Victor Horsley Memorial Lecture

OR

THE INSULATION OF THE NERVOUS SYSTEM.*

BY

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WITHIN a few days it will be exactly ten years since Victor Horsley died. The circumstances of his death, however lamentable they may seem to us who lost him, were not, perhaps, very different from what he himself might have wished. He was at work in the direct service of his country, he was using his whole strength in the relief of suffering, while his mind and body kept unabated their astonishing and characteristic vigour. In commemorating this great man our attention is attracted to three separate aspects of his life. We think of him as a physiologist and as a surgical pioneer, and we think of the personality which lay behind and informed these and all the activities of his crowded years.

His work for science and for surgery has long been incorporated with the general body of knowledge and has its lasting place. For his personality there is no such lodgement, and those in whose memory it lives so vividly are already, after the passage of even ten years, a heavily reduced company. I therefore gratefully accept this chance to make my small record of a man who in my knowledge of men was unique in this—that he combined an inflexible belief in his own standards and a truly apostolic zeal in all public affairs, with a disposition that was in its essence boyish and simple and in every private relation easy and mild and kind.

METHODS OF INVESTIGATION IN NEUROLOGY.

The pioneer work of Horsley in the surgery of the central nervous system has had and must continue to have important remote and secondary effects upon the development of neurology. Whenever a region of the body has been made accessible to surgery, a new insight into its pathology has resulted from the fresh experience that has been acquired of morbid processes in the living and especially of the earlier stages of disease. This has been abundantly shown in the case of the abdomen and in the case of the thorax. In that of the central nervous system it is perhaps as yet less obvious, but it is already unmistakable and will become increasingly so as experience accumulates.

While most of us would no doubt agree that important practical knowledge is to be acquired in this way, there are probably few who look to it with much hope for the discovery of principles of general scope and fundamental significance. As a possible source of any wide expansion of neurological theory it is just and natural to look to laboratory methods and the study of animals rather than to methods of the bedside and to the study of man himself in his reactions to injury and disease. In the familiar and not always philosophically made comparison between the experimental and clinical methods it is usually, however, overlooked that the latter has of necessity a virtue which is in some degree its special possession. The student whose material is man is drastically handicapped by the limited extent to which experiment is open to him. He must take his problems as he finds them, and deny himself the help of almost all the preliminary simplifications which are the essence of the laboratory worker's advantage. At the same time, however, the conditions of his work impose upon him a knowledge of his material at once so intimate and so wide as to constitute a situation probably unique in the whole field of science. When we consider the intensity of watchfulness which the quite ordinary practice of neural

surgery calls for and obtains it must be obvious that the behaviour of the human brain in the various circumstances of injury and disease is far better known than that of any other animal. Indeed, one of the characteristic difficulties of the clinician comes from this very abundance of the stuff of observation, and he is likely to be overwhelmed by its bulk and rendered inattentive by its familiarity, losing amongst details his sense for larger groupings, and amidst the everyday his eye for the significant. Nevertheless the history of science shows that one important source of general ideas has been just this very circumstance of a close intimacy with a large range of observed facts.

The familiarity with the behaviour of the central nervous system that has been possible since it has been accessible to surgical exploration and treatment is capable of reacting in an important way on our attitude to neurological theory.

THE ABSTRACT METHOD IN NEUROLOGY.

There are few departments in biological science in which what we may call abstract methods of thought are more naturally and inevitably used than they are in neurology. By abstract methods I mean methods in which the single or grouped items of experience are for convenience of thought represented by abstracted summaries of themselves or symbols, which have a handiness for working on in the mind that the raw undigested facts cannot possess. The discovery of the uses of abstraction was an event of fundamental importance in the evolution of science, and in the early Greek natural philosophers we can see with what exultation was welcomed the extension it gave to the powers of the mind. Perfectly legitimate and indeed indispensable as the method is, it is obviously not applicable to all material of inquiry with equal ease and safety. With what certainty and precision the qualities of number, space, and motion allow of abstraction is seen in the noble achievements of mathematics, physics, and astronomy—achievements which, through their most recent extensions in atomic and in stellar physics, have finally established the overwhelming prestige of the method and its effective leadership in science.

