Diseases of the Nervous System

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Introduction

Many medical students consider clinical neurology complex and mysterious as well as a particularly formidable academic hurdle, while it is often regarded by medical practitioners as directed chiefly to fruitless differentiation between obscure and untreatable degenerative diseases. Both views are far from the truth. The clinical neurologist spends most of his time in the diagnosis and management of illnesses characterized by such important and common symptoms as headache, dizziness, and attacks of loss of consciousness, which are at least as accessible to treatment as those under the care of his colleagues in other specialties. Furthermore his discipline entails the logical application of a working knowledge of the anatomy and physiology of the nervous system at a fairly simple level, while the pathological processes with which he deals evoke physical signs less equivocal and more elegant than those encountered in any other branch of medicine. It is for these reasons, rather than because of the frequency of epilepsy and migraine, that clinical neurology has earned an important place in every undergraduate curriculum, especially on the continent of Europe and in the foremost medical schools of the United States.

Many students undoubtedly encounter difficulty in mastering the principles of this part of their clinical instruction. This is partly because the student usually comes to clinical neurology long after the conclusion of his formal anatomical studies, which were in any case conducted apart from the clinical context that could give them meaning, and have probably left little more than a blurred recollection of often irrelevant detail.

These are the reasons for our presentation of the subject in a somewhat unorthodox form, broadly based on the integrated medical curriculum recently introduced in the University of Newcastle. One principle is that as far as possible the contributions of basic science and the special investigations are worked into the texture of instruction and presented as intrinsic aspects of a clinical presentation rather than as isolated subjects on their own account. Another is that instruction

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proceeds from the clinical expressions of the simplest pathological concepts such as physical injury, impaired blood supply and identifiable infection to the more complex and problematical parts of clinical neurology where the present weakness of the subject in aetiological knowledge is apparent. The book is designed for reading rather than for reference: our presentation is selective rather than comprehensive, and rarities are mentioned only when they have some intrinsic importance or illustrate a principle.

The authors wish to thank many friends and colleagues for suggestions and criticisms; Miss Dorothy Mustart for preparing the diagrams; Dr J.B. Foster, Dr Peter Hudgson, and Dr Geoffrey Pearce for lending illustrations; and Dr Gordon Gryspeerdt and Professor Bernard Tomlinson for allowing us to use their radiological and pathological material. We hope that our written account reflects the approach that students have enjoyed in such a presentation of the subject, and that collaboration of two clinical neurologists of different backgrounds but similar outlook has helped to avoid the occasional lacunae inseparable from any entirely individual view of a complex subject.

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CHAPTER 1

The Form and Functions of the Nervous System

The functions of the nervous system are infinitely more varied than those of any other organ or system and are served by many thousands of millions of neurones, interlinked in an orderly but inconceivably complex manner. The student who has mastered the essentials of the comparatively simple pumping action of the heart or the rather more involved regulating functions of the kidney is naturally daunted by the prospect of exploring the impact of disease on this labyrinth, whose functions range from the control of sweating to those of memory, speech and consciousness. A further obstacle is that while other organs vary in no important respect throughout the mammalian kingdom, the human brain is very different from that of even the most advanced of other primates. Partly for this reason, much that has been learnt from animal experiments has no immediate application to the understanding of the normal or diseased nervous system in man. These limitations, imposed on student and professor alike, obscure our understanding of neurological disease, but also permit some simplification of the necessary basic knowledge. It is, for example, unnecessary to memorize all that is known or surmised about the connections of the red nucleus in the cat, since this has no certain clinical application. Nevertheless, it is impossible to embark on the study of neurology without a sound understanding of those elements of neuro-anatomy and physiology currently known to be clinically relevant. In the following account it will be assumed that the student has already received considerable instruction on the structure and function of the nervous system, but insufficient enlightenment on those aspects likely to prove useful in clinical medicine.

