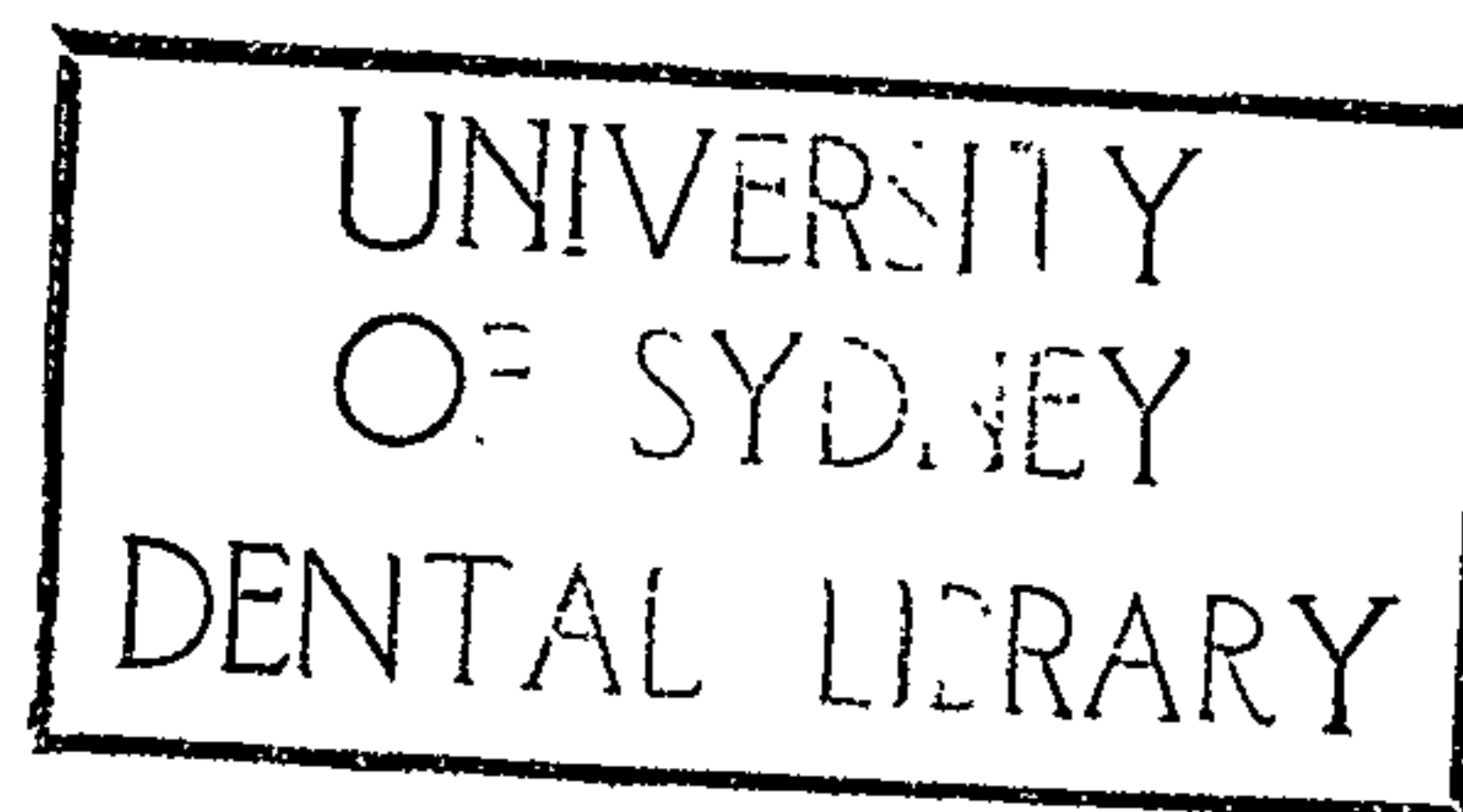


A STUDY OF INFERIOR DENTAL NERVE
REGENERATION FOLLOWING TRAUMATIC INJURY

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A THESIS SUBMITTED FOR THE DEGREE OF
MASTER OF DENTAL SURGERY



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1981.

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1. ACKNOWLEDGMENTS

1. First and foremost I must thank Dr. Robert Cook, Senior Dental Surgeon and Oral Surgeon, Royal Melbourne Hospital, and Dr. Bruce Levant, Senior Oral Surgeon, Prince Henry Hospital, Melbourne, who suggested this project and encouraged me to carry out this research. In addition, Dr. Bruce Levant assisted me with the use and interpretation of the nerve stimulator. Dr. Robert Cook was most generous to permit me to assist with the surgery and management of the osteotomy patients, the majority of whom were his private patients. Dr. Robert Cook also allowed me to study these patients and to take readings and measurements of the return of sensation.
2. I thank my supervisor, Prof. Geoff Stacy of the Department of Oral Surgery and Oral Medicine, University of Sydney, who made valuable suggestions during the project and his continued support in the writing of this thesis.
3. I am grateful to Mr. Wayne Fitzherbert for his generous contribution with the typing, duplicating and binding of this volume, and in addition, to his secretary, Mrs. Sheila Barfoot, who typed the entire thesis.
4. The Royal Melbourne Hospital and Prince Henry Hospital freely and generously gave me permission to test and study their patients who were undergoing treatment for injuries due to trauma. Their help is most appreciated.
5. Mr. Terry Oakley, the photographer at the Victorian Plastic Surgery Unit at Preston and Northcote Hospital devoted much time to the preparation of the majority of the photographs for this thesis and his assistance is gratefully acknowledged.
6. Mr. Bill Kaegi, Chief Technical Officer, Histology Department, University of Melbourne, kindly prepared, sectioned and stained several inferior dental nerves and for this assistance I am very grateful.
7. I would like to thank Prof. Sir Sydney Sunderland for the helpful discussion which contributed to the success of this project.
8. My thanks to Miss Joan Longhurst of the Department of Oral Surgery and Oral Medicine, University of Sydney, for her suggestions regarding the production and format of this thesis, and to Miss Janice Matthews of the Department of

Oral Surgery and Oral Medicine, University of Sydney, for the invaluable help in the mounting of the figures.

9. Last but not least, I would like to express my gratitude to Dr. H. Barry Collin, Reader, Department of Optometry, University of Melbourne, for the pearls of wisdom offered and for his continued moral support. I am also greatly indebted to him for the photography of the histological slides and completion of this thesis.
10. Finally, I would like to thank the patients without whom this research and this thesis would not have been possible.

2. PREFACE

The consequences of damage to sensory nerve fibres depend on the nature, site and severity of that injury. Rupture or contusion of the inferior dental nerve invariably produces altered sensations and the symptoms which accompany such an injury are generally those of anaesthesia or paraesthesia in the area of distribution of the mental nerve i.e., the lower lip and chin.

The subsequent return of normal sensation depends upon the regeneration of the injured fibres of the inferior dental nerve together with renewal of its ability to conduct all peripheral nerve impulses to the central sensory cortex. The time required for return of normal sensation can vary from days to weeks, or years. Sometimes the damage is permanent.

In recent years, records at the Royal Melbourne Hospital show a noticeable increase in the number of patients suffering from symptoms of mental nerve anaesthesia/paraesthesia. This is attributable to the gradual increase in the incidence of fractures between 1975 and 1979 (Table 1) and of elective surgery to the mandible. However, in the former of these there was a significant reversal of this trend in the years 1978 and 1979 due to the better enforcement of the law regarding the compulsory wearing of seat belts and the introduction of random breath alcohol tests. The increase in the number of mandibular osteotomy procedures now being undertaken for correction of mandibular prognathism explains many of the cases of elective surgical origin.

The condition of mental anaesthesia/paraesthesia can also occur following the surgical removal of impacted mandibular third molars where the roots of the teeth are in close proximity to the inferior dental nerve.

One may well ask why this condition is of any great clinical concern. It must be realised that the condition of anaesthesia/paraesthesia may be accompanied by other very unpleasant sensations (neuralgia, causalgia) which on occasions can become unbearable for the patient and demand investigation and long-term management. Anaesthesia and paraesthesia can also be socially embarrassing as the following examples illustrate.

(a) A patient may have difficulty in drinking from a vessel without dribbling,

particularly in the early days following nerve damage.

- (b) The patient may be unaware that saliva dribbles from the corner of his or her mouth.
- (c) The patient may have difficulty in clearly enunciating some words.
- (d) There may be a distinctly strange impression that the lip is swollen and this sensation can become an embarrassing obsession.
- (e) There may be difficulty in shaving and in applying lipstick.
- (f) Patients have been known to burn themselves when the temperature of food or drink is not quickly assessed. For this reason also, smoking may be a hazard.
- (g) If the condition is present in a child there can be an inclination for that child to chew such a paraesthetic lip, causing repeated injury which can be complicated by infection.

The problem facing the clinician is, first, one of accurate assessment of the extent of impairment of sensation so that sound professional advice, including an accurate prognosis, can be given during the period of uncertainty and difficulty in patient management. In this respect an accurate prognosis based on present clinical assessments cannot be given. Secondly, for medico-legal reasons, the clinician needs to be able to define accurately the degree and extent of sensory impairment. Such an assessment may be very difficult to achieve with any degree of accuracy using present methods. Thirdly, in order to make meaningful comparison from one consultation to the next, the clinician needs to be able to record accurately the area and degree of sensory impairment in order to make any objective judgement as to improvement or otherwise in the condition at the next visit. All these considerations are important from the viewpoint of successful patient management.

The procedures used at present for the evaluation of sensory function are inadequate and provide only an imprecise means for detecting and determining the onset and for following the course of recovery of the injured nerve. The establishment of a reliable method which can be used to assess a case involving trauma to the inferior dental nerve would give the clinician a valuable clinical tool which could be used for the purposes of prognostication and patient reassurance.

In my own clinical experience with this problem, I became concerned about these inadequacies in assessment and found in consultation with my colleagues that

they also faced similar problems. They could give me very little further assistance. In addition, on consulting the literature there seemed to be very little of practical relevance. These findings reflected the overall paucity of available knowledge to which the dental profession had ready access and it became evident to me that this area of knowledge needed to be fully reviewed.

The aim of this thesis, therefore, was to review an area of seeming deficiency in the dental literature and to investigate beyond the presently available clinical tests and diagnostic criteria by supplementing these with an electrical skin stimulation test. It was my hope that this latter method would provide a more accurate assessment upon which reliable clinical judgments and prognosis could be based. It will be seen that this hope has been realised.

A glossary of terms, although not exhaustive, has been included for the convenience of the casual reader. Any clinical understanding or advancement of this subject must rest firmly on a sound knowledge of the basic sciences involved. Hence, the inclusion of sections on relevant neuro-anatomy, neurophysiology and pathology.

TABLE 1

JAW INJURIES AT THE ROYAL MELBOURNE HOSPITAL

	<u>MANDIBLE</u>	<u>MID 1/3</u>	<u>MANDIBLE</u> <u>AND MID 1/3</u>	<u>TOTAL</u>
1975	73	17	4	94
1976	112	26	14	152
1977	123	23	18	164
1978	87	34	11	137
1979	105	35	7	147

3. GLOSSARY OF TERMS

<u>Afferent:</u>	Bringing to or into; denoting certain arteries, veins, lymphatics and nerves.
<u>Amoeboid</u>	Resembling an amoeba in appearance or characteristics of irregular outline with peripheral projections.
<u>Analgesia:</u>	Loss of sensibility to pain.
<u>Anastomosis:</u>	A natural communication, direct or indirect, between two blood vessels or other tubular structures; also, by extension, a passage of nerve fibres from one nerve to another. An operative union of two hollow or tubular structures.
<u>Anaesthesia:</u>	Total loss of sensation, especially of sense of touch, in skin or mucous membranes as a result of some nervous lesion or other abnormality.
<u>Antidromic:</u>	Relating to propagation of an impulse along an axon in a direction the reverse of the normal.
<u>Atrophic:</u>	Relating to atrophy.
<u>Atrophy:</u>	A wasting of tissues, organs or the entire body.
<u>Autograft:</u>	Autotransplant: tissue or an organ transferred by grafting into a new position in the body of the same individual.
<u>Autolysis:</u>	The enzymatic digestion of cells (especially when dead or degenerate) by enzymes present within them (autogenous).
<u>Autonomous:</u>	Autonomic.
<u>Autonomy:</u>	Independence of outside control, or of control by the cerebrospinal nerve centers; functional independence.
<u>Autoradiography:</u>	Radioautography.
<u>Axodendrite:</u>	An unmyelinated process given off from the axon of a nerve cell.
<u>Axodendritic:</u>	Referring to the synaptic relationship of an axon with a dendrite.
<u>Axolemma:</u>	Mauthner's sheath, the delicate plasma membrane of the axon.
<u>Axonotmesis:</u>	Interruption of the axons of a nerve followed by complete degeneration of the peripheral segment, without severance of

the supporting structure of the nerve. Such a lesion may result from pinching, crushing, or prolonged pressure.

Axoplasm:

Neuroplasm of the axon.

Capsule:

A membranous structure consisting usually of dense collagenous connective tissue, which envelopes an organ or part.

Causalgia:

A burning pain associated with glossy skin. The name given by Weir Mitchell to a type of severe burning pain; it is most frequently seen following nerve injuries.

Centrifugal:

In a direction away from any centre; efferent. Denoting the direction of the force pulling an object outward (away) from an axis of rotation.

Cholesterol:

The most abundant steroid in animal tissues, especially in bile and gallstones.

Chromatolysis:

The disintegration of the granules of chromophil substance in a nerve cell body which may occur after exhaustion of the cell or damage to its peripheral process.

Conduction:

The act of transmitting or conveying certain forms of energy, such as heat, sound, or electricity from one point to another, without evident movement in the conducting body.

Degeneration:

Retrograde d.

Degeneration with chromatolysis of nerve cells after division of their axons.

Wallerian d.

Degeneration of a nerve fibre separated from its trophic centre; the nerve cell is characterized by proliferation of the nucleus of the interannular segment and by segmentation of the myelin, ending in atrophy and destruction of the axon.

Demyelination, Demyelinization:

Destruction or loss of myelin from the medullary sheath of Schwann.

Dendrite:

Dendron: One of the branching protoplasmic processes of the nerve cell.

Eccentric:

Abnormal or peculiar in ideas, action or speech.

<u>Efferent:</u>	Conducting (fluid or a nerve impulse) outward or centrifugally.
<u>Ellipsoid:</u>	An oval condensation of reticular cells surrounding the second part of the penicillate artery of the spleen. The outer end of the inner segment of the retinal rod.
<u>Endoneurium:</u>	Henle's sheath; sheath of Key and Retzius; the connective tissue support of the individual nerve fibres within a fasciculus.
<u>Endothelial:</u>	Relating to the endothelium.
<u>Endothelium, pl. Endothelia:</u>	A layer of flat cells lining especially blood and lymphatic vessels; it corresponds to the mesothelium of the serous cavities.
<u>Epicritic:</u>	Denoting a set or system of sensory nerve fibres, supplying the skin and oral mucosa, by means of which one is enabled to appreciate the finer degrees of the sensations of touch, pain and temperature, and to localize the same; distinguished from protopathic.
<u>Epineurium:</u>	The connective tissue surrounding a nerve trunk and binding together the fascicles; it contains the blood vessels and lymphatics and usually fat cells.
<u>E.S.S.:</u>	Electrical skin stimulation.
<u>Exteroceptor:</u>	One of the peripheral end organs of the afferent nerves in the skin, or mucous membrane, which respond to stimulation by external agents.
<u>Funiculus:</u>	A small cordlike structure, such as one of the bundles of nerve fibres the aggregate of which compose the nerve trunk.
<u>Fusiform:</u>	Spindle-shaped; tapering at both ends.
<u>Heterograft:</u>	A graft transferred from one species to another.
<u>Hoffman's sign:</u>	In latent tetany mild mechanical stimulation of the trigeminal nerve causes severe pain; Hoffman's reflex, digital reflex; snapping reflex; flexion of the terminal phalanx of the thumb and of the second and third phalanges of one or more of the fingers when the volar surface of the terminal phalanx of the

	fingers is flicked.
<u>Homograft:</u>	A piece of tissue or an organ transferred from one member to another member of the same species, not identical twins.
<u>Hyperesthesia:</u>	Oxyesthesia; excessive sensibility to touch, pain or other sensory stimuli.
<u>Hypesthesia:</u>	Hypoesthesia; diminished sensibility.
<u>Hypoesthesia:</u>	Hypesthesia.
<u>Interoceptor:</u>	One of the sensory end organs (receptors) situated within the walls of the respiratory and gastrointestinal tracts or in other viscera.
<u>I.D.N.:</u>	Inferior dental nerve.
<u>Lipogenic:</u>	Relating to lipogenesis; fat-producing.
<u>Lipogenous:</u>	Lipogenic.
<u>Maturation:</u>	A stage of cell division in the formation of sex cells during which the number of chromosomes in the germ cells is reduced to one-half the number characteristic of the species, meiosis, reduction division. The process of achieving full development or growth.
<u>Mesenchymal:</u>	Relating to the mesenchyme.
<u>Mesenchyme:</u>	An aggregation of mesenchymal cells. A primordial embryonic tissue consisting of mesenchymal cells, usually stellate in form, supported in a homogeneous ground substance.
<u>Microbody:</u>	A body about 0.5 μ m in diameter, surrounded by a membrane and containing oxidases.
<u>Microtubule:</u>	A cylindrical cytoplasmic element 100 to 270A in diameter and variable in length; microtubules increase in number during mitosis.
<u>Modality:</u>	Any form of electrical or physiomedical therapeutics. Various forms of sensation, e.g., touch, vision, etc.
<u>Morphology:</u>	The science which treats the configuration or the structure of animals and plants.
<u>Myelin:</u>	A mixture of lipids (cholesterol, phospholipids, sphingolipids,

phosphatides, plasmalogens) and neurokeratogenic protein material arranged in layers around the axons of medullated nerve fibres.

Myelination:

Formation of a myelin sheath of a nerve fibre.

Myoneural:

Relating to both muscle and nerve; denoting the nerve terminations in muscular tissue.

Neurapraxia:

Injury to nerve resulting in paralysis but unattended by degeneration and followed by rapid and complete recovery of function.

Neuritis:

Inflammation of a nerve, marked by neuralgia, hyperesthesia, anaesthesia, or paraesthesia, paralysis, muscular atrophy in the region supplied by the affected nerve, and by abolition of the reflexes.

Neuroectoderm:

That part of the ectoderm which is separated from the superficial ectoderm to form the neural tube. In the human embryo this separation occurs in the 4th week of gestation.

Neuroectodermal:

Relating to the neuroectoderm.

Neurolemma:

Neurilemma; sheath of Schwann; a tubular cell that enfolds myelinated and unmyelinated nerve fibres. In myelinated fibres it forms the lamellae of myelin.

Neuroma:

An old, general term for any neoplasm derived from cells of the nervous system; on the basis of newer knowledge pertaining to the cytologic and histologic characteristics, such as neoplasms are now classified in more specific categories, e.g., ganglioneuroma, neurilemoma, pseudoneuroma, and so on.

Neuroplasty:

Plastic surgery of the nerves.

Neurotmesis:

Complete division of a nerve.

Neurotomy:

Operative division of a nerve.

Ranvier's node:

Interruptions occurring at intervals in the myelin sheath of a nerve fibre.

Organelle:

Cell organelle; organoid (3); one of the specialized parts of a protozoan or tissue cell serving for the performance of some

individual function; these subcellular units include all types of mitochondria, the Golgi apparatus, cell centre and centrioles, granular and agranular, endoplasmic reticulum, lysosomes, plasma membrane, and certain fibrils, as well as plastids of plant cells.

<u>Paraesthesia:</u>	An abnormal spontaneous sensation, such as of burning, pricking, numbness, etc.
<u>Perikaryon:</u>	The cytoplasm periplant, protoplasm surrounding the nucleus. The body of the odontoblast, excluding tubules.
<u>Perineurial:</u>	Relating to the perineurium.
<u>Perineurium:</u>	The connective tissue sheath surrounding a fascicle of nerve fibres in a peripheral nerve. It consists of concentric layers of closely united flattened cells which alternate with layers of fine collagenous fibres having a predominantly longitudinal direction.
<u>Phagocyte</u>	Carrier cell, scavenger cell; a cell possessing the property of ingesting bacteria, foreign particles and other cells.
<u>Plexus:</u>	A network or interjoining of nerves and blood vessels or of lymphatic vessels.
<u>Postganglionic:</u>	Posterior to or beyond a ganglion.
<u>Preganglionic:</u>	Situated before or preceding a ganglion.
<u>Proliferation:</u>	Growth and production of living cells.
<u>Proprioceptor:</u>	One of the peripheral end organs of the afferent nerves in the deeper structures, such as the muscles, tendons, and joints.
<u>Protopathic:</u>	Denoting a set or system of peripheral sensory nerve fibres furnishing a low order of sensibility, enabling one to appreciate pain and temperature to a not very delicate extent, and not definitely localized; distinguished from epicritic.
<u>Radioautogram:</u>	Autoradiogram; the graphic record obtained by placing a radioactive material (e.g., thyroid tissue after the administration of radioiodine) in contact with or in close proximity to a photographic emulsion and developing the exposed film or plate.

<u>Radioautography:</u>	The making of a radioautogram.
<u>Reinnervation:</u>	The restoration of nerve control of a paralyzed muscle or organ by means of regrowth of nerve fibres either spontaneously or after anastomosis.
<u>Retrograde:</u>	Moving backward. Degenerating; reversing the normal order of growth and development.
<u>Segment:</u>	To divide and redive into minute equal parts.
<u>Segmentation:</u>	Dividing into segments; the state of being divided into segments. Cleavage.
<u>Somatic:</u>	Relating to the soma or trunk. Relating to the wall of the body cavity, parietal. Relating to the body; corporeal, physical.
<u>Summation:</u>	The aggregation of a number of similars; totality.
<u>Sympathectomy, Sympathetectomy:</u>	Excision of a segment of a sympathetic nerve or of one or more sympathetic ganglia.
<u>Synapse:</u>	The place where a nerve impulse is transmitted from one neurone to another. The termination of an axon in relation to the membrane of a nerve cell.
<u>Syncytium:</u>	A multinucleated protoplasmic mass formed by the secondary union of originally separate cells.
<u>Tinel's sign:</u>	A sensation of tingling, or "pins and needles", felt in the distal extremity of a limb when percussion is made over the site of an injured nerve, it indicates a partial lesion or early regeneration in the nerve. It is sometimes called "distal tingling on percussion" abbreviated to DTP.
<u>Thermesthesia:</u>	Thermoesthesia
<u>Thermoesthesia:</u>	Thermesthesia; thermal or thermic sense; temperature sense; the ability to distinguish differences of temperature.
<u>Transection:</u>	Cut across.
<u>Trans-synaptic:</u>	Indicating transmission of a nerve impulse across a synapse.
<u>Trophic:</u>	Resulting from interruption of nerve supply.
<u>Ultrastructure:</u>	Fine structure; structures or particles seen with the

ultramicroscope or the electron microscope.

ua:

Microamps.

Viscera:

Plural of viscus.

Visceral:

Relating to the viscera; splanchnic.

Viscous:

Viscid; sticky; adhesive; marked by high viscosity.

ln(LN) :

Log

4. NEURO-ANATOMY OF THE PERIPHERAL NERVE

(i) THE PERIPHERAL NERVOUS SYSTEM

Most of the cell bodies of the peripheral nerves are massed in or near the central nervous system, namely the spinal cord and brain. The processes of some of these cells lie within the central nervous system while others extend beyond it and lie largely or wholly outside it. It is this part which is termed traditionally the peripheral nervous system. A sound knowledge of the anatomy and function of the various nerves is essential for the correct interpretation of any neurologic signs and symptoms of dysfunction. A clinician with such detailed knowledge can deduce logically the site of any damage or lesion. The basis for any clinical reasoning and treatment planning in a particular case arises from such basic but detailed knowledge of the relevant anatomy and physiology.

