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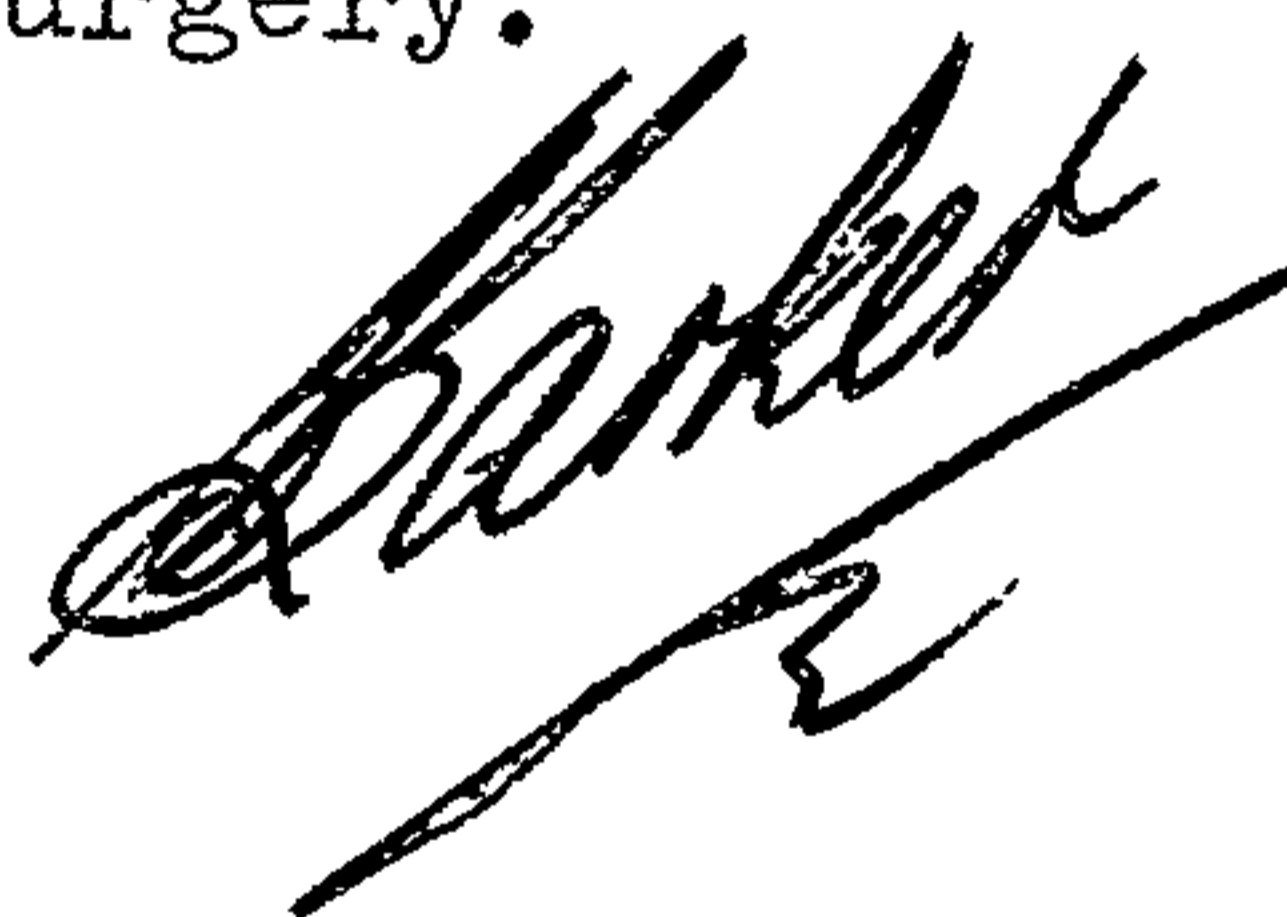
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THE PHYSIOLOGY  
AND AETIOLOGY  
OF FACIAL PAIN

—  
B. C. W. BARKER

1961

This critical review of the literature concerning the Physiology and Aetiology of Facial Pain, is submitted in accordance with the requirements for the degree of Master of Dental Surgery.

A handwritten signature in cursive script, appearing to read "Baker", with a long horizontal flourish extending to the right.

## PREFACE.

It is only in relatively recent times that investigation into the pain experience has allowed an understanding of its basic mechanisms. This knowledge is deficient in many aspects, and it is difficult, if not impossible, to dogmatise on many of the observed phenomena.

The distressing nature of pain necessarily limits experimental investigation in man, although outstanding contributions have been made in this field by Lewis, Wolff, White and Sweet.

Physiologists, anatomists and workers in allied sciences have elucidated many aspects of the pain mechanism, but the information gleaned by objective clinical observation of patients suffering from specific and non specific pain states and of patients who have undergone surgery affecting pain pathways, has been of inestimable worth.

Deductions from such observations have allowed a "working hypothesis" to be formulated in many instances which at least allows rational therapy to be instituted.

To the dental surgeon, a knowledge of pain syndromes affecting the oro facial and cephalic regions and an understanding of their aetiology and management is of first importance.

This knowledge, however, must rest on an understanding of the phenomena associated with the pain experience as such. Accordingly, preliminary sections in this review have been devoted to considerations of neurophysiology and the anatomy of pain pathways both macroscopic and microscopic, in order that the nature of pain be more readily comprehended and elucidated.

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## CHAPTER 1

### THE MEANING OF PAIN

Oro facial pain is the most common complaint of the patient to the dentist. In view of the multiplicity of possible aetiologic factors and the often confusing symptomatology, diagnosis and management may constitute a most difficult problem.

The mechanism of pain is complex and an understanding of the pain experience must be based on a knowledge of the normal physiology of nervous tissue, the anatomy of pain pathways, both peripheral and central and a familiarity with the specific and non specific entities associated with facial pain.

The difficulty which patients find in trying to convey sufficiently precise ideas as to the sensation felt, adds to the problems of diagnosis. Some of the main characteristics of the pain experience will therefore be considered in this chapter.

An exact definition of pain has confounded mankind since the dawn of history. It is significant that Sir Thomas Lewis (100) in the preface to his study of pain, states that:-  
"....Pain, like similar subjective sensations, is known to us by experience and described by illustration. Reflection tells me that I have so far from being able satisfactorily to define pain, of which I here write, that the attempt could serve no useful purpose."

Perusal of the literature gives the impression that one must think of pain as being compounded of a pure sensation and an emotional reaction.

"A disturbed sensation causing suffering and distress."  
(New Gould Medical Dictionary).

"Suffering, either physical or mental, an impression on the sensory nerves causing distress, or when extreme, agony."  
(Stedman's Medical Dictionary).

Macphee (105) quotes Behan as saying that "Pain is the mental interpretation of some abnormal and generally harmful process which is occurring in the organism."

Head defined pain as "...the oldest defensive reaction, and potentially painful stimuli are the basis of all primitive reflexes."

Another definition states that pain is "The subjective warning sensation accompanying a nocuous physical stimulus."

Balme sums up the situation as follows:-

"The problem of pain has challenged the thought of scientists and philosophers in all ages, but in spite of all that has been written on the subject, no definition has yet been formulated which adequately describes what we mean by this experience. The difficulties of such a definition are obvious, for although primitive in character, pain is essentially a sensation in which both physiological and psychological processes play a part. Each of these factors will vary with the temperament, the intellectual range of the individual and the susceptibility of the individual. Moreover, they will vary in the same individual at different times and under the stress of different emotions.

There is thus no absolute criterion, subjective or objective, by which we can determine what pain really is, and we must therefore fall back upon an analysis of what we normally describe as a painful sensation."

Pain is now regarded as a specific sensory experience mediated through nerve structures which are separate from those which subserve other sensations such as touch, pressure, heat or cold. This, however, is a relatively recent concept.

As recently as the turn of the 20th century, it was still considered debatable whether pain was indeed a sensation, or exclusively a feeling reaction, akin, but opposite to, that of pleasure. The idea of pain as being synonymous with mental

anguish persists to this day. There was a strong school of thought which maintained that pain was not a sensation but a form of feeling, not to be classed with sensations such as touch or temperature. In other words, it was denied that there was such a thing as a pain tract; there were no peripheral end organs or nerves in existence which on irritation alone could produce pain (174).

This erroneous concept can more readily be understood if we consider the etymology of the word 'pain'. It is derived from the latin 'poena' which means 'penalty'. This illustrates the ancient belief that pain is an unpleasant feeling which is the result of our sins (70).

This type of thinking about pain is amply documented in all of the written records of antiquity. The attitude to pain for many centuries was, in general that it had a chastening effect, and was in some way 'good for the soul'.

Following on the work of Sir Charles Bell early in the 19th century, when it was discovered that the dorsal roots of the spinal nerves brought impulses to the central nervous system and that the ventral roots of the spinal nerve carried impulses from the central nervous system to the peripheral organs, the way for research into the true nature of pain sensation was opened.

A concept subscribed to in the past was a belief that pain sensation resulted from excessive stimulation of such sensory receptors as those of touch, pressure, cold, heat etc. This was the 'Intensive Theory' of Wundt.

Several investigators, whose work shall be reviewed in greater detail in succeeding chapters, were responsible for a gradual change from this view.

Pioneers such as Blix, Goldscheider (1885) and Von Frey (1896) noted that when skin is explored with stiff hairs, pain alone may be elicited from certain areas. They forwarded the view that human skin contains specific minute spots where stimulation, by whatever method, yielded only that sensation

which was characteristic for the spot - either cold, warmth, pressure or pain.

This 'punctate theory' is no longer credited but conclusive evidence of the specificity of pain as a sensation was finally provided by Woollard (181) and his colleagues who were able to stain characteristic nerve terminals in a section of human skin removed from an area in which pain was the only sensation which could be elicited from a variety of stimuli.

These workers demonstrated that cutaneous pain is subserved by the finer medullated and non medullated nerve fibres bearing free nerve endings. In areas where pain only is elicited, fine nerve fibres were seen giving rise to superficial nerve nets, arranged in a plexiform interlocking manner.

As Huxley and Wells state - "Pain is an alarm signal and its biological importance is reflected in the anatomical fact that, whereas warmth and cold and touch are senses confined to particular patches of skin, the pain network is unrestricted and pervades the whole surface of the body."

It is thus clear that the pain experience is first a sensation derived from noxious impulses traversing specific pathways.

Confirmation of this theory that pain is a specific sensory experience with its own neural structures and properties, can be seen by considering the following clinical facts.

- 1) That pain does not result from overstimulation of fibres serving other sensations is demonstrated in patients who have lost the perception of pain or pain only in limited regions of the body, as a result of accidental injury of the spinal cord or after surgical transection of the spinothalamic pathways. Pain alone may be absent, in such cases, in circumscribed areas without associated loss of temperature or touch (174).
- 2) Certain analgesic agents are capable of specifically raising the threshold of pain up to 80% above the control level while they lowered or left unaltered the threshold for perception

of touch, hearing, smell, two point discrimination and the perception of vibration.

3) There is much evidence to indicate that certain structures are equipped for, and give rise to, the sensation of pain only e.g. the teeth, middle meningeal artery and the arteries of the face. Afferent fibres from the structures conduct only those impulses which result in pain. On the other hand, there are certain areas from which pain cannot be elicited e.g. the parenchyma of the brain.

4) A consideration of the differing effects of asphyxia and procaine block on nerve trunks illustrates how ischaemia causes cessation of thermal impulse conduction prior to those of pain, while anaesthetic solution abolishes pain conduction first.

The two modalities are apparently conducted by neural mechanisms of differing physiological properties. These will be considered in detail later.

We must therefore accept the concept that pain is a separate entity and a specific modality, having its own threshold. It is a specific sensory experience mediated through nerve structures which are different from those which mediate other sensations such as touch, pressure, heat and cold (180). Excessive stimulation of these other mechanisms may also produce pain but it does so by exciting the pain pathways as well as that for the other sensation in question.

The peripheral receptors for pain show little specificity towards the type of stimulus which will elicit a response. When tissue is distorted, the pain endings are activated while being stretched, while damaged cells liberate chemical substances into the tissues which then stimulate pain nerve endings.

Pain must not be classed as a pure sensation, however for there is a concomitant emotional and psychological affect. Pain is quite different from normal emotions such as elation or sorrow, in that it is always felt in some part of the body. That is, pain is peripherally projected or referred to some

part of the body with varying degrees of precision. It is always an unpleasant sensation and usually operates against a background of a multiplicity of visceral reflexes and hormonal changes. Pain is therefore intermediate between sensory perception on the one hand and an unpleasant emotional experience on the other. (184).

Pain sensibility under normal circumstances of everyday existence is a valuable warning of bodily injury and thus serves a protective function. Indeed, Sherrington defines it as "the psychical adjunct of an imperative protective reflex."

Pain is therefore a protective sensory phenomenon, the cause of which may arise in the periphery of the body but its end is in the consciousness.

Goldscheider (1885) may be freely quoted on the function of pain:-

"....Pain makes us realise that some external danger is threatening, which we may still avoid, or that harm has already been done to the body requiring our care, if we would still escape more serious consequences. Pain arises as a warning signal whenever we are exposed to such conditions of life as by their continued influence would involve general disturbances of health. Pain appears before or simultaneously with, the outbreak of disease, warning man that his body is in a diseased condition and requires care. Pain, the symptom of organic disease, imperatively urges the patient to nurse the diseased organ.....// Pain is a harsh but useful law of nature, but like all natural laws, is unyielding in its constancy, blind in its disregard, brutal and cruel. Pain appears, not only in the guise of benevolent warning, but also as a troublesome torment. Even in incurable disease, in affections in which the realisation of ill health is useless to the patient in as much as no-one can control the disease, pain is present, ruthlessly destroying all enjoyment of life without offering any physical advantage whatsoever by way of compensation. In the most dangerous disease pain is often absent, thus lulling the patient into a sense of security, only to appear and call for abolition by

artificial means after the patient has undergone an operation in order to save his life.'

Pain is therefore regarded as belonging to that order of phenomena which are usually termed conditions of general sensation, such as hunger, thirst, tickling and nausea. They are all distinguished by a high degree of pleasurable or unpleasurable sensation and do not inform us concerning our environment by sensory perceptions but above all attract our attention to the altered state of our own body (169).

Although serving a protective function, pain does not appear to be essential to a suitable biological adjustment (180). Persons congenitally without the ability to experience pain and people who have had pain pathways surgically interrupted, adequately adjust themselves to their environment by substituting other sensations as warnings (116). Indeed, we ourselves have learnt to estimate intensity of sensations so that a stimulus likely to arouse pain can be avoided (80).

The intensity of pain is not directly proportional to the severity of tissue damage. Persons critically ill as with terminal neoplastic disease, and those gravely injured, do not inevitably experience intense pain. Usually, however, pain serves as beneficial function in helping the body to avoid harmful agencies that threaten his safety and well being.

Unfortunately, as Goldscheider stated, pain does not always stop when it has accomplished its protective function, and it may then become destructive. Indeed, many of the painful conditions from which the human being suffers cannot be avoided or eluded no matter how intelligent the individual may be.

Under certain conditions and circumstances pain, once started, seems to maintain itself and as Leriche has taught, it produces vaso-constriction which in turn may redouble the pain and give rise to a vicious cycle (171).

The management of pain constitutes a serious clinical problem not only because of itself as a distressing experience, but also because continued pain has been demonstrated to have a

deleterious action upon vital organs such as the heart and kidneys (180).