NEURONE AND NERVE IMPULSE

The neurone, the basic element of nervous tissue, consists of a cell

body containing the nucleus, a variable number of branching dendrites, and an axon. The intense metabolic activity of the cell is reflected in the numerous mitochondria in the cytoplasm, and by the presence of basophilic Nissl granules containing ribose nucleoproteins. The axon, which varies in length from a few millimetres to almost a metre, is maintained by the continuous synthesis of axoplasm by the cell body, and therefore degenerates if the cell body is destroyed. The dendrites and the cell body receive synaptic connections from other neurones, often in enormous numbers, and the axon conveys the nerve impulse, sometimes to effector organs but more often to other neurones.

The interior of the neurone is electrically negative relative to the exterior. This actively excludes sodium (the sodium pump) while maintaining a relatively high concentration of potassium within the cell. The nerve impulse originates in the region of the cell body adjacent to the axon, and is induced by a brief loss or reversal of the resting electrical gradient, a process known as depolarization. Stimuli reaching the neurone through the synapses may have either an excitory or inhibitory effect, the former tending to depolarize the membrane and the latter to maintain the resting potential. The nerve impulse does not cross the synapse, but transmission is effected by the liberation from minute vesicles of a chemical that then acts on the cell membrane. The nature of the stimulus, whether excitatory or inhibitory, almost certainly depends on the chemical liberated, but relatively little is known of the chemistry of transmission in the central nervous system. Acetylcholine has been identified as the transmitter substance in peripheral autonomic ganglia and in one central neuronal system, but other substances are certainly concerned.

We may picture the neurone exposed to conflicting impulses at high frequency and fluctuating intensity, and discharging along its own axon only when the balance swings so far towards excitation as to cause depolarization of the cell membrane. Propagation of the nerve impulse is quite unlike the conduction of an electric current along a wire. Depolarization, involving a brief reversal of the resting electrical gradient, spreads along the axon and both this active process and the maintenance of the resting state require the expenditure of energy and the consumption of oxygen. Many axons are surrounded by lipid sheaths of myelin. In peripheral fibres this is laid down spirally by the neurilemma or Schwann cells, while in the central nervous system the oligodendroglia apparently perform a similar function. Many fine peripheral fibres have no myelin sheath, but are surrounded by a layer

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of Schwann cell processes. In all myelinated peripheral fibres the myelin sheath is interrupted at intervals of less than a millimetre by the nodes of Ranvier, the junction between successive Schwann cells. Although much more difficult to demonstrate, similar nodes are present in the central nervous system. It is thought that active propagation takes place at the nodes, causing successive depolarization of each segment of axon and more rapid and economical transmission. Loss of the myelin sheath prevents efficient propagation of the impulse. Conduction velocity also varies with the diameter of the fibre and in large peripheral myelinated fibres may reach 60 metres per second (125 m.p.h.).

NEUROGLIA

The electron microscope has revealed that the central nervous system consists of an astonishing interlacing of branching processes of neurones and glial cells with little or no recognizable extracellular space, a finding in conformity with its lack of any lymphatic system. The glial cells are not merely supportive tissue, but are undoubtedly involved in the metabolism of the nervous system. Tissue culture studies have thrown some doubt on the original rigid classification, but the microglia appear to be phagocytic histiocytes and the oligodendroglia concerned with the formation of the myelin sheath. The astrocytes are often closely related to capillaries, but their precise metabolic role is not well understood.