When, however, we make living matter and living organisms the subject of study we find that though we can by no means dispense with the use of abstraction it is far less effective in application and has disadvantages which it does not seem to possess in the inorganic world. In biological inquiry an abstract conception, though professedly no more than a convenient summary of experience and constantly subject to the censorship of facts, is apt to acquire a quasi-vitality of its own through which it loses its immediate dependence on experience and comes to dominate instead of serving. The danger arises not so much from the extreme cases of conceptions which easily show as flagrantly inconsistent with facts, but from ideas primarily good and sound which have been endowed with a prestige that in their very nature they could not deserve. That an overvaluation of the abstract conception as an implement of research can deceive even the very elect could be shown by many eminent examples. The biological writings of Herbert Spencer are perhaps as good an instance as comes readily to mind, and it is easy to trace in them how this very weakness has led within a few years to their greatly diminished influence. To find so distinguished a man in a state of reprobation may well make humble people look anxiously to their own doctrines; and indeed which of us, for example, can ask himself without a qualm what is the *exact* meaning he attaches to the abstract conception of evolution which has dominated the biological world for half a century?

When we turn to neurology we find the currency and influence of abstract conceptions very great—as, for example, in the theory of aphasia, in Hughlings Jackson's interpretation of cerebral functions, in Monakow's doctrine of diaschisis, and so forth. All these are doubtless, in their essence and originally, good and valuable conceptions; it is another matter, however, how far their function as professed summaries of experience is kept distinct from their charm as mere intellectual patterns. It is thus peculiarly necessary for neurology to submit itself to the

* The second Victor Horsley Memorial Lecture, delivered at the House of the British Medical Association on Friday, July 9th; Sir John Bland-Sutton, Bt., F.R.C.S., was in the chair.

discipline of frequent returns to the comparatively primitive and clumsy method of direct and concrete thinking. Such efforts should, I think, be guided by two principles. The first is the obvious one that a constant and docile reference to experience is indispensable. The second is perhaps less obvious and is less simple to state; it accepts the free use of hypothesis as essential to neurological progress, but it enjoins that in drawing up our necessarily more or less abstract conceptions of the nature and working of the nervous system we should incline to the use of ideas of a definitely biological type, and should as far as possible avoid concepts that in their very nature can have no direct resemblance to what actually happens in the body. In giving to our neurological ideas this concrete and realistic tone we shall always depend to a great extent on an intimate familiarity with the appearances and behaviour of the actual nervous tissues. The knowledge of this kind we possess to-day may well be regarded as having in great part grown out of Horsley's work.

The surgical neurologist is perhaps fortunately placed for considering the nervous system in an attitude of mind at once general and concrete; while he lacks the special knowledge of the anatomist, the physiologist, and the pathologist, he is also free from their special preoccupations; while the behaviour of the nervous tissues in injury and disease is a matter of familiar knowledge, it is prevented from becoming commonplace by the narrow margin of safety within which he works and the serious consequences that follow when it is exceeded. Thus is almost forced on him the development of views which, whatever they may lack in the way of abstruse detail, will at any rate always tend to be strictly realistic.

INJURIES TO THE LIMITING STRUCTURES OF THE NERVOUS SYSTEM.

In illustration of this general point of view I propose to call attention to a small group of facts which while they are of more or less common knowledge are perhaps more especially within the observation of the surgeon. They are concerned with the responses of the nervous system to certain injuries.

Division of a Nerve.

It is a very old observation that when a mixed peripheral nerve is cut its central end becomes swollen into a bulbous mass of dense fibrous tissue. It seems sometimes to be thought that this is only an occasional result of a nerve section and is especially to be looked for when persistent pain has followed the injury. This is, of course, not the fact. The bulbous end is the invariable and inevitable result of a nerve section to which it is the necessary and so to say physiological response. When we inquire into the exact nature of this so-called amputation neuroma we find that in immediate consequence of the section the nerve fibres ramify and grow out from the cut end so that there issues from this a veritable spray of fine naked axis cylinders. The result of this invasion is to call forth an energetic response from the adjacent non-neural tissue leading to the formation of a peculiarly dense fibrous material that resists the spread of the nerve fibrils and finally encloses them in an impenetrable capsule. Within this limiting substance the growth of axis cylinders continues, but since there is no exit it can result only in the formation of an intricate and aimlessly convoluted network.