Pain is not merely a local sensation but an impairment of the activity of the total body.

Weir Mitchell, a surgeon during the American Civil War, writing on the destructive nature of pain says "....There are few persons who are not physicians, who realise the interference that long continued and unendurable pain may have upon the body and mind.

Under such torments the temper changes, the most amenable grows irritable, the soldier becomes a coward, and the strongest man becomes scarcely less nervous than the most hysterical girl."

Different people feel pain in different degrees. The labourer feels pain less than the cultured intelligent person (116). Perhaps the intelligent person has the same threshold for perception of pain, but his more vivid imagination and his memory of past experiences gives the painful sensation a greater emotional meaning.

Racial factors too are significant and we find that the highly civilized people are more affected than savages by physical torture.

The lower in the scale of life one goes the less intensely does pain seem to be perceived but it does not seem possible to decide at what level of life pain ends. Even amoebae show irritability but whether this is a reflex response or an example of negative chemotaxis without sensation is impossible to say. Observation of lower forms of life, such as lizards, suggests that radical traumatic injuries, such as leg amputations, cause only passing interference with the animal's activities (105).

Fear of pain may accentuate the sensation when the hurt does occur. A child may imagine pain when a tooth is merely touched with a mirror. This may be only imagination, but who shall say it is less real to the child? "A burnt child fears the fire," and this fear of pain in the young is usually due to recollection of a previous painful experience. It is thus

important to avoid hurting a child for 'psychic scars' caused by painful experiences are impossible to fully eradicate.

As Sir James Paget said:- "Pain expected, watched for, long thought of, will come."

In theory, our present knowledge of anatomy should enable the surgeon to relieve all varieties of intractable pain by the specific interruption of afferent pathways. This is unfortunately not always the case.

Frequent failure to benefit post herpetic and other neuralgias of the face, and certain intensely disagreeable sensations sometimes following injury to the peripheral nerves, serves to remind us that we still have much to learn.

The sensory system subserving pain is unique. In the circumstances of normal life, it is quiescent, and no impulses traverse the pain pathways to the sensorium unless tissues somewhere are being distorted or damaged. This is in contradistinction to other sensations e.g. touch or thermal modalities, which are constantly supplying information to the central nervous system. The pain experience is therefore always pathological and the complaint of pain always has some real basis, however exaggerated by psychogenic factors.

Pain is difficult to describe quantitatively and qualitatively and it usually exceeds the patient's didactic skill to convey precise information as to the symptoms of his suffering.

This is in consequence of varying factors:-

1) Pain is a subjective symptom and therefore variable in different patients. Pain may be exaggerated or minimised which is purely an individual interpretation of intensity. In view of this individual variation, it is doubtful if much can be gained by assessing pain severity. Although severe pain may indicate a grave disorder, this is not invariably so. Severe pain such as in intestinal colic may be a passing event and of relatively trivial concern. On the other hand it is known that minor degrees of pain are often provoked by very serious

diseases (100).

2) In view of the difficulty in describing pain, the patient usually resorts to other forms of sensory experience in his description. Pain may therefore be described as burning, pricking, pressing, bursting, stabbing or throbbing which are terms proper to the description of thermal tactile pressure and vibratory sensations (184). Apart from reference to associated sensations, the patient usually includes reference to time relationships (uniform, variable, constant, intermittent), space relationships (localised, diffuse or spreading) and adds some assessment of what he considers to be the degree of pain (182).

Associated sensations are usually felt for the stimulus which elicits pain, will quite often activate other receptors in the same area capable of responding to that particular physical stimulus e.g. severe heat produces thermal sensation followed by pain.

3) It is important to determine the type of pain from the sufferer for this is fundamental to diagnosis. Broadly speaking there are two types of pain (80) (180).

In general, cutaneous or superficial pain differs from visceral pain in possessing a bright, pricking burning or itching quality which is highly localisable. It seems to exert an exhilarating action and commonly incites the individual to fight or flight, and this is in keeping with its protective function. Visceral or deep pain on the other hand is characterised by a deeper, diffuse aching quality which seems to exert a depressing effect, is commonly associated with nausea and followed by withdrawal, inactivity and rest. One may rationalise that this is also to be expected; deep pain from an inflamed viscus is best treated by rest to the part rather than sudden activity.

In no instance is localisation of deep pain as exquisite as is that of pain from the skin. The additional fact that deep pain - and here we must include the pain arising from the teeth - may be referred remotely, gives rise to some difficulties in diagnosis and we must be familiar with the sites of reference

from specific structures and the segmental distribution of pain.

That pain may be referred widely from the site of origin is well shown by Wolff et al (79). These workers illustrated how stimulation of the mucosa covering the middle turbinates or around the ostium of the maxillary sinus leads to pain felt in the cheek. Again, mucosal lesions in the ethmoidal recess produces pain in the cheek together with toothache in the upper molar teeth, while similar lesions in the inferior turbinate lead to pain in the cheek and in all the upper teeth of the same side (184).

A pain's duration throws light on its mechanism and may be of use in separating superficial from deep pain. The picture of a time intensity curve of pain has significant associations. This curve portrays the manner in which pain starts, the rapidity of its culmination, the duration and smoothness of its height and the manner of its decline. Thus superficial pain may come and go in a flash, as when skin is pricked, or it may be felt in rhythmic pulses as in pulpal inflammation. Again, it may be experienced as a longer and less rhythmic phase as in intestinal colic (100).

It must be emphasised that the cause of pain is rarely known immediately and with certainty unless such pain is provoked at the surface of the body. Pain is rarely of localising value except in general terms, for 'superficial' pain may, in fact, be due to a lesion of the peripheral nerve endings, the nerve trunk, the nuclei or central connections. The facial pain may be identical in terms of description in the case of each of these many possible sites (106). The qualitative aspects of pain may not localise the source of the lesion except to indicate that it is either at the site of the pain or in the neural pathways which extend from the periphery to the cortex.

Apart from superficial pain, it will be recalled that deep pain also cannot be distinguished from each other by the quality, and the localisation has neither the constancy nor the individuality enabling us to regard it as specific. The understanding of

pain mechanisms poses many problems, some of which we are now able to clarify. Many aspects of the pain experience however, must remain in the realms of speculation.

Sicher (142) poses several pertinent questions apertaining to the dental pain mechanism and it is worthwhile listing them and making it our goal to seek explanations for these in succeeding chapters.

- 1) Why are two people so different in their sensitivity to pain?
- 2) How can so many different stimuli such as heat, cold, chemical irritants, and so on cause pain?
- 3) Why is pain the only reaction of pulp and dentine to any stimulus of sufficient intensity?
- 4) How can we explain the sensitivity of dentine?
- 5) Why does a local anaesthetic so often produce analgesia and not anaesthesia?
- 6) Why is it so difficult to anaesthetise pulp and dentine?
- 7) Why is pulpitic pain so often only vaguely or indeed not at all localised as against the precise localisation of periodontal pain?
- 8) What is the explanation of referred pain?

It is necessary to consider the problem from anatomical, physiological and histological aspects and apply our findings to the interpretation of facial pain.

CHAPTER 2

NEUROPHYSIOLOGICAL CONSIDERATIONS (173) (183) (185)

Pain sensation has its own neural mechanism and, as is true of other senses, the neurone is the structural and histologic unit.

The Structure of the Neurone.

The term neurone describes a nerve cell, that is, the cell body, and its processes, the dendrites and the axon. The cell as such, possesses a cell membrane and cytoplasm, but it has a very irregular shape due to the numerous short dendrites which may be more than 1 mm in length. All neurones are embedded in a cellular matrix consisting of glial cells and blood vessels.

The cytoplasm of nerve cells is fibrillated, the so called neurofibrils extending from the dendrites through the substance of the cell into the axon. Embedded in the cytoplasm are Nissl granules consisting of nucleoprotein and containing organically combined iron. Fatigue, the action of certain poisons and sections of the axon results in chromatolysis, that is, the disappearance of the Nissl granules.

The axon arises from the axon hillock which is distinguished by the absence of granules, and it runs, as a rule, for a considerable distance before branching. It may extend 1 metre in length and gives off numbers of branches in its course, terminating by dividing into many telendendrites, forming a terminal arborization. Some sensory axons, however, terminate by a single ending. The nutrition of the axon depends upon its intact connection with its cell.

The medullated axon consists of the following structures from within outwards -

(i) A central core of semi-fluid axo-plasm containing minute rodlets arranged parallel to the long axis of the fibre and giving it a fibrillar appearance. There appears to be a specialised boundary layer of axoplasm called the axon membrane which separates the intracellular contents from the extracellular fluid and is the functional surface membrane. It is

probably the site of the action potential recorded from the nerve.

(ii) The white myelin sheath, which is made up of concentric sheaths of protein interspersed with layers of lipoid, mainly lecithin, is radially arranged. This sheath is interrupted at regular intervals by the nodes of Ranvier. The distance between the nodes increases during growth and inter nodal distance is proportional to the diameter of the fibre. This fact has an important bearing on the discussion of velocity of impulse transmission.

The Action Potential which accompanies the nerve impulse can only be picked up from such fibres at the nodes of Ranvier where the myelin sheath is absent.

(iii) The sheath of Schwann, which is a homogenous membrane closely adherent to the myelin, is bent in at the nodes.

Midway between the nodes is nucleated cytoplasm, - the cells of Schwann.

The axons, during development of the neural mechanism, grow out in company with a peripheral column of proliferating Schwann cells. The axons invaginate these cells and become completely enveloped in them. The myelin develops after this stage and only occurs if the axon diameter exceeds 2  $\mu$ . Fibres less than this remain unmyelinated. As the axon enlarges, the Schwann cell coils around it and these coils form the myelin sheath which, as stated is a lipoprotein. This view, which has been substantiated by electron microscopy shows that there is no separate myelin sheath - the latter being purely a derivative of the Schwann cell.

The small non-myelinated fibres of the somatic nervous system will assume importance as belonging to the group conducting 'slow' or 'second' pain.

In the central nervous system, the envelopment of the axon is effected by astrocytes, which are glial cells. Fibres of the Central Nervous System possess nodes as do peripheral cells and there is thus no structural difference but only a difference in

the type of cell concerned.

Sections of peripheral nerve reveals that the Schwann cell is surrounded by fibrous endoneurium and the individual axons are bound into fasciculi by fibrous perineurium. The fasciculi are enclosed in a boundary layer of epineurium.

The only function of the nerve fibre is to conduct the nerve impulse. Experimentally, the fibre can be stimulated at any accessible point on its course.

The nerve impulse set up at the point of stimulation travels distally as well as centrally. Under natural conditions, however, the nerve impulse is usually generated in the nerve cell and travels distally along the axon. The main exceptions are the afferent neurones; in these the impulse is set up by appropriate stimulation of sensory terminals.

#### The Resting Potential of Nerve.

If a micro electrode is placed in a single axon of large diameter and another is connected with the external layer of the Schwann cell, a potential difference is observed between the two electrodes, that is, the charge inside the resting nerve is not the same as that outside, and the magnitude can be determined by connecting the electrodes to an amplifier and cathode ray oscillograph.

The surface membrane is said to be polarised for it maintains a potential difference between its outer and inner surfaces. Its magnitude is about 50 - 60 millivolts and is called the resting potential. When the fibre is not conducting impulses, the interior is negative to its exterior. (Fig. 1). This is a universal characteristic biological property of all living cells. The resting potential of a neurone, however, is greater in magnitude than in any other cell.

The resting potential is due to the fact that ions are unevenly distributed between the tissue fluid and the cytoplasm. In the tissue fluid is found a predominance of sodium chloride and calcium while in the cytoplasm we find potassium and organic ions.

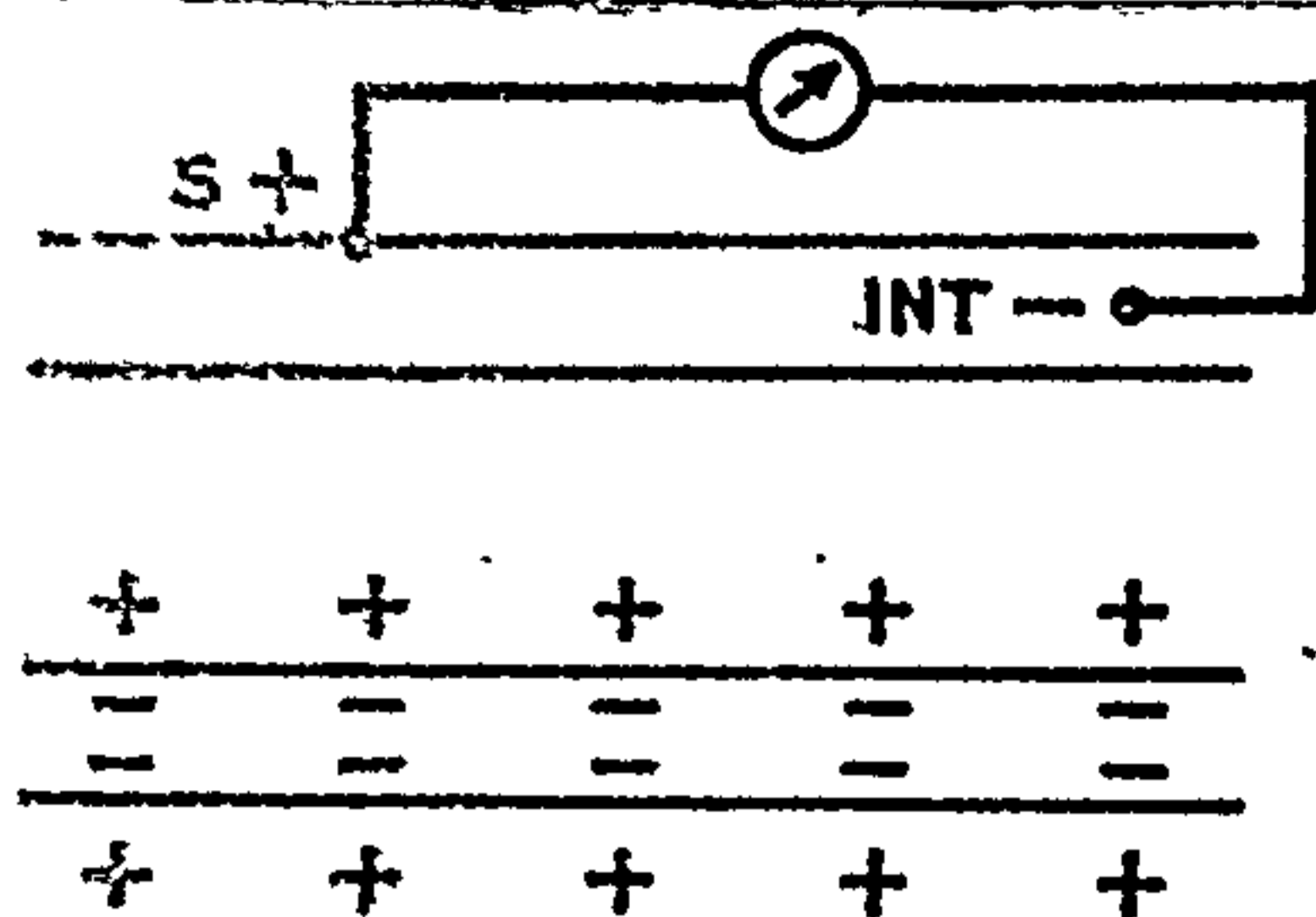


FIG. 284.—Diagram to show Polarization of the Surface Membrane of the Resting Nerve Fibre.