Peripheral Nerve Trunks

In their passage to the periphery, nerve fibres do not run independent courses as single units, but are collected into bundles or funiculi (Fig.1), with which are associated other tissues and structures, to form peripheral nerve trunks. The component parts contributing to the formation of peripheral nerve trunks are: nerve fibres (sensory, motor, autonomic), funiculi, connective tissue (endoneurium, perineurium, epineurium), blood vessels, lymphatics and nervi nervorum (Sunderland, 1968) (Fig.1).

Peripheral Nerve Fibres

The peripheral nerve fibres vary in calibre from very fine unmyelinated to thick myelinated fibres. On the basis of histological examination and from physiological experiments these are divided into three groups, A, B and C. The myelinated A fibres are further subdivided into five groups which partly overlap one another α , β , γ , and δ recently ϵ in order of decreasing conduction velocities and diameter. The B group consists of myelinated efferent autonomic fibres and the C group unmyelinated fibres (Brodal, 1969). The diameter of the A group of fibres is between 1-20 μ , that of B group 1-3 μ and the C group of fibres are between 0.5-1.5 μ . The conduction velocity in myelinated fibres is measured in metres per second and is obtained by multiplying the diameter of the fibres by six (Hursh, 1939).

It was Gasser (1935) who indicated that the velocity with which an impulse is conducted in a nerve fibre is related to the diameter of the fibre and therefore the thicker the fibre the faster is the conduction velocity. In large myelinated fibres impulses are propagated with a speed of some 75-120 metres per second and in the finest myelinated fibres the velocity is only 0.3-1.5 metres per second (Brodal, 1969).

Afferent Nerve Fibres

The endings of peripheral nerve fibres are scattered profusely throughout the body. The cutaneous endings are called exteroceptors, those ending in muscle tendons and joints are known as proprioceptors, and a third whose endings are in the viscera, are called interoceptors. Nerve impulses from exteroceptors, proprioceptors and interoceptors are conducted centrally by primary sensory neurones and are distributed as necessary for reflex responses and for transmission of sensory data to the brain (Barr, 1974). These neurones are referred to as somatic afferents and visceral afferents.

Efferent Nerve Fibres

There are also two kinds of efferent neurones. The somatic efferents terminate in motor end plates or in skeletal muscle fibres whilst the visceral efferents have a special feature in that two neurones take part in the transmission from the central nervous system to the viscera. These are known as pre-ganglionic and post-ganglionic fibres. It is the post-ganglionic fibres of the autonomic system that accompany the peripheral sensory nerves (Barr, 1974).

Specific Nerve Types

(a) Sensory fibres

Sensory nerve fibres carry the peripheral dendrites of posterior root ganglion neurones. They are represented by both non-myelinated and myelinated type fibres. The latter range in thickness from $2\ \mu$ to $30\ \mu$ and on the basis of histological examination and physiological experiment have been arranged into three groups $2\ \mu$ to $6\ \mu$; $6\ \mu$ to $12\ \mu$ and those exceeding $12\ \mu$. Non-myelinated and finely myelinated fibres predominate in the peripheral sensory nerves. Sensory nerves have been divided into a cutaneous and a deep system on the basis of the distribution of their

endings. Those that run in the cutaneous branches terminate in the skin while those travelling in the muscular and deep branches of the main nerve trunk innervate the muscles, tendon, connective tissue and bone (Sunderland, 1968). The cutaneous sensory fibres terminate either freely (free nerve endings) or in a wide variety of specialized end organs or receptors in the epidermis and the sub-epidermal layer of the dermis and mediate sensations of touch, pain, warmth, cold and pressure (Gasser, 1935). Pure cutaneous nerves and branches are richer in fine unmyelinated fibres than the motor or mixed nerve fibres. The density of innervation of the cutaneous surface varies from area to area and each receptor is innervated by several nerve terminals and each nerve terminal may innervate more than one receptor. Further, the various receptors within the same morphological group provide a basis for minor variations in a particular sensory modality (Walshe, 1948). The fibres that accompany the deep branches innervate muscle spindles, tendon organs and joint capsules and are relatively thick and myelinated. Besides mediating the sensation already mentioned they also subserve stretch (Gasser, 1935).

On a structural basis sensory endings have been further divided into (i) a non-encapsulated group of simple undifferentiated terminal arborizations, and (ii) encapsulated types which are more specialized (Barr, 1974).

Non-encapsulated endings

These are found in the epithelia, serous membranes, connective tissue, tendons, joints and viscera. The simple free nerve endings in the skin are small fibres of group A and group C. They form a plexus in the dermis and continue into the epidermis as unmyelinated fibres (Brodal, 1969) (Fig. 2). These endings respond to sensations of pain and temperature both of which are warnings of real or potential injury and are known as nociceptive senses. Modifications of these simple nerve endings are sensitive to touch such as those belonging to the Group A fibres of medium calibre. These form a plexus in the dermis and terminate in the epidermis as Merkel's discs, and up to fifty of these may be related to one simple nerve fibre. Further examples of non-encapsulated endings are those related to

Free endings

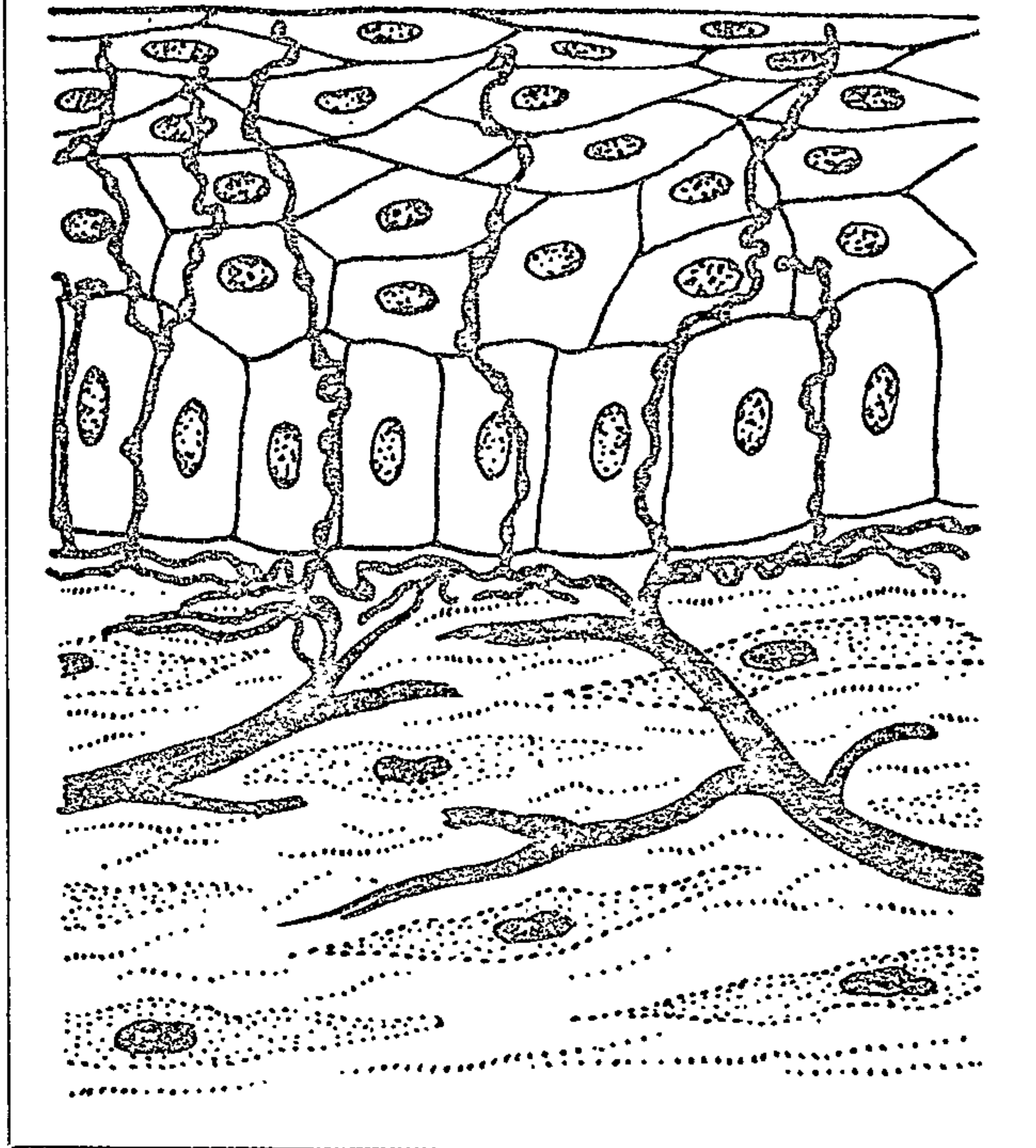


Figure 2.

Note plexus formation in the dermis and unmyelinated fibres extending between the epithelial cells towards the surface. (From Junquera et al).

proprioception and found in association with joints. The terminal ramifications of these Group A sensory fibres are rather complicated and some of the B Group fibres, especially those associated with the viscera (indicating fullness of stomach, bladder and rectum), belong to the non-encapsulated group (Barr, 1974).

Encapsulated endings

Examples of the encapsulated endings are those associated with the Meissner corpuscles, Pacinian corpuscles, neuro-muscular spindles, neurotendinous spindles and sensory end-bulbs (Barr, 1974) and these endings are enclosed within a covering (the capsule) of connective tissue rich in fibrils (Brodal, 1969).

(i) Meissner's Corpuscles (Fig.3).

These are exquisitely sensitive tactile endings found in the dermal papillae and projecting into the epidermis at select sites, e.g. around the mouth, nipple and external genitalia. They are ovoid in shape and $50\ \mu$ by $100\ \mu$ in size. From one to four Group A fibres of large diameter enter the deep pole of the corpuscle, give up their myelin and then pursue an irregular course among the epithelioid cells (Barr, 1974). They enable a person to detect that two points on the skin are touched, even though separated only by millimetres, i.e., the two point discrimination test (see Chapter 10).

(ii) Pacinian Corpuscles (Fig. 4) (Synonym: Corpuscle of Vater-Pacini)

They serve as mechanoreceptors and are sensitive to light pressure and are found in ligaments, in joint capsules and subcutaneous connective tissue. They are ellipsoidal in shape and visible to the naked eye (Brodal, 1969) with a cylindrical cone surrounded by numerous lamellae, bounded sparsely by collagen fibres and separated by spaces containing fluid (Barr, 1974). The cone is notable for

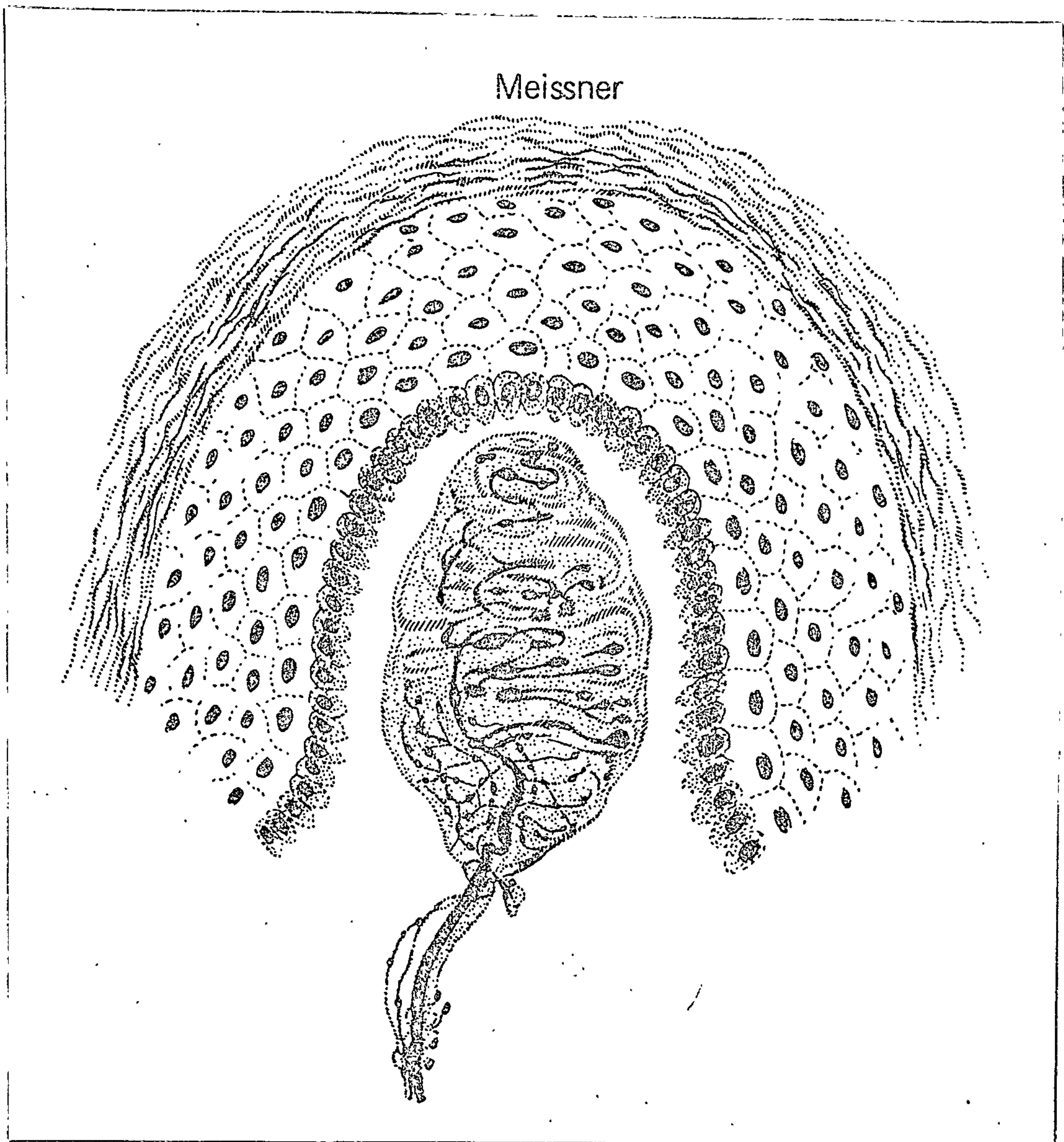


Figure 3. Note the relationship of corpuscle to the dermal papilla. (From Junquera et al).

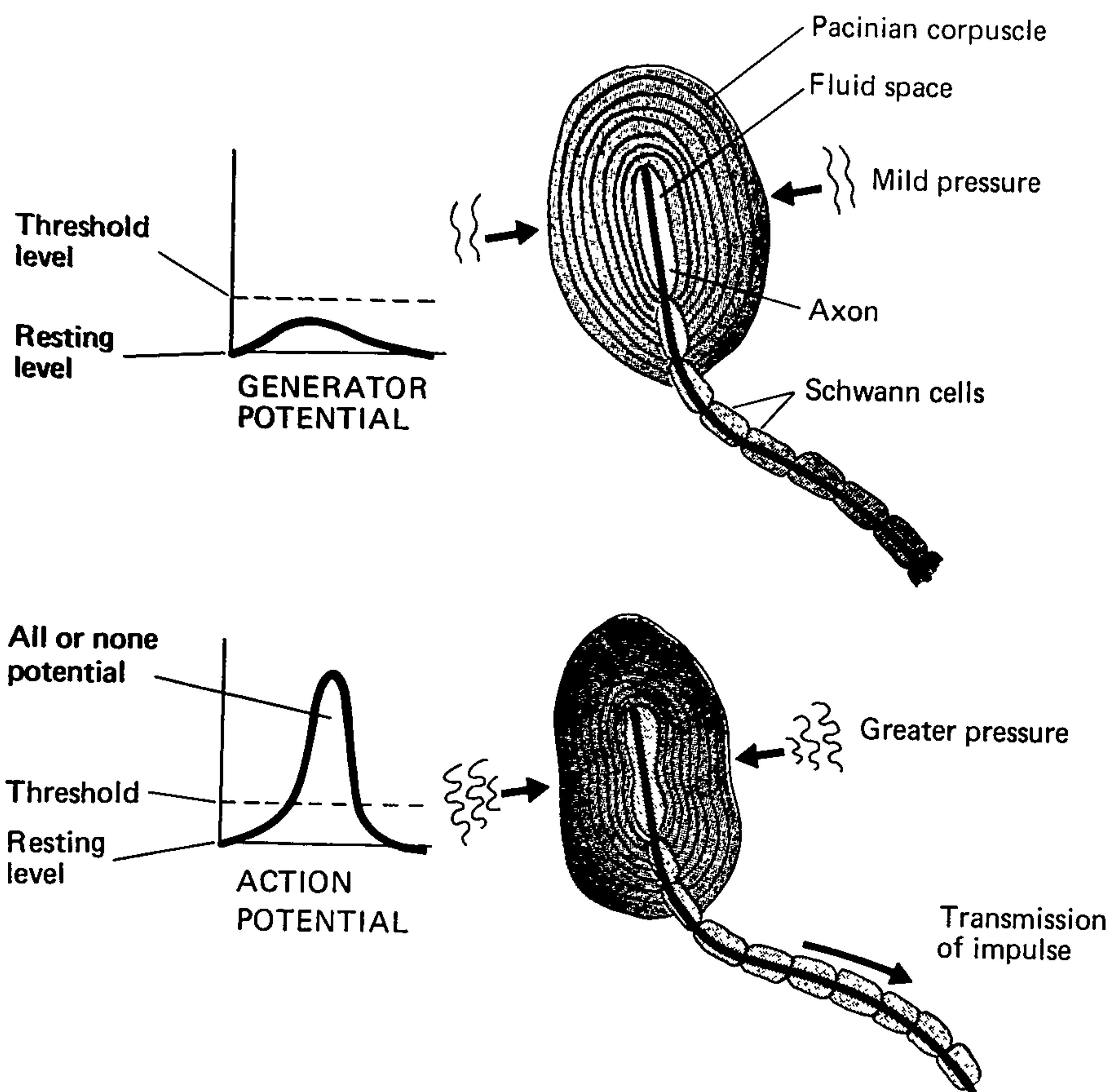


Figure 4. Pacinian Corpuscle. Note Group A myelinated fibre which becomes unmyelinated after entering corpuscle. (From Junquera et al)

containing an unusual number of mitochondria. A large Group A fibre enters each corpuscle at a point at which the myelin terminates. They function as receptors for vibration and for sensations of fullness of hollow organs (Barr, 1974).

(iii) Neuromuscular Spindles (Fig. 5)

These receptors are both structurally and functionally very complex and contribute to muscle function in several ways. They provide sensory data for spinal reflex adjustments of muscle tonus, and contribute to the cerebellum for motor functions and for sensori-motor integration at the cerebral cortical level (Barr, 1974). They are a fraction of a millimetre wide and up to six millimetres long and are inserted in considerable numbers parallel with the fibres of voluntary muscles. Each spindle is supplied by two afferent fibres of the A group. The larger fibre of the A group loses its myelin as it enters the capsule and the dendrite, called the annulospiral ending, winds around the wide portion of the intrafusal muscle fibres (Fig. 5). The other fibre which is the smaller of the two, branches terminally and ends some distance from the mid-region and is known as the flower-spray ending. These spindles are unique sensory endings in several respects, the most significant being that they also have an efferent or motor innervation. The extrafusal fibres make up the main mass of the muscle, and are innervated by axons belonging to the A group and of α size while the intrafusal fibres are innervated by axons belonging to the same group but of γ size. The spindles also play an important role in muscle function. The simplest role played by these spindles is that of a receptor for the stretch or extensor reflex (knee jerk and jaw jerk tests) (Kennedy, 1970).

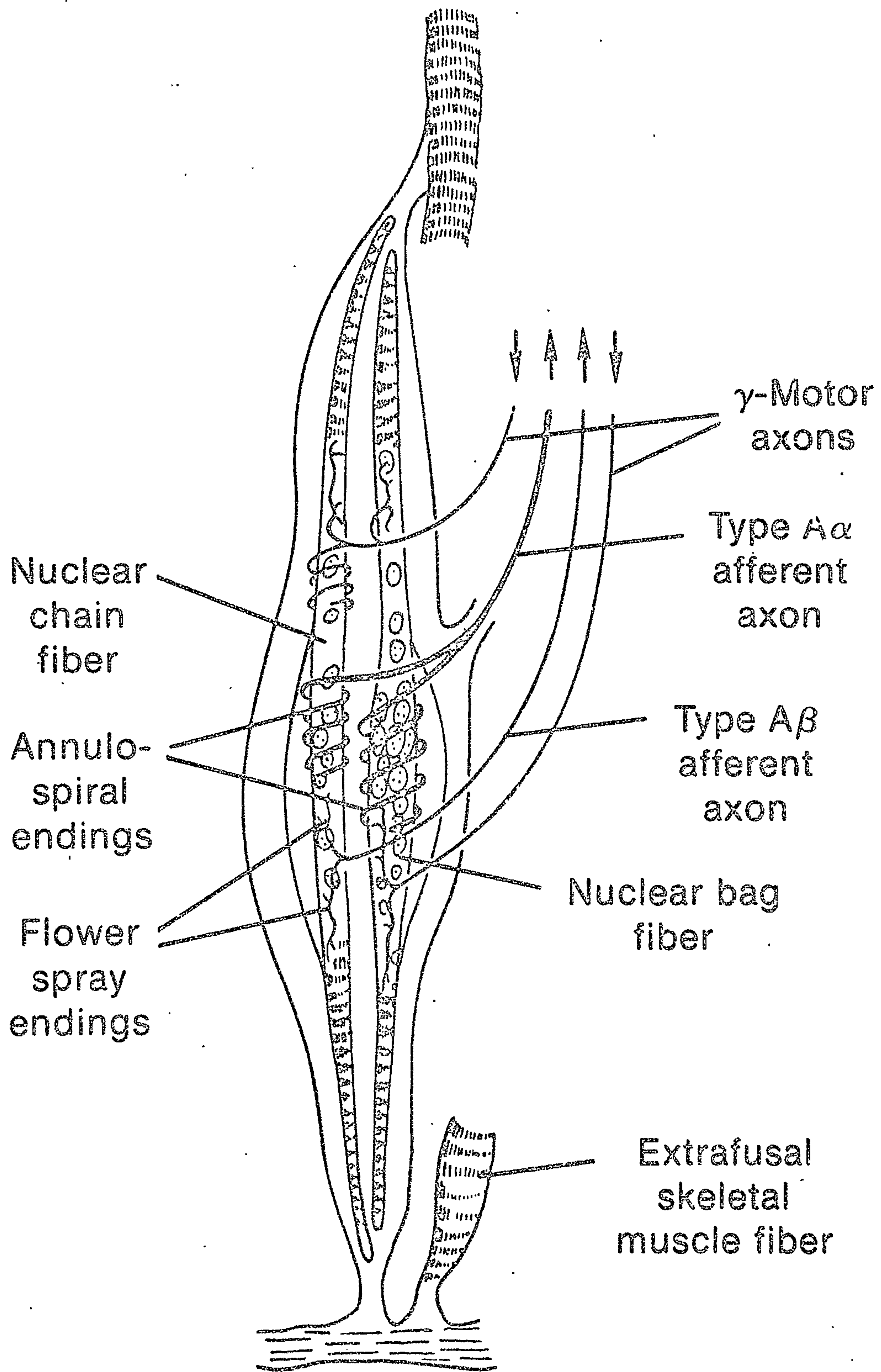


Figure 5. Diagram of muscle spindle showing various nerve endings.

(iv) Neurotendinous Spindles (Fig. 6)

These are sometimes known as Golgi tendon organs and are most numerous at the muscle attachment of the tendon. A large group A fibre enters the spindle and its branches end in the intrafusal tendon fibres. The endings are stimulated by tension on the tendon, greater tension being required than for excitation of neuromuscular spindles by stretch. The afferent impulses have an inhibiting effect on the motor neurones causing relaxation of the muscle to which the particular tendon is attached thus providing a balance in the total integration of reflex activity. This provides protection against damage to muscle or tendon because of excessive tension (Barr 1974).