Breaches of the Spinal Theca.

It occasionally happens, usually perhaps in connexion with the avulsion of a spinal nerve, that a subcutaneous laceration of the spinal dura occurs. More commonly the surgeon has an opportunity of studying the effect of breaches of the theca in cases where a laminectomy with incision of the membranes has to be followed by a second similar operation after some weeks or months. We find then that wherever the cerebro-spinal fluid has been able to escape into the tissues it has been everywhere walled off by a dense impervious membrane, so that, according to the extent to which the fluid has made its way, there will be a more or less complicated series of cyst-like spaces

communicating with the intrathecal cavity. It is the wall of these cystic extensions of the theca that is of interest, for it shows all the characters of the normal dura. It is of a dense, fibrous substance, its inner surface is smooth and glistening, and its outer surface, instead of merging with the surrounding tissues like a scar, is easily separable from them along a well marked line of cleavage.

Regeneration of the Cerebral Dura.

It is not uncommon for a second cerebral operation to be necessary in a case in which the dura mater has already been opened or removed. If the second operation is done after an interval of about six weeks or more it will be found that the gap, however large, that was left in the dura at the first operation has been closed by the formation of a new membrane having all the characters of normal dura as above described. Among such characters the most striking, and perhaps the most conclusive of the nature of the new membrane, is its differentiation from the overlying scalp, so that the latter can be stripped away from it with ease and without bleeding. It is interesting to note that at one time a great deal of surgical ingenuity was expended on evolving a plastic surgery of the dura, in which gaps were closed by the insertion of fascial grafts. Such grafts were always remarkably successful because a new dura would have formed quite naturally and equally well without them.

Here we have a group of three well defined facts established by countless observations and capable of confirmation at any time. They bring evidence from different parts of the nervous system disclosing even to superficial consideration a clear common tendency. The conclusion to which all point is that breaches of the normal coverings of the nervous tissues allowing contact between the latter and other tissues of the body result of necessity in energetic local reactions. The obvious function of such reactive processes is to re-establish the normal discontinuity between neural and somatic tissues and to break the contact that has caused the disturbance.

We have met, then, with a mechanism of a definitely physiological type which may well prove to be concerned with the very nature of the nervous system. Our next inquiry will naturally be, What is the immediate agent of the reaction we are concerned with? In the case of the divided nerve it seems clear that the escaping naked axis cylinder is the actual irritant substance; in the case of the spinal theca it is evident that the cerebro-spinal fluid is the effective agent; in the case of the cerebral dura it is probable that in ordinary conditions with an intact arachnoid, fluid exuding through this is the excitant, though the contact of the brain itself is doubtless also effective. It is seen, then, that there is a common property possessed by naked nerve fibres, by cerebro-spinal fluid, and almost certainly by the brain substance itself, which enables these to set up in the somatic tissues an energetic reaction the tendency of which is to insulate the one from the other. There is evidence that the neural side of the contact, while effective as an irritant, does not contribute to the newly formed tissue which, whether in the form of the fibromatous material of the bulbous nerve or in that of the extemporized dura, is of purely non-neural origin though obviously a highly specialized material and no mere scar.

FUNCTIONAL EFFECTS OF BREACHES IN INSULATION.