S= surface electrode; INT.=electrode in interior of nerve fibre.  
 The upper part of the diagram shows how the resting potential has been measured.  
 INT. is negative relative to S.  
 The lower part of the diagram shows the distribution of the charge across the nerve membrane. The external surface is positively charged and the internal surface is negatively charged.

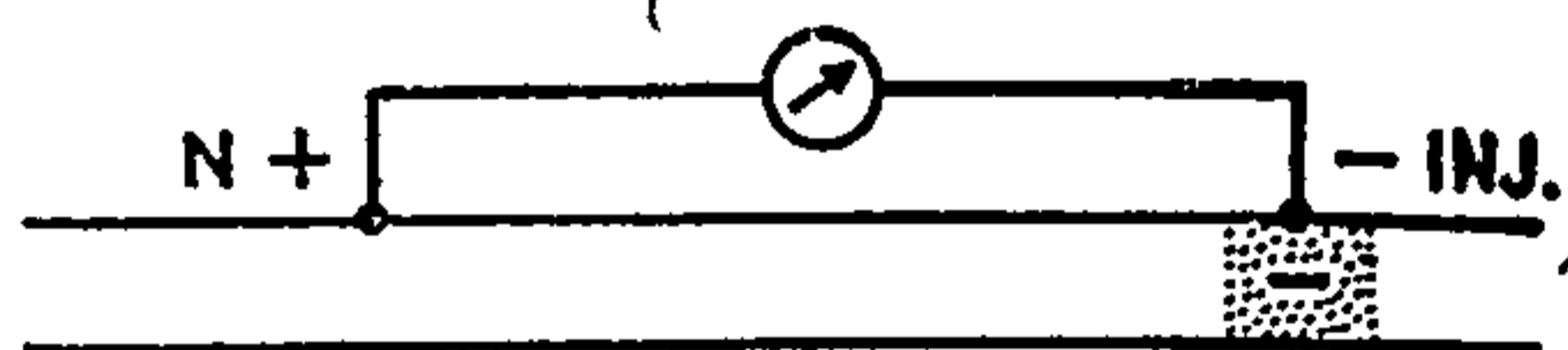


FIG. 285.—Injured Area of Nerve Fibre is Negative relative to Normal Area.

The diagram shows how the injury potential is measured.  
 N=normal. INJ.=injured areas.  
 Both electrodes are placed on the external surface of the fibre. INJ. is negative with respect to N.

Fig. 2. If the interior of the fibre is connected with an injured surface on the fibre, the interior and the damaged surface point are found to be at the same potential i.e. they are equally negative. The surface electrode in this position is, in effect, registering the inner potential of the fibre and is seen to be negative in relation to the electrode on a normal part of the surface.

This illustrates how the metabolism of the neurone maintains the potential difference across the surface membrane, under resting conditions, by active exclusion of excess positivity.

This ionic imbalance is not due to the impermeability of the Schwann cell or axon but rather there is a continuous interchange of all ions which is kept in the observed concentration by:-

(i) The mobility of ions. Sodium and Chloride ions show only a slow migration and maintain small concentrations within the cell.

(ii) Continuous movement at different velocities of ions out of the cell. The cell constantly pumps sodium and chloride ions out and allows potassium ions into the cell. The energy for this pumping action is supplied by the metabolism of the neurone.

The rate of energy release decides the magnitude of the resting potential and therefore the gradient of ionic equilibrium. This resting metabolism is effected by a supply of glucose which provides for continuous oxidation and release of energy, and oxygen, which is supplied from the blood. Thus a change in the oxygen or glucose concentration in the blood causes a change in the resting potential of all nerve cells.

The oxygen supply to the brain, though large, is not greatly in excess of cerebral needs. Any reduction in the flow, or in the oxygen tension in the blood soon leads to disturbed brain function.

The metabolism of the brain and of nervous tissue generally, is peculiar. It can apparently only metabolise carbohydrates and cannot in itself store glucose. This is distinct from many other cells which will oxidise fats etc, if glucose is unobtainable. Nervous tissue is therefore very dependent for its energy on the contemporaneous blood sugar. Hypoglycaemia produces symptoms mainly of cerebral dysfunction.

Within the nerve cell, glucose is phosphorylated to hexose phosphate and then to pyruvic acid which enters the tricarboxylic cycle to form CO<sub>2</sub>, water and energy. If oxygen is not available, lactic acid is formed with a lower value of energy produced. The resting potential at low arterial oxygen

is thus changed.

Pyruvic acid oxidases, which are necessary in the enzymatic degradation of glucose, require thiamine or vitamin B. Thus we see that oxygen, pyruvic acid oxidase and thiamine as a coenzyme are required for energy release within the axon. Deficiency of any one factor produces derangement of the nervous system and ultimately permanent damage.

The excitability of neurones depends upon the resting potential and is decreased if the resting potential is depressed.

Thus it can be seen that excitability varies firstly with the electrolyte balance of the body as a whole and secondly on the metabolic processes which allows the neurone to maintain its resting potential.

With regard to the former, it is a known fact that surgery affects the nervous system in many patients due to alteration in the salt balance.

#### The Nerve Impulse.

Nerve fibres signal events by transmitting impulses. Each impulse consists of an area of activity whose intensity, duration and speed of conduction are remarkably constant in any one fibre. It is an incompletely understood physico-chemical change and involves an alteration in the electrical state of the surface of the fibre; a change in the transverse electrical resistance; a very small increase in heat production and increases in oxygen consumption and CO<sub>2</sub> production with concomitant chemical changes.

Of all these physico chemical changes, the electrical potential change is the easiest to record. It is the most certain indicator of the development and propagation of the nerve impulses and probably represents the essential process involved in transmitting the impulse along the fibre.

The impulse must be distinguished from the stimulus, which is the external force - either electrical, chemical or mechanical - which sets up the impulse. The chemical changes in nerve fibres

are probably wholly or mainly concerned with the recovery processes which follow activity.

### The Action Potential.

If a stimulus of sufficient intensity be applied to any part of a neurone, then activity is transmitted throughout, from the point of stimulation in both directions. Activity in the direction from the periphery towards the Central Nervous System is orthodromic. Antidromic direction is contrary to normal activity and is rarely seen.

When an impulse is set up, the membrane becomes depolarised i.e. as the impulse passes down the nerve, the resting potential is abolished for one or two milliseconds. This disappearance of the resting potential is called the Action Potential and is the electrical signal of the passage of a nerve impulse through the nerve.

This action potential is seen in its simplest form when two electrodes - one externally and one internally on the nerve - are connected to a recording system.

(Electrodes may be placed on intact nerve and action potentials on opposite sides of the base line are then set up as the impulse passes first one and then the other electrode. Since an impulse occupies about 4 cms of nerve at a time, there will be some interference between the two halves of the resulting double diphasic action potential unless the electrodes are farther apart than this).

The action potential is seen in the first half millisecond as a reversal of sign to about 40 mv. i.e. a change in potential from - 60 to 40 mv., which is a total change of 100 mv. (Fig. 3).

A reversal of potential is thus seen and the inner electrode becomes positive relative to the outer. There also follows small negative and positive after potentials.

This implies a change in ionic relationships which could be effected:-

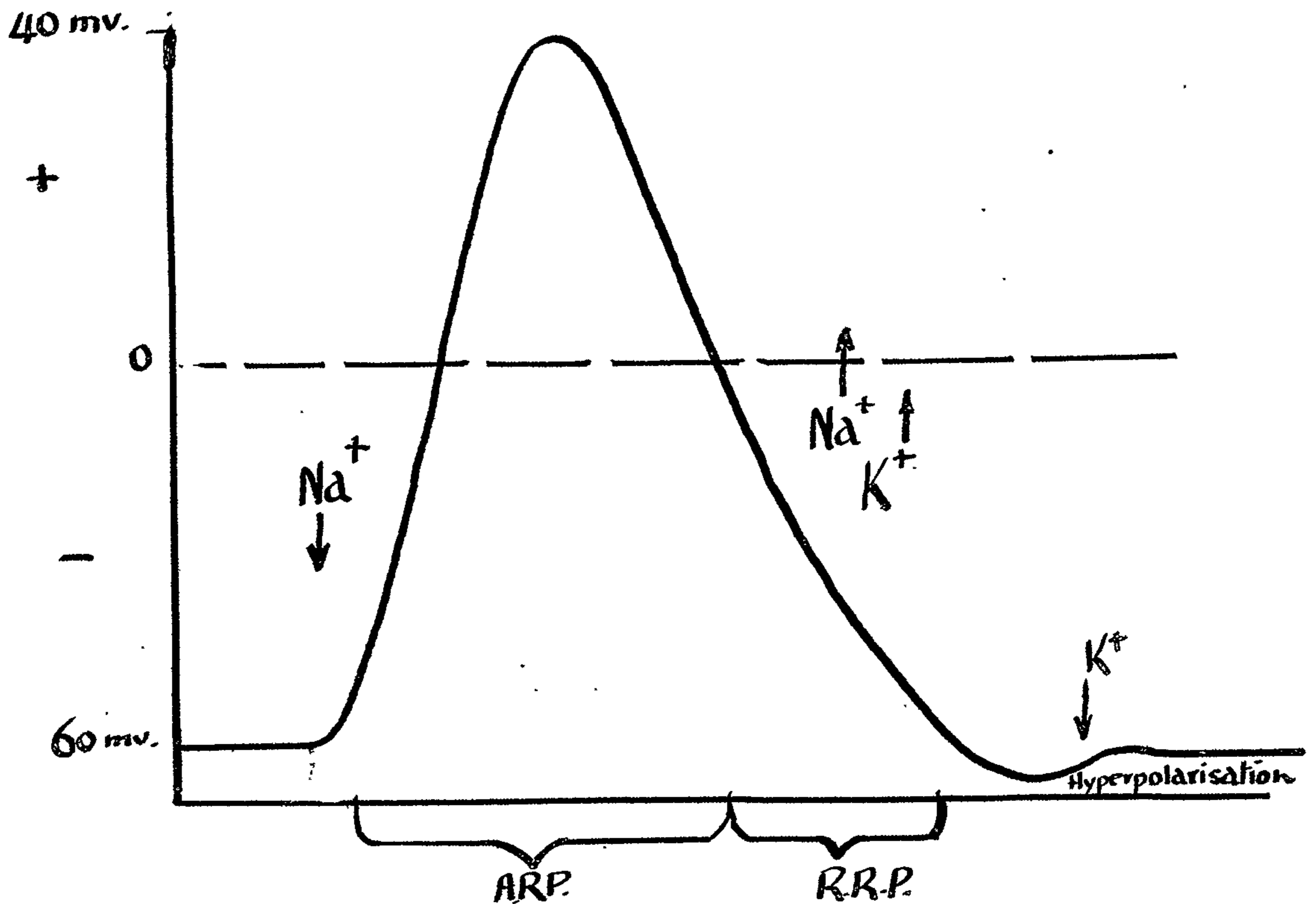


Fig. 3. Diagrammatic representation of an action potential showing depolarisation and abolition of the resting potential, due to entry of positive ions into the neurone.

Subsequent repolarisation is preceded by a hyperpolarisation period due to expulsion of excess positivity.

Acetyl choline permits selective diffusion of potassium ions back into the neurone, restoring the resting potential.

(i) By loss of negative ions from the interior. The chloride ions, however, are small in proportion and could not effect this great reversal of potential.

(ii) The change is in fact due to entry of positive ions into the neurone. Hodgkin and Cass have suggested that during excitation, the axon membrane changes its relative permeabilities to potassium, sodium and chloride ions. In the resting state, the relative permeabilities are in the ratio 1.0 : 1.04 : 0.45, and these changes to 1.0 : 20 : 0.25.

The axon membrane thus temporarily becomes selectively permeable to Na and relatively impermeable to  $K^+$

The external concentration of  $Na^+$  is 150 times greater than that internally and thus we can see that little energy would be required to admit it. The  $Na^+$  concentration inside the fibre then exceeds that outside, and this reversal of the resting ratio reverses the sign of the resting membrane polarisation i.e. the surface becomes negative relative to the interior.

The generation of the action potential is thus supplied by immigration of sodium from the outside, and the energy required is provided by the stimulus.

The production of a nerve impulse can be seen when a fibre is experimentally stimulated by means of a brief pulse of current. Figure (4) shows how the current flows from the electrode connecting to the anode through the fluid outside the membrane, through the membrane to the interior of the fibre, and then out again to the electrode connected with the cathode. The electrical charge set up in the neighbourhood of the electrodes is called electrotonus - catelectrotonus at the cathode, and anaelectrotonus at the anode. Electrotonus is a localised electrical change i.e. at the point examined where there is a reversal of resting potential, we find a battery of longitudinal potential difference. It is maximal at the electrode and diminishes in magnitude exponentially with distance from the electrodes.

On switching the current on and off, it rapidly builds up and subsides. Increasing the strength of the current

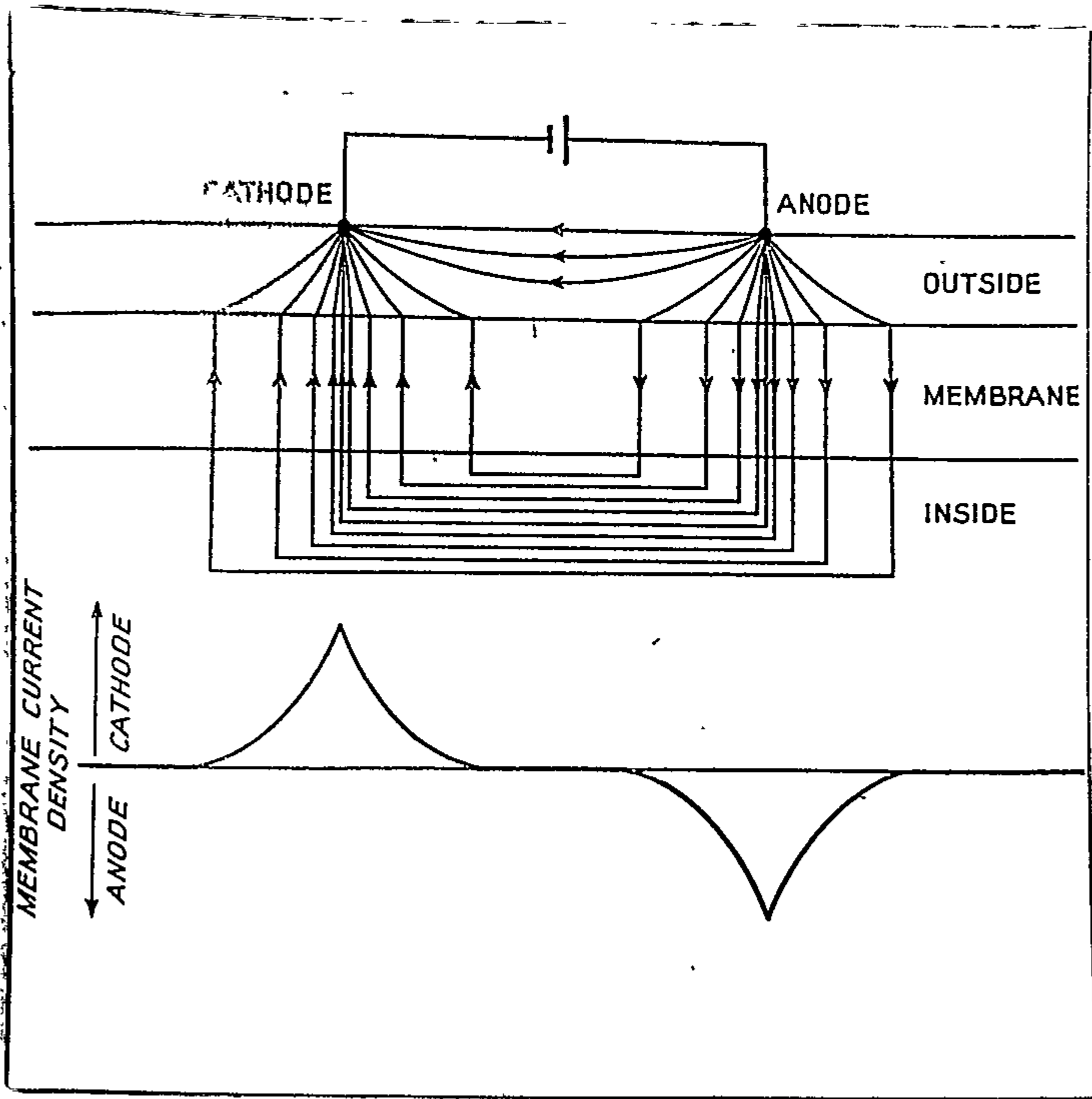


Fig. 4. Diagram of current distribution in nerve during passage of a brief pulse of current.