(v) Sensory End-Bulbs

These vary in shape and in size from 50-100 μ in diameter and their morphology and function are poorly understood. A small to medium calibre Group A fibre pierces the capsule and breaks up into numerous branches. They are widely distributed in the body, e.g., the dermis, subcutaneous tissue, serous membranes and joint capsules. They have received numerous names and are commonly called end-bulbs of Krause (Fig. 7) which are receptors for coolness and end-bulbs of Ruffini (Fig. 8) which are for warmth. Evidence that these are special temperature sensors is not conclusive as they appear to participate in touch, pressure, temperature and proprioceptive sensibilities and are obviously in need of further study (Barr, 1974).

(b) Motor fibres

These fibres are often called motoneurones and originate from their perikarya which are situated in the ventral horns of the spinal cord and in the motor nuclei of some of the cranial nerves in the brain stem. They

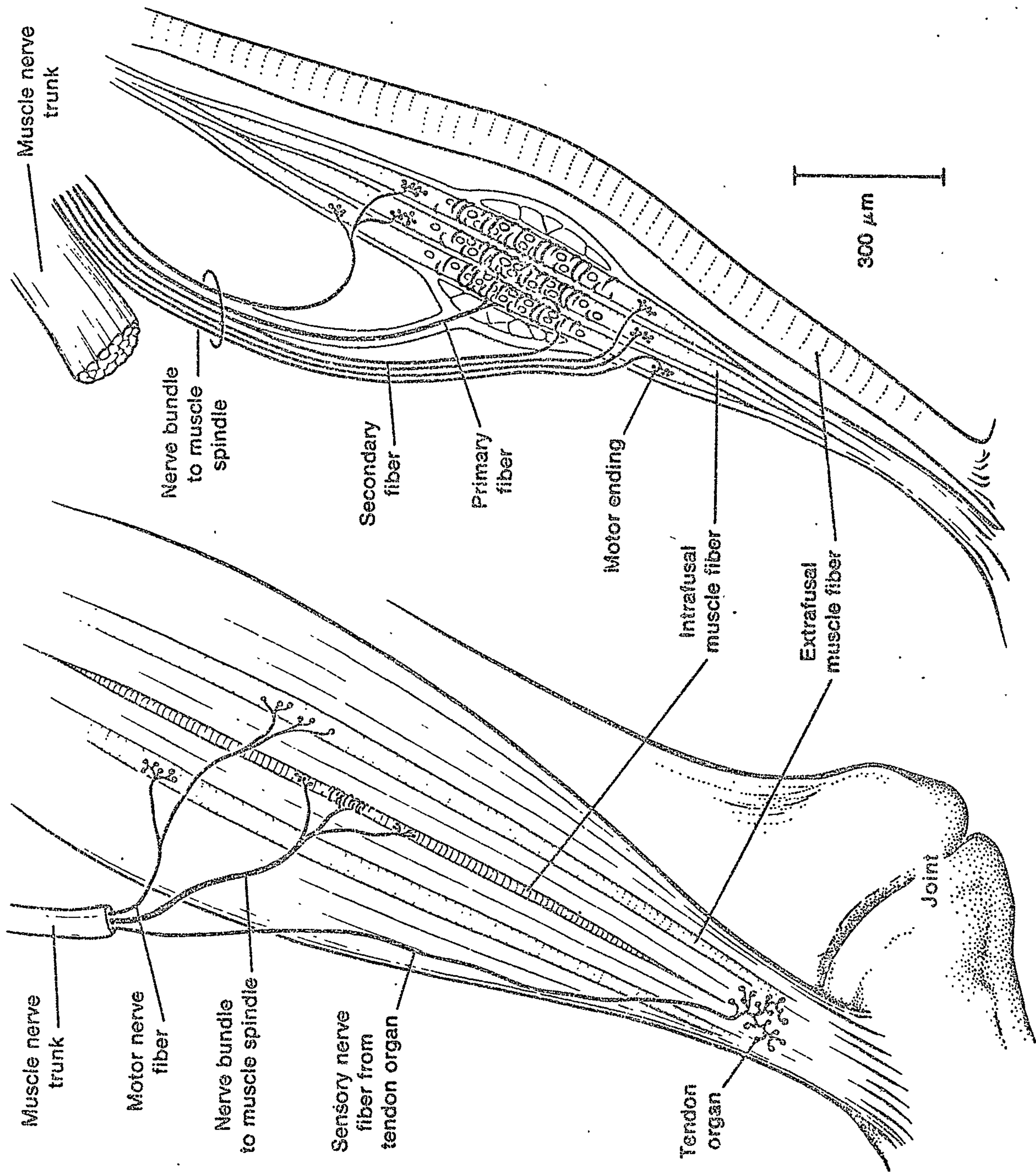


Figure 6. Diagrammatic representation of nerve endings in tendons.

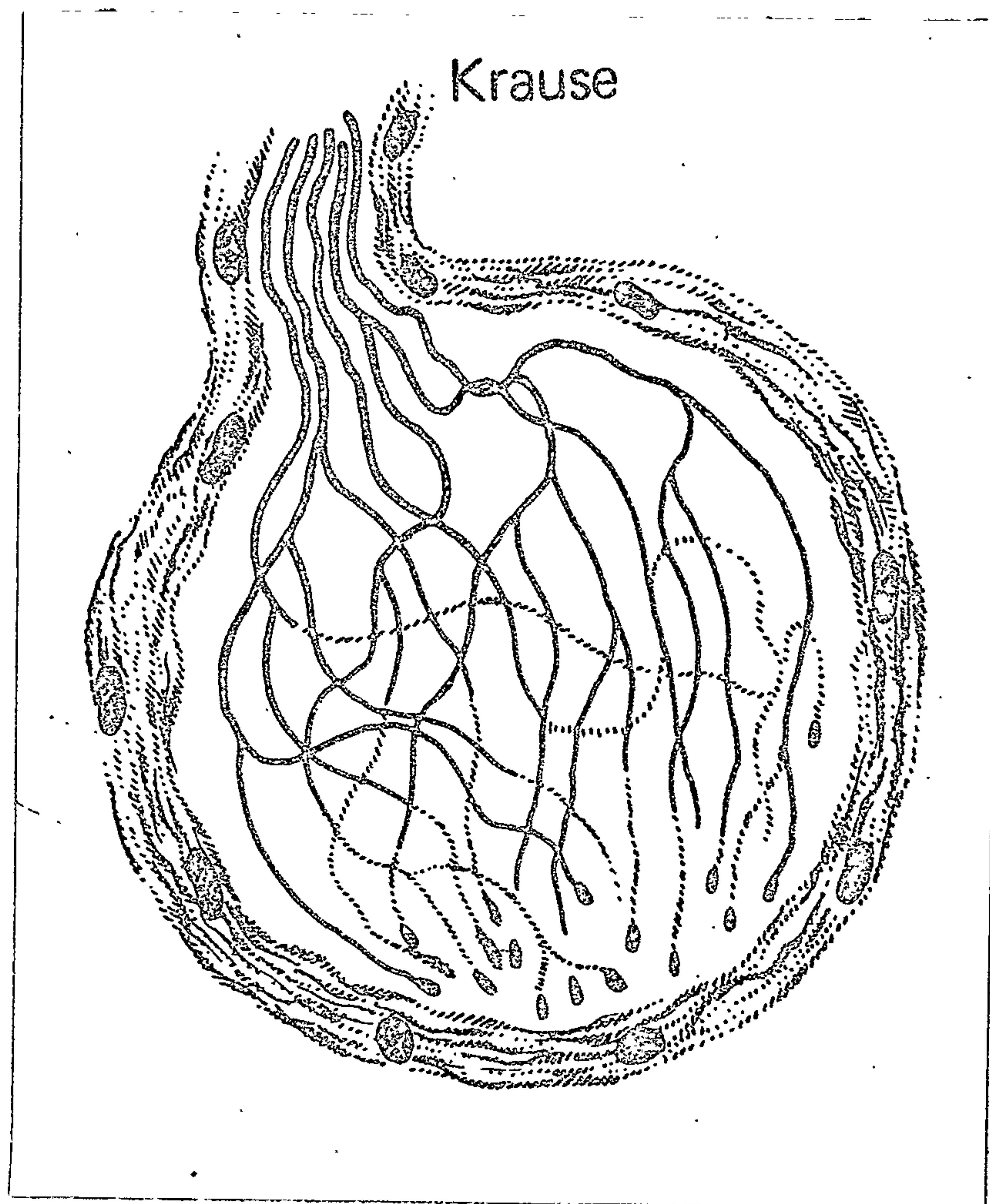


Figure 7. Configuration of End-bulb.
(After Junquera et al).

Ruffini

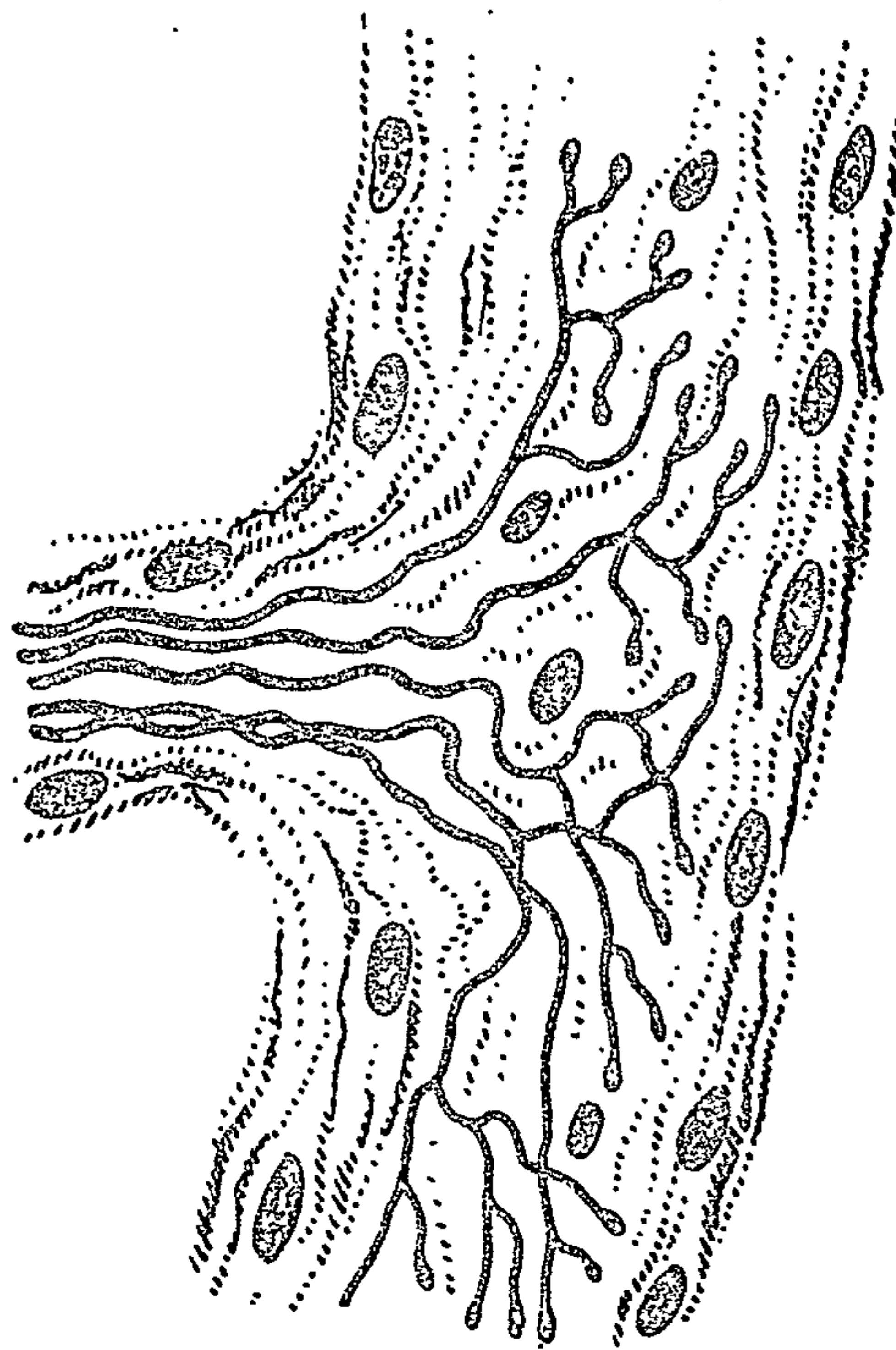


Figure 8. Configuration of End-bulb.
(After Junquera et al).

terminate in the neuromuscular endings of skeletal muscles (Brodal, 1969). Seventy percent of these fibres are between $10\ \mu$ - $17\ \mu$ in diameter. These large motor fibres are commonly referred to as α fibres while the remainder are of $2\ \mu$ - $8\ \mu$ diameter and are called small motor nerve fibres, namely γ fibres (Eccles and Sherrington, 1930). The larger fibres $10\ \mu$ - $17\ \mu$ are known to innervate the extrafusal fibres of the muscle while the small fibres terminate in the intrafusal fibres of the muscle spindle (Kuffler et al., 1951). According to Sherrington the motoneurones are the "final common pathway" for all those impulses from many sources which are transmitted to the skeletal musculature of the body (Barr 1974).

The Motor Unit

The term "motor unit" was introduced by Sherrington and comprises a motoneurone, its axon and the muscle fibres it supplies. Its size varies, as a single ventral horn cell may supply from a few muscle fibres up to a thousand or more. This latter occurrence is brought about by the extensive branching of the axon within the muscle or close to it (Eccles and Sherrington, 1930). Sunderland and Laverack (1953) claimed that some axons may also branch peripherally along their courses. Cooper and Daniel (1963), from their studies on muscles, stated that the intrafusal fibres of the spindles of man are of two types: nuclear bag and nuclear chain. Annulospiral fibres innervate the nuclear bag fibres while the flower-spray endings the nuclear chain fibres.

Motor End Plates

The terminal arborizations of the motor nerve fibres are found in the muscles and are called motor end plates. The end plates consists of two parts - a nervous part and a muscular part - separated from each other by a cleft $200\text{--}300\text{\AA}$. This myoneural junction in many respects resembles a synapse in the central nervous system. The nervous part i.e., the ultra structure of the axonal expansion within the end plate ends in a number of grape-like swellings and contains synaptic vesicles and mitochondria while in the muscular part of the end plate there are several nuclei and numerous mitochondria. It is established that the transmitter substance at the end plate is acetylcholine (Brodal, 1969).

Peripheral Motor Neurone Lesions

Depriving a muscle of its motor supply results not only in its paralysis but sets off a sequence of changes in its histological structure, physiological properties and chemical constituents. The morphological changes following denervation are therefore degeneration, atrophy and replacement. As a rule one muscle fibre is supplied by one axon only and has a single end plate. When the nerve fibre is cut the motor end plate and the fibre undergo degeneration (Feindel et al., 1952).

(c) Autonomic Fibres (Sympathetic and Parasympathetic - Fig. 9)

The concept of the Autonomic system originally was that it comprised only structures outside the central nervous system (C.N.S.). It is futile now, with the discovery of the rami communicantes, to subdivide the autonomic nervous system into somatic and visceral systems as it was ascertained that certain cells in the brain stem and spinal cord send axons to the autonomic system. In addition, the cerebral cortex also influences its functions (Brodal, 1969). Brodal quotes an old but general definition by Greving in 1928 which he seems to think adequately covers its function. The autonomic nervous system is designated as "the entire mass of those nerve cells and fibres which are concerned in the innervation of the internal organs, in so far as they are made up of smooth muscles or belong to glandular organs. They subserve the regulation of processes which usually are not under voluntary influence".

The characteristic feature of this system is that the efferent conducting pathway from the central nervous system (C.N.S.) to the innervated organ, is always constituted by two succeeding neurones, one preganglionic with its perikaryon in the central nervous system and the other postganglionic with its perikaryon outside. The nerve cells within the C.N.S. which are concerned with autonomic functions are morphologically different to those subserving the somatic process and are frequently found arranged as definite cell groups or nuclei (Brodal, 1969).

The autonomic system is further subdivided anatomically and functionally into sympathetic and parasympathetic systems.

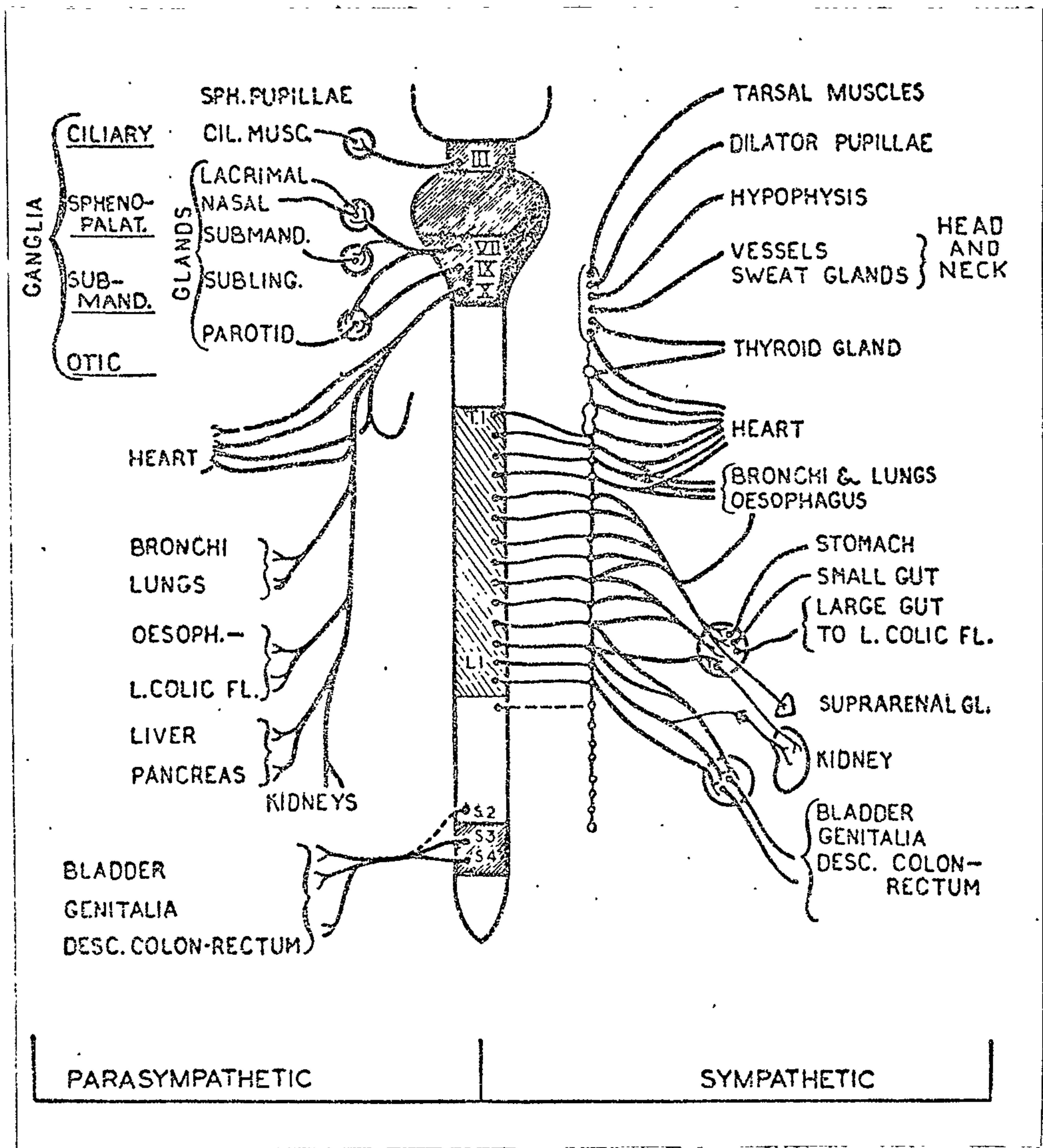


Figure 9.

Traditional diagram of the autonomic nervous system. (Grant's Method of Anatomy)

Sympathetic fibres

Sympathetic fibres originate in the intermediolateral cell column of all thoracic spinal segments and the upper two or three lumbar segments. The sympathetic fibres of peripheral nerves are the postganglionic processes of the neurones of the ganglionated sympathetic trunk (Barr, 1974). They leave the cord via the ventral root and by way of little trunks called white rami communicantes as preganglionic fibres and enter the paravertebral or prevertebral ganglia (according to their position) disposed in the form of chains on either side of the vertebral column (Ham, 1974). The number of postganglionic fibres that leave the ganglia is considerably greater than the preganglionic fibres that enter the ganglia. According to Langley 1900, in general, these fibres are non-medullated and the number of medullated fibres present is relatively few in comparison with amphibia (Sunderland 1968). Sympathetic fibres pass to the blood vessels, hair muscles and glandular structures of the skin by way of the cutaneous nerves and to deeper structures via the deep branches of the main nerve trunks. They delicately adjust the circulation to meet the functional demands of the tissues, regulate the production of secretions from glandular structures and activate the erectores pili of the muscles of the skin causing the erection of hairs and the goose flesh effects at the surface of the body (Barr, 1974).

Parasympathetic fibres

In the parasympathetic division, the preganglionic fibres originate from two sources, i.e., from the cells of the nuclei of the gray matter in the medulla and midbrain and from the cell bodies found in the lateral column of the sacral portion of the spinal cord. The preganglionic fibres are long and end in small ganglia closely associated with the gland or muscle. The post-ganglionic fibres are therefore short, except in the head region where the ganglia are not within or close to the associated structures and therefore longer (Ham, 1974). The role of the parasympathic system is to bring about changes that are designed to conserve and restore the energy sources of the body, i.e., they decrease the rates and force of the heart

beat, lower the blood pressure and augment the activity of the digestive system (Barr, 1974).

(d) The inferior dental nerve (innervation of the lip chin area) (Fig. 10A).

The inferior dental nerve (IDN) is the intermediate branch of the mandibular nerve which is the third division of the trigeminal nerve (Sicher and Du Brul, 1970). The origin of the trigeminal nerve, the fifth cranial nerve, is in the brain stem halfway between the lower and upper borders of the pons in its centro-lateral aspect. The nerve travels centrally and ascends through the pontine cistern and pierces the dura mater below the attachment of the tentorium cerebelli. The nerve is made up of two bundles, a Portio major associated with sensory function and a Portio minor related to motor function. About 1 cm from the Pons the Portio major swells to form the Gasserian ganglion from which the mandibular branch arises. The mandibular division is the biggest of three divisions of the trigeminal nerve and is a mixed nerve. It contains the entire motor portion. It leaves the skull through the foramen ovale and divides into several branches, the inferior dental nerve being one of them (Brodal, 1969).

The inferior dental nerve then descends between the two pterygoid muscles, behind and slightly lateral to the lingual nerve, winds around the lower border of the lateral pterygoid muscle, turns sharply outward and downward to reach the inner surface of the mandible to reach the mandibular foramen which it enters. Before it disappears into the mandibular canal it releases the mylohyoid nerve. This nerve is always described as a motor nerve but Sicher and Du Brul (1970) say that it contains sensory fibres and in most persons a thin sensory nerve is seen to supply the skin on the inferior and sometimes on the anterior surface of the mental prominence (Fig 10B(a)). Further, in 10% of the cadavers examined, a twig of the terminal sensory branch of the mylohyoid is seen to enter the mandible in the mental region and may participate in the nerve supply to the lower incisors.