When we see such well defined mechanisms for the sealing of breaches in neural insulation we naturally should expect to find such breaches to be of great functional importance and capable of causing serious disturbance in the tissues unnaturally brought into contact. There is in fact evidence that some effect on function is produced, but it is not to the mere prevention of this that we can look to explain the actual existence of these mechanisms themselves; that seems to depend, as we shall see, on some far more fundamental causation. The chief evidence of disturbed function is seen in the case of the divided nerve. Here there are symptoms suggesting persistent excitation of the cut end. These are always present from the first, but they vary greatly in intensity. The sensation of the presence of the limb after an amputation is universal, and it always lasts for several weeks. Not uncommonly it is

painful, and then it tends to be more persistent and may last for years. The facts suggest that the exposed nerve fibres of the stump are excited by contact with the tissues, and that in the bulbous end the stimulation effect gradually dies down until a state of equilibrium is established in which the new tissue sealing off the nerve end is practically as inert towards the nerve as is its normal sheath.

It is natural to suppose that after a wound of the brain which allowed a scar of non-neural origin to come into close contact with the brain substance a state of excitation might be set up. The frequency of traumatic epilepsy in cases of direct scarring of the brain is perhaps suggestive, but I know of no evidence that allows us to take the case beyond a mere suspicion.

On the somatic side of a breach of neural insulation there is no disturbance of function beyond the mere reaction already described. It is, indeed, characteristic of this that it is always and only strictly local. There is nothing in the way even of a diffuse or spreading fibrosis; the new tissue, whether it be an amputation neuroma or a new segment of dura and although it is of somatic origin, becomes sharply differentiated from the tissues it is derived from, and can be separated from them easily without cutting. We see, therefore, that although breaches of neural insulation are immediately dealt with by energetic, effective, and highly specialized mechanisms, the actual disturbances of function produced by such breaches do not seem to be very important.

INSULATORY ARRANGEMENTS IN THE NORMAL NERVOUS SYSTEM.

If the evidence I have cited bears the meaning I have given it and we can regard as of high importance to the body the maintenance of neural insulation, then we can look for confirmation in normal structure and expect to find dispositions in relation to the nervous system which are insulatory in function. From the nature of the reaction we have seen to be set up by breaches of insulation we may infer that the influence against which insulatory mechanisms are provided is chemical in kind, and this inference may serve as a guiding principle in the search.

Insulation of the Peripheral Nerves.

Beginning our survey with the peripheral nerves we may at once dismiss from consideration the medullary sheath, which, whatever its physical insulatory function may be, is clearly not in question as a chemical insulant, since non-medullated nerves lie as peacefully and as inert in the tissues as the medullated. The case is different, however, with the neurilemma. Here we have a sheath common to all nerves outside the central axis, and continuous without a break from spinal cord or brain to end-organ. The motor nerve fibre is clothed from within the central nervous system to the muscle fibre, where the neurilemma completes the sealing off of unnatural contacts by becoming continuous with the sarcolemma itself. The sensory fibres are similarly clothed throughout their length; at their peripheral termination they enter end-organs all of which throughout a great variety of structure show—with one suggestive exception—so marked an encapsulatory arrangement that one cannot but think that here the need for insulation must be especially vital. The one sensory nerve fibre which is known to terminate in an end-organ which is not of a strongly capsular type is the fibre that serves the sense of pain. This fibre ends in a free arborization in the tissue to which it is distributed, and this terminal part is uncovered by neurilemma. It cannot but strike us as significant, though I shall not take up the point further at the moment, that this anomaly of a sensory fibre making naked contact with the somatic tissues should be a character of the fibre concerned with pain, a form of sensibility that in itself is so profoundly anomalous.

The view that the neurilemma is the chemically insulating structure we are looking for is confirmed by the fact that within the central nervous system, where insulation is otherwise provided, it is defective or altogether absent. A point further suggestive of the importance of insulation in the

peripheral nerves is the evidence we have that there is an upward drainage along their trunks, so that the products of their metabolism are probably kept from contact with surrounding tissues and are conveyed into the central theca.

Insulation of the Central Nervous System.