Upper diagram shows the distribution of current flow from anode (+) to cathode (-) through the interstitial fluid, across the membrane and in the axoplasm.

Lower diagram shows membrane current density. It is greatest at the cathode and anode and declines in an exponential manner with distance from the electrodes. Nerve excitability is increased at the cathode (catelectrotonus) and decreased at the anode (anelectrotonus).

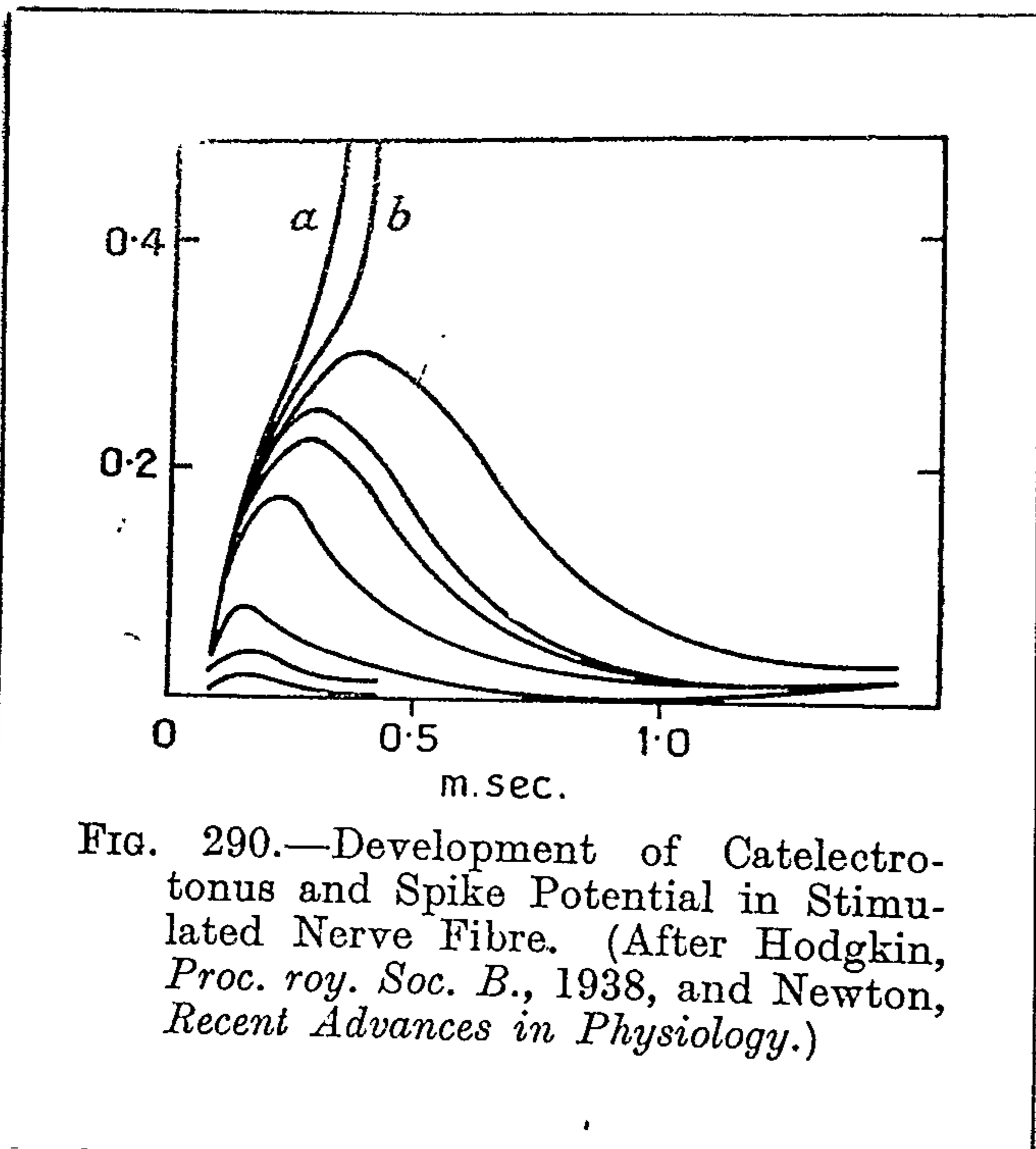


FIG. 290.—Development of Catelectrotonus and Spike Potential in Stimulated Nerve Fibre. (After Hodgkin, *Proc. roy. Soc. B.*, 1938, and Newton, *Recent Advances in Physiology.*)

Fig. 5. Electrical changes produced in nerve at the stimulating electrode (cathode) by progressively increased stimuli.

Ordinate: magnitude of response as a fraction of the full spike potential. Note the progressively increasing local catelectrotonus.

With the strongest stimuli employed (a, b) the catelectrotonus develops into a full spike potential of which only the onset is shown (183).

progressively increases the electrotonus - at the cathode it is associated with increased excitability of the fibre and at the anode decreased excitability.

When cataelectrotonus reaches a certain magnitude, an impulse is generated at the cathode as shown by the appearance of a propagated spike potential (Fig. 5). It seems that the current flow at the cathode alters the state of the membrane and when this so called depolarisation reaches a critical magnitude, an impulse is set up.

#### Propagation of the Impulse.

The spike potential acts like a travelling stimulating cathode (Fig. 6). The intensity of the energy in an electrotonic field is always greater than the threshold of the nerve.

At the boundary of the active region of the fibre, that is, at the site of production of the spike potential - a local closed electrical circuit is set up, the current flowing from the positive resting region to the negative active region. This local circuit in front of the active zone is identical with the local circuit set up at the cathode i.e. it is a region of momentary cataelectrotonus.

When this cataelectrotonus reaches the requisite magnitude, it alters the membrane sufficiently for impulse and spike potential to be set up. The spike or action potential acts then as the stimulus to the zone of nerve fibre immediately adjacent to it. Thus, the action potential and impulse are progressively propagated along the fibre.

To sum up:-

- (1) Propagation is initiated when an action potential is at its peak.
- (2) Propagation depends upon the formation of electrotonic fields -

If the fibre is myelinated, we see obstruction to ionic movements and ionic flow is restricted to the nodes of Ranvier. Myelin is a powerful electric insulator, and there is a distortion

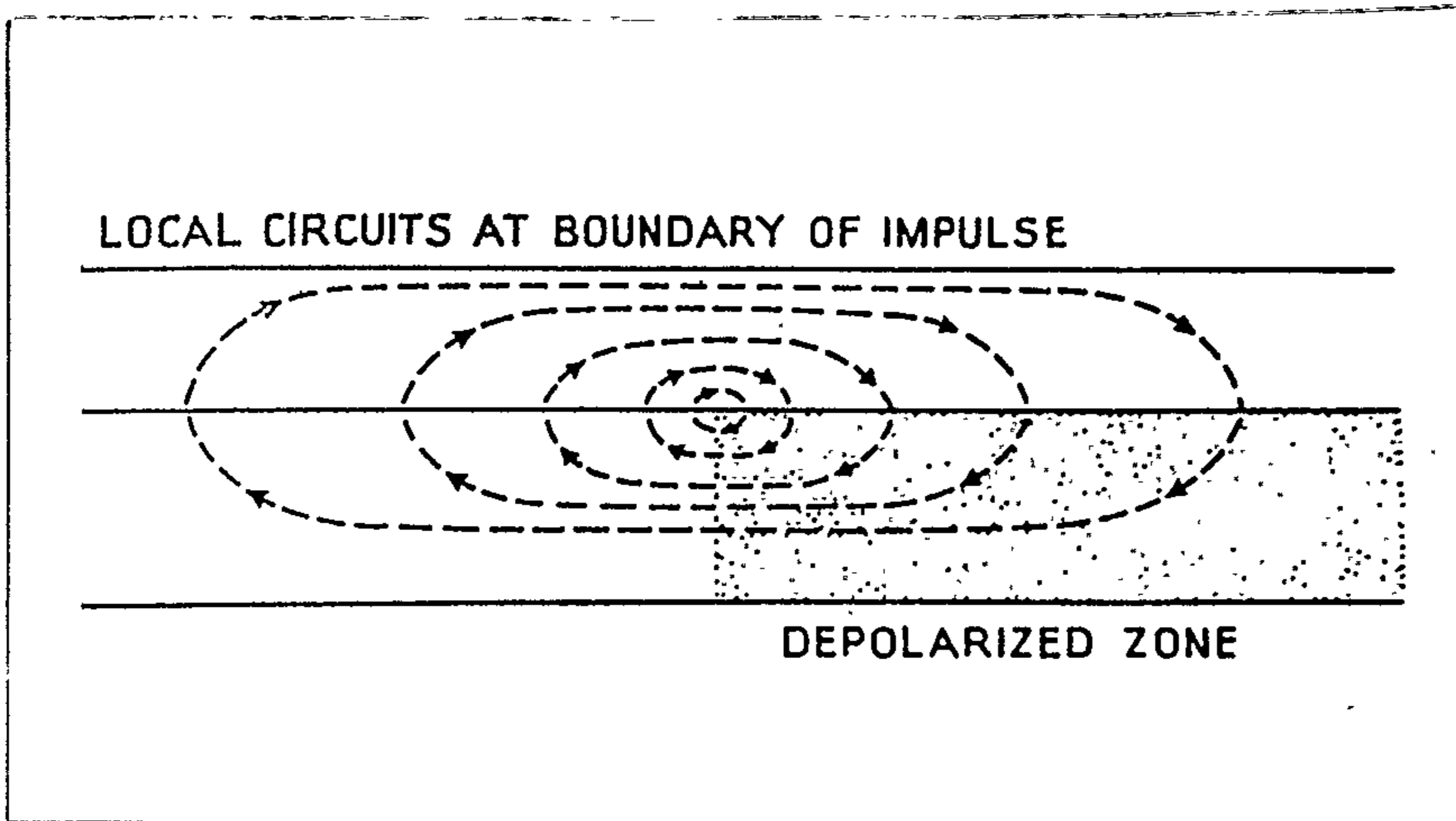


Fig. 6 Propagation of the nerve impulse. The impulse is moving from right to left in the nerve fibre. The depolarised zone is the site of the spike potential. It generates a current flow in the adjacent part of the fibre which sets up first a catelectrotonus, then a spike potential.

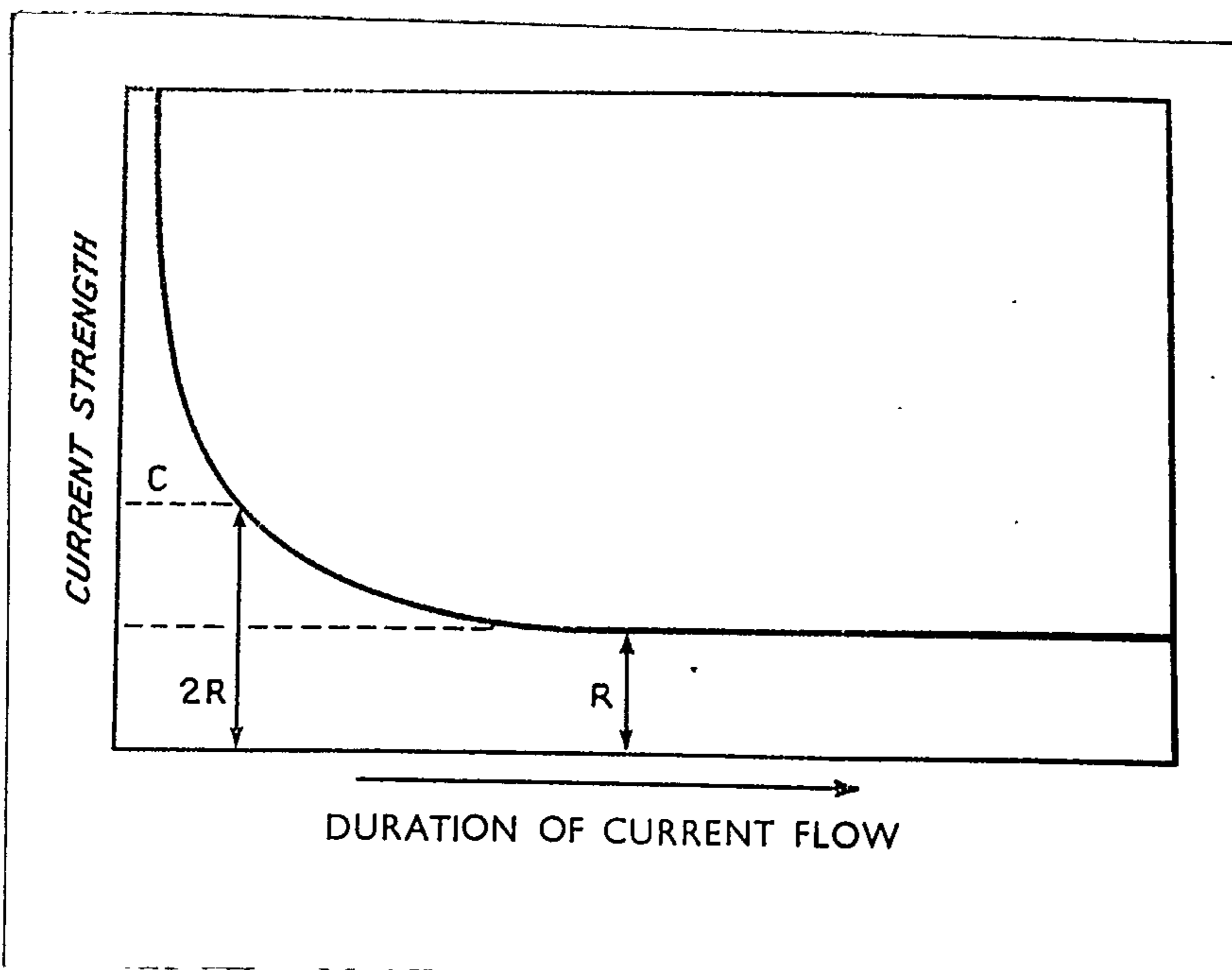


Fig. 7 (page 30) Strength - Duration Curve. Rheobase and Chronaxie. The curve shows the relationship between strength of stimulation and the minimum duration of stimulation necessary to set up an impulse.  
R = Rheobase, C = Chronaxie

of the electrotonic fields in current flowing from node to node into elliptical fields. There is no centre in these elliptical electrotonic fields, but two epicentres, and the fields coincides with each node. The impulse thus jumps rapidly from one node to the next i.e. it is saltatory.

