of the neural plate, and for motor fibres to the more medial musculature to leave the plate nearer the midline, and as a consequence one finds that it is in the dorsal half of the neural tube that the sensory fibres terminate (their cell bodies lying in the *dorsal root ganglia* on each side of the tube), while the cell bodies of the efferent motor fibres lie in the ventrolateral part of the neural tube, and this arrangement is evident in the adult spinal cord (Fig. 1.3**d**). Here one can see in cross-section the *ventral* and *dorsal horns*, consisting of masses of *grey matter* (mostly cell bodies), a less prominent central region concerned with the neural control of visceral function, and a surrounding sheath consisting of *white matter*, mainly bundles of nerve fibres running longitudinally up and down the cord.

At the cephalic end of the neural tube, a modification of this basic plan occurs. The central fluid-filled canal, which is very small in the spinal cord, widens out at two separate points to form hollow chambers or *ventricles*: at the same time it migrates back to the dorsal surface of the neural tube, so that the ventricles are open on their dorsal side. This surface is covered by the *choroid membrane*, the site of production of the cerebrospinal fluid that fills the canals and ventricles of the brain. The more caudal of the ventricles is called the fourth ventricle, and the region around it is the *hindbrain* or rhombencephalon; it is connected to the more rostral third ventricle by the *cerebral aqueduct*. The region round the aqueduct is called the *midbrain* or mesencephalon and that round the third ventricle is the *forebrain* or prosencephalon (Fig. 1.4). Subsequently, the third ventricle produces a pair of swellings at the front end, which become inflated into the *lateral ventricles*: the neural tissue surrounding them forms the *cerebral hemispheres* (telencephalon) while the rest of the forebrain is called the diencephalon. The hindbrain is likewise divided into two regions: the caudal part is called the *medulla*, and the rostral part of it (metencephalon) is marked by the outgrowth of the *cerebellum* over the dorsal

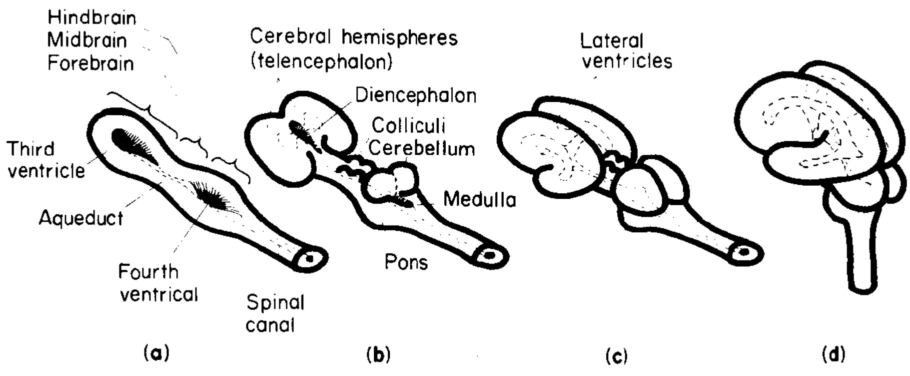


Fig. 1.4 The notional steps leading from neural tube to human brain. **(a)** The opening of the canal to and from the third and fourth ventricles. **(b,c)** The growth of the cerebellum, and of the cerebral hemispheres with their associated lateral ventricles. **(d)** Human brain, showing greatly enlarged cerebral hemispheres, and flexion of the neural tube