When we turn to the central nervous system we find that the method of individual insulation no longer prevails, but that the whole mass of the central axis is protected as one unit. Plainly, of course, it is the meninges which are chiefly concerned. Of these we have already seen that the dura has so important a function that accidental defects in it are repaired with very remarkable rapidity and completeness. The *mechanically protective* function of the dura, which doubtless has its importance, can scarcely be regarded as explaining its peculiarly impervious texture, its double endothelial surface, and the marked line of cleavage that separates it even when newly formed from the surrounding tissues. All these, however, acquire meaning when they are regarded as evidence of its *chemically insulatory* capacity. Effective as the dura doubtless is in its way, it deals only with one relatively small part of the problem of insulation. If we are right in supposing that all neuro-somatic contacts are inadmissible and that the blood and blood vessels belong to the somatic side of the frontier, the nutrition of so large a bulk of nervous tissue as the central nervous system must involve dispositions altogether unique in the body, and we should expect, in regarding the circulatory mechanisms of the part from this point of view, to meet with features of a very special kind.

The cerebro-spinal fluid and its circulation, the existence and disposition of the multiple membranes of the brain, and the absence of a recognizable lymphatic system in the ordinary sense of the term, constitute a picture which is unique, and has admittedly defied thorough explanation. Let us consider it in relation to the avoidance of undue contact between neural and non-neural elements.

THE CEREBRO-SPINAL FLUID.

Let me briefly review the strange facts of the physiology of the cerebro-spinal fluid as they are now known. The cerebro-spinal fluid is an extremely dilute secretion profusely poured out by the choroid plexuses of the cerebral ventricles. It flows through the central cavities of the brain and issues therefrom through the roof of the fourth ventricle into the subarachnoid space. Through this so-called space, which has rather the structure of a cellular sponge-work, it courses partly into the spinal canal, but chiefly upwards and forwards over the brain, to escape into the venous circulation through the arachnoid villi that project into the various lateral extensions of the superior longitudinal sinus. As is well known, any obstruction to the flow in any part of this intricate course downwards within the brain and upwards outside of it inevitably leads to an accumulation of the fluid and to hydrocephalus. Such obstructions are easily produced and common.

The cerebro-spinal fluid with its circulation, whatever function it may be there to perform, shows itself, then, to constitute a weak spot in the cerebral organization that as it were invites pathological attack. That the cerebral apparatus should contain an arrangement in some ways so seriously disadvantageous, suggests that the mechanism must have some deep functional significance that is indispensable to the physiology of the body.

There is no lymphatic system in the ordinary sense in the brain or spinal cord, and no flow outwards through the cerebro-spinal envelopes of anything corresponding with lymph occurs anywhere. It seems clear that products of nervous metabolism find their way into the cerebro-spinal fluid in the subarachnoid space; there is, in fact, strong clinical evidence that this fluid has a definite toxicity for the rest of the body, for when it is liberated into the tissues high fever is apt to occur during the short period before absorption is arrested by the inevitable reaction in the tissues that produces encystment. It is thought that metabolic products reach the cerebro-spinal fluid along the so-called perivascular lymphatics. These remarkable structures are

tubular extensions of the subarachnoid space which accompany and enclose the vessels that penetrate the brain to their finest ramifications. The interpretation of their meaning has long been regarded as a great difficulty, but if we accept the view that somatic structures like the blood vessels cannot be admitted to direct contact with the nervous tissues it is natural to regard the perivascular lymphatics as mechanisms to insulate the blood vessels from this contact. It may be assumed from what we know of the nourishment of tissues in general that there is some kind of leakage from the cerebral tissues comparable with lymph as found everywhere else and presumably of a not dissimilar concentration. This fluid will find its way to the subarachnoid space, presumably by the perivascular channels. The disposal of such a material may well be regarded as an exacting task. It is impregnated with products of nerve metabolism and is an eminently "neural" fluid capable of producing energetic reactions in any somatic tissue it meets. Thus there can be no question of its entering the blood stream in the relatively high concentrations that are satisfactory for lymph, and Nature meets the case by providing for its being heavily diluted before it is allowed to join the somatic blood in the cranial sinuses.