PROPAGATION IN MYELINATED FIBRES IS THUS FASTER THAN IN UNMYELINATED TYPES AND INCREASE IN INTERNODAL LENGTH RESULTS IN MORE RAPID PROPAGATION. THE FACT THAT CONDUCTION VELOCITY VARIES DIRECTLY WITH FIBRE DIAMETER HAS AN IMPORTANT BEARING WHEN WE CONSIDER THE FIBRE TYPES SUBSERVING PAIN SENSATION.

In attempting to explain the phenomenon of the action potential the membrane theory has been proposed. It is suggested that the cell membrane may consist of radially arranged long chain fatty acids or lecithin molecules with a potential gradient of 50000 volts/cm. across it.

If this potential is diminished, the packing of the radial molecules might well change, so altering the membrane permeability. When an impulse passes, there is certainly a drop in electrical resistance across the membrane. This resistance has been measured directly and found to fall to 1/40th of its resting value. The structure of the membrane is not greatly altered but apparently flaws appear in it.

Excitation probably occurs whenever the charge on the cell membrane has been reduced to a critical level. At this instant, the membrane becomes permeable, and the remaining charge is abolished by the migration of the positive and negative ions which pass through the membrane.

Currents now flow towards this permeable region from the edges of the active area outside the membrane and away from it inside the fibre. This reduces the charge on the adjacent parts of the cell membrane and if the area excited is large enough, the charge at the adjacent edges will fall below the critical level and the cell membrane there too will become permeable.

This process continues and the wave of excitation spreads out. After a period of activity, the cell rebuilds the charge

on its surface and restores its impermeability by methods which will be described shortly.

Direct evidence of the existence of local currents which travel ahead of the impulse and begin the process of excitation was found experimentally by stopping the impulse at a narrow cold block on the nerve. Although the impulse itself was unable to pass, the local current spread ahead beyond the block and appeared as a small potential 1/8th of the size of the normal action potential and then died out after conduction over a few mm.

This small potential was able to increase the excitability of the nerve to 95% of the threshold, and was in fact due to a local response set up below the block.

By means of these local currents or circuits, i.e. electrotonic fields, an impulse can jump a narrow region of complete block. The spike potential is arrested when it reaches the block but the local circuits can pass through it to excite the normal nerve fibre beyond.

If a region of a nerve fibre is depressed, for example, by local anaesthetic or injury, the affected region, when stimulated by the arrival of the electrotonic wave, responds with a subnormal spike potential, which is the best the depressed region can produce. If a length of fibre is only partly narcotised, the action potential and impulse travel through it with a uniformly diminished intensity, but on reaching normal tissue again, the forerunning electrotonus generates a spike potential of normal magnitude once more.

#### Changes in excitability after a nerve impulse.

At the peak of the action potential, there is a preponderance of sodium inside the neurone, and the neurone is absolutely refractory, however strong the stimulus. Thus the absolute refractory period corresponds roughly to the duration of the spike.

The peak declines slowly to below the normal resting

potential and then returns to normal. This is due to expulsion of  $\text{Na}^+$  and  $\text{K}^+$  since the mechanism does not distinguish between them, and excess positivity is lost. This falling phase thus falls lower than normal, and the level may fall to - 80 mv.

K then diffuses slowly back into the neurone, restoring the resting potential to - 60 mv.

The period from the top of the spike to the commencement of this hyperpolarisation is a relative refractory period, and is 7 - 10 times as long as the absolute refractory period. In large fibres, the absolute refractory period is about 0.4 to 0.5 millsecs, and the relative refractory period is about 2 millsecs. At first, a very strong current is necessary to excite the fibre in the relative refractory period, and it responds with a subnormal spike. The strength of the minimal exciting stimulus progressively falls until excitability returns to normal.

The period of hyperpolarisation which occurs after the relative refractory period is sometimes referred to as the negative after potential, and during this time the fibre is more excitable. This is sometimes followed by a positive after potential during which the fibre is in a subnormal state, and both excitability and conduction velocity are depressed.

FIBRES OF LARGEST DIAMETER RECOVER MORE QUICKLY THAN FIBRES OF SMALL DIAMETER AND CONSEQUENTLY THE UPPER LIMIT OF IMPULSE FREQUENCY WHICH THE SMALLER FIBRES CAN TRANSMIT IS LOWER.

It is to be noted that the magnitude of the spike potential set up in a nerve fibre is maximal, providing that the strength of the exciting stimulus is threshold. That is, a nerve fibre responds to a threshold stimulus to the utmost of its ability under the conditions of the moment. This is the All or None relationship.

#### The Mechanism of Nerve Recovery.

Whereas the energy supplied for the action potential is effected by the stimulus, much energy must be released to expel the  $\text{Na}^+$  and  $\text{K}^+$  when the action potential reaches its peak. This is not due to increased glucose, or oxygen metabolism, for

this mechanism is only concerned in the maintenance of the resting potential.

The system concerned is the breakdown of high energy phosphate systems, i.e. the breakdown of creatine phosphate to A.T.P. and A.D.P.

The creative phosphate is stored at rest, and is derived from normal oxidation of glucose. Glucose is partly oxidised to CO<sub>2</sub> and water, and partly enters with energy production for synthesis of high energy phosphate systems. The sudden burst of energy therefore is provided by breakdown of creatine phosphate to A.T.P. and A.D.P. releasing 10,000 cal/molecule.

After transmission of the impulse, the return of K<sup>+</sup> into the neurone depends upon an alteration in the permeability of the membrane. Whereas energy processes would return Na<sup>+</sup> and K<sup>+</sup> together, this process is selective and therefore is non-energetic. Na<sup>+</sup> ions are larger than K<sup>+</sup> ions, and thus a small increase in pore size would permit diffusion of the potassium only. This is effected by the action of acetyl choline on the membrane. The sole function of acetyl choline is to effect repolarisation after hyperpolarisation. The nerve increases production of this substance during the first stage of repolarisation.

The enzyme choline acetylase and choline is always present in nerve, and acetic acid is a bi-product of glucose metabolism. The energy released by CrP breakdown thus supplies energy for synthesis of acetyl choline as well as for the expulsion of positivity.

Diffusion of acetyl choline into the tissue fluid is prevented by choline esterase in the Schwann cell, and acetyl choline is converted back to acetic acid and choline. The diffusion of potassium ions then ends.

It can be seen that the administration of anticholinesterases allows acetyl choline to appear in the tissue fluid and the nerve is then in a permanently refractory state.

### Stimulation of Nerve Fibres.

In the intact animal, nerve cells are excited by more or less specialised endings such as tactile or Paccinian corpuscles or by other nerve cells. The end organ has a very much lower threshold for stimulation and it, in turn, excites the nerve fibre. It is supposed that the natural stimuli produce the same sequence of changes in the nerve endings i.e. a localised cataleptotonus followed by a propagated action potential.

The end organ must be able to deliver a very strong stimulus to the nerve fibre, since some endings e.g. pressure receptors in the periodontal membrane of teeth, can excite their fibres during their relative refractory period, when thresholds are above normal.

The smooth relation between the frequency of response, and the intensity of stimulation between 5 and 300 impulses/sec is probably due to the special properties of the endings in which excitation is built up more slowly with weaker stimuli. With higher rates of response a stronger stimulus produces a higher rate of discharge, because each stimulus is able to excite earlier than the relative refractory period.

Some observations on the <sup>in</sup> vitro stimulation of nerve fibres serves to illustrate the meaning of threshold stimulation.

Whether we artificially excite a nerve by chemical, thermal, mechanical or electrical stimuli, the nerve responds in the same way by setting up an impulse of constant shape, size and duration.

The stimulus must be of a certain minimal value, i.e. it must be threshold and once threshold has been reached, an increase in stimulation will not cause a change of a more optimal nature to the impulse.

The effectiveness of an electrical stimulus depends upon strength, duration and rate of rise. In order to excite, the current must rise at more than a certain critical rate. If the current is slowly rising, it may fail to excite even if it reaches eventually a strength well above that necessary with steeply rising current. A nerve accommodates itself to the current in

such a way that there is a gradual increase in threshold to which excitation can occur. The current must therefore have a minimal gradient in order to excite, and electrical stimuli in common use rise sharply to their maximum value.

Below a certain strength called the rheobase, no shock will excite, however long it is allowed to continue. A strong current produces a response after a short time of flow, but as the strength is reduced, a longer duration of flow is required to stimulate. This relationship between the current strength and the duration of current flow necessary to stimulate is shown in the strength duration curve in Fig. 7. (page 24).

The weakest current strength which can excite a tissue if allowed to flow through it for an adequate time is called, as stated, the rheobase, and a shock which is just rheobasic will always excite after a finite interval which is called the utilisation time.

If we use a current strength which is equal to twice the rheobase, the duration of the current flow which stimulates the tissue under these conditions is called the chronaxie<sup>or</sup> excitation time. Chronaxie values are useful indicators of the relative excitability of the tissues. Thus the chronaxie of nerve fibres is considerably shorter than that of skeletal muscle.

If, in order to avoid the disturbing effects of setting up a nerve impulse, a short shock of 95% threshold strength is applied to the nerve, the excitability of the nerve is raised for about 1 m/sec. This can be detected by applying a second shock of the same strength, through the same electrodes. This is called local excitatory state. Its maximal duration is called the summation interval. If two such shocks are applied within the summation interval, neither of which is capable of setting up an impulse alone, excitation of the nerve will occur. PERHAPS THIS HELPS IN THE UNDERSTANDING OF CUTANEOUS HYPERALGESIA, WHICH WILL BE DISCUSSED IN A LATER CHAPTER. LOW THRESHOLD STIMULI RADIATING FROM AN INFLAMED AREA MAY RESULT IN HYPERALGESIA AND RESPONSE TO STIMULI WHICH ARE NORMALLY NON-NOXIOUS.

Analysis of compound Action Potentials.

When a peripheral nerve is stimulated, there is never seen a single action potential. Rather a compound action potential is observed which is the superimposition of the numerous individual action potentials of the stimulated fibres. As the exciting stimulus is progressively increased a larger number of fibres respond. Finally, a strength of stimulus is reached which excites all the nerve fibres and increasing the stimulus further does not increase the response of the whole nerve.

Fibres in a nerve have differing thresholds which account for the increasing response as stimulation is increased.

The classic experiment of Gasser and Erlanger in 1927 (67) formed the basis of our present knowledge of the connection between action potential, conduction rate, and fibre diameter. Working with a cathode ray oscillograph, they found that the electroneurogram i.e. the shape of the action potential, led off from a nerve trunk and recorded on a rapidly running film had a different shape in the motor and sensory roots.

In the posterior roots, the wave was drawn out in three different peaks which they called alpha, beta, and gamma. They attempted to reconstruct the form of the electroneurogram setting out from a fibre analysis of the respective roots.

This reconstruction tallied closely with the recorded shape of the electroneurogram (145).

Gasser and Erlanger thus ascertained that the anatomical classification of fibres according to size corresponded with the physiological classification according to speed of conduction, and formulated the basic concept that conduction velocity varies directly with fibre diameter.

According to Gasser and Erlanger the alpha, beta, and gamma peaks corresponded to three classes of nerve fibres with a diameter down to 5  $\mu$  and a conduction velocity of respectively 80, 50 and 30 metres/sec.

By further studies on peripheral mammalian nerves these workers revealed another two classes of fibres with such a slow conduction rate that they had not been recorded in the previous experiment. They called the latter two classes B and C fibres.

Precise recordings of compound action potentials now reveal that the A group is composed of alpha, beta, gamma and delta subgroups and a fifth group which is very irregular, called the epsilon group.

Gasser's original experiments could not differentiate these latter groups.

About 54% of the total number of fibres contribute to the alpha -beta elevation, 11% the gamma, and 35% to the delta and epsilon elevations. These elevations are purely a result of differing fibre diameter (velocity metres/sec =  $K \times$  axon diameter). Among the A fibres then, there is a continuous series of velocities from 90 metres/sec down to 10 metres/sec.

All these medullated fibres of the A group in somatic nerves appear to be fundamentally of the same kind. The individual action potentials are the same in configuration i.e. their constituent spikes, negative after potentials and positive after potentials are identical and have the same proportions one with respect to another. Parallel to the after-potentials, the excitability cycles i.e. the cycles of altered threshold following a response, are also alike.

Homogeneity among all medullated fibres, is, however, not true (66). It has been mentioned that Gasser observed a group of fibres termed B fibres which were relatively slowly conducting and medullated.

The peak elicited by the B fibres was not found in electro-neurograms of the posterior roots but only in the electroneurograms of peripheral nerves (145).

Although Sjoquist states that this B peak is due to branching of the fibres peripherally, it is now believed that the B group is associated practically entirely with the autonomic

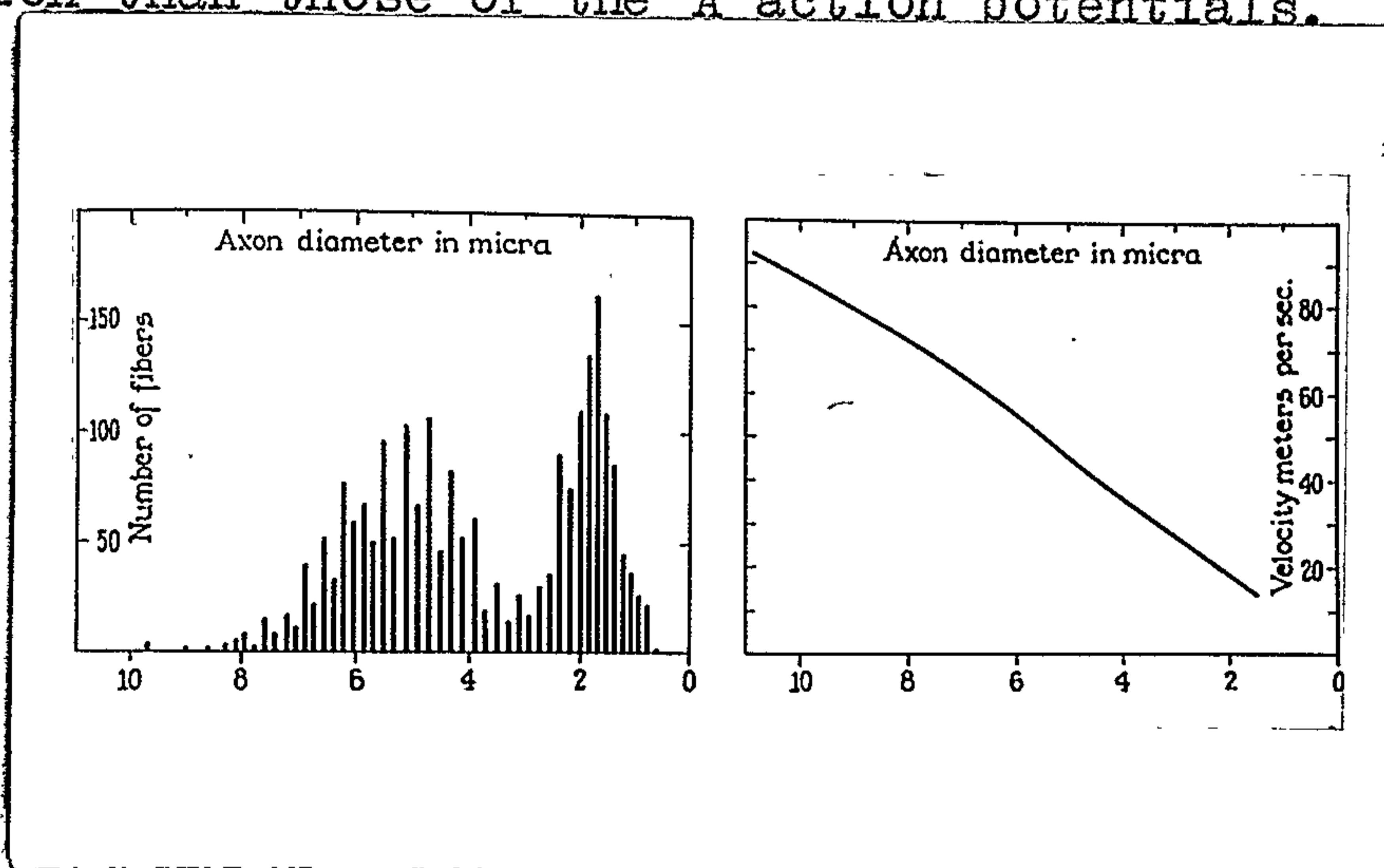
system and are the medullated fibres connected with the viscera in peripheral nerves. Obviously they would not be found in the posterior roots of somatic nerves.