The inferior dental nerve during its passage through the mandibular canal

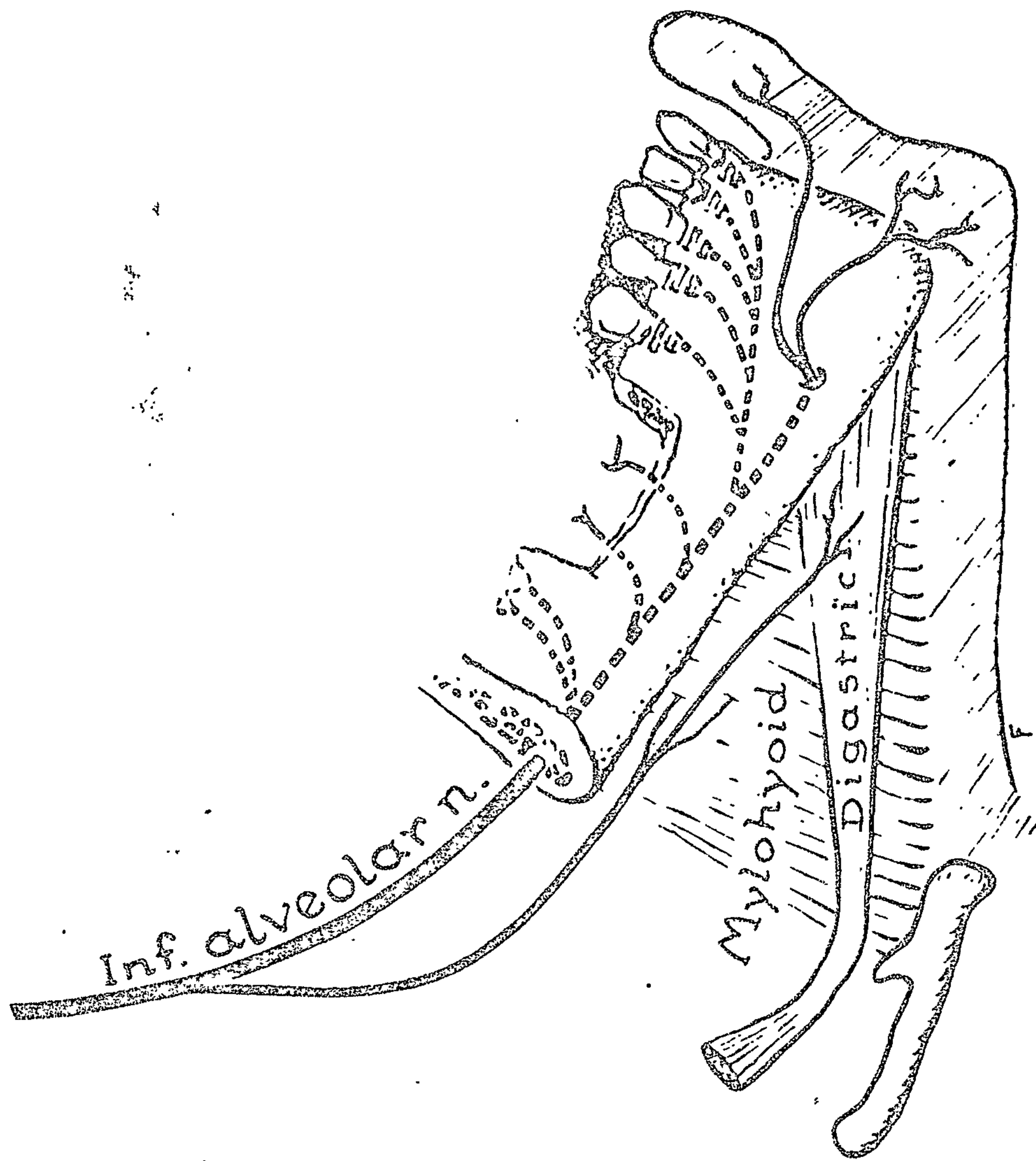


Figure 10A. Innervation of lip/chin area.

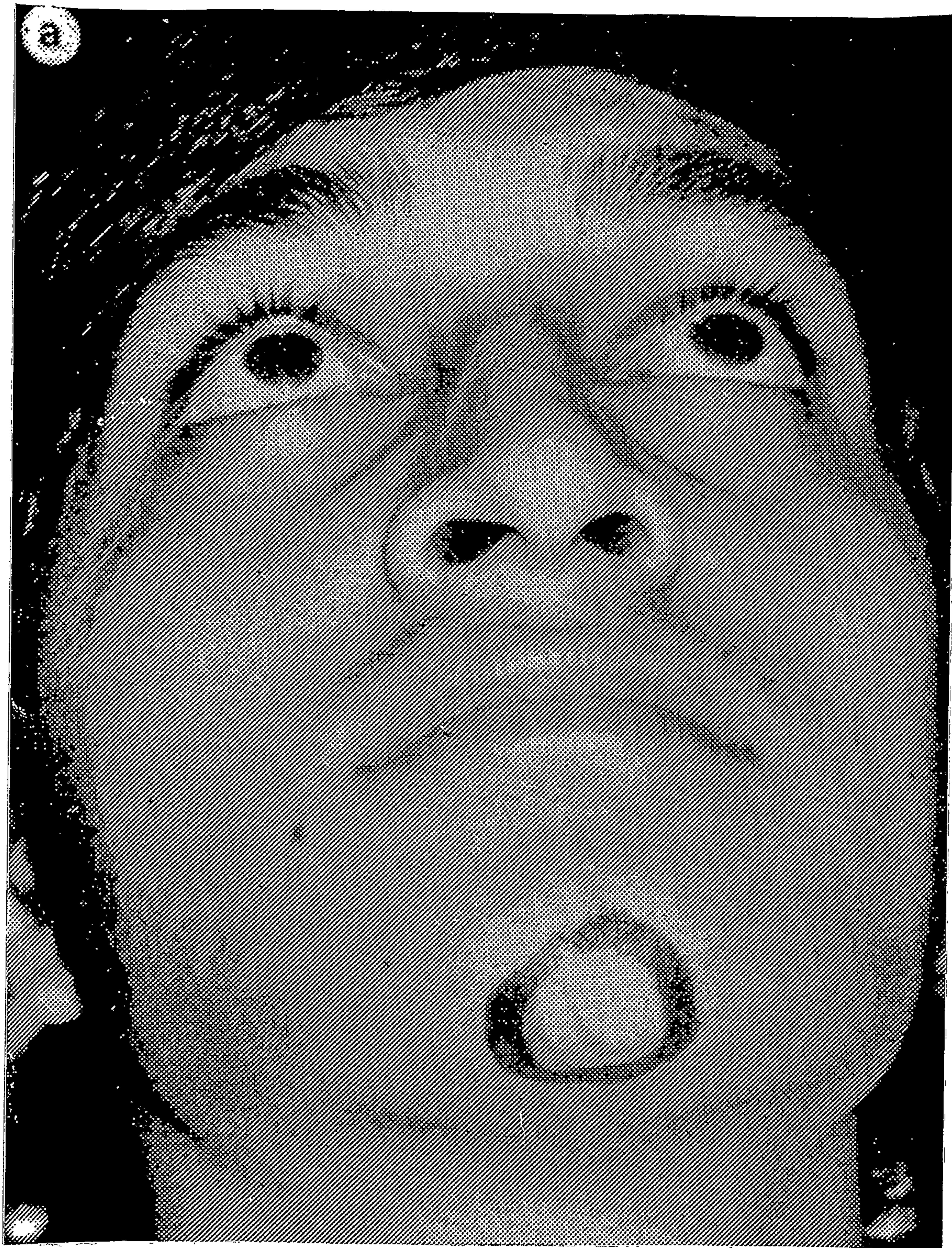


Figure 10B(a). Region shown to be innervated by the
(a) mylohyoid nerve. (Robert and Harris, 1973)

gives off numerous dental branches and is arbitrarily divided into posterior, middle and anterior sets. These form a loose inferior dental plexus and their terminal branches enter the roots of the lower teeth to supply their pulp. Some of the terminal branches perforate the interalveolar septa to supply the periodontal ligaments of adjacent teeth and end in the gingival papillae. Where the buccal gingiva is not supplied by the buccal nerve it received fibres from the perforating interdental nerves.

Having traversed the length of the mandibular canal the inferior dental nerve divides into two terminal branches, the incisive dental branch for the lower incisors and mental branch. The mental branch (Fig. 10B(b)) leaves the body of the mandible through the mental foramen and usually divides into three branches. Two of these course anteriorly and upwards into the lower lip to supply the skin and mucous membrane of the lip and mucosa of the labial alveolar surface. The other turns forward and downwards to the skin of the chin. Anatomists are in agreement that in the majority of cases these nerves cross over the midline of the lip chin area by about 1-2 mm which suggests that this central area may have a dual nerve supply.

Last (1966), Cunningham (1967) and Sicher and Du Brul (1970) all describe that the transverse cervical nerve (anterior cutaneous nerve of the neck) arising from C_2 and C_3 emerges with the great auricular nerve, curves around the posterior border of the sternocleidomastoid and enters the superficial fascia. It quickly breaks up into a number of slender twigs to innervate the skin in the midline of the neck from the chin to the sternum. However, none makes any mention of its innervating the lip. Sicher and Du Brul (1970) on the other hand indicate that in most people the mylohyoid nerve is a mixed nerve and contains sensory fibres. These sensory fibres continue in most persons as a thin sensory nerve towards the chin, where it supplies the skin on the inferior and sometimes on the anterior surface of the mental prominence. (Fig. 10B(a)).

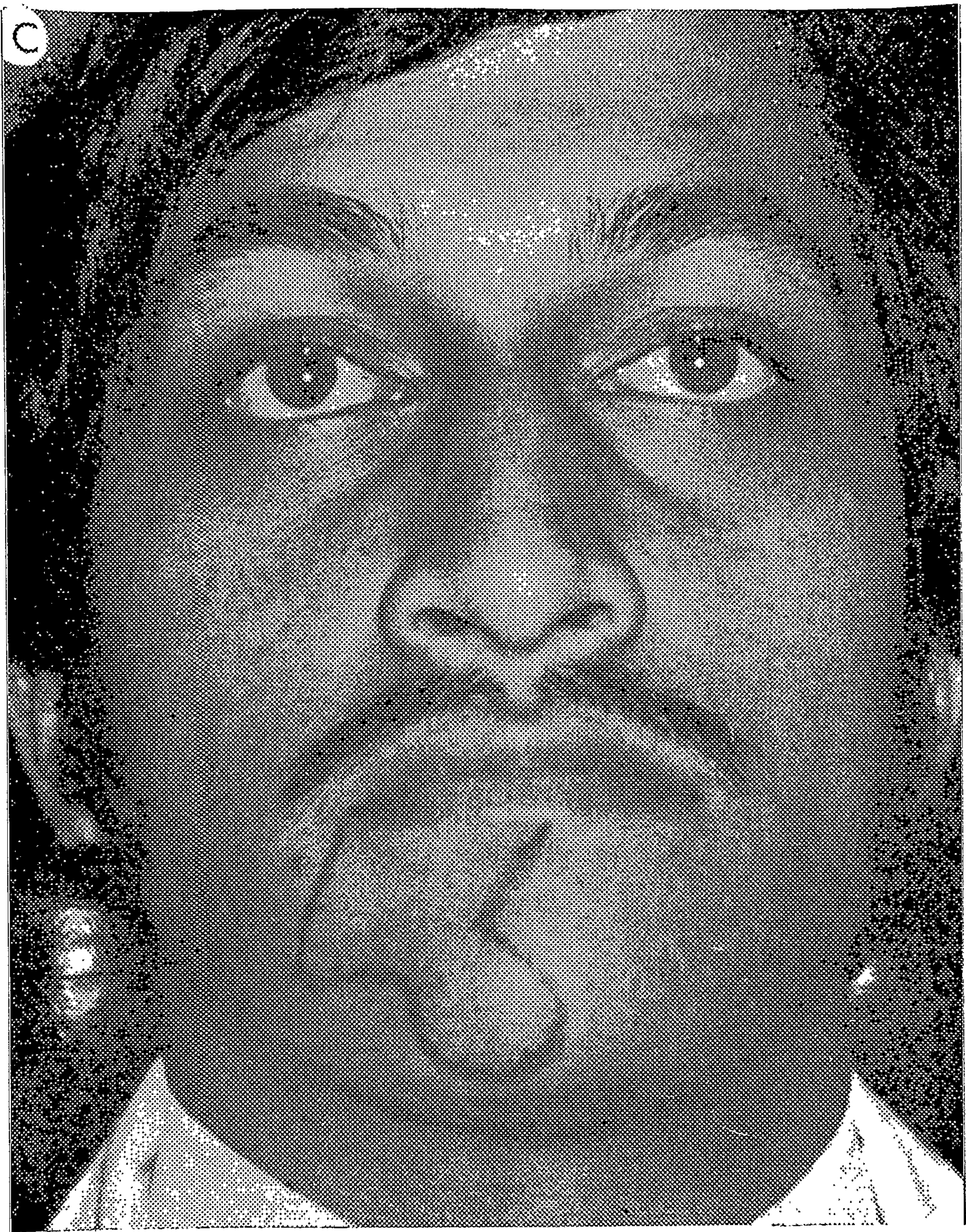


Figure 10B(b). Region shown to be innervated by the
(b) inferior dental nerve.
(Robert and Harris, 1973)

(ii) HISTOLOGY OF THE NEURONE (Fig. 11)

The nervous system is a highly specialized tissue. The special signalling properties of the receptor in the system give it the capacity to react to physical or chemical agents and transmit the resulting excitation from one locality to another via its long processes - the axons. In the nerve centres, where these signals arrive, they are translated into sensations or responses and thus co-ordinate the functions of the various organs so that the integrity of the body is maintained.

The cells that carry out these special functions are called neurones. Each neurone consists of a central cell body (q.v.) which houses the nucleus surrounded by its protoplasm called perikaryon (Fig. 11). The cytoplasm of the neurone is drawn out into several short radiating filamentous processes called dendrites and a single long process of variable thickness and length, an axon, measuring from less than a millimetre to over a metre. Immediately surrounding the axon is a multi-layered sheath of myelin (in the case of myelinated fibres). Enfolded in this sheath are the Schwann cells and external to these is an encircling connective tissue covering, the endoneurium (Fig. 1). The neurone is the structural and functional unit of the nervous system and arises from a single embryonic cell, the neuroblast (Arey, 1974). In the perikaryon are several organelles which contribute to the effective functioning of the neurone. The axon may or may not emit one or more collateral branches along its peripheral course (Fig. 11) and terminates by breaking up into a number of terminal filaments or telodendrites (Fig. 16). The cell bodies of the neurones and their branching processes differ in size, shape and function thus producing countless types of neurones. The size of the perikaryon varies from $5\ \mu$ for the smallest cells in the complex circuits to $135\ \mu$ for large motor neurones. The pattern of branching of the dendrites may be exceedingly profuse and intricate and therefore varies greatly, and is distinctive for neurones composing a specific cell group or nucleus (Barr, 1974).

Central Cell (Fig. 12)

The function of the central cell, apart from providing a large area of membrane surface for the generation, induction and transmission of the nervous impulse is chiefly to ensure the maintenance of nutrition of the various processes and their branches which constitute the essential conducting mechanism of the neurone (Barr, 1974). The cell membrane is made up of a plasma membrane composed of

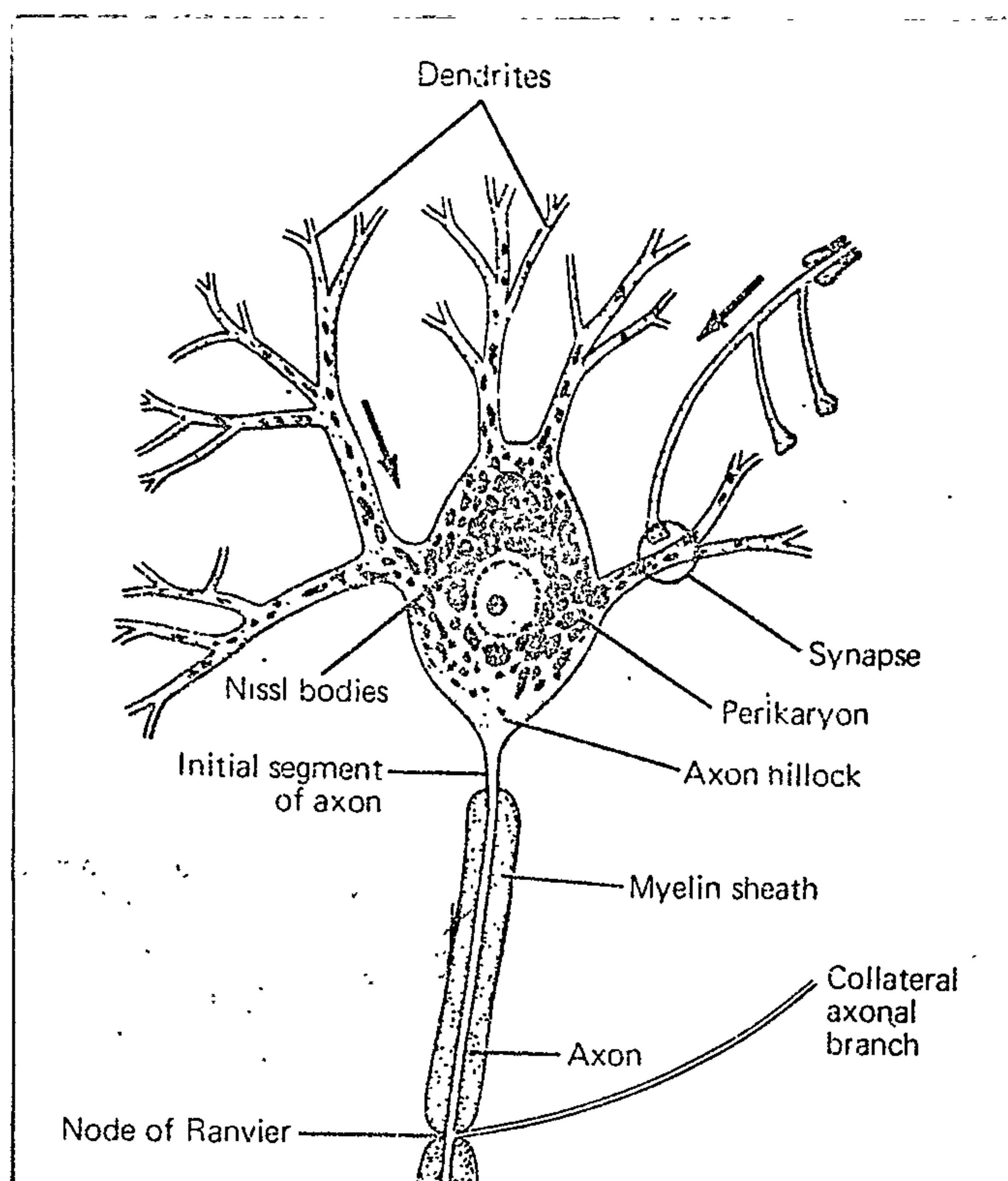


Figure 11.

Component parts of a typical peripheral neurone.

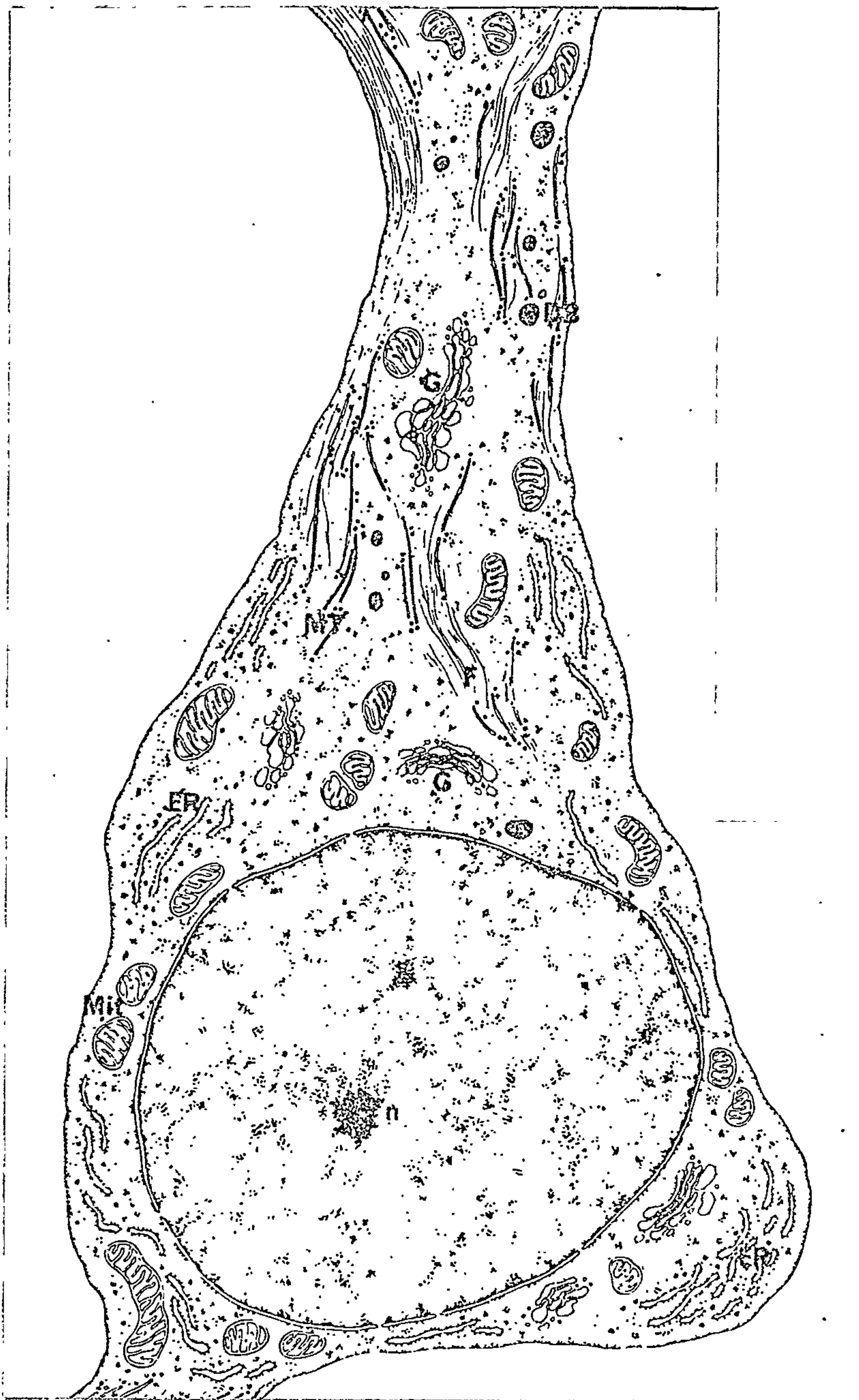


Figure 12. Diagram of central cell body with its organelles as follows:

n - nucleolus in nucleus; Mit - mitochondria;
 ER - Endoplasmic reticulum and Nissl granules;
 G - Golgi apparatus; F - neurofilaments;
 MT - Microtubules; DB - dense bodies.

(Adapted from HAM Histology 1974)

lipid and protein molecules together with an external "cell coat" consisting of glycoprotein and sialic acid. The membrane is semi-permeable to some ions, thus giving rise to (i) a resting membrane potential when the cell is at rest and (ii) generation of an action potential under suitable conditions (see chapter on Neurophysiology) (Barr, 1974). In the cytoplasm of the cell body surrounding the nucleus are found numerous filamentous, membranous, and granular organelles. These are the neurofibrils, Nissl bodies, Golgi apparatus, mitochondria, and the centrosome and various inclusions (Fig. 12).

The Nucleus

The nucleus is large, pale, spherical or slightly ovoid with a double nuclear membrane (Hartmann 1954) and contains finely particulate chromatin (Bloom and Fawcett, 1975). The nucleus is more often than not centrally placed in the perikaryon, an exception being the cells of the nucleus dorsalis in which it is eccentrically placed. There are also a few binucleate nerve cells and these can be found in the sympathetic ganglia. A single prominent nucleolus is observed and its role is the synthesis of ribonucleic acid (RNA) and the transfer of RNA to the cytoplasm (Barr, 1974). In man, but not in all mammals, the sex chromatin of the female is prominent and is located near the nucleolus or at the periphery of the nucleus (Bloom and Fawcett 1975).