The most characteristic feature of the cerebro-spinal fluid as it exudes from the choroid plexuses is its remarkably low solid content. It is by far the most watery secretion produced by the normal body, and one might almost say it is an attempt by Nature to secrete pure water. It contains a small amount of the diffusible substances of the blood, but practically nothing else. So strong is the tendency to keep the fluid watery that the choroid plexuses have a truly astonishing impenetrability to drugs and other foreign substances circulating in the blood. Even the bile pigments in cases of jaundice fail to find a passage. This fluid, practically amounting to nothing but water, is secreted in large quantities; on rare occasions I have had the experience of seeing as the result of accident what was perhaps a large fraction of the total secretion of cerebro-spinal fluid discharged on the surface. The amount of fluid escaping has been very large and the consequent inanition correspondingly profound. The normal function of this great flow of water we may suppose with some confidence to be to flush through the whole subarachnoid space and to dilute the products of cerebral metabolism to such a degree that the resulting fluid can be safely admitted to the general blood stream. This view gets some confirmation from the evidence we have that the fluid in the subarachnoid space has a larger solid content than the fluid in the ventricles.

It is interesting to reflect that the source of this mysterious secretion which has given so much difficulty to the chemical physiologist may turn out to be no more abstruse a thing than Nature's nearest approach in the animal body to a spring of plain water; if this should be so, it may also remind us of the small and amusing coincidence that one part at any rate of the tortuous channel through which the fluid runs—the *aqueduct of Sylvius*—has since the very early days of anatomy borne a singularly exact and appropriate name.

In our review of certain aspects of the nervous system we have found reason to regard as of fundamental importance the preservation of an impenetrable barrier between the whole of the nervous system and the rest of the body. This barrier we have seen to be made up of a number of highly special structures and mechanisms. Its function is on the whole to prevent contact between the neural and the non-neural, but is also in certain places to permit it. These places are only two: first, where the motor nerve end comes into contact with the muscle fibre, and secondly, where the naked arborization of the pain nerve meets the tissue in which it is distributed. The nervous system is thus kept apart from the body, as we may say, in order that when the two are permitted to meet the reaction shall be the more energetic. It is in fact, then, of the very essence of nervous tissue that it should be different from the other tissues, so that it can irritate and be irritated by them. This necessity for a certain "strangeness" of the nervous system may possibly throw some light on its curious embryology. The origin of the nervous system, as

an epiblastic tube originating on the surface of the body and then sinking into its substance, has been investigated chiefly from the morphological point of view, and great ingenuity and research have been expended on it. It may be worth suggesting, however, that the problem has also a functional side, and that the epiblastic origin of an organ that is ultimately to be deeply embedded in mesoblastic tissues possibly has the function of contributing its strangeness, and therefore its effectiveness, to the nervous system as a whole. This quasi-hostility between neural and somatic, between brain and body, is a suggestive and perhaps a disturbing thought, but we shall not attempt here to follow it out.

NEURAL INSULATION IN PATHOLOGY.

It is more convenient at the moment to consider certain pathological evidence that has some bearing on the conclusions we have already reached.

That the central nervous system differs from other organs in having a certain inaccessibility has long been recognized in connexion with syphilis. The difference between the strictly extraneural mesoblastic infection of the meningeal gumma on the one hand, and the intraneural parenchymatous infection of general paralysis on the other, shows that the frontier between the two regions is as sharply marked pathologically as it is physiologically. Moreover, the relative inefficacy of antisyphilitic treatment in the parenchymatous infection reminds us that the frontier is also impassable for many drugs.

The dura and arachnoid are in some sense intermediate tissues, for they show a certain tolerance for both neural and non-neural contacts, the arachnoid having slightly greater affinities for the former, and the dura perhaps for the latter. That they are, however, fundamentally non-neural in their behaviour, and probably also in their nature, is suggested strongly by their relations to certain tumours. The glioma is probably the one truly neural tumour that affects the central nervous system. Although it behaves within the brain as a malignant infiltrating growth, its spread is restrained by the neuro-somatic barrier, so that while in exceptional cases it may affect the meninges and skull by pressure atrophy it can never invade them or extend to the tissues of the body. On the other hand, the so-called "dural endothelioma," which is relatively so common as a growth involving arachnoid and dura, frequently shows the power to infiltrate the skull and overlying parts as a malignant neoplasm; but although it may press deeply into the brain it never invades it, being restrained as effectively in the one direction as is the neural glioma in the other. The behaviour of these two tumours has long been familiar, but seems always to have been accepted as very much a matter of course. It is perhaps more reasonable to regard it as one of the most significant anomalies in the whole of pathology.