These B fibres, associated with the viscera, are medullated fibres with a different set of fundamental properties to the A group.

To complete the survey of fibre types, it will be recalled that a very large unmyelinated component exists. The ratio of unmyelinated to myelinated fibres varies from 4:1 to 1 : 1 (66). These unmedullated fibres belong to the category known as C fibres, originally noted by Gasser as being fibres of slowest conduction rate (67).

These fibres conduct impulses at velocities between 2 - 0.6 metres/sec and their properties are in sharp contrast to the A fibres.

- (i) Spike duration for the A fibres is 0.4 - 0.5 m/sec; for the C fibres 2.0 m/sec.
- (ii) Termination of the negative after potential - 12-20 m/sec for A fibres; 50 - 80 m/sec for C fibres.
- (iii) Termination of positive after potentials - 40 - 60 m/sec for A fibres and 1000 + m/sec for C fibres.
- (iv) All parts of the C action potentials are much longer in duration than those of the A action potentials.



Figures 8 and 9 illustrate that the prominence of the features of an action potential is no index to the importance of

the fibres they represent. Figure 8 shows a fibre distribution curve of a nerve and it can be seen that more than half the number of fibres present are of the smaller diameter from 4 - 0.5  $\mu$ . In view of the slower conduction rate of these fibres (Fig. 9) they show up as insignificant delayed minor elevations in the compound action potential and yield little to the action potential in comparison with the first high elevations of the large sized fibres.

Collectively, by virtue of their numbers, these fibres have a great capacity for carrying independent signals and among them we must look for the bearers of a large fraction of sensory messages.

Why sensory messages should be mediated by fibres of such different constants is not clear. Obviously there is a decided variation in time taken by the messages to reach the central nervous system and this must be necessary for the integration mechanism. Some impulses arrive ahead of the others and probably determine which of the possible neurone chains are to be occupied in effecting an appropriate reaction.

The utility of fast impulses arriving first to control the position of parts of the body in space can be appreciated so that these parts will be ready for the finer reactions determined by the detailed information mediated by fibres of slower conduction.

The fastest sensory impulses originate in muscles and are concerned with proprioception.

The question as to what group of fibres are concerned in the mediation of pain sensation is not a simple one, for it will be shown in the succeeding chapter that pain may be of the 'fast' or 'slow' variety. If one touches the finger near the nail bed against a hot electric bulb, there are felt two distinct flashes of pain, the one coming almost at once, and the other after a discernable delay (180). The second may be more intense and prolonged. A similar double flash can be felt after a needle prick.

The conduction of pain impulses must therefore be mediated by at least two fibre types which have differing conduction velocities.

When a needle of constant weight is caused to fall upon the skin from a constant height, there occurs first a burst of large 'spikes' mingled with smaller 'spikes', both at high frequency, and then a subsequent discharge at a decreasing frequency lasting several seconds. In this late discharge spikes of small size are relatively more common, with a predominance of C spikes.

It is apparent that touch and pressure receptors have been stimulated by the needle prick as well as pain, and perhaps other non specific excitations.

The following experimental evidence suggests that pain is conducted in the fibres of smaller diameter, both medullated and unmedullated.

- 1) The fibres subserving pain have been demonstrated in a convincing way by Weddell et al (181). Following section of a sensory nerve, the area from which pain cannot be evoked is smaller than that for touch and temperature. From a patient who had previously experienced a nerve lesion of this sort, a portion of skin from which pain only could be elicited was examined histologically. A superficial net with fine fibres branching to give rise to beaded endings made up the sum total of its neural content. These free terminals connected with a superficial plexus made up of unmyelinated and thin myelinated fibres. These small fibres contrast sharply with large fibres innervating the Krause bulbs and other elaborate endings.
- 2) Ranson and Billingsley (122) showed that after section of the small fibres of the lateral division of a dorsal root, stimulation of the remaining fibres failed to elicit nociceptive reflexes, while on the contrary, after section of the large fibres in the medial division, the reflexes were left intact.
- 3) Heinbecker, Bishop and O'Leary (85) experimented with a lightly anaesthetised cat and administered progressively

increasing shocks to a peripheral nerve. It was found that the nociceptive reflexes became marked when the delta fibres were brought into activity - smaller fibres requiring larger stimuli to excite. This finding points clearly to the importance of the delta fibres producing the reaction although it does not accord these fibres an exclusive property (66).

4) More direct evidence of the association of pain impulses with delta A fibres has been obtained by Heinbecker et al (86) in an experiment performed on a human subject. Twelve (12) shocks in 5 seconds at a delta stimulating strength applied to an exposed nerve brought forth facial contortions and groans whereas slightly weaker stimuli at higher frequency failed to produce these disturbances.

5) The 'C' fibres are also capable of setting up nociceptive reflexes. Clark, Hughes, and Gasser (31) found that in a deeply anaesthetised animal, the stimulus exciting C fibres as well as delta A fibres produces much larger reflexes than one exciting only A fibres.

While the production of reflexes affords no direct proof of the involvement of fibres in pain mediation, the reaction is one to be expected if the fibres have that function.

6) In Tabes Dorsalis, injury to dorsal nerve roots may abolish fast pain and leave only the slow pain sensation.

From the foregoing, it seems that pain impulses are carried by both myelinated (delta A) and unmyelinated (C) fibres.

Conduction in C fibres is 1 - 2 metres/secs while conduction velocity in medullated A fibres is 15 - 20 metres/sec.

We are thus able to differentiate a slow group of impulses and a fast group, and herein lies the explanation of the double response to pain which was first described by Goldscheider in 1892.

In 1933 Zottermann (187) found, by distending the cuff of a sphygmomanometer apparatus around the upper arm to a pressure above the systolic, and leaving it in place for 40 mins., it was

possible to produce differential anaesthesia of the hand and fingers. At a certain stage only pain sensation is left, and this pain sensation which persists, is felt only after a delay. This delay compares accurately with the calculation of what the delay would be expected to be if the impulses were carried in C fibres.

While C fibres seem to be associated with the transmission of 'second pain', the delta A fibres must not be assigned an exclusive role for the transmission of 'first' pain.

Zottermann (188) found that the potentials observed in a cat on stroking the skin with a wisp of cotton, all belong to the delta category. These findings indicate that the delta A fibres are instrumental in the mediation of touch as well as of pain.

It also seems that there are some fairly large sized fibres other than those of the delta A group which carry pain impulses.

In perineural cocaine anaesthesia, the order in which block is noted is in direct proportion to fibre diameter. Bishop et al (86) found that the order in which sensations are lost are as follows;- slow pain (C fibres), cold, warm, pain and pressure or touch.

Some pain therefore appears to survive cold (fibre size 4 - 5  $\mu$ ) and is itself survived only by large pressure fibres (size 8  $\mu$ ). The inference is therefore that there are some pain fibres larger than those of the delta A group.

It is therefore difficult to assign any one sensation with definite elevations on the electroneurogram, for fibres subserving different modalities are widely distributed throughout the range of fibre size.

Sjoquist (145) draws attention to the fact that fibres of peripheral nerves may branch, the daughter fibres having a smaller diameter than the parent ones. Such branches may well be less than 3  $\mu$  and bear no relation to pain transmission. The position is further complicated when we consider that it is

possible for small myelinated nerve fibres, to have conduction rates corresponding to the C fibres (conduction rate varies with the square area of the fibres, not with fibre diameter) and these may not in themselves be associated with pain transmission.

In summary it may be said that nocuous stimulation sets up a prolonged discharge of impulses with little sign of adaptation, conducted in two main types of fibres -

- (a) Very fine unmyelinated C fibres.
- (b) Thin medullated A fibres of the delta epsilon group.

The correlation between fibre size and modality of sensation are, however, not as good as one might hope. It seems that:

- (i) Larger medullated fibres than those of the delta epsilon group may also carry pain impulses.
- (ii) The delta A fibres may transmit touch and temperature as well as pain.
- (iii) C fibres may transmit temperature impulses in addition to pain.

Wright (182) generalises as follows:-

"The whole of the apparatus concerned with the conduction of pain impulses and their relations in the nervous system appear to be equally slow, for the maximum rate at which painful sensation can be felt as intermittent is approximately 15 stimulations/second. Though the responses to pain are comparatively rapid when they do occur, compared with other sensations the delay in the nerve mechanism is long."

	Relative spike height	Relative conduction rate	Relative diameter
Touche .....	10	100	10
Taste .....	6-1	60-40	7-6
Heat .....	4-2	40-20	6-5
Cold .....	2-1.5	20-15	5-4
Pain.....	1 and less	10 and less	4 and less

Fig. 10. Sjoquist's analysis of fibre diameter in relation to spike height conduction rate and probable function (145).

The table listed below represents currently held views on the functions of differing fibre types:

Group A: 2 < 25u myelinated  
alpha, beta, gamma and delta subgroups  
Largest fibres are proprioceptive sensory and somatic motor nerves i.e. the afferent and efferent connections with striated muscles.  
Smaller fibres are cutaneous sensory subserving heat, cold (5 - 4u), touch (12 - 8u) and pressure (8 - 6u). Small delta fibres are concerned with first pain (2 < 5u; some larger).

Group B: 5 < 15u myelinated.  
Form bulk of preganglionic trunks in the autonomic system.

Group C: 2u or less unmyelinated  
Subserve slow pain sensibility e.g. from the periodontium and perhaps some temperature sensation. Also seen in postganglionic sympathetic efferents.

THE PHYSIOLOGICAL CHARACTERISTICS OF DIFFERING FIBRE TYPES.

Physiological properties of large and small fibres differ markedly. Considering that pain is mediated in general by the smaller fibres, it is of interest to note certain points of difference which distinguish these from larger fibres subserving other senses as well as somatic motor functions.

Point (1) Excitability varies directly with fibre diameter. The larger fibres respond to a smaller stimulus i.e. they have a lower threshold due to a greater potential difference over the fibre, e.g. application of a hot instrument to the skin produces a sensation of heat, followed by a burning pain if contact is maintained.

Point(2) Conduction velocity varies directly with the fibre diameter -

$$V \text{ m/sec} = 6 \times \text{diam. } \mu$$

Reference will be later made to 'first' and 'second' pain. The former is carried by large fibres with higher conduction velocity than the smaller diameter fibres signalling 'after' or 'second' pain.

Point (3) The resting potential differs in different fibres and the heights of action potential differ also.

The height of the action potential is directly related to fibre size, whereas the duration of the action potential varies ~~in~~ inversely. The smaller fibres take longer to repolarise in view of their smaller energy release. This accounts for the following fact.

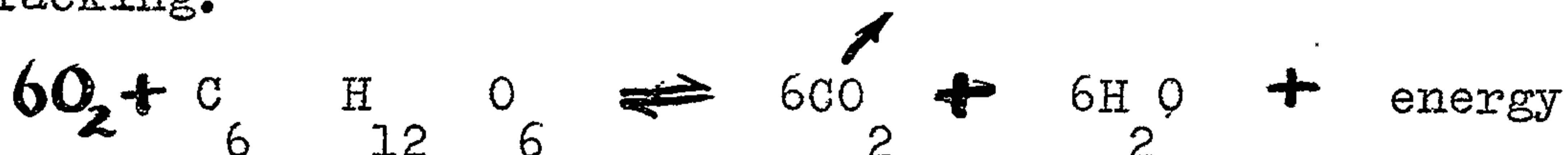
Point (4) The refractory period varies inversely with fibre size. That is the larger fibres can transmit up to 800 impulses per second, whereas the small fibre may only be able to transmit 100 impulses.

The differing quality of periodontal and pulpitic pain is partly due to the fact that the pain conducting fibres in these situations differ in size and therefore in rapidity of impulse transmission.

Point (5) The rate of metabolism is directly related to fibre size. The larger fibres have greater oxygen and glucose requirements and are therefore first affected by oxygen lack. Excitability and conduction is reduced during oxygen lack and the first fibres to be affected comprise the motor and proprioceptive sensory systems.

Thus in asphyxia, the 'fast' pain impulses are blocked before the 'slow' pain mediated by the C fibres.

The effects of carbon dioxide and decreased *ph* is interesting. Following CO<sub>2</sub> infusion or increased acidity of the tissue fluid, there occurs first a period of increasing, fluctuating amplitude of the action potential, followed by decreased amplitude. CO<sub>2</sub> affects the permeability of nerve sheaths and allows increased Na movement in response to a stimulus. It also leads to an increase in the breakdown of high energy phosphate systems within the nerve during repolarisation. Thus we notice increased CO<sub>2</sub> concentrations leads to increased vasomotor effects and laryngeal spasm etc. This temporary increase in neural excitability is followed by decreased excitability due to the eventual exhaustion of creatine phosphate. The A.D.P. is not regenerated because energy from oxygenating processes is lacking.



CO<sub>2</sub> must be removed continuously for the reversible reactions to continue. CO<sub>2</sub> in the blood in excess of 5% results in loss of function.

This heightened excitability of nervous tissue in the presence of low pH may partly explain the increased sensitivity and difficulty in anaesthetising an inflamed area. Other factors, however, are probably of greater importance. Such as the direct stimulation of pain endings by tissue break down products and the lessened effect of local anaesthetic in an acid environment.

Point (6) | Susceptibility to local anaesthetic agents varies inversely with fibre diameter. The smaller sensory fibres are

blocked first, and pain is diminished before motor function is lost. Local anaesthetic does not decrease metabolism or creatine phosphate breakdown in any way, and the effect must lie in interference with ionic exchange. Ionic transfer cannot occur over the myelin sheath but can take place only at the nodes of Ranvier. Thus unmyelinated (pain) fibres are blocked by local Anaesthetic more quickly than myelinated fibres for penetration can occur over the whole length not only at the nodes. Possibly some combination of the local anaesthetic with portion of the axon sheath and Schwann cell reduces ionic permeability.