Neurofibrils, Neurofilaments and Microtubules

Under the light microscope, neurofibrils appear as slender interlacing threads coursing through the cytoplasm from one dendrite into another or into the axon (Palay and Palade, 1955). In electron micrographs these same neurofibrils are seen to be formed by an aggregation of slender neurofilaments about 75-100 Å in diameter. They lie parallel to the long axis of the axon and dendrites and can be followed into the finest terminal ramifications of all the processes (Bloom and Fawcett, 1975). At even higher magnification they appear as minute tubules with a 30 Å thick dense wall and a clear centre. In addition, there are also microtubules about 200-300 Å thick and these are involved in the rapid transport of essential metabolites from the cell body throughout the neurone (Barr, 1974) (see

Chapter 8). Both the neurofilaments and microtubules are arranged in tracts resembling roadways (Bloom and Fawcett, 1975).

Nissl Bodies

These have been named after Franz Nissl (1860-1919), a Heidelberg neurologist, who first described them in the last century. These Nissl bodies are clumps of basophilic substance (Ham 1974) and the principle constituent is ribonucleoprotein (Bloom and Fawcett 1975). The Nissl bodies show important changes in pathological conditions (Bloom and Fawcett, 1975). The amount of Nissl material increases with the size of the neurones. There are coarse clumps in motor neurones whereas the Nissl material is more finely distributed in sensory neurones. Nissl substance is present in the dendrites but is absent in the axon hillock and the axon itself (Barr, 1974). A Nissl body consists of an aggregation of flattened membranous cisternae of rough endoplasmic reticulum with numerous ribosomes and polysomes scattered between the adjacent cisternae (Ham, 1974). The ribosomes contain RNA and participate in the synthesis of structural and enzymatic proteins. Through axoplasmic flow at a rate of 1 mm per day, they leave the perikaryon to replace protein that is degraded through cellular activity, notably in the axon. They are therefore important during growth of the neurones and during regeneration of peripheral nerve fibres (Barr, 1974).

Golgi Apparatus

Using light microscopy, this appears as an irregular network of coarse strands arranged in an arc or a complete circle around the nucleus halfway between it and the cell surface. Under the electron microscope, the Golgi network appears as clusters of closely apposed, flattened cisternae arranged in stacks and surrounded by multitudes of small vesicles. This arrangement was first demonstrated in these cells by the Italian histologist Camillo Golgi in the last century and the Golgi apparatus was said to contain the enzyme thymine pyrophosphatase. In secretory cells, there is good evidence that the products of secretion are "packaged" in the Golgi area, including incorporation of the carbohydrate moiety of the secretory product (Barr, 1974).

Mitochondria

These are spherical, rod shaped or filamentous bodies and vary in diameter from $0.1\ \mu$ to $1.0\ \mu$. They are scattered everywhere intermingling with Nissl bodies and neurofibrils (Palay and Palade, 1955; Bloom and Fawcett, 1975). They are the repository of enzymes, including the respiratory and phosphorylating enzymes of the Krebs citric acid cycle, and are involved in several aspects of cell metabolism (Barr, 1974). Their number varies from cell to cell, and in different parts of the same cell, and they are especially numerous in axon endings. Their fine structure resembles that of mitochondria of other cells but those in the nerve cells display two peculiarities, (i) their cristae (numerous folds projecting into the organelle to increase its surface area) often run parallel to the long axis of the mitochondria instead of being consistently transversely orientated and (ii) the dense matrix granules are absent or infrequent (Bloom and Fawcett, 1975).

Centrosome

The spherical centrosome contains a pair of centrioles and plays an important role in the dynamics of mitosis (Barr, 1974). It is seldom observed under the light microscope but occasionally encountered under the electron microscope in adult neurones but, as neurones do not proliferate in the mature state, its role in the adult nerve cell is unknown. This is not the case during embryonic development when the pre-neuronal cells are multiplying (Bloom and Fawcett, 1975).

Inclusions

Two pigments are known to appear in nerve cells - (i) lipofuscin which first appears in post-natal life in the ganglion cells and later in the cells of the CNS. These yellowish-brown granules are said to be related to the aging process; (ii) melanin is mostly found in the substantia nigra, a motor nucleus in the mid-brain, the significance of which is uncertain. It appears at the end of the first year, increases until puberty, and remains relatively constant thereafter (Barr, 1974; Ham, 1974). Glycogen, another product, is found in embryonic neurones but is not present in a

histochemically demonstrable quantity in adult nervous tissue (Bloom and Fawcett, 1975).

Axon (Fig. 13)

There is one axon to each neurone and it arises from the axon hillock which is devoid of Nissl bodies. It differs from the dendrites of which there are several to each neurone. Connection with the cell body is a pre-requisite for the life of the axon. It tapers gradually at the periphery and the cytoplasm is a viscous fluid known as axoplasm. In it are neurofilaments, microtubules, scattered mitochondria and patches of smooth surfaced or agranular endoplasmic reticulum which are continuous with those in the cell body (Barr, 1974). There is an absence of the Golgi apparatus and components related to protein synthesis but these are actively formed in the cell bodies and transported down the axon at a fairly regular rate (Droz and Leblond, 1963). These materials are essential for the efficient functioning of the axon. It has a uniform diameter throughout its length, but tapers near the end organ. Its diameter increases in proportion to its length. The nerve fibres of the axon vary from 0.2μ to 20μ in diameter. Along its course the axon may or may not emit collateral branches at right angles to the main axon. This is unlike those branches of the dendrites which branch out at an acute angle. The terminal arborizations of the axon are composed of primary, secondary and other branches, their buds varying greatly in number, shape and distribution. They surround the body of the post synaptic neurone in the form of a basket or twist around the dendrites like a clinging vine. Through its endings the axon transmits nerve impulses to other neurones or to muscle or gland cells. The response of the effector cells is always activity, but the response of the other neurones may be a varying degree of either excitation or inhibition. There are many types of axon endings and the same axon may terminate in several different ways, and synapse with several different neurones (Bloom and Fawcett, 1975). The membrane around the axon is known as the axolemma, is a continuation of the cell membrane of the nerve cell, and is directly concerned with the

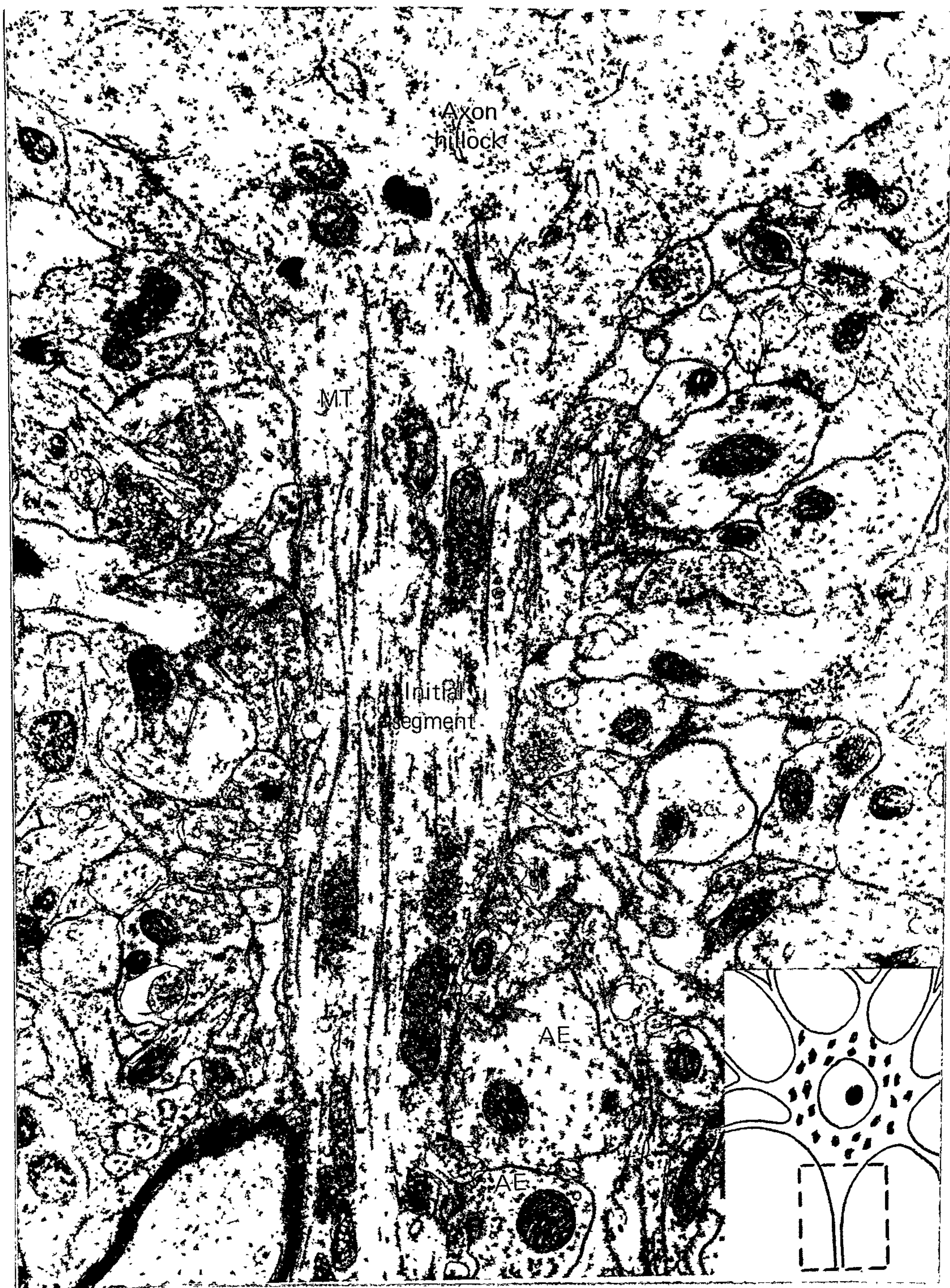


Figure 13. Electron micrograph of "trigger zone" i.e. the axon hillock and initial segment of the axon. (From Junquera et al)

transmission of nerve impulses. The membrane is differentially permeable to ions and there is a high concentration of K^+ and a low concentration of Na^+ and Cl^- within the fibre (Webb and Young, 1940). The axon carries the response of the neurone away from the cell body in the form of a propagated action potential. The axon hillock and the initial segment of the axon from which the potential arises are sometimes called the "trigger zone" (Fig. 13). The axons of many nerve cells have a prominent myelin sheath which is highly refractile in the fresh condition and appears black in tissue fixed in osmium tetroxide (Bloom and Fawcett, 1975).

Dendrites (Fig. 14)

Dendrites are either direct extensions of the perikaryon or remote arborizations, as in the peripheral branches of a sensory ganglion cell in which case a length of axon is interposed between the perikaryon and the dendrite arborization. Their branching may be exceedingly profuse and intricate and provides most of the receptive surface of the neurone. Branches are thick when emerging from the cell body and taper gradually towards the ends. They may be divided into primary, secondary, tertiary and higher orders of branches of various shapes and sizes, and are distributed in diverse ways. The surface of many dendrites is covered with innumerable minute thorny spines or gemmules which serve as sites of synaptic contact for the reception of nerve impulses from other functionally related neurones (Barr, 1974). They possess Nissl bodies, mitochondria, neurofilaments, microtubules and endoplasmic reticulum. The latter three become progressively scanty towards the end of the dendrites (Fig. 15). Thus the dendrites play a crucial role in the ability of the neurone to integrate information received from its many inputs which may be excitatory or inhibitory (Bloom and Fawcett, 1975).

The Nerve Sheath (Figs. 16A, 16B)

The axons of many nerve cells have a prominent myelin sheath. It is not part of the neurone but rather a part of the ensheathing cell, the Schwann cell, and is a product of it (see Chapter on Regeneration). Under the light microscope nerve fibres are divided into myelinated and unmyelinated

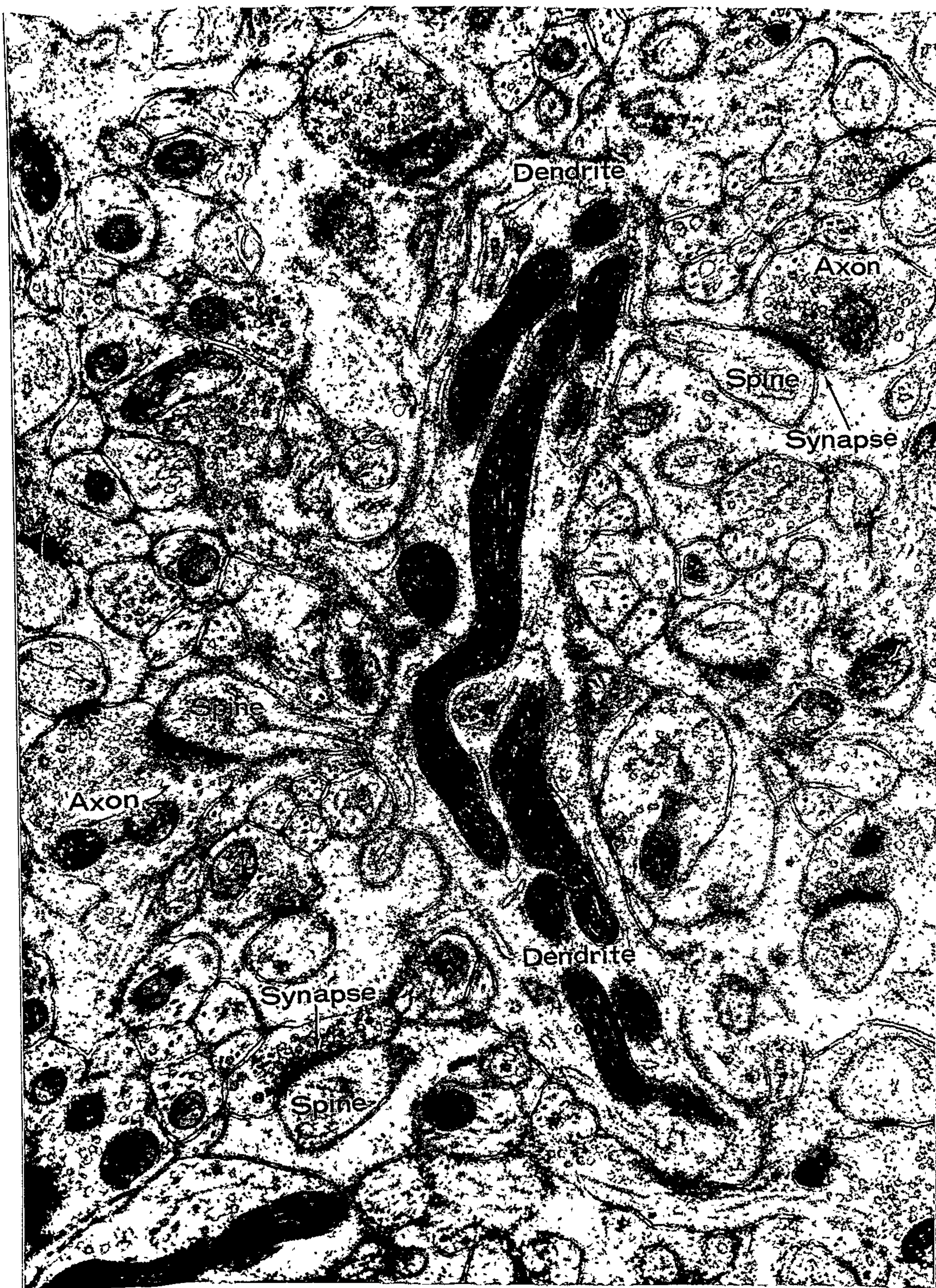


Figure 14. Electron micrograph of a dendrite showing conspicuous mitochondria, spines projecting laterally and axons forming synapses with dendrite. (From Bloom and Fawcett 1975)

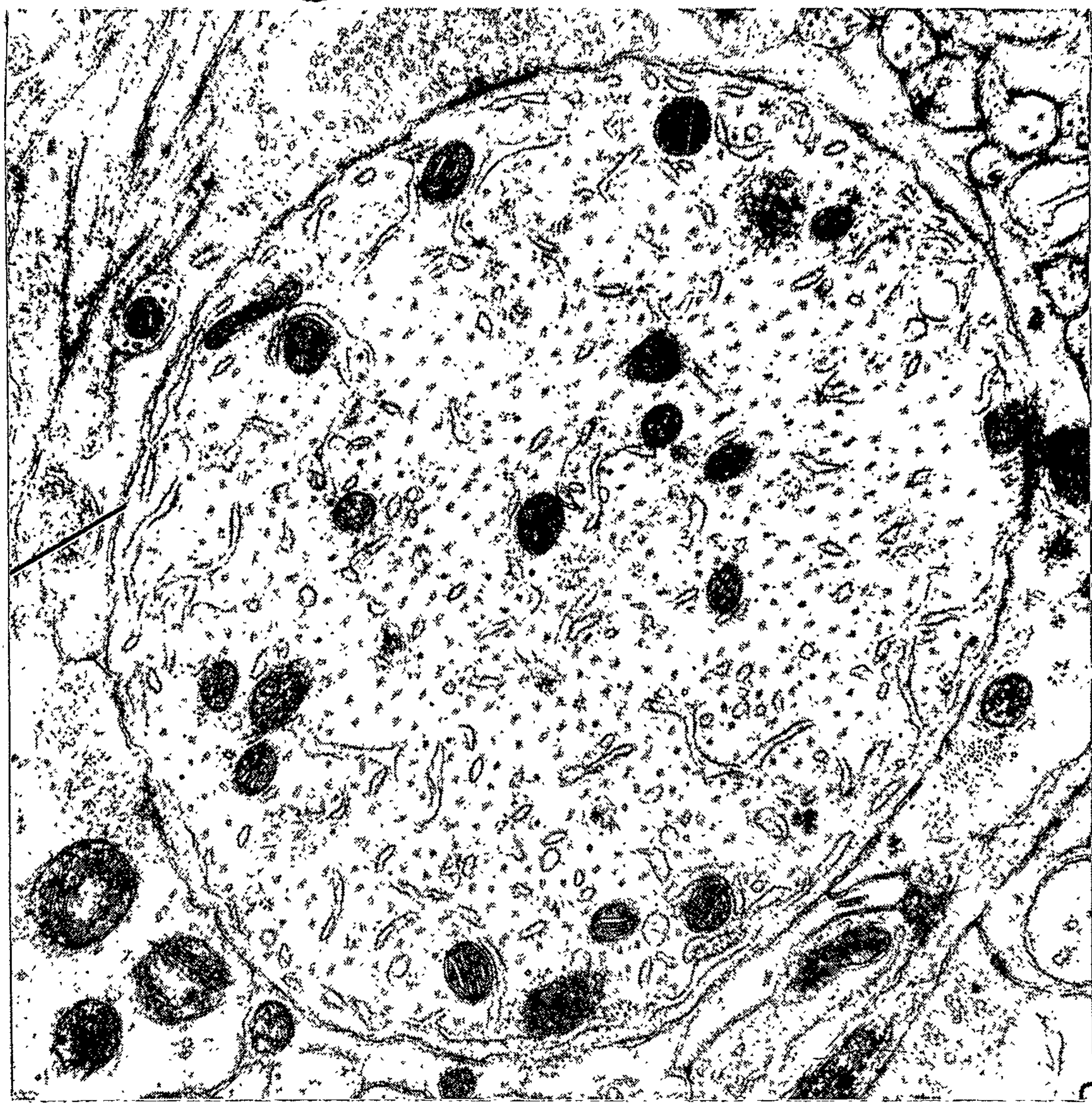


Figure 15. Cross-section of a primary dendrite showing mitochondria, tubular elements of endoplasmic reticulum and profiles of microtubules. (Bloom and Fawcett 1975)

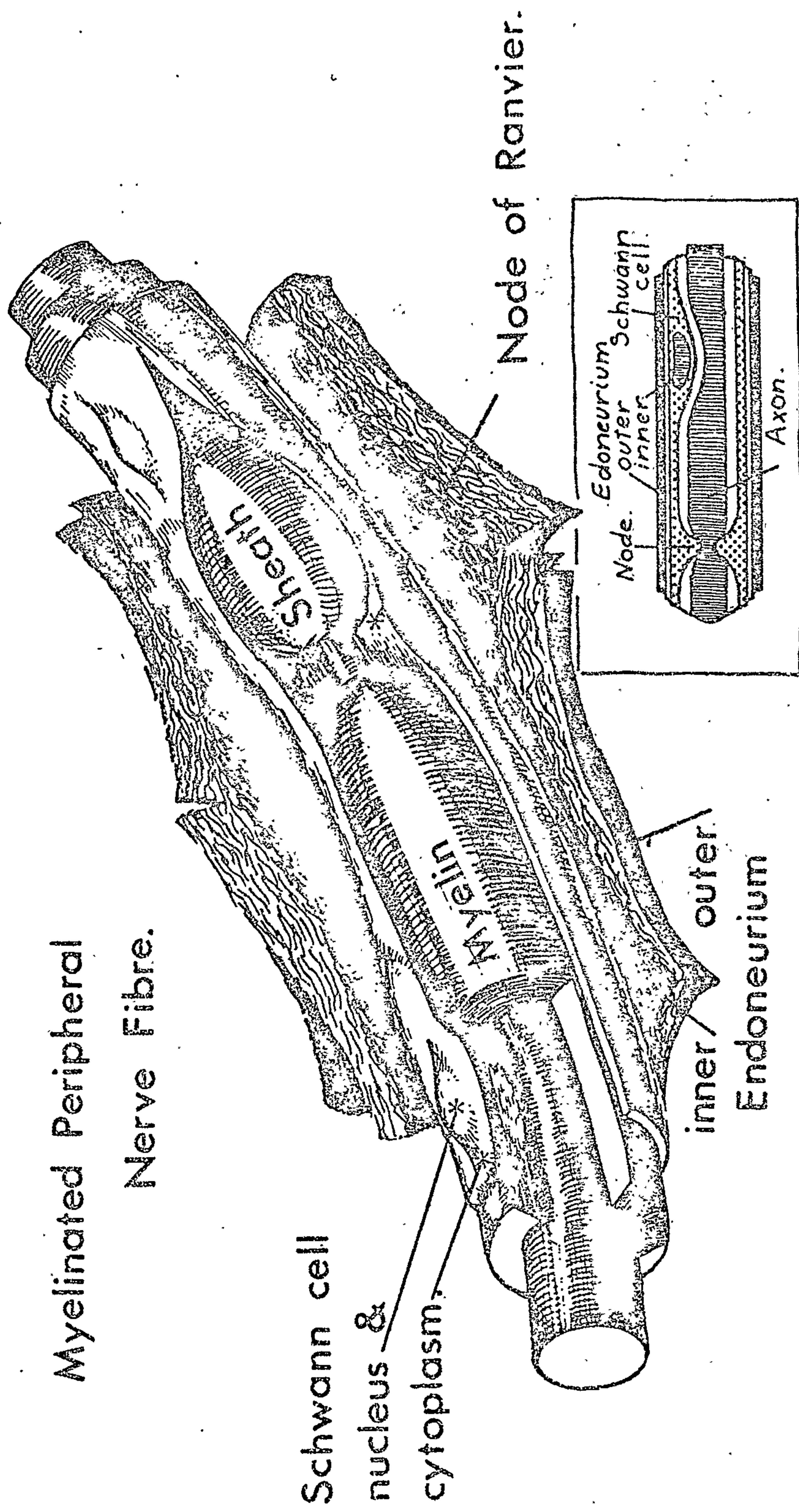


Figure 16 (A) Diagram of a nerve fibre showing prominent myelin sheath and other histological features referred to in text.
(From Nerve and Nerve Injuries, Sunderland, 1978)



Figure 16(B) Cross-section of a normal sensory nerve showing:

- AU - 'unmyelinated' fibres (but showing a very fine layer of myelin)
- Am - myelinated fibre
- M - myeline
- S - Schwann cell cytoplasm

(Electron micrograph from Satinsky, Pepe and Liu, 1964)

nerves according to the presence or absence of myelin, but under the electron microscope it has been shown that even the unmyelinated types have a very thin layer of myelin (Ham, 1974) so that the terms 'myelinated' and 'unmyelinated' are relative only (Fig. 16B).