METABOLISM

In the complex metabolism of the nervous system certain main streams can be identified. The most immediate is the provision of energy to maintain the relative exclusion of sodium and the electrical potential without which a neurone ceases to function. This is provided by the breakdown of high-energy phosphate compounds that must be constantly renewed by the catabolism of glucose. The process of glucose breakdown, glycolysis, is essentially similar in all tissues and proceeds through the citric acid cycle, catalysed by the agency of enzyme chains. Vitamin B^1 (aneurin) has been identified as a coenzyme concerned in the breakdown of pyruvate, an essential stage in the cycle, and it was the observed effect of deficiency of this vitamin that led to the important concept of the biochemical lesion. This implies that function is dis-

turbed by a potentially reversible disorder of metabolism, in this instance a block in glycolysis leading to accumulation of pyruvate and failure to provide cellular energy. The importance of such lesions is being increasingly recognized. The lack of an enzyme or its inactivation by abnormal metabolites leads not only to failure of the normal step in the metabolic chain, but to accumulation of 'toxic' concentrations of normal tissue constituents. These in turn may block other enzymes, leading to a spreading chemical and functional disorder. If this is sufficiently prolonged permanent neuronal damage ensues, but if the original metabolic block can be recognized and corrected the adverse effects can be mitigated or reversed.

The nervous system differs from muscle in that anaerobic glycolysis does not occur and the removal of hydrogen ions linked with oxygen to form water is continuously necessary. The brain is therefore peculiarly vulnerable to any interruption of its supply of oxygen, without which the neurone rapidly dies, apparently consuming its own substance as a final source of energy. A continuous supply of glucose is also essential, for although glycogen is present in the brain there is no provision for carbohydrate storage comparable to that of muscle or liver. In conditions of rest the adult brain, comprising little more than 2% of the body weight, is responsible for one-fifth of the total consumption of oxygen and two-thirds of the consumption of glucose.

Glucose is indeed virtually the sole source of energy, as although brain slices can be induced to utilize other substrates this does not occur in life. Other potential sources of energy are prevented from accumulating in the central nervous system by the operation of the blood-brain and blood-cerebrospinal fluid barriers. These are homeostatic mechanisms ensuring that the neurones enjoy a relatively stable biochemical environment, shielded to some degree from fluctuations in the general metabolism. Although the precise means by which this is effected remain unknown the barrier is an active process by which unwelcome metabolites that have diffused into the brain are returned to the plasma.

Surprisingly, the rate of protein synthesis in the adult brain is comparable to that in the liver. Much of this must be accounted for by the continuous synthesis of axoplasm in the cell body and its extrusion down the axon. There are suggestions from animal experiments that the physical basis for the storage of information may lie not in reverberating electrical circuits, but in the elaboration of specific proteins. The clinical significance of this intense metabolic activity is quite uncertain.

Knowledge of the chemistry of synaptic transmission is only beginning to contribute to our understanding of disease, partly because there is no certainty about the agents involved. There is evidence that acetylcholine, dopamine, noradrenaline, gamma-amino butyric acid and possibly glycine and serotonin play some role in transmission. Gamma-amino butyric acid appears to be a universal neuronal depressant but other probable transmitter substances have been shown to be capable of both inhibition and excitation, depending on the receptor mechanisms of the individual neurone. It is probable that many of the very numerous drugs that act on the nervous system exert their effect by modifying the release of or response to transmitter substances. Even the most complicated pharmacological action on the brain must result either from excitation or inhibition of neurones, but a drug may exert opposing effects at different anatomical sites or even on different populations of cells at a single site such as the descending reticular formation. The mode of action even of simple sedative drugs is imperfectly known, and nearly all therapeutic actions have been discovered by trial and error.

The metabolism of amino-acids is of central importance, being linked with the synthesis of transmitter substances, with protein metabolism, and with the citric acid cycle. The principle free amino-acid in the brain is glutamic acid, probably derived from glucose, and capable of combining with ammonia to form glutamine. The conversion of glutamic acid to gamma-amino butyric acid requires the coenzyme pyridoxal phosphate which has been shown to be absorbed as pyridoxine or vitamin B^6. The functions of glutamic acid that have been partially unravelled therefore include the detoxification of ammonia and almost certainly an important part in the regulation of neuronal excitability.