General Anaesthetics, however, reduces motor function before pain, i.e. the larger fibres are blocked first and paralysis occurs before analgesia. General Anaesthetics rapidly penetrates myelin and affects myelinated fibres first.

Nerve has great tensile strength due to the elasticity of the endoneurial and perineurial sheath. Thus Local Anaesthetics must pass through many outer layers to the axons. Although of rare occurrence, the epineurium of a nerve may be pierced; the Local Anaesthetic is deposited in close relation to the endoneurium and due to longitudinal spread may disseminate widely even as far as the Central Nervous System.

Often difficulty is experienced with lower molar teeth in eliminating dentinal and pulpal sensitivity by local anaesthesia. This difficulty is often erroneously attributed to the fact that fibres of the inferior alveolar nerve destined for the pulps are situated at the axis of the nerve and therefore are not readily accessible to the anaesthetic drug. In actual fact the dental branches of the alveolar nerve lie on its anterior and then on its superior surface.

It is possible that the pulp and dentine resist easy anaesthesia because of the large size of the pulpal pain fibres (Chapter 3), these belonging to the A group of heavy fibres in contradistinction to the thin 'C' group pain fibres of the periodontal membrane.

The difficulty experienced in blocking the pulpal nerves

of a tooth which is in an inflammatory state is difficult to explain. It is a common and extremely annoying clinical experience to find that a block anaesthetic far away from the inflamed area does not eliminate pain from the pulp even though signs of regional anaesthesia are apparent and neighbouring non inflamed tissues are fully analgesic.

It seems that nerve fibres, that are at the time of anaesthesia actively conducting impulses of high frequency, are refractory to the anaesthetic drug. Sicher suggests that the chemico electrical surface changes occurring during impulse transmission may interfere with the surface action of the anaesthetic molecules (142).

#### Transmission of Nervous Impulse from Neurone to Neurone.

In order to comprehend some of the extreme and varied somatic and visceral responses to pain, we must consider some basic concepts concerning the transmission of afferent impulses in the Central Nervous System. Such considerations, though superficial, will enable us to understand the manner in which impulses are referred so widely in the sensorium and perhaps to comprehend the mechanism of referred pain - a subject which must be dealt with at length in a separate chapter.

In the Central Nervous System, impulses pass from one neurone to another, and conduction is always unidirectional, i.e. the impulse always passes from the terminals of the axon of neurone I to the dendrites and soma of neurone II. The junctional region between the terminals of neurones I and II is called the synapse.

The nerve cell receives impulses which reach it from a number of different directions, for a large number of afferent impulses must reach a cell for it to be excited. In the Central Nervous System cells which can be excited by a single afferent fibre do exist, e.g. in the lateral geniculate body but are rare.

Histologically, we see that the afferent motor fibres, which impinge on the surface membrane of, for example, a ventral horn cell, end in small varicosities called synaptic terminals

or boutons terminaux. The cell body has a number of short processes on dendrites, which increase the total available area on which afferent nerve fibres may end. There is no physical continuity at the synapses but intimate contact exists. Two membranes therefore intervene between the two neurones - the membrane of the cell body and the membrane of the impinging nerve filaments.

One ventral horn cell may receive synaptic terminals from many hundreds of afferent fibres. The cell in the ventral horn is therefore a convergent point. Transmission of the impulse from neurone to neurone depends on the processes occurring at the synapse and acetyl choline appears to play an important part.

There is an interval between the arrival of an impulse at the synapse and the setting up of an impulse in the Central Nervous System neurone. This synaptic delay is about 0.2 to 0.9 m/sec and it is about 5-10 times as fast as in the autonomic system.

Conduction across a synapse is much more susceptible to poisons than is conduction along a nerve trunk. For instance, the general anaesthetics and barbiturates interfere with conduction as some synapses in the Central Nervous System and anoxia depresses the synapses of the Central Nervous System profoundly. This is in marked distinction to the autonomic ganglionic synapses.

The arrival of an impulse at a neurone produces a prolonged increase in excitability of the cell. This is termed a period of residual facilitation which lasts 10 - 15 m/secs.

Dillon (43) states that this residual facilitation lowers the threshold for future stimulation of afferent nerve fibres. "When once the resistance of any given path to a nerve impulse has been overcome by one stimulus, the synapse resistance is reduced and the pathway can be used with greater ease by succeeding stimuli."

Sherrington envisages the development of a central excitatory state.

According to Sherrington, the arrival of an excitatory

stimulus to the Central Nervous System is followed by the setting up of a C.E.S., which outlasts the impulse which set it up. When a volley of impulses reaches a nerve cell, it is supposed that C.E.S. is built up and when it reaches a critical level, the cell discharges. This reduces the amount of C.E.S. present which has to build up before the cell can discharge again. Hence, the frequency of efferent impulses depends on the rate of the building up of C.E.S. which in turn depends on the number of afferent impulses which reach the centre in a given time.

The persistence of C.E.S. on motor neurones depends on continuous bombardment of impulses which continue to arrive for some time after the initial volley. This maintained bombardment is due to the presence of delay paths whereby impulses are diverted through numerous accessory synapses and arrive at the motor neurones after various intervals. This is the principle of reverberating chains effected by multiple internuncial neurones.

As shown in the figure<sup>(11)</sup>, many internuncial neurones may intervene between primary afferent neurones and the effector or connector neurones, and afferent impulses in the spinal cord may flow through many channels before reaching the ventral horn cells.

These interneurones, beside playing an obvious part in the relaying mechanisms, play a considerable part in the processes of central summation and after discharge. In considering Fig. (11) we see that a single stimulus applied to the appropriate afferent nerve sets up a single afferent impulse which enters the spinal cord in a dorsal nerve root, or the cranial equivalent. This single impulse may be converted to four impulses, each bombarding the spinal afferent (or connector) neurone in close succession. Also we see by means of the arc Aa that an excitatory cycle can be established by means of which the motor or efferent neurone might be subjected by a nervous bombardment for an endless period of time unless some inhibiting agent supervenes. Thus can be seen how central facilitation or C.E.S. is rapidly built up and maintained.

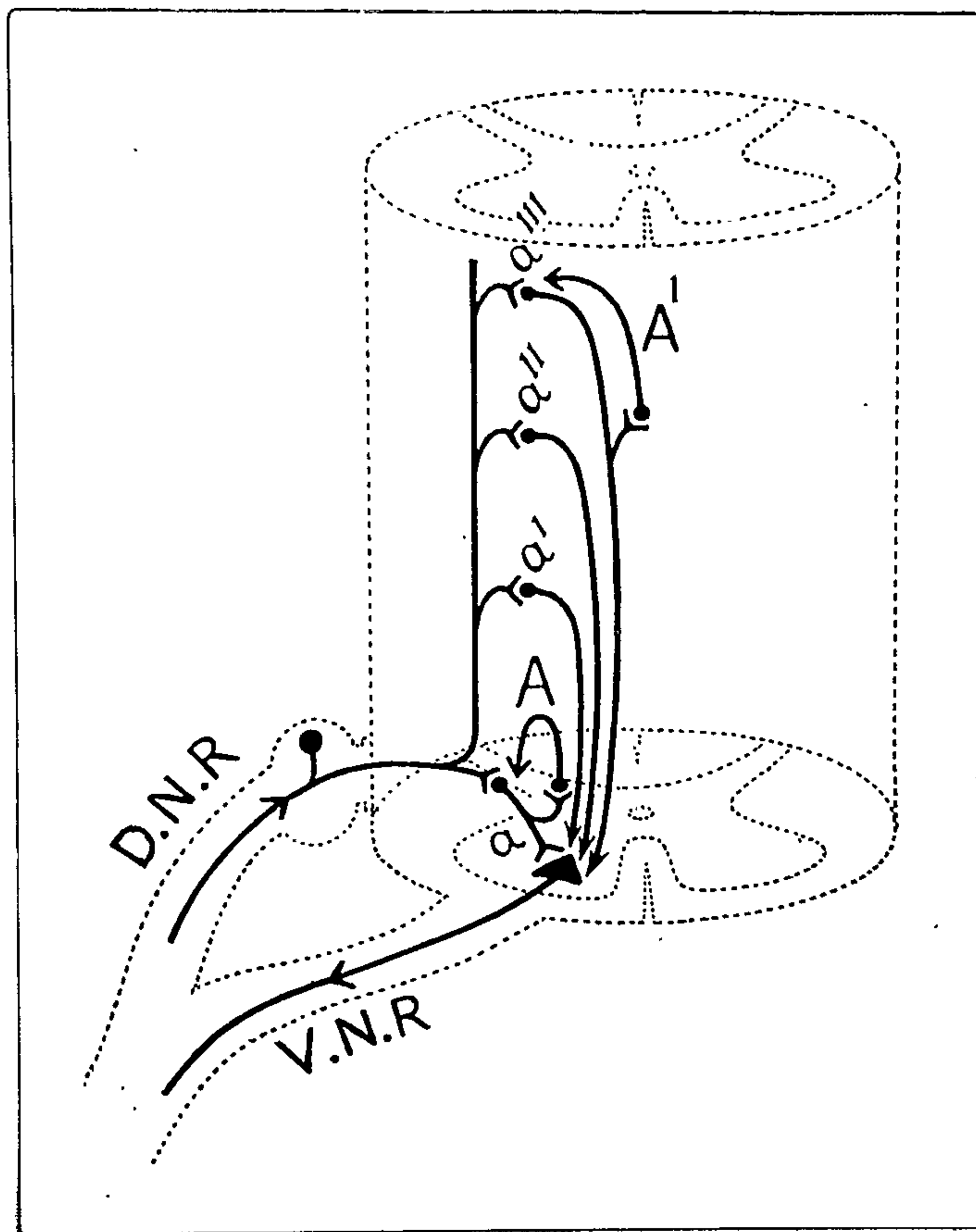


Fig. (11) Role of Internuncial neurones in reflex action (183).

D.N.R. = Dorsal Nerve Root

V.N.R. = Ventral Nerve Root

a, a<sup>i</sup>, a<sup>ii</sup>, a<sup>iii</sup>, A, A<sup>i</sup> = Internuncial Neurones.

The shortest reflex arc is a. Longer reflex arcs involving delay paths are shown via a<sup>i</sup>, a<sup>ii</sup>, a<sup>iii</sup>; A and A<sup>i</sup> are 'reverberators' which may constantly reexcite a and a<sup>iii</sup>.

The importance of facilitation in powerful reflex responses is apparent. The greater reflex effect of a second volley of impulses can be explained by the arrival at the motor horn cell of these impulses coincident with the arrival of other impulses, which are set up by the conditioning volley but have been delayed in reaching the anterior motor horn cells by passing through longer chains of the internuncial pool.

When the intensity of stimulus is only just great enough to evoke a reflex, the response is quite localised, and confined to a small group of muscles. If, however, the stimulus becomes more and more intense, the response becomes more and more widespread, involving groups of muscles widely remote. The excitatory process is then regarded as spreading more widely in the Central Nervous System and this is referred to as irradiation and might be attributed to the development of a larger and more widespread diffusion of the C.E.S., involving a larger number of irritable structures in the Central Nervous System.

It is seen that each afferent axon acts on a certain number of neurones at threshold value, and on a certain number of other neurones in the vicinity at a subliminal value. If a further axon is stimulated in this region, it is feasible that the fringes may reach liminal stimulation and thus the sphere of excitation will spread.

WHEN WE LATER CONSIDER THE NEUROANATOMY OF THE CRANIAL NERVES, THESE CONCEPTS CONCERNING THE IRRADIATION OF THE C.E.S. AND THE SPREAD OF EXCITATION TO SUBLINIMAL FRINGE WILL HELP TO FORM A HYPOTHESIS OF REFERRED PAIN.

Another aspect which must be considered is that of spatial summation. When an impulse reaches a cell, it sets up a localised synaptic potential which, when it attains threshold value, directly excites the cell and causes it to discharge. If it is a subliminal stimulus it fails to fire the cell, but a subliminal synaptic potential may summate with other subliminal synaptic potentials which have been set up simultaneously in an adjacent part of the cell membrane, and reach threshold level. This is the principle of spatial summation and in brief, we may

say that, if two stimuli, each of which is too weak to stimulate when applied separately, are applied simultaneously to adjacent parts of an afferent field, they may evoke a reflex response. This, of course, is an aspect of convergence of common neurones.

Further, as the synaptic potential endures for some time, a sequence of impulses might conceivably build up subliminal potentials stepwise to threshold value. This facilitatory effect of subliminal volleys applied within a few m/sec in adjacent areas is known as temporal summation.

It is doubtful whether temporal summation occurs to any great extent, in the Central Nervous System, but spatial summation certainly does. It is apposite to enquire more fully to this phenomenon, and consider its application to cutaneous pain (174).

There are two aspects of spatial summation. The first, which has been reported for vision, and for heat sense, is that the intensity of stimulus increases or decreases with decrease or increase in the size of the area stimulated.

Although experience teaches that a noxious impulse may summate under certain circumstances, there is at present no quantitative evidence on this point for pain sensation.

The second aspect of spatial summation which has been demonstrated for vision and for cutaneous temperature sensation, is that the sensory threshold is decreased or increased as the size of the area stimulated is increased or decreased. The usual explanation of this effect is that the subthreshold impulses of separate end organs are summated in the Central Nervous System to produce a sensation.

As will be seen, however, cutaneous pain threshold in man is relatively stable, and is dependent alone upon the strength of the stimulus, and not upon the size of the area stimulated. That is, pain threshold is independent of the number of end organs stimulated, and pain sense does not really exhibit the phenomenon of spatial summation. Furthermore, the intensity of two pains existing at the same time is no greater than that of the more

intense of the two. This distinguishes cutaneous pain physiologically from cutaneous temperature sense. It implies that the intensity of pain depends upon the intensity of the stimulus, and not upon the size of the area involved, as with cutaneous temperature sense. (However the total distress to the individual as distinct from pain as such, is dependent both upon the intensity of the stimulus and the size of the painful areas, and other factors).

It may be rationalised that this lack of spatial summation for pain is to be expected. Lack of spatial summation of pain provides that the organism will not be overwhelmed by noxious impulses and so prevented from effective action. Through pain, the organism is warned of the imminence of tissue damage - the limit of safety has already been passed and immediate action is required. A stimulus twice the pain threshold value results in tissue destruction, whereas there is a wide range of stimuli between the threshold for warmth, and the pain threshold. The fine gradations of perception with temperature sensation is therefore not permissible for pain sensation, and spatial summation had no application in it.

#### Pain and Reflex Action.

Impulses set up by nocuous stimuli, in addition to arousing sensations of pain, also set up widespread reflex effects, the common aim being the defence of the animal against the damaging influence. Even in spinal animals in which pain sensation is non-existent, reflex effects are observed (183). The reflex response to a painful stimulus may be simple e.g. reflex contraction of muscles or it may be extremely complex involving somatic and visceral effects ( Chapter V ).

When there is competition between reflexes, those which are set up by nociceptive impulses are as a rule prepotent and have pre-emptive rights over other reflexes (182). Thus when reflex competition is taking place, the nociceptive flexor reflex overcomes the proprioceptive extensor thrust reflex or the proprioceptive reflex which is responsible for quadriceps tone in decerebrate rigidity (183).