Our final pathological illustration takes us back to the peripheral nerve. We have already seen that this is the only part of the nervous system where a breach of insulation produces immediate and definite disturbance of function. The neurilemma seems fortunately, however, to be an exceedingly effective barrier between neural and somatic tissues. There is clinical evidence that a relatively slight subcutaneous injury can lead to the formation of a neuro-fibroma presumably through damage to the neurilemma; but this is a rare event of little practical importance, and failing gross injury the insulatory mechanism is wholly satisfactory. That this is the result of effective restraint rather than inertia on the side of the nervous system is perhaps shown by that fortunately rare complaint multiple neuro-fibromatosis or Recklinghausen's disease. In this condition it has been shown that every fibromatous formation, localized or diffuse, contains nerve fibrils which, presumably by their irritant qualities, have given rise to the fibrosis, much as might a foreign body or a micro-organism of highly attenuated virulence. It seems clear that it is the presence on a large scale of nerve fibrils outside their normal insulating sheath which is the proximate cause of the morbid state. It may be doubted whether the neural leakage is a primary manifestation or is due to an essential weakness or collapse of the insulating

function of the neurilemma. Whether the failure of this sheath is primary or secondary, absolute or relative, no one who has seen a severe case of the disease can doubt that any general collapse of the peripheral insulatory mechanism makes the life of its unfortunate subject almost insupportable.

INSULATION AND THE PHYSIOLOGY OF PAIN.

I have already called attention to the remarkable fact that there is one kind of sensory fibre which ends in a free arborization in naked contact with the tissues. Our last task in dealing with the insulation of the nervous system is to examine a little more in detail the striking anomaly that in their end-organs the pain fibres make this unique exception to the rule that sensory fibres are insulated up to and including their end-organs.

This anatomical uniqueness of the pain fibre in its end-organ is matched by the uniqueness of the physiological characters of pain sensibility, and it is very natural that we should desire to correlate these two anomalies. Pain sensibility is remarkable in three respects: first, in the quality of the sensation itself; secondly, in its threshold of sensitiveness; and thirdly, in the nature of its appropriate stimuli. (a) The *sensation of pain* is peculiar in that it has a sudden and as it were explosive way of bursting into consciousness, in that it calls urgently and often irresistibly for some kind of motor response, and in that it is in its very nature distracting so as to be incompatible with quiet contemplation or steady judgement. (b) The *threshold for pain stimuli* is remarkably high, so that in comparison with other forms of common sensibility the stimulus has to be relatively energetic to call forth the characteristic sensation. (c) The *stimuli* that call forth pain sensations are remarkable for being very miscellaneous. In every other kind of sensibility but pain, the normal response is to a single well defined physical change—pressure is evoked by weight, touch by movement, cold by loss of heat, warmth by access of heat. The ordinary stimulants of pain, on the other hand, such as pressure, pin-pricks, cold, heat, and the electric current, make up a thoroughly odd class, the members of which show no common character. They are all capable of producing the characteristic sensation before, and usually long before, an intensity of stimulation is reached that can be shown to be harmful. That many of the stimuli would be harmful in greater intensities can scarcely, therefore, be regarded as forming a common physical basis, but must rather be explained as merely a consequence of the normally high threshold.

When we consider these peculiarities we can hardly regard them as those of a highly differentiated mechanism, but rather as those of one relatively crude. All sensibility may well have been of this kind in organisms to which the distracting explosive qualities of the sensation would be no detriment. If we look upon the peculiarities of pain as an evidence of crudity rather than of differentiation it is relatively easy to correlate them with the uninsulated end-organ of the pain fibre, which we must regard as less differentiated and cruder than the complex end-organs of the other fibres. Pain sensibility would thus owe its special character to being the function of a nerve fibre of a peculiar kind, which while relatively insensitive responds in an exaggerated way when its threshold is reached. Presumably these characters are to be associated with the uninsulated end-organ, and we may suspect that it is this lack of insulation which gives to the fibre its characteristic features of blunt sensitivity and emphatic response.