The ionic equilibrium involving the relative concentrations of potassium and sodium on either side of the cell membrane is influenced by the concentrations of other electrolytes. Calcium stabilizes the cell membrane, preventing depolarization, and a lack of extra-cellular ionic calcium has the opposite effect, causing repeated spontaneous firing of the neurone. Carbon dioxide, produced in the brain by glycolysis or conveyed in the blood stream has a similar stabilizing effect on the membrane and therefore a depressant action on neuronal activity. Its accumulation is prevented by the action of the enzyme carbonic anhydrase which catalyses its combination with water to form carbonic acid.

About half the dry weight of the brain consists of lipids, many of which are specific for nervous tissue and apparently synthesized there.

Cholesterol and the cerebrosides, containing a carbohydrate radical, and sphingomyelin which contains phosphorus, are all relatively concentrated in the white matter. The metabolism of these substances is only slowly being elucidated but their function in the formation of the myelin sheath is established. Once formed the myelin complex appears to be stable in health and is relatively little involved in active metabolism. Disorders of lipid metabolism are therefore particularly important in the early years of life when myelin is being laid down, and in those disease processes in which the myelin sheath is destroyed. Abnormal accumulation of lipids may therefore result from breakdown of myelin, or from disturbance of the normal lipid metabolic pathways during the period of development.

Investigation of the biochemistry of the brain in health and disease is rendered difficult by the operation of the blood-brain barrier and the inaccessibility of the central nervous system. Little is so far known of the different metabolic activities of specific organs and systems in the brain. Biopsy techniques must necessarily be of limited value, permitting little more than an estimate of the metabolites present in the specimen at the moment it was taken. This can be but a poor reflection of the dynamic processes whose distortion must cause or accompany most forms of cerebral disease.

For purposes of description it is conventional to write of the sensory and motor aspects of the nervous system almost as if they existed in isolation. This is entirely artificial. The function of the nervous system is the reception, integration and perception of sense data, external or internal, and the organization of the appropriate response. This may indeed be motor but may also be secretory or concerned with such mental processes as memory or thought.

THE AFFERENT SYSTEM

A large proportion of the afferent impulses reaching the central nervous system does not give rise to any conscious 'sensation'. Of those that do it is convenient to speak of fibres conveying sensations of touch or pain, but it must be remembered that such fibres simply convey nerve impulses no different from others, and that there can be no sensation of touch or pain, unless these are interpreted as such by the brain.

Numerous specialized receptor organs are present in the skin, hair

follicles, muscles, tendons, joints, connective tissue and viscera. In the skin some receptors appear to be structurally adapted to respond to specific stimuli, and it is well known that sensitivity to pain and thermal stimuli varies greatly from point to point within small areas. However, attempts to demonstrate that one type of receptor is specific for a given type of stimulus have proved inconclusive. Areas containing nothing but a network of bare nerve fibres may be exquisitely sensitive to all forms of stimulus. It may be the pattern of stimulation in space and time that is responsible for the different sensations actually experienced, rather than the stimulation of specific receptors.

One specialized receptor organ must be described in more detail. It is the muscle spindle—the spiral sensory organ that encircles a group of small specialized muscle fibres, the so-called intrafusal fibres (Fig. 1). These fibres have a motor supply distinct from that of the bulk of the muscle, conveyed by fine fibres which, because of their size, fall into the gamma group. They are better referred to as the fusimotor fibres. Although further refinements are constantly being described, the essence of the muscle spindle is that the two ends of the intrafusal fibre can contract, while the centre, surrounded by the primary sensory receptor, cannot. When the fusimotor fibres discharge, the central portion including the receptor, is consequently stretched. The sensitivity of the receptor is therefore variable and under the control of the fusimotor fibres. When the muscle is stretched the spindles initiate afferent impulses which pass up fast-conducting fibres to the spinal cord. Spindles have been identified in nearly all voluntary muscles, and play a most important part in all aspects of movement.