Myelinated fibres (Figs. 16A, 16B)

Immediately surrounding the axon of myelinated nerve fibres is a multilayered sheath consisting of a Schwann cell-myelin complex internally and a connective tissue layer, the endoneurium, externally. Myelin is highly refractile, which enables identification of its presence under light microscopy. Its presence or absence exerts an important influence on the physiological properties of the neurone (Bloom and Fawcett, 1975). The sheath is interrupted at various points along the nerve fibre into segments (internodes) by nodes of Ranvier (described later in this section) and nearly all of those fibres belonging to groups A and B are said to be myelinated. The thickness of the myelin sheath tends to be directly proportional to the diameter and length of the axon and it is found that the greater the diameter of the nerve fibre the faster is the conduction of the nerve impulse (Young, 1942).

X-ray diffraction studies show that the myelin consists of alternating protein and lipid layers and the lipids have been identified chemically as cholesterol, phospholipids and cerebrosides. The myelin sheaths are laid down during the later part of foetal development and during the first year postnatally. The amount of myelin increases from birth to maturity. The present concept of the formation of the myelin sheath is that first the cytoplasm of the Schwann cell surrounds the axon. Then, there is an unfolding of the double layered Schwann cell membrane and a subsequent rotation of from a few to fifty turns of the membrane around the axon depending on the diameter and length of the axon (Fig. 17). The actual mechanism of the formation of the spiral is still unsettled. Some say the direction of the spiral is clockwise in some internodes and anti-clockwise in others (Bloom and Fawcett, 1975). As the rotation occurs the cytoplasm is squeezed out between the layers of cell membrane except for the

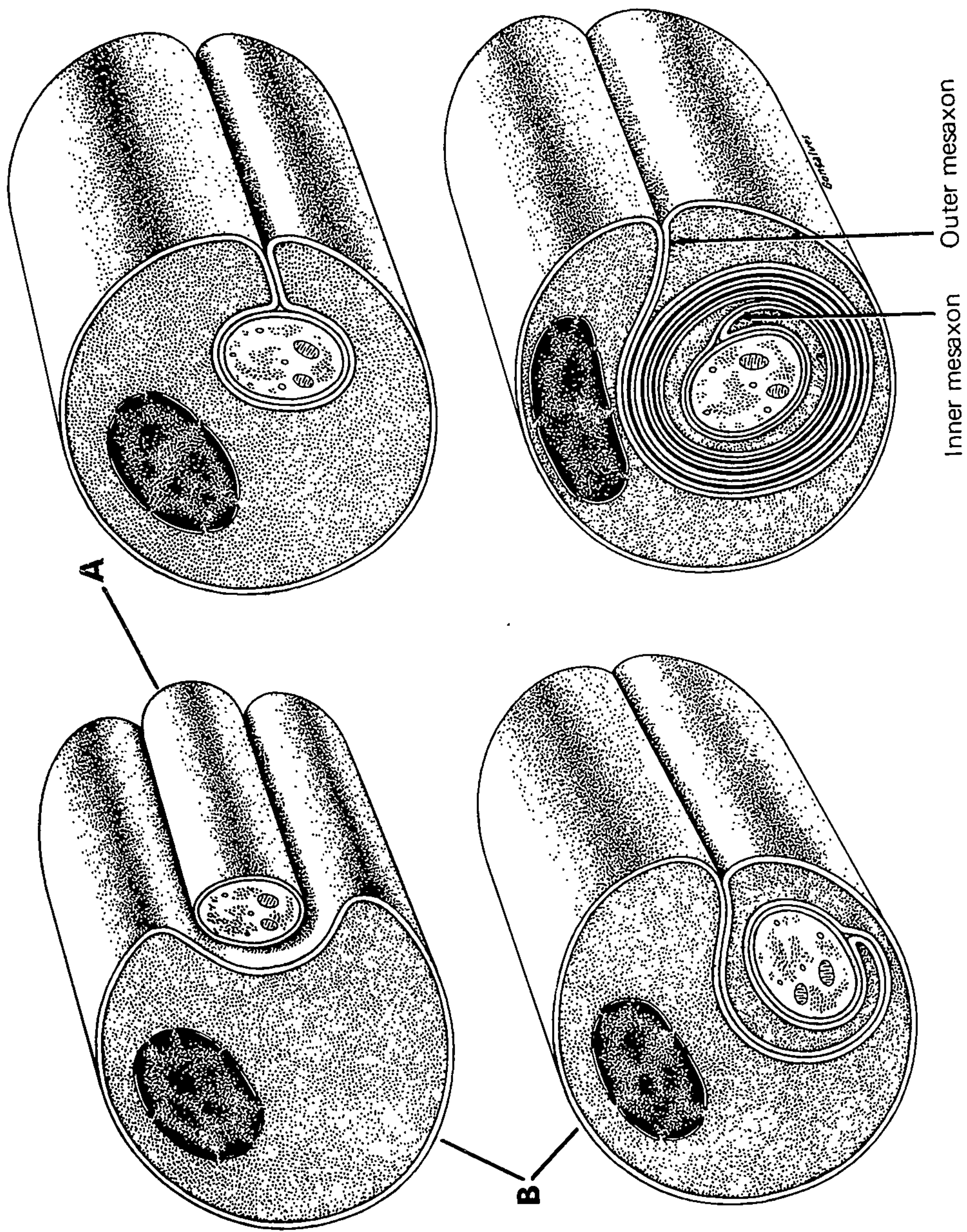


Figure 17. Diagrammatic representation of the process of myelination.
A - Axon B - Schwann cell (From Junquera et al)

surface cytoplasm which is abundant around the nucleus of the Schwann cell. The two inner protein layers fuse through a mesoaxon to form the major dense line 25 Å in thickness, indicated in Fig. 17. The less dense layer, about 100 Å wide, consists of a double thickness of the lipid layer of the cell membrane. The fused outer protein layers become exceedingly thin to form the intraperiod line in the middle of the lighter lipid layer (Barr, 1974). Under the electron microscope the compact myelin appears as a series of light and dark lines (Fig. 18). The myelin of each segment - between the nodes of Ranvier - is interrupted by oblique funnel-shaped clefts called incisures of Schmidt-Lantermann (Fig. 20). The functional significance of these is unknown, but several are seen in each Schwann segment. Glees (1943), from his investigation, states that these incisures open when a nerve trunk is stretched. Their behaviour under these conditions suggests that they function to prevent abnormal distortion and fracturing of the myelin segments. The regions between the separated lamellae consist of Schwann cell cytoplasm continuous with that forming the outer sleeve of the fibre on the one hand and with the thin, inconstant layer of cytoplasm next to the axon on the other (Bloom and Fawcett, 1975).

Unmyelinated fibres

Unmyelinated fibres are contained within a chain of Schwann cells external to which is the encircling connective tissue the endoneurium. The boundaries between adjacent Schwann cells are indistinct. These fibres are of smaller diameter than the myelinated types and up to a dozen unmyelinated fibres may occupy deep recesses in the surface of the same Schwann cell (Bloom and Fawcett, 1975) (see Fig. 19). This is in contrast to myelinated nerves where there is only one fibre to a Schwann cell (Ham, 1974). Unmyelinated axons and dendrites of large calibre are usually distinguished by the presence of a great number of neurofilaments in the axon (Bloom and Fawcett, 1975).

Schwann Cell (Sheath of Schwann, Neurilemma Sheath) (Fig. 16)

Schwann cells, like the neurones, are of ectodermal origin and derived

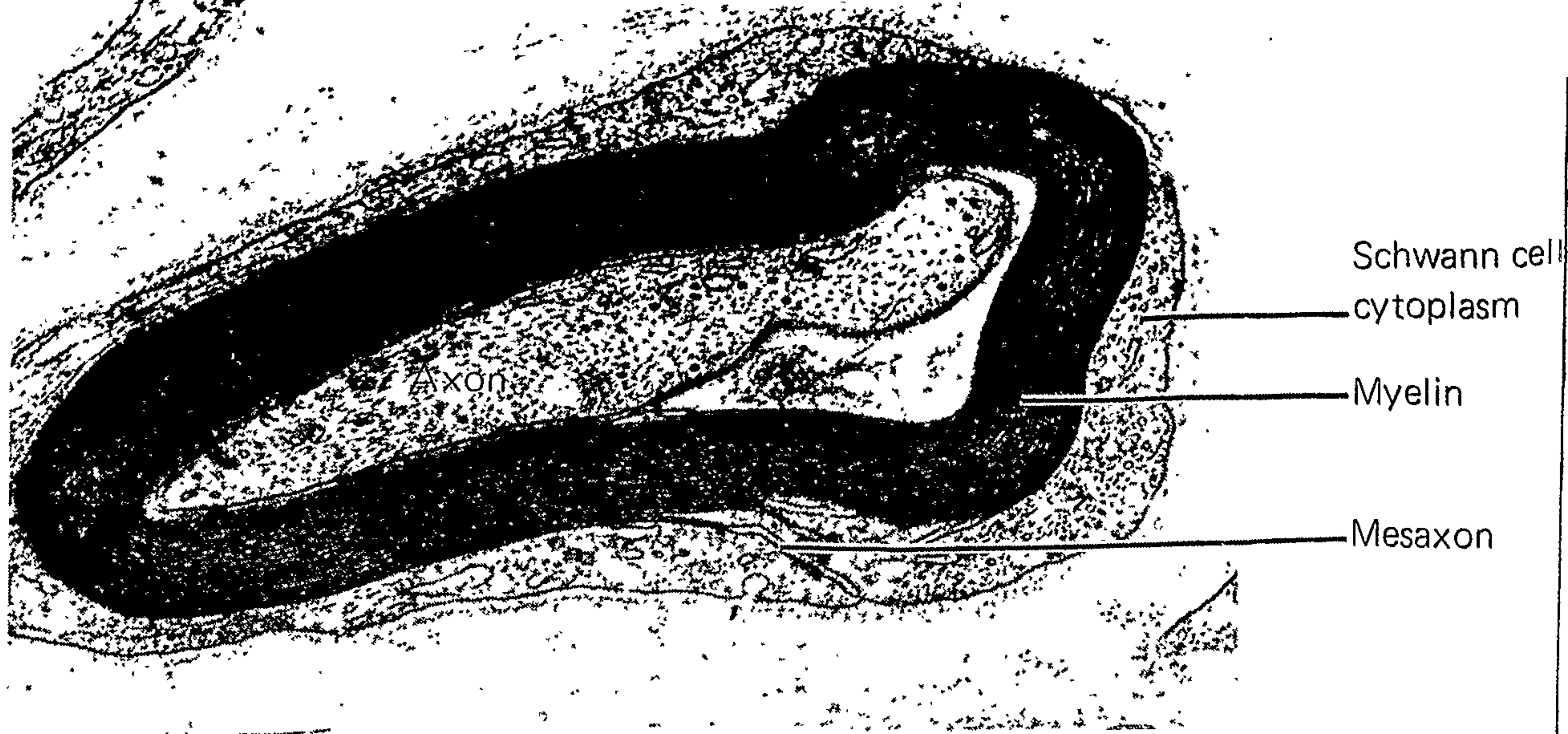


Figure 18. Electron micrograph (X20,000; X80,000) showing laminated myelination. (From Junquera et al)

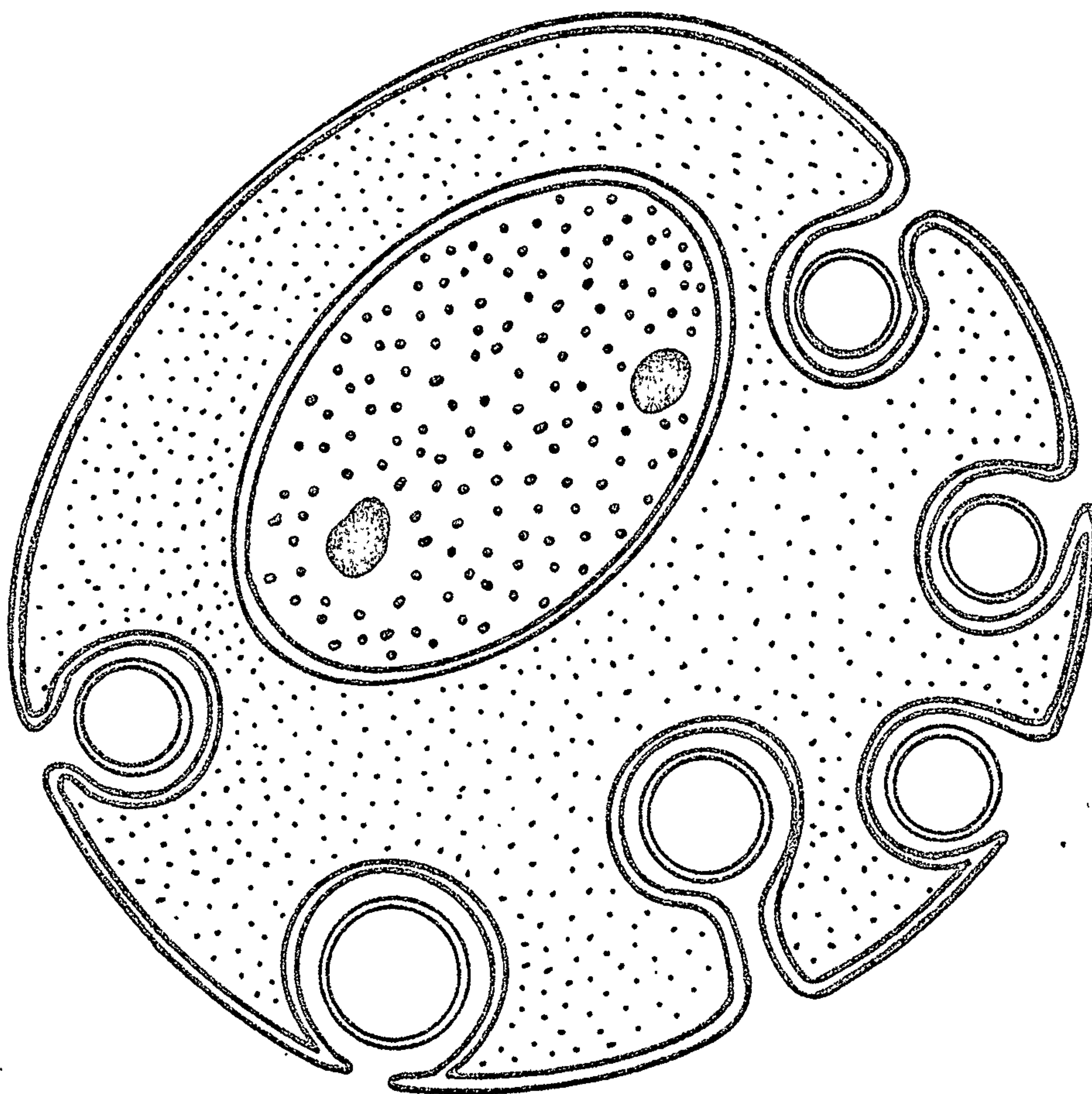


Figure 19. Diagram to show envelopment of numerous unmyelinated axons by one Schwann cell.
(From Junquera et al)

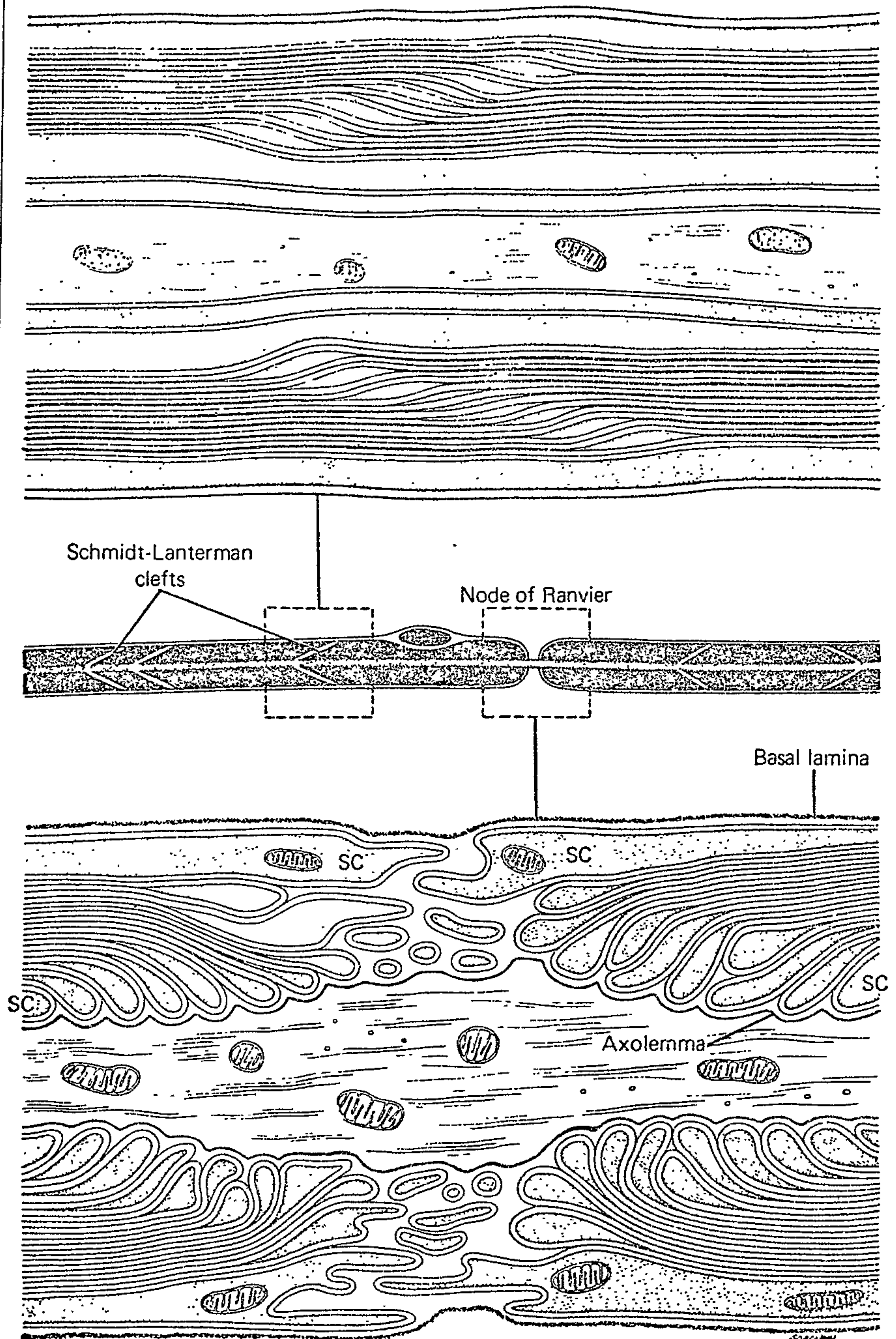


Figure 20. Diagram showing histological detail of Schmidt-Lanterman clefts and a Node of Ranvier. (After Junquera et al)

SC - Schwann cell cytoplasm

from the neural crest. During development of the neural mechanism, the axons grow out in company with a peripheral column of Schwann cells into which they invaginate and become enveloped (Arey, 1974). All peripheral axons are enclosed by a sheath of Schwann cells (the neurilemma sheath), a homogenous membrane, which invests the axon almost from its beginning to near its peripheral termination. It is the toughest and most rigid part of the nerve fibre. In the adult the nuclei of Schwann cells are flattened and in the cytoplasm the organelles recognised are Golgi apparatus, mitochondria and endoplasmic reticulum. Because the myelin and the Schwann sheaths appear distinct on the light microscope they were considered as separate structures, but the electron microscope shows that the myelin is actually part of the Schwann cell (Bloom and Fawcett, 1975). Like the myelin sheath, the sheath of Schwann is interrupted at regular intervals by nodes of Ranvier which are points of discontinuity between successive Schwann cells along the length of the axon. In myelinated axons each internodal segment of the sheath between two consecutive nodes of Ranvier is therefore composed of a Schwann cell with its myelin lamellae. Schwann cells are indispensable for the life and function of peripheral nerve fibres and besides being protective and myelin forming, are said to have a nutritive role (Arey, 1974). These cells are also proliferative and therefore very important in nerve regeneration. These features are discussed in Chapters 7 and 8.

Nodes of Ranvier (Figs. 16 and 20).

These are associated with myelinated fibres and at these points along a nerve fibre there is no myelin. The sheath of Schwann dips down towards the fibre and therefore the axon is partially uncovered (Robertson, 1962). Nodes of Ranvier are present in the C.N.S., but there is no sheath of Schwann cells here and the myelin is produced by the oligodendrocytes. The nodes are involved with the transmission of nerve impulses at great speed. This is considerably reduced in unmyelinated fibres with no nodes of Ranvier (Ham, 1974).

The internodal segments are shorter in the terminal portion of the fibre.

The longer and thicker the fibre the longer are the internodal segments. Internodal lengths may vary in fibres of the same diameter and may be up to one millimetre. Similarly, successive internodes in the same fibre may have different lengths (Vizoso and Young 1948). With growth and development the number of internodal segments remains constant but the length increases (Siminoff, 1965). In contradistinction to these observations, remyelination of regenerated axons in the adult produces internodes that are short and about the same length for all fibres regardless of their calibre (Vizoso and Young, 1948). If an axon gives off collateral branches, this takes place at the nodes of Ranvier (Bloom and Fawcett, 1975).