We possess a possible source of further light on this problem in the phenomena that accompany the recovery of function in sensory nerves after division and immediate suture. It is well known that this process, as observed under experimental conditions in the human subject by at least three independent groups of investigators, is accompanied by remarkable modifications in all forms of sensibility. It is impossible to refer to these modifications in detail, but it gives them in a broadly approximate way—and I speak from actual personal experience of them—to say that they are generally in the direction of the peculiarities shown by normal pain; in other words, the modified sensations compared with the normal are more explosive and more urgent, they have a higher threshold,

and they call for some kind of motor response. The explanation of these and the other modifications that are to be observed during recovery of sensory nerves has differed with different investigators. It is far too much a matter of detail to discuss these differing hypotheses here, but there is one criticism to be offered of some that is relevant to the general attitude we have tried to support. This criticism is that there has been a tendency to approach the problem in too abstract a way. It has been assumed that the question is one of the mere return of functions that are present in the normal and in the form in which they are then present—modifications in the character of sensation being ascribed to such factors as the order of return and the rate of return of different functions, and the modification in character of one form of sensibility to the presence or absence of another. This is to assume that the processes and incidents of regeneration itself have nothing to say to the problem; and that the struggle between the advancing nerve fibres and the reaction they arouse from the line of suture onwards can be ignored. To take it for granted that the naked growing fibres can pass through this difficult and prolonged ordeal without any alteration in their function, and to limit the problem in this way to strictly and exclusively neural factors, seems to me a method less concrete and practical than the case demands.

An alternative hypothesis, which is at any rate more comprehensive and more simple, can, however, be put forward. The general tendency of all forms of sensation yielded by a regenerating nerve to develop a certain resemblance to pain reminds us that regenerating fibres resemble pain fibres in a lack of complete insulation. It is probable, therefore, that imperfect insulation tends to render all fibres less sensitive than normal, but more apt when effectually stimulated to respond in an exaggerated explosive way. With the advance of regeneration the fibres serving touch, heat, and cold, become once more connected with end-organs, and then their insulation, by the junction of the neurilemma with the capsule of the end-organ, can be completed. The completely insulated fibre, having lost its temporary resemblance to the pain fibre, becomes once more sensitive to the finer stimuli and ceases to yield exaggerated responses.

The process of regeneration thus seems capable of causing a regression of function in all kinds of nerve fibres to a cruder type that in the normal is represented only by pain. This regression occurs because during regeneration insulation must necessarily be defective. According to this hypothesis normal pain and the sensibility of regenerating nerves give us an insight into the ancestry of common sensation. Primitive sensibility of all kinds we may suppose to have been like pain in us; it had a relatively high threshold, but it was effective because its sensations were urgent and explosive and, of course (also like pain in us), were exactly localized. Among such sensations fine discrimination was plainly impossible. With the development of the completely insulated nerve and end-organ the fibres thus equipped became capable of yielding sensation to finer and to specialized stimuli, and of a quality no longer explosive but able to be submitted to discrimination; at the same time the large number of pain nerves remained in their primitive state to warn the body of strong stimuli by urgent sensations among which there was no power and no need for discrimination because their function was to excite immediate response.

The great and manifest difference between the vertebrate and the invertebrate nervous systems is that the former is centralized and the latter is scattered throughout the body. The facts I have quoted and the inferences I have drawn suggest the hypothesis that, side by side with centralization and rendering it possible, insulation also must have proceeded. Insulation on the one hand must have been made increasingly necessary by the growing differentiation of neural from somatic tissues, and on the other hand must have helped to sharpen this very difference. It is not, therefore, surprising that a function so fundamental is not only recognizable in the structure and behaviour of the normal nervous system, but is also evidently at work in morbid processes and constitutes at once a help and a limitation to the work of the surgeon.