The afferent fibres originate in the cell bodies in the posterior root ganglia, and in similar ganglia related to the cranial nerves. On leaving the ganglion the axon divides, one branch being directed peripherally to the sense organ and the other centrally to the spinal cord or brain. The fibres vary greatly in diameter and thus in conduction velocity. The central branches of the spinal afferent fibres form the posterior roots, which divide into smaller rootlets and enter the spinal cord on its postero-lateral aspect.

Each posterior root receives fibres from a more or less well defined area of skin, the dermatome (Fig. 2). These areas overlap and there is certainly some individual variation. The important landmarks can be summarized as follows: the first cervical root (C1) has no sensory component, and the C2 area extends over the back of the scalp almost to the vertex; C3 and 4 include the neck and upper part of the shoulder, while

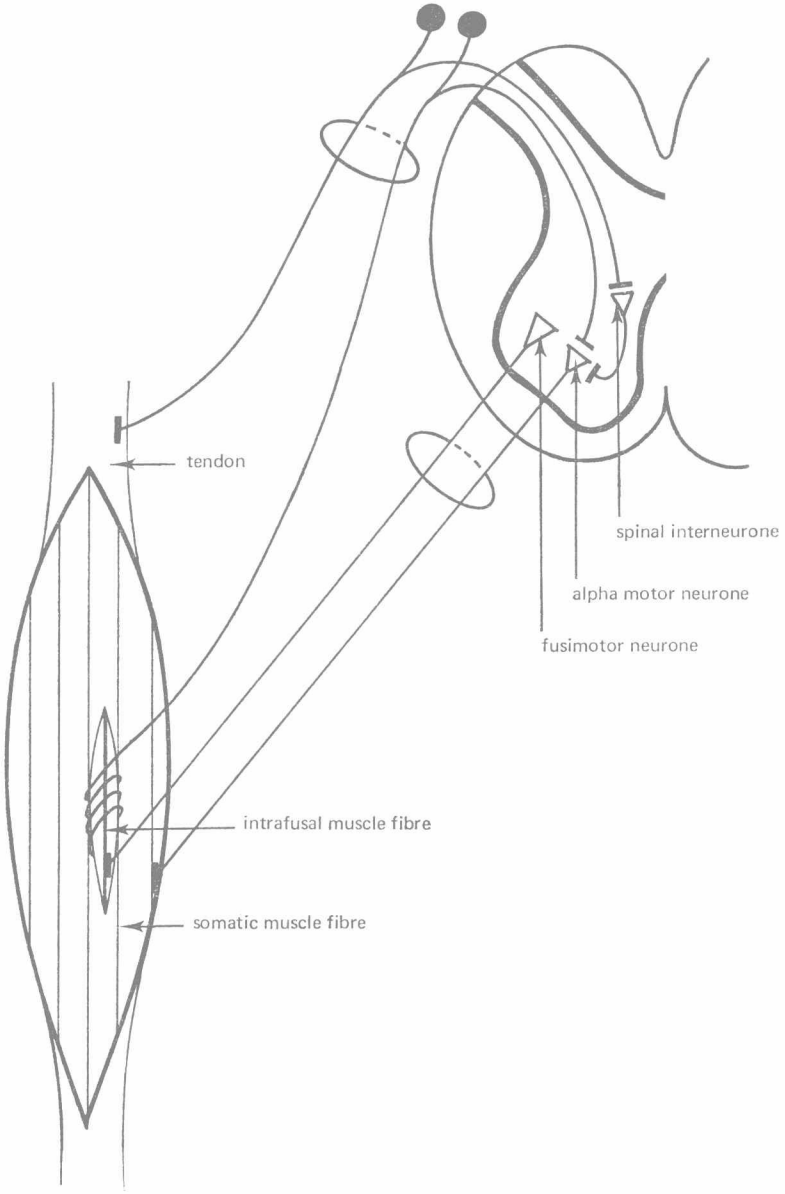

FIG. 1. The muscle spindle: a simplified diagram showing how the sensitivity of the primary sensory organ can be influenced by contraction of the somatic muscle fibres and of the intra-fusal fibres.

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