This, however does not apply to such necessary reactions as breathing, although nocuous impulses may markedly modify the rate and depth.

Unmodified types of reflex response to pain are listed below (182).

- (i) Withdrawal of the animal from the irritant. Gradation from the simple flexor reflex and crossed extensor reflex to actual flight is seen, depending upon the strength of the stimulus plus the effect of other senses. Autonomic reactions may be extreme.
- (ii) Removal of the irritant e.g. the scratch reflex for surface irritation, lacrimation, cough or sneezing reflex in the case of irritation of less accessible membranes. When involving the whole animal we see killing of the irritant or thrusting it aside. Associated with this are visceral reflexes such as increase in blood pressure, pulse rate and blood sugar.
- (iii) Immobility. This occurs in the animal if stimulation persists. There are the familiar responses of reflex spasm of the muscles associated with the part.

Reflexes are often described as inevitable responses to afferent stimuli, This description is true only when the general character of the reaction is considered, but when examined in detail, the reflex response usually shows a considerable measure of variability and is modified by environmental factors. In other words, many reflex actions are controlled or inhibited by the higher centres in the sensorium.

The higher centres, which so modify reflex activity can be influenced by a wide range of afferent stimuli. It is generally stated that reflex responses to stimuli become more variable in pattern as the centre lies at a higher level in the central nervous system.

It is maintained that the posterior horn neurones are more than simple relay stations, but are capable of either facilitating or inhibiting the sensory impulse before reaching the second neurone.

Some form of integration and inhibition of sensory impulses does occur. It is supposed that in the normal individual the central nervous system favours the transmission of finer sensibilities, while the pain impulses are inhibited up to a point. That is, unless the pain impulses are strong enough to dominate, the entire sensory pattern of painful sensation does not register in perception or in consciousness.

This is understandable, for if it were not the case, all painful stimuli of whatever intensity would call forth involuntary protective reactions, and higher learning and discriminative reactions would be interfered with to an extent that the normal individual would become abnormal (81).

CHAPTER 3

INNERVATION OF ORO-FACIAL TISSUES

The end organ of the receptor neurone for pain differs from that of other sensations such as heat, cold, pressure etc. Much controversy has existed in the past as to whether pain is a sensation as such with its own neural mechanism or whether it develops from excessive stimulation of other sensations such as touch or pressure.

The first critical studies in the field of cutaneous pain were carried out independently by Blix (1885) and Goldscheider (1885) who formulated the concept of specific 'pain spots'. Using fine needles, they found that points especially receptive to painful stimuli were present in cutaneous areas and conversely that a fine needle could be stuck painlessly into many points on the skin. These pain points, Goldscheider stated, may be aggregated as closely as 200 to the sq. cm. On the tip of the nose or the sole of the foot they amount to between 40 - 70 per sq. cm.

Goldscheider regarded pain as part of a pressure pain continuum of experience i.e. that pain develops from a threshold sensation which is pressure in quality.

This work was expanded by Von Frey (1896) who by using stiff stimulating hairs applied to the skin was able to add further evidence of the specificity of pain as a sensation. Von Frey claimed that he could distinguish points where the sole response was a sense of pain, and other spots in which it was a sense of pressure. He was also able, he thought, to correlate the distribution of cold, warm and pressure spots in the skin with a respective frequency of Krause's corpuscles for cold, Ruffini's endings for warmth and with a special nerve ending around hair roots and Meissner's corpuscles for touch. Von Frey, then, expounded the view that pain is an independent modality.

Evidence as to the type of receptor responsible for signalling pain was conclusively demonstrated by workers such

as Woolard (181) and Weddell (17)) et al. who were able to stain the nerve terminals in a section of human skin removed from an area in which pain was the only sensation which could be elicited from a variety of stimuli.

This problem of cutaneous pain sensibility must therefore be considered under three headings:

1. The cutaneous end organs for pain and their arrangement.
2. The possible association of these receptors with sensations other than pain e.g. touch.
3. The explanation of Goldscheider's 'pain spots' i.e. whether such localisation is a central effect or due to the peripheral arrangement of the nerve endings.



A. Merkel's disc, subserving touch. B. Free endings, subserving pain, scattered throughout deeper layers of epidermis. C. Meissner's corpuscles, subserving touch. D. Nerve fibres, subserving pain. E. Krause's end bulbs, subserving cold. F. Nerve endings subserving warmth (sometimes called Ruffini's endings). G. Nerve fibres and endings on hair follicles, subserving touch. H. Ruffini's endings, subserving pressure. I. Sympathetic nerve fibres innervating a sweat gland. J. Pacinian corpuscles subserving pressure. K. Golgi-Mazzoni endings, subserving pressure. L. Nerve trunks containing thick and thin fibres. M. Sebaceous gland. N. Sweat gland. O. Sympathetic nerve fibres supplying erector pili muscle.

Drawing composed from methylene-blue and reduced silver preparations. The functional interpretations summarized above are based upon observations by Woollard, Weddell, and Harpman, *J. Anat.*, 1940. Figure reproduced by permission of the editor.

We do not agree that the free endings necessarily subserve only pain sensation.

Fig 12.

1. THE CUTANEOUS END ORGANS FOR PAIN:

In addition to the complex endings which are generally accepted as the specialised receptors for heat, cold and pressure, the skin shows multitudinous branching unmyelinated and finely beaded plexiform endings. Such endings are found at dermal and epidermal levels.

**That** the receptive mechanism for pain is contained in this plexiform arrangement of nerve fibres with free nerve endings has long been accepted. This is the only type of sensory innervation having the almost ubiquitous distribution of the pain sense. Again, the conclusions reached in Chapter 2 show that the receptor mechanism lies among the fine medullated and nonmedullated C and delta A fibres.

Woolard found pain to be the most superficial as well as the most extensive in depth of the various modalities, and a perusal of the arrangement of these pain fibres will readily explain this.

Interlacing plexuses of unmyelinated fibres spread horizontally in the subepidermal regions and from this network, fine, beaded terminals pass superficially between the cells of overlying tissue strata (184). Some actually end in the cytoplasm of the cells and can be readily acted on by chemical changes in the cells produced by noxious agents (183).

Each sector of the network represents a syncytium of branches from a single unmyelinated or finely myelinated fibre so that each afferent fibre with its terminal syncytium constitutes a sensory unit. The plexus from each fibre interlocks with adjacent plexuses in a most complicated manner (181).

Free nerve endings are present around the blood vessels and in the aponeurotic sheaths of skeletal muscle and probably subserve pain in these localities.

These free nerve endings subserving pain are exteroceptors (81). The meaning of this word has been extended to include cutaneous, chemical and distance receptors.

At this stage it may be stated that there is an overlap of cutaneous pain nerve territories (100). It is known that if the nerve to a limb be severed, the area of total loss of cutaneous sensibility is much smaller than would be anticipated from the known anatomical distribution of the nerve.

Relation of the receptors of pain to the sensation of touch and other modalities.

Throughout the body plexiform arrangements of nerve fibres are found bearing free nerve terminals in the form of simple terminal twigs, loops, brushes or minute skeins (162). These are present in the epidermis, in the mucous membrane and in many deeper tissues, somatic and visceral, but not all. The terminal portions of this ramification are in all sites unmyelinated; but further back, myelinated fibres may enter into it. It has been thought that all of this plexiform arrangement of nerve fibres subserved pain reception - touch perception being defined as the function of specialised endings such as endings about hair follicles and Meissner corpuscles.

Much controversy has recently arisen, however, as to whether touch reception may be also mediated by these free nerve terminals. It has been argued that the sense of touch on the skin is even more nearly ubiquitous than that of pain, and that minimal threshold stimulus of the widely disseminated unmyelinated endings in the skin evokes an initial sensation of touch. Whether the same endings or different but histologically similar ones are concerned with the diffuse capacity to appreciate pain remains to be demonstrated.

Various workers have expressed views concerning this. Heinbecker, Bishop and O'Leary (86) state that sensibility of the skin consists of four fundamental modalities - touch, pricking touch, warmth and cold. Pain, they say, is the affective quality resulting from more than threshold stimulation of the pricking touch group.

Weisengreen (169) believes that pain and touch are different degrees of the same sensation and is unwilling to look

upon pain as a distinct sense with afferent tracts peculiar to itself. He considers how sensory impressions made on nerve purely of special sense may rise to the height of being painful, and therefore deducts that pain is the central expression of a certain grade of irritation, in any centripetal nerve. There is, he states, "every probability that the sensory nerves are competent to carry inward a variety of impressions which owing to the peculiar nature of the excitations which they cause in the nerve are capable of appreciation only by the separate centres devoted to their perception..."

This view is untenable when we consider that the central tracts conducting pain and temperature impulses can be destroyed, while those subserving touch, pressure and proprioception remain intact.

Lewis and Pochin in 1937 (99), concerning the double response from skin, say that the first response may be touch or pain, whereas the second is unequivocally pain at all times.

Waterston (167) in 1933 stated that within the twofold structure of the skin, there is a division of sensory function - the epidermis being the organ of touch and the corium being that of superficial pain.

Wooland et al in 1940 showed that whereas no pain is aroused by shaving off as much epidermis as may be removed with a razor without causing bleeding, nevertheless this is not the entire story. They feel that first pain (see Chapter 2,6) is excited in the epidermis, and second pain subepidermally; both the epidermis and dermis are therefore organs for pain reception though perhaps for pain for different quality.

As far as the distribution of pain fibres subserving fast and slow pain is concerned, Tower (162) believes that the larger medullated fibres conducting fast pain are distributed mainly in the epidermis; the smaller medullated and unmedullated pain fibres are confined mainly to the dermis. Again, she states that the fast fibres have more widely distributed terminals than the slow fibres. It seems, however, that some less sensitive

areas of the body surface may receive only, or predominantly, one type of pain innovation and that of the slow variety. Tower goes on to state that the fibres subserving fast pain i.e. first or superficial pain have a contact quality at threshold, whereas deep, slow or second pain does not.

Clarification of these conflicting views i.e. whether mechanisms for fast and slow pain exist at different levels in the skin and whether the fast pain terminals have a threshold touch quality, may be attempted by examining sensations elicited from the cornea.

The cornea contains only fine unmyelinated nerve endings which ramify both beneath and within the epithelial layer.

Von Frey in 1896 and Lewis (100) in 1942, and others, have stated that from the cornea one may elicit pain but not touch.

Goldscheider, however, finds that threshold stimulation of the cornea results in touch. White and Sweet (171) support this view.

In patients following bulbotrigeminal tractotomy, the cornea becomes completely analgesic to pain. It retains its sensitivity to touch however and it therefore seems likely that in these cases, central pathways persist by means of which stimuli arising from naked unmyelinated endings are interpreted as touch. It appears then, that the central connections of any given nerve fibre have a decisive role to play and that the degree to which naked nerve terminals of a given area subserve touch as well as pain may vary.

It has been shown that the fibres subserving pain and some touch sensation (Chapter 2.) may be histologically indistinguishable. It also seems rather impracticable for a single fibre to mediate the two sensations - especially considering the touch sensation from the cornea when the pathways for pain have been interrupted. It seems reasonable to visualise the interweaving nerve plexuses in the skin as subserving both pain and touch, but the parent nerve fibres for each modality must be separate and

have different central connections.

The results of Lewis and Pochin may thus be explained. The variable first response i.e. either touch or pain was probably the result of threshold stimulation of nerve plexuses subserving one or the other (or both simultaneously) of the two modalities.

Another controversy concerns whether or not overstimulation of specific receptors of touch (in relation to hairs), cold, warmth and perhaps light and sound, register as painful. Is pain in this relation the affective quality resulting from much more than threshold stimulation of such receptors? With respect to the specific touch receptors including hairs, the evidence is fairly conclusive, at least in animals, that overstimulation in itself does not appear to inevitably result in pain.

The pain associated with intense heat and cold stimulation is fully acknowledged - with increasing intensity the temperature sensation disappears and only burning pain results. Perhaps it is as Trotter and Davies (quoted by 162) in 1909 believed, that hot or cold are themselves combined experiences of warm and pain and cool and pain.

More acceptable evidence is gained on a nerve histological basis. There has been a natural suspicion that the fine accessory fibres sometimes found in encapsulated organs such as those of Meissner Paccini, Ruffini and Krause - fibres which have been shown to be of a somatic, not sympathetic derivation - might serve pain reception, and the main fibres specialised sense (quoted by 162).

Woolard (181) and his co-workers commented on the similarity of the accessory fibres to the free nerve endings of the sub-epidermal plexus.

Assuming these accessory fibres are responsible for the pain of overstimulation of the sense concerned, another problem presents itself. Do pain fibres respond to a wide range of stimuli including thermal and mechanical disturbances or are there various pain endings differentially responsive<sup>ve.</sup> to different stimuli?

Although this is dealt with in greater detail in Chapter 6 it may be stated that pain nerve endings, possibly in view of their simplicity, have high thresholds and when the stimulus of whatever nature causes tissue damage, the resulting chemical products furnish the stimulus received by the free nerve endings.

The localisation of cutaneous pain.

Blix and Von Frey thought that each pain 'spot' or at the most, a small group of spots, was innervated by a single fibre which in turn made connections with other nerve fibres ascending the neural axis in chain formation finally to reach the cerebral cortex, where a disturbance initiated at the cutaneous end of this chain would be interpreted and localised.

It is well known, however, that the area of total sensory supply of any peripheral nerve is widely overlapped by that of adjacent nerves. A similar situation is noted with the fields of individual fibres in the same nerve.

Weddell in 1941 (170) provided an histologic demonstration that each sensory 'spot' on the skin is in fact innervated by endings from several different nerves.

Tower (162) introduced the concept of the 'sensory unit' as contrasted with the single afferent nerve ending. She states that a sensory unit consists of many nerve endings, all branches of a single nerve fibre connecting with a single cell in the dorsal root ganglion. Many sensory units overlap in a given area - each unit being distributed over a terminal area of several sq. mm. or cm. Although such terminal ramifications overlap and interlock intricately, there is no fusion between different fibre units.

In view of this overlapping of separate units, stimulation applied to one point results in transmission centrally through several afferent fibres at once. (184) (116). The pattern of excitation so produced, wherein fibres excited minimally encircle fibres excited more strongly, is relayed to the sensorium where, by central analysis, localisation might be arrived at. A tiny

area of skin might give rise to a pattern of excitation differing sufficiently from its neighbours to permit of localisation and two point discrimination. The nervous system appears to operate on a principle of analysis or synthesis of constellations of activity in many nerve cells and fibres (162). That the 'spot' is an entity in consciousness is not in question. It does not follow that this spot need be an element in peripheral innervation. Consciousness may be imagined to synthesise the sensory impressions coming in over the multiplicity of fibres innervating any normal area of skin, into the concept of the 'spot', which is then projected on to the periphery for the specific purpose of localisation.

It seems that the finer the overlapping pattern of nerve fibres presumably the finer the analysis that can be arrived at.

Also it is obvious that any stimulus which is capable of exciting the pain sensitive network in the dermis, must simultaneously excite some of the other specialised endings in the area. Herein lies the main reason for the greater degree of qualitative discrimination in respect of painful stimuli applied to the skin as compared to the crudity of the painful experience aroused by dental stimulation (184).

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