Synapse (Figs. 21, 22, 23)

The nervous system is a complex chain of neurones arranged to permit transmission of impulses from one neurone to another in one direction only. This is because of the chemical mediation at these sites. The site of transmission is the synapse, a term introduced by Sherrington in 1897, meaning a conjunction or connection. The synapse may be axodendritic, axosomatic or axoaxonic (Brodal, 1969) (Figs. 21 and 22). Recently the presence of dendrodendritic synapses and synapses between adjacent perikarya, has been indicated (Bloom and Fawcett, 1975). The number of synapses in a neurone varies considerably and the terminal branches of the axon are referred to as synaptic end bulbs or boutons terminaux. Axodendritic synapses are usually excitatory, while axosomatic and the less frequent axoaxonic synapses are likely to be inhibitory (Barr, 1974). The end bulb is the termination of the axon and under the electron microscope is seen to be surrounded by the axolemma. The part in close proximity to the post-synaptic neurone is called the pre-synaptic membrane, whilst the other is referred to as the post-synaptic membrane. The end bulb is seen to be rich in mitochondria, indicating a high rate of oxidative phosphorylation (Brodal, 1969) with bundles of neurofilaments present in some (Barr, 1974). Unique constituents at the pre-synaptic endings are numerous vesicles which vary from 200 Å to 650

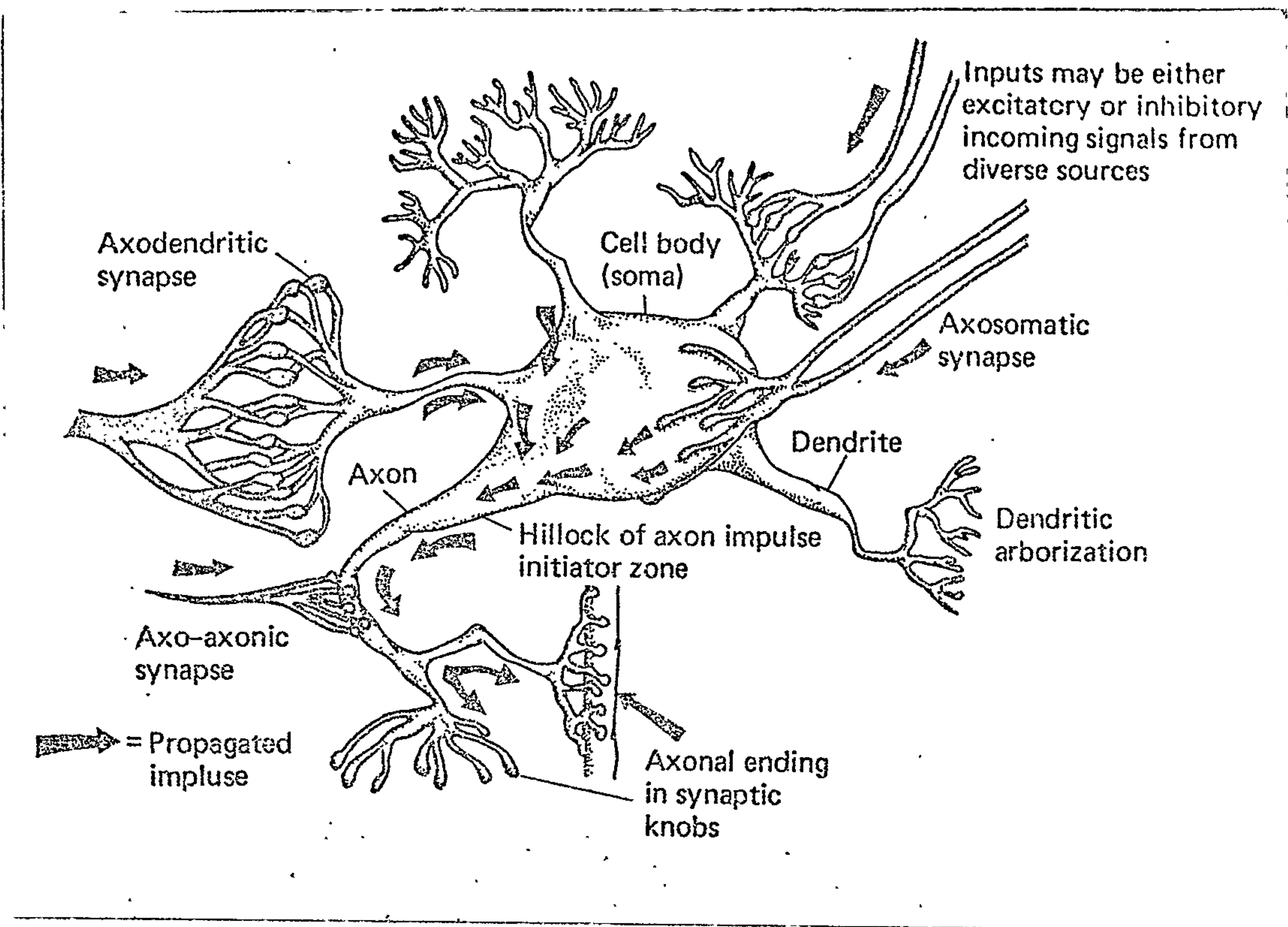


Figure 21. Variations of synaptic connections diagrammatically represented.
(From Junquera et al)

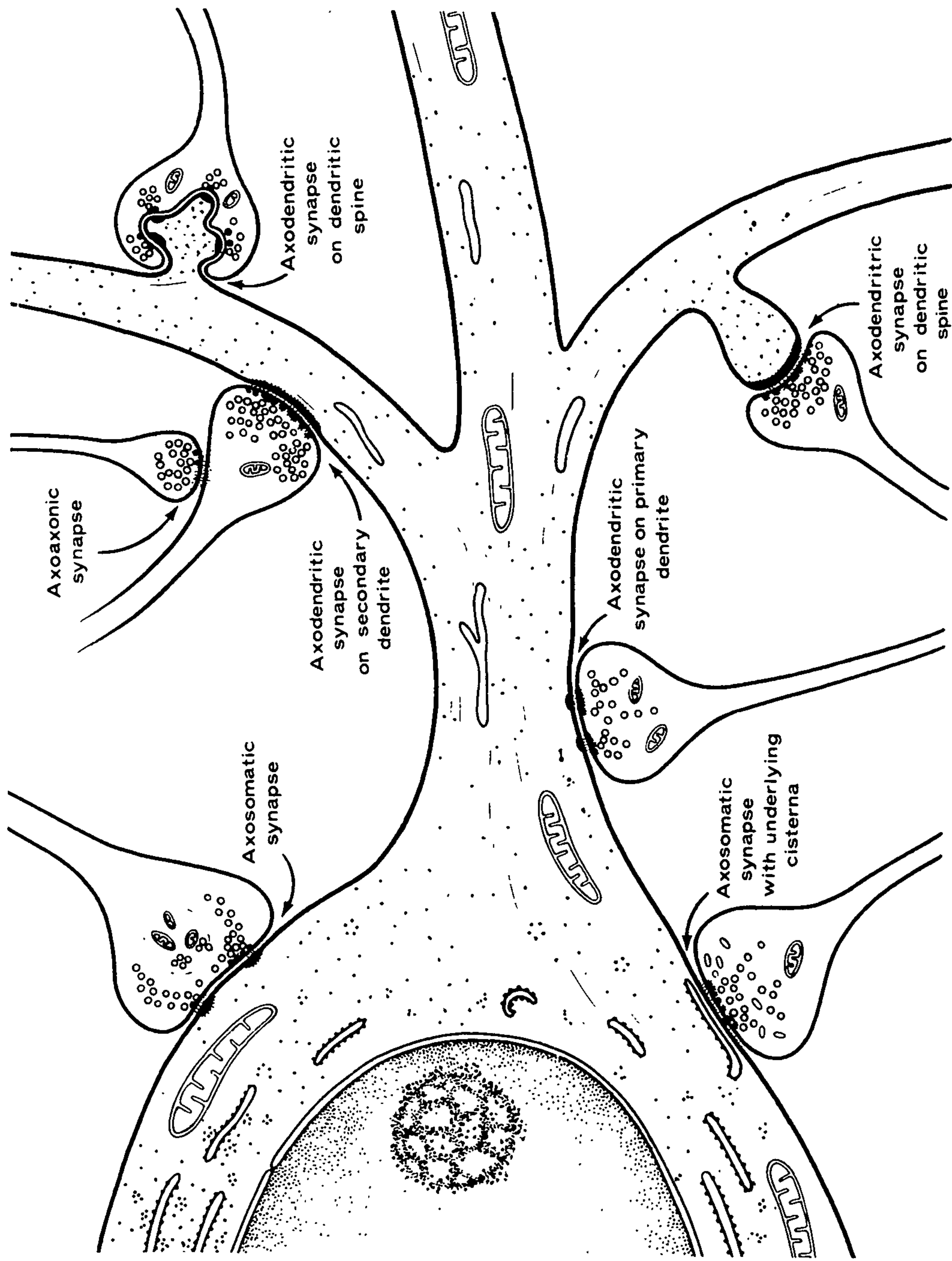


Figure 22. Enlarged diagrammatic detail of the various connections shown in Figure 21. Note positions of synaptic clefts and vesicles as seen in electron micrograph Figure 23. (From Bloom and Fawcett 1975)

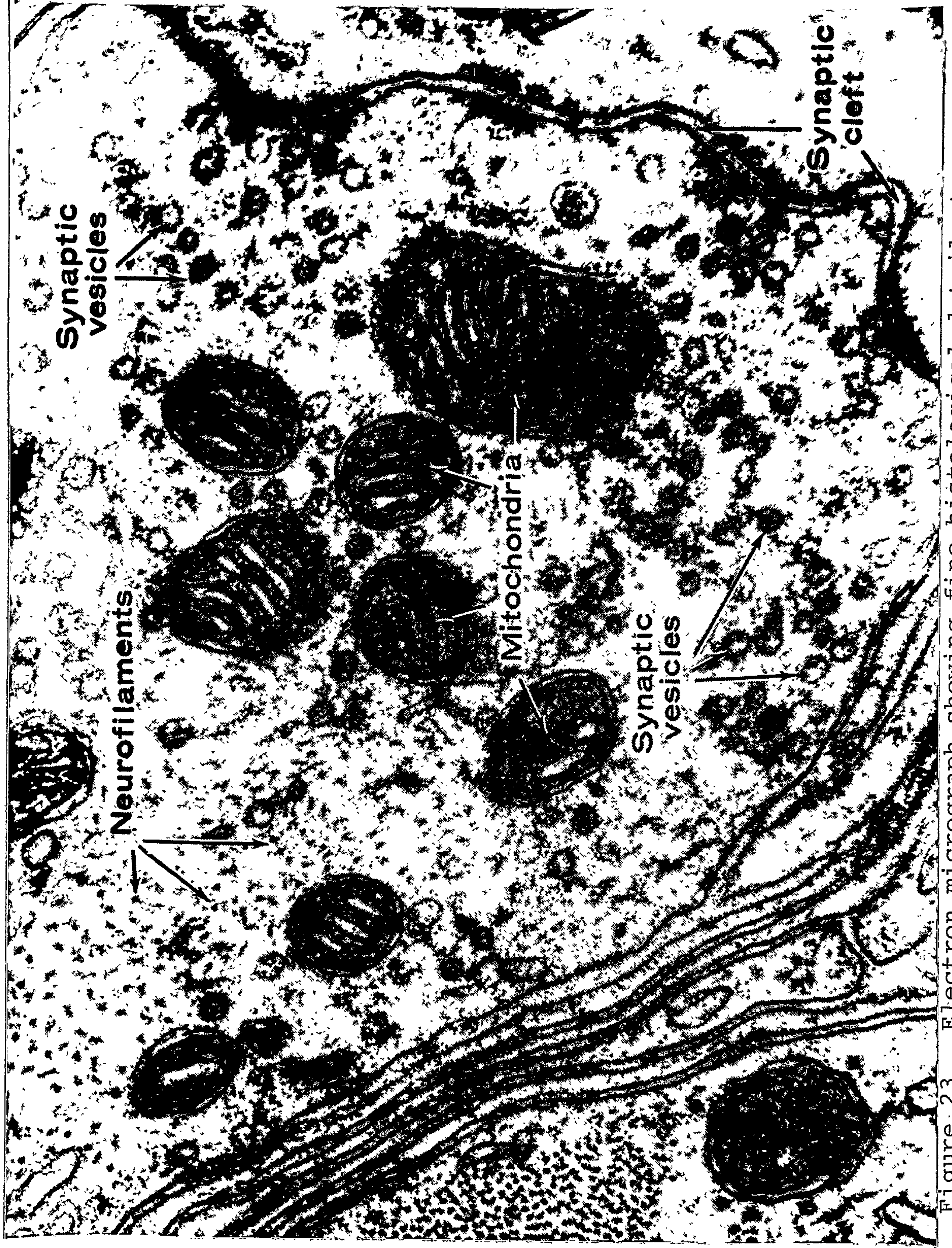


Figure 23. Electron micrograph showing fine histological detail at a synapse.
(From Bloom and Fawcett 1975)

Å in diameter (Ham, 1974). These are thought to contain the chemical mediator for the transmission of impulses across the synapse. At the synapse the pre- and post-synaptic membranes show specializations in the form of electron dense condensations of material (Brodal, 1969). The membranes are closely apposed and separated by a narrow synaptic cleft of about 200 Å (Fig. 23).

(iii) FUNICULUS

Definition

A funiculus is a bundle of nerve fibres invested by a strong sheath called the perineurium (Fig. 24). It may contain all three types of nerve fibre namely sensory, motor and sympathetic, but one or two of the types may be absent (Sunderland, 1968).

Funicular Intercommunications

It is uncommon for human peripheral nerves to be composed of a single funiculus. The human peripheral nerves have several funiculi which, by repeatedly uniting and dividing, engage in plexus formation (Fig. 25) along the full length of the nerve (Sunderland et al., 1959). The funicular pattern alters so rapidly that transverse sections of the nerve taken more than a few millimetres apart fail to represent precisely the same pattern (Sunderland, 1968). Plexus formations do not invariably lead to a dispersal of the fibres, for in some cases the process is actually reversed so that fibres which are widely scattered over several funiculi at distal levels are gathered into one or two bundles further proximally. Funicular intercommunications can be reduced to three fundamental types depending on their fibre composition. (1) Bundles whose constituent fibres are derived solely from one branch. Fibres representing individual branches first pursue an independent course along the nerve for various distances above the site of branching, either as a single funiculus or as a compact bundle group in which the funiculi engage in plexus formations. (2) The second type involves members of one bundle uniting with the immediately adjacent bundles. Here minor changes occur over short distances. (3) In the third type intercommunication results in bundles being composed from several

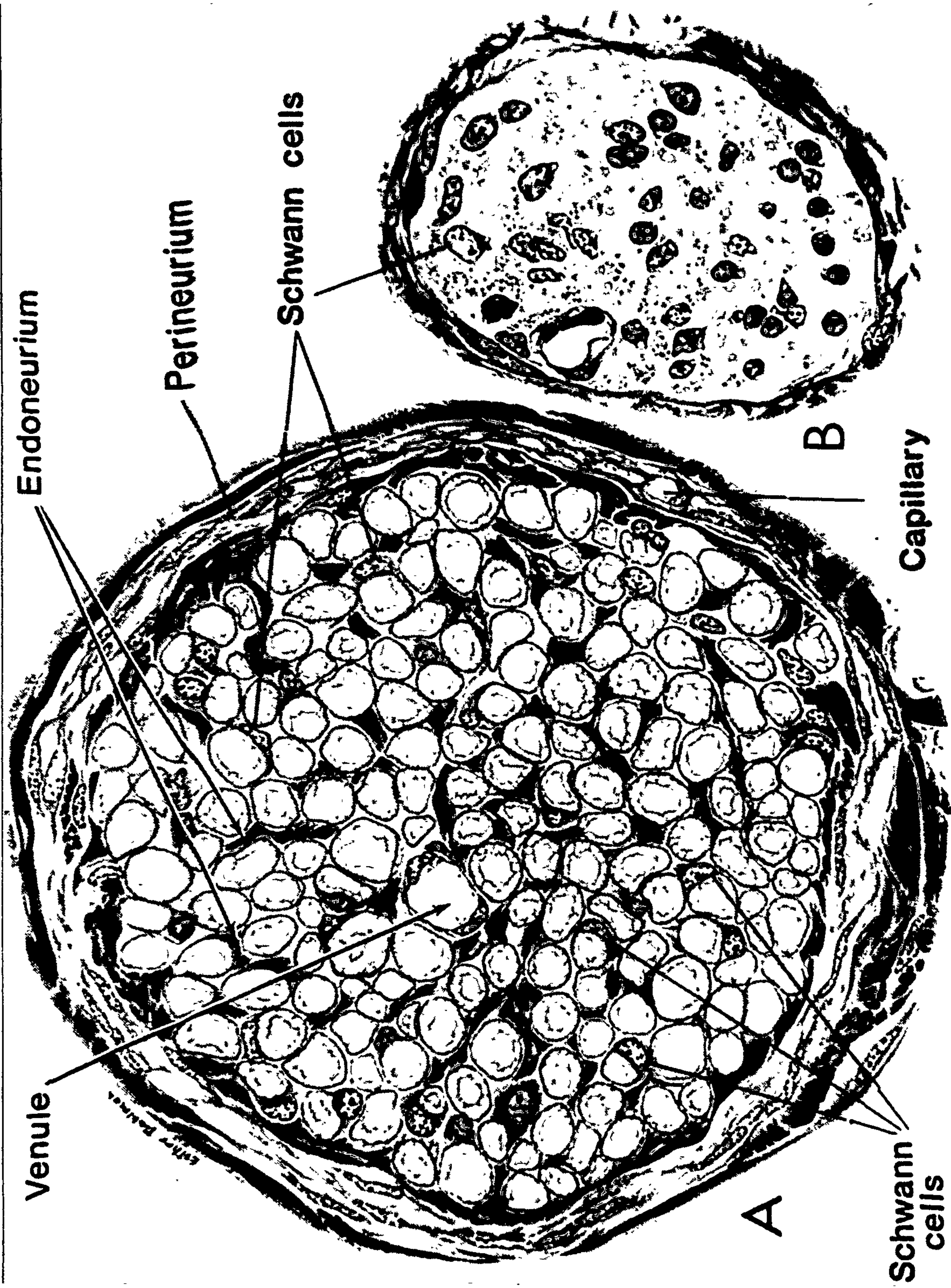


Figure 24. Constituent parts of a Funiculus. (From Bloom and Fawcett, 1975)

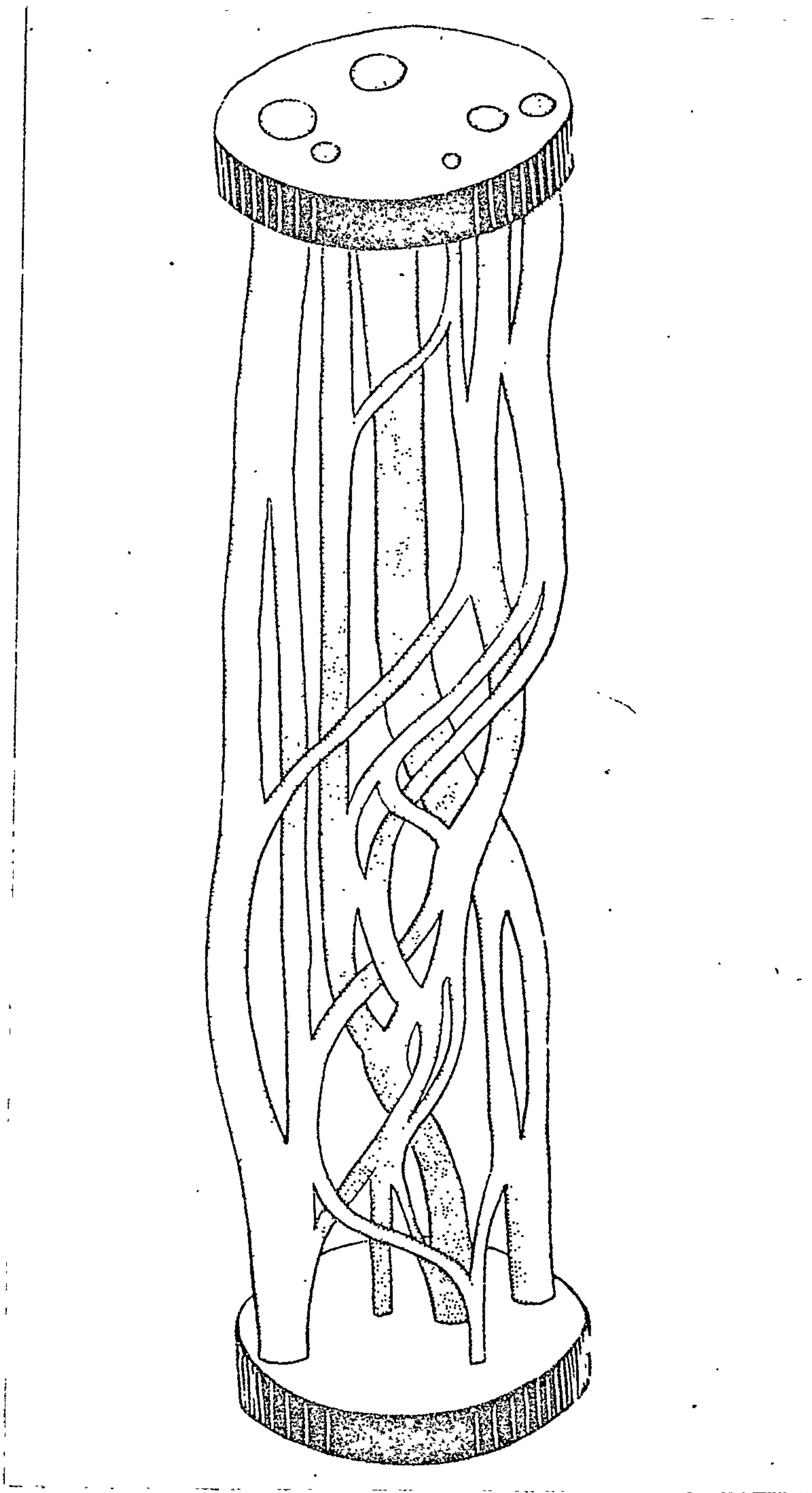


Figure 25. Funicular plexus formations as found in a 3 cm segment of a peripheral mixed nerve.

different branches in varying combinations and proportions. The longer the course of the fibres of a branch within a nerve trunk the greater is the scattering and intermingling of its fibres at proximal levels. Thus, the source of the fibres contained in a funiculus depends on the level at which an analysis is made, e.g., at the axillary outlet it is usual for the majority of the funiculi to contain representative fibres for most if not all of the peripheral branches (Sunderland 1968). Further down, regrouping of the fibres results in muscular and cutaneous elements occupying different funiculi. Still further down groups of funiculi contain nerve fibres destined solely for specific cutaneous and muscle branches.

The Consequences of Intra-funicular Damage (Fig. 26)

From the foregoing it can be seen that the consequences of intra-funicular damage in which the endoneurial tubes are ruptured, may differ in each clinical situation. When the funiculus contains fibres from one or two functionally related sources regenerating fibres are confined within the funiculus and all routes lead to the same or functionally related tissue. In funiculi composed of intermingled fibres from several different and functionally unrelated sources the entry of axons into foreign tubes will distort the fibre pattern, and this will seriously impair the functional efficiency of regeneration, despite the fact that the injured funiculi may be in continuity. Thus at proximal levels the fibres from the most distal structures are intermingled and widely distributed over the funiculi whereas the fibres from branches of high origin are more discreetly localized. Therefore, high lesions are more serious for distally innervated structures than they are for the proximally innervated structures. Thus the level of the lesion becomes a factor influencing the extent and quality of the recovery (Sunderland and Ray, 1948).

The Funicular Composition of the Inferior Dental Nerve

(a) Historical Information

Studies by Rood (1978) of the transverse section of the human I.D.N. from within the pterygomandibular space of a fresh cadaver gave the number of fibres in a dentate mandible to be 15,513. The diameter of these fibres ranged from 2 μ to 15 μ and the distribution graph indicated two peaks, one

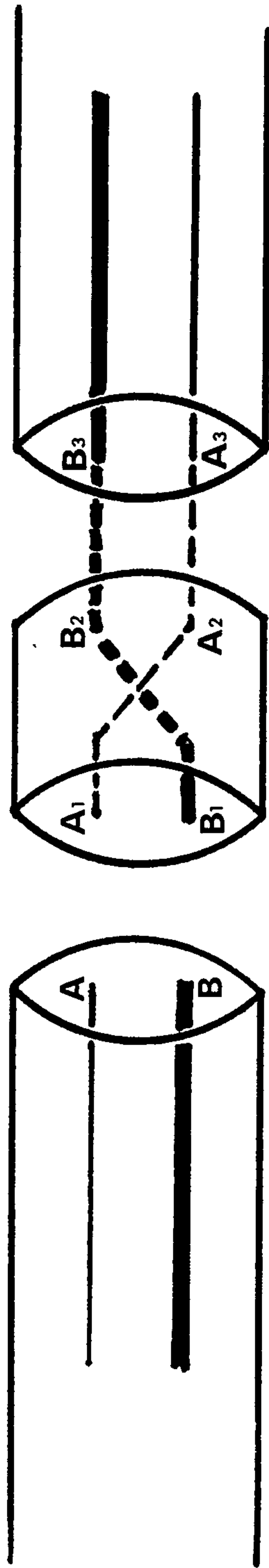


Figure 26. Diagram to illustrate the possible alterations of funicular pathways (A,B) at the time of regeneration following minor loss of tissue. E.g. a 2mm loss of tissue is sufficient to alter the juxtapositioning of funiculi and therefore complicate or affect the quality of regeneration.

at $2\ \mu - 4\ \mu$ and the other at $8\ \mu - 9\ \mu$, indicating a bimodal distribution of the fibre size. Murphy and Grundy (1969) counted 9506 fibres in the human IDN and the distribution had a mono-modal pattern. However, their study was on an edentulous mandible and it was noticed that the fibre distribution and pattern in these two studies were different. The majority of fibres in the larger count of Rood (1978) consisted of fibres of smaller calibre and according to De Lange and his co-workers (1969) and Frommer (1972), it is these fine fibres that are principally involved in the innervation of the dental pulps. In the edentulous mandible these fibres would have degenerated thus causing the reduction in the total number of fibres and the change in pattern.

Studies on the myelinated fibres of the I.D.N. of a young sheep by Murphy and Thompson (1966) showed a progressive increase of fibres commencing from the mandibular foramen to the mental foramen. However, the mean diameter of the fibres decreased but this was accompanied by an overall increase in the number of funiculi indicating a progressive splitting of the funiculi into smaller units.

(b) Experimental Investigation

(i) Source of material

In my own study of the funicular pattern of the I.D.N. the specimens were all from edentulous mandibles. The first of these was from a cadaver which had been preserved for some period of time. The second from a mandible resected due to carcinoma of the floor of the mouth. The third was from an autopsy specimen, death having occurred only a few hours previously. Approximately 15 cm of nerve was removed in each case using a conventional straight dental hand piece, a bur, chisels and osteotomes to remove bone commencing from the mental foramen and proceeding distally to the mandibular foramen.

(ii) Processing

All three nerves were fixed in 10% buffered formal saline for 24 hours. Lengths of nerves taken at various levels were embedded in

paraffin and transverse sections cut at 5 μ . These were stained with Haematoxylin and Eosin and by the Kluver-Barrera (Luxol fast blue) methods for myelinated fibres. Two staining techniques were used, the former for general tissue structure and the latter for localization of myelin sheaths. In addition the specimen from the autopsy was prepared and stained by the Gutman and Sanders(1943) method for myelin and transverse sections cut at 8 μ .

(iii) Histological findings (Figs. 27 A and 27 B)

Tissue sections were taken at three levels (Fig. 27 A) and the funicular pattern photographed by light microscopy. Careful examination of the tissue sections (Fig. 27 B (a), (b), (c)) showed that it was technically impossible to accurately measure the diameter and count the number of individual fibres present in each funiculus. Such a study would require fresh well-preserved material and would constitute a project too extensive to be included in this thesis. The number of bundles of fibres at each level was counted and these are shown in figure 27 B (a), (b) (c).

In figure 27 B (a) there are 5 easily recognizable bundles whilst in 27 B (b) there are 7 and in 27 B (c) approximately 21 bundles of fibres are discernible.

It can be noted that the size of the bundles varies. Although there are more bundles at the more distal levels 27 B (b) and (c), some of these bundles appear larger than at level 27 B (a) whilst others are smaller.

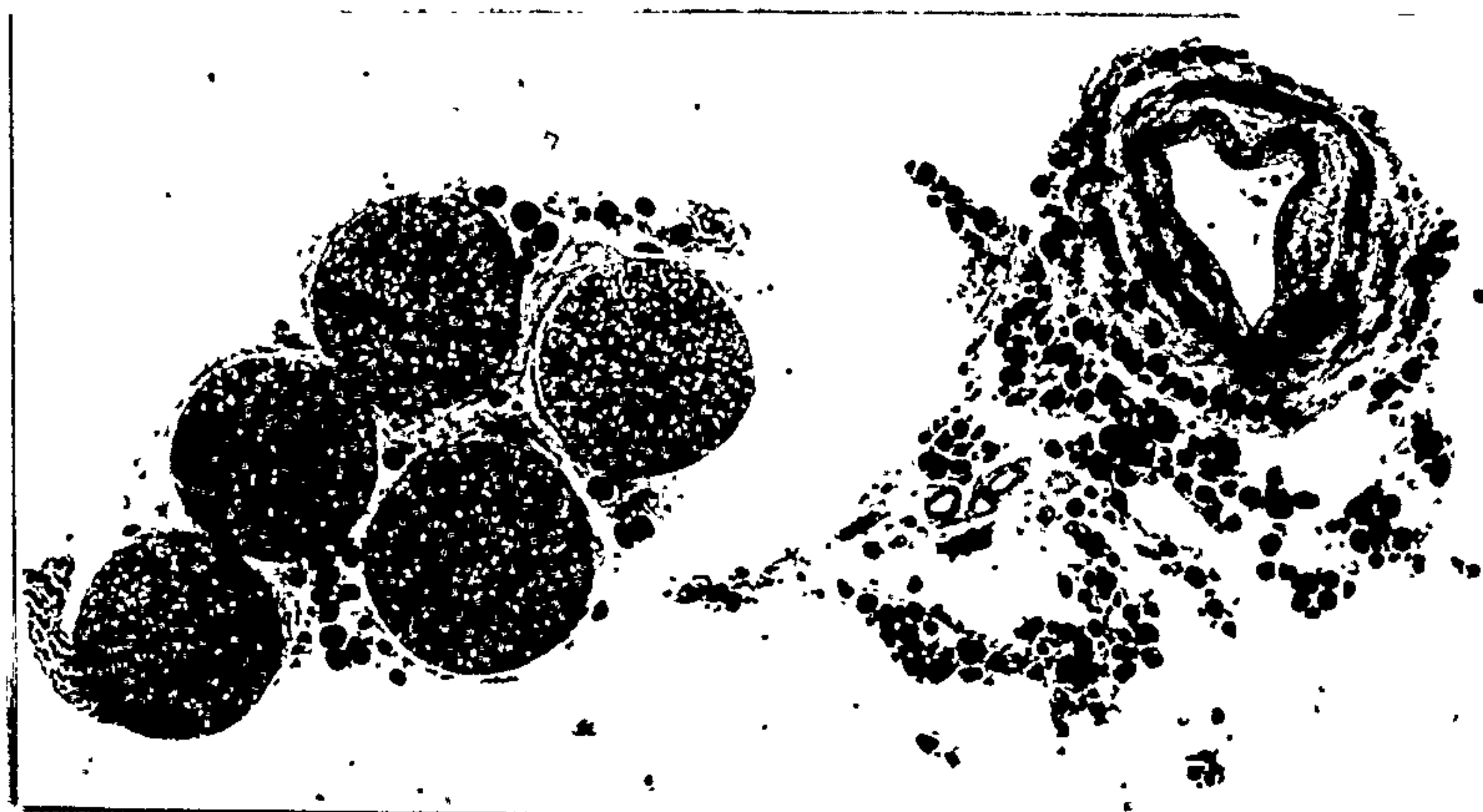
(iv) Conclusions

- (1) There was considerable variation in the number of bundles of funiculi at different levels in the nerve.
- (2) There was an overall increase in the number of bundles observed in sections taken more distally in the nerve. This is the result of the splitting of the funiculi into smaller units. In addition, there may be an increase in the total number of individual fibres.

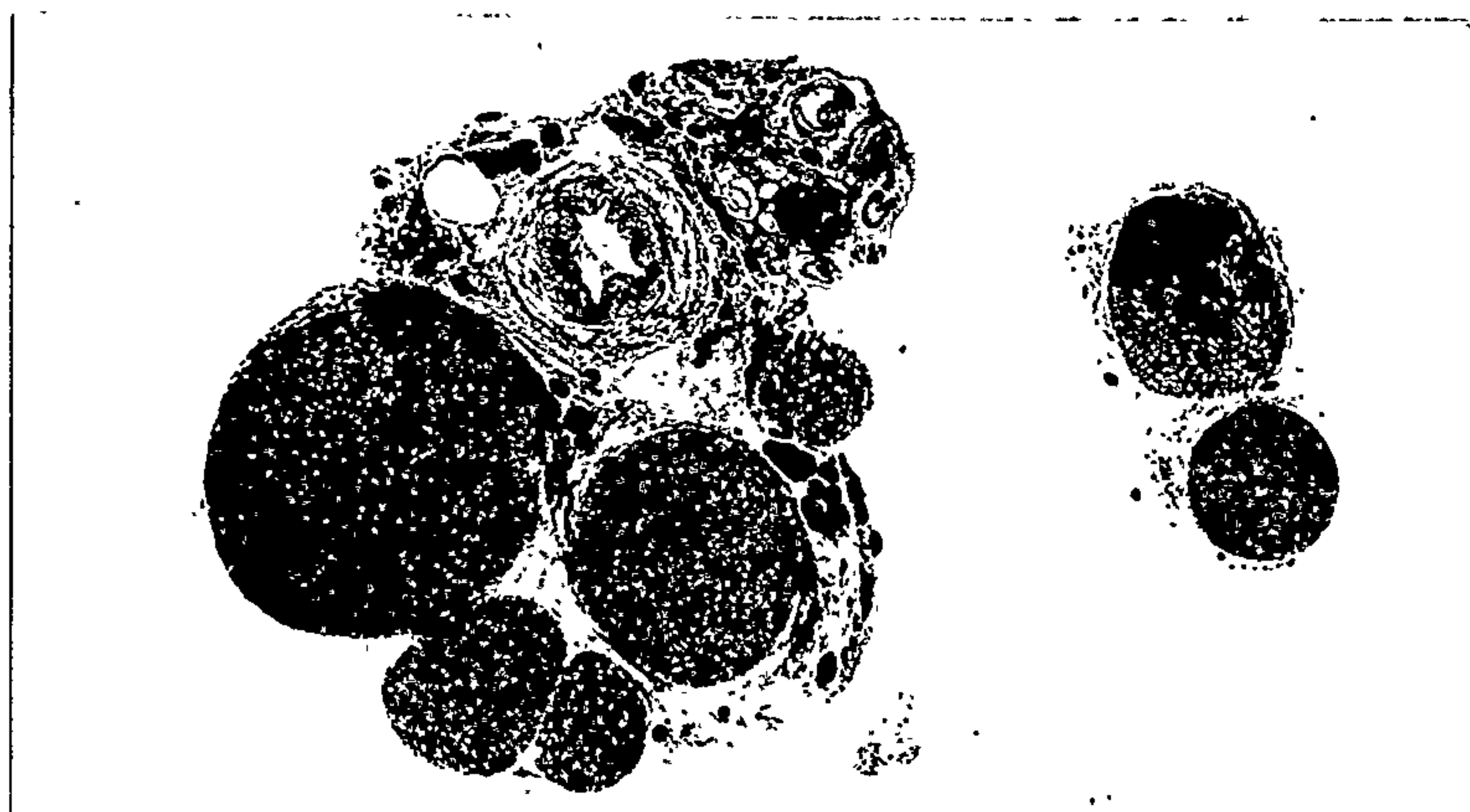


Figure 27A. Mandible illustrating levels of sectioning of inferior dental nerve.

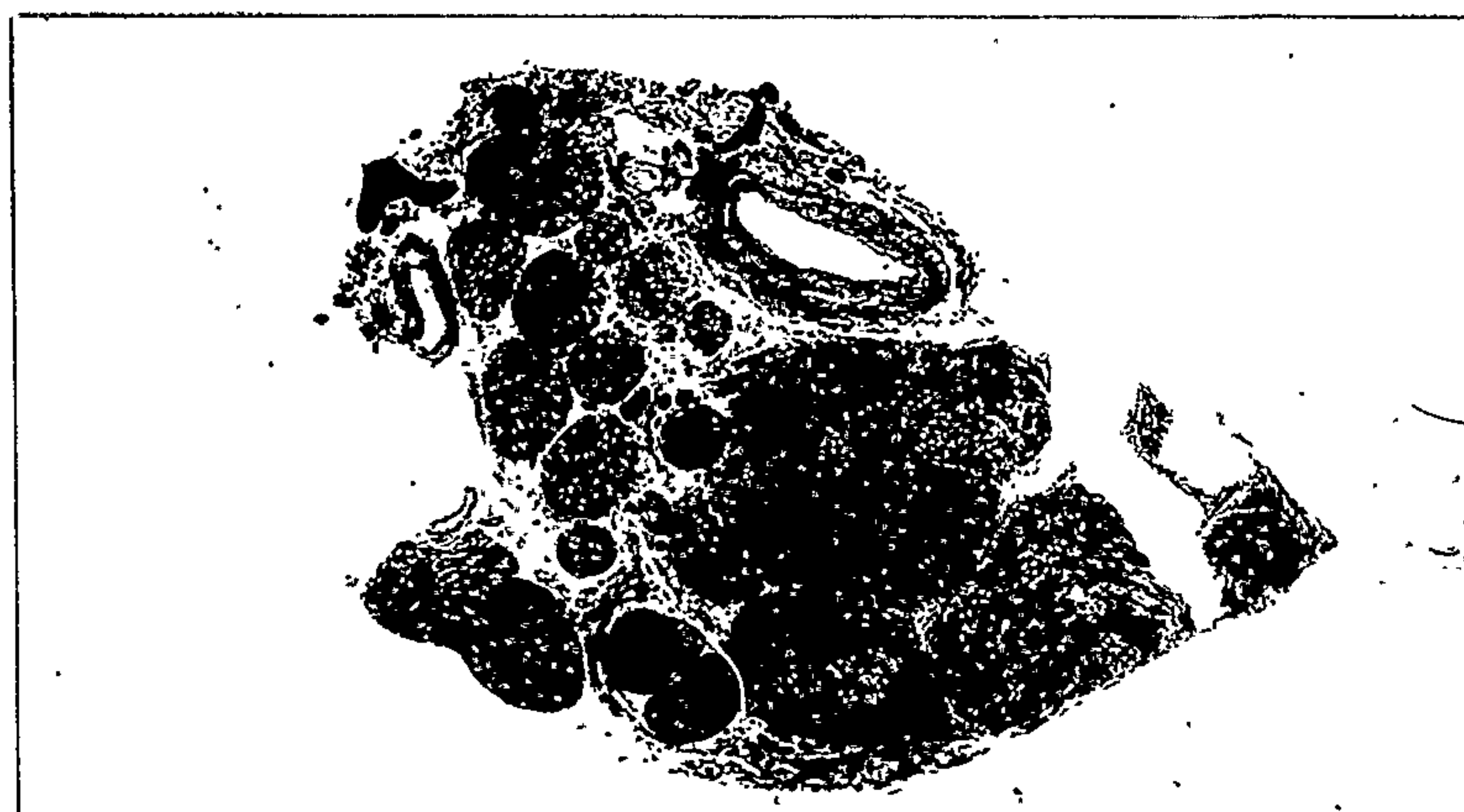
Figure 27B. The funicular pattern of the inferior dental nerve.



(a) At mandibular foramen.



(b) At the molar area.



(c) At the mental foramen.

Stain used: Gutmann & Sanders method for myelin (1943)
Light microscopy X21.875.

- (3) The presence of larger bundles distally may indicate a recombining of fibres or funiculi prior to their splitting into smaller units as the nerve moves peripherally.

The Consequences of Intra-funicular Damage to the I.D.N.

The consequences of intra-funicular damage to the I.D.N. is similar to that described for other nerves above (Chap.4 (iii)).

I.D.N. damage associated with mandibular injuries may range from 1st to 5th degree involvement, i.e., from a simple rapidly reversible conduction block at one end of the scale to severance by a bony spike or rupture from violent traction at the other end. In a nerve trunk the fibres on the outside have the largest diameter, travel the furthest and are affected first. Those on the inside are affected last. This has been demonstrated in the case of the I.D.N. by the inferior dental nerve block which affects the lips first and full analgesia of the lip and premolars is obtained whereas the third molar remains unaffected for a longer period. Roberts and Sowray (1970) are of the opinion that the analgesic has not reached the innermost fibres of the I.D.N. Likewise, I believe that the anaesthesia/paraesthesia of the lip/chin area produced in this study I have just completed may be due to this very reason, i.e., it is the outermost fibres of the I.D.N. that are being more often subjected to trauma in fractures and surgery of the mandible, thus producing an anaesthetic/paraesthetic state of the lip/chin area. The I.D.N. is a peripheral nerve and in its course to innervate the teeth and lip/chin area is mostly protected in a bony canal. Therefore, it is uncommon for the I.D.N. to suffer serious injury. Frequently the injury is one of first or second degree, and in a closed fracture a lesion of continuity commonly occurs and spontaneous recovery results. Further, as it is purely a sensory nerve the tendency for the regenerating fibres to enter foreign tubes is non-existent and therefore there is less distortion of the fibre pattern.

At the levels at which the injury occurs, the nerve is well surrounded by bone. Therefore, intra-funicular damage and neuroma formation is unlikely to occur. However, in very severe injuries, e.g., fourth or fifth degree, the tendency for neuromas to occur is greatly enhanced. In addition, as the I.D.N. is not a mixed nerve, the paths of the regenerating fibres are directed towards the same or

functionally related tissue. Consequently functional efficiency of regeneration is not seriously impaired.

(iv) CONNECTIVE TISSUES

A peripheral nerve trunk consists of nerve fibres, each enclosed in an endoneurial sheath, and bound together into bundles or funiculi by perineurium. These bundles are in turn embedded in a loose areolar connective tissue framework which is the epineurium (Fig. 28). The endoneurium, epineurium and perineurium constitute the connective tissues of peripheral nerves and each possess individual structural and functional peculiarities. Sectioning of a nerve involving these structures introduces a series of complications that adversely affect regeneration and make failure more probable than success (see Chapter Nerve Injuries).

Epineurium (Fig. 28)

The epineurium contains collagen and elastic fibres which run longitudinally. The areolar tissue which separates the funiculi and holds them loosely is condensed at the surface of the trunk and forms a definitive investing sheath which limits the nerve from surrounding structures to which it is loosely attached, giving it mobility in its bed. This slackness and elasticity ensure that the contained nerve fibres are not subjected to abnormal tension during limb movement. The epineurium, by providing a loose matrix for the contained funiculi, also acts to cushion them against deforming forces.

Adipose tissue is often found to form a conspicuous element in interfunicular tissue which varies in content and location within the same nerve and from individual to individual (Fig. 28). From a cross-sectional study of the epineurium and funiculi along a nerve trunk, Sunderland and Bradley (1949) noticed that the epineurium varies in amount from individual to individual and from nerve to nerve and at corresponding levels in the two sides of the body. Further, there is more epineurium where the nerve crosses joints and the amount of epineurium present increases with the number of funiculi present.

Perineurium (Fig. 28)

The perineurium which invests each funiculus is relatively thin but dense and

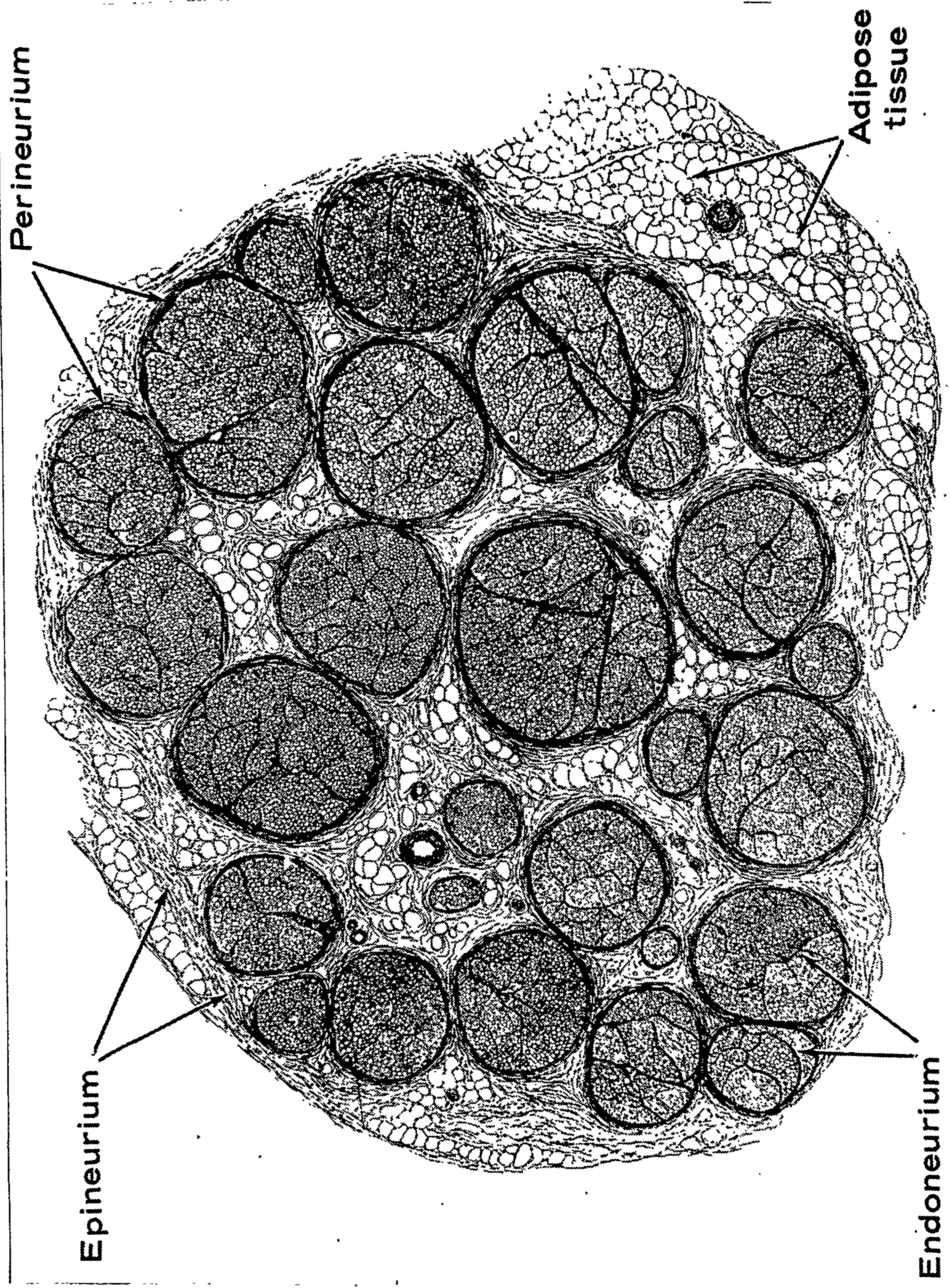


Figure 28. Section of a peripheral nerve showing the arrangement of connective tissues. (From Bloom and Fawcett, 1975)

distinctive. It is a sheath of fibrous tissue composed of elastin and collagen fibrils which are disposed about the bundles, circularly, obliquely, and longitudinally (Glees, 1943). There is no abrupt line of demarcation of the perineurium externally where it merges with the epineurium but internally it is sharply demarcated from the contents of the funiculus, except where the fine processes or septa pass internally to blend with the epineurium. The inner demarcating membrane is made up of flattened polygonal mesothelial cells, one to two layers in thickness, and is easily distinguished from the collagen fibres of the perineurium.

The perineurium thus forms a tubular sheath for the contents of the bundle and permits some movement of the fibres inside the funiculus. There is a linear relationship between the diameter of the funiculi and the thickness of the perineurium. Also, the number of funiculi increases as their size decreases (Sunderland and Bradley, 1952 b).

The function of the perineurium is to protect the nerve fibres it encircles, and the circular and oblique connective tissue fibres resist and maintain a positive intra-funicular pressure. Breaching the perineurium leads to an immediate herniation of the intra-funicular tissue thus demonstrating this positive pressure (Sunderland, 1946 b). The intra-cellular pressure which exists between the cell body and its processes during the proximo-distal flow of the axoplasm is transmitted to the delicate endoneurium and through it to the perineurium (Lubinska, 1956). One sees this during Wallerian degeneration. When the myelin sheath and axoplasm disintegrate, the intra-funicular pressure falls and there is loss of elastic tension in the perineurium resulting in the shrinkage of the funiculus. The reverse occurs with regeneration (Lubinska, 1952 b). The perineurium plays the major role in maintaining the integrity of a nerve trunk under tension (Sunderland and Bradley, 1961).

Endoneurium (Figs. 1, 16, 24, 28)

This is composed mostly of collagenous tissue and is the supporting connective tissue inside the funiculus. It forms septa which divide the funiculus into smaller groups, carrying the intra-funicular blood capillaries (Fig. 29). It also forms the thin delicate external limiting membrane of individual nerve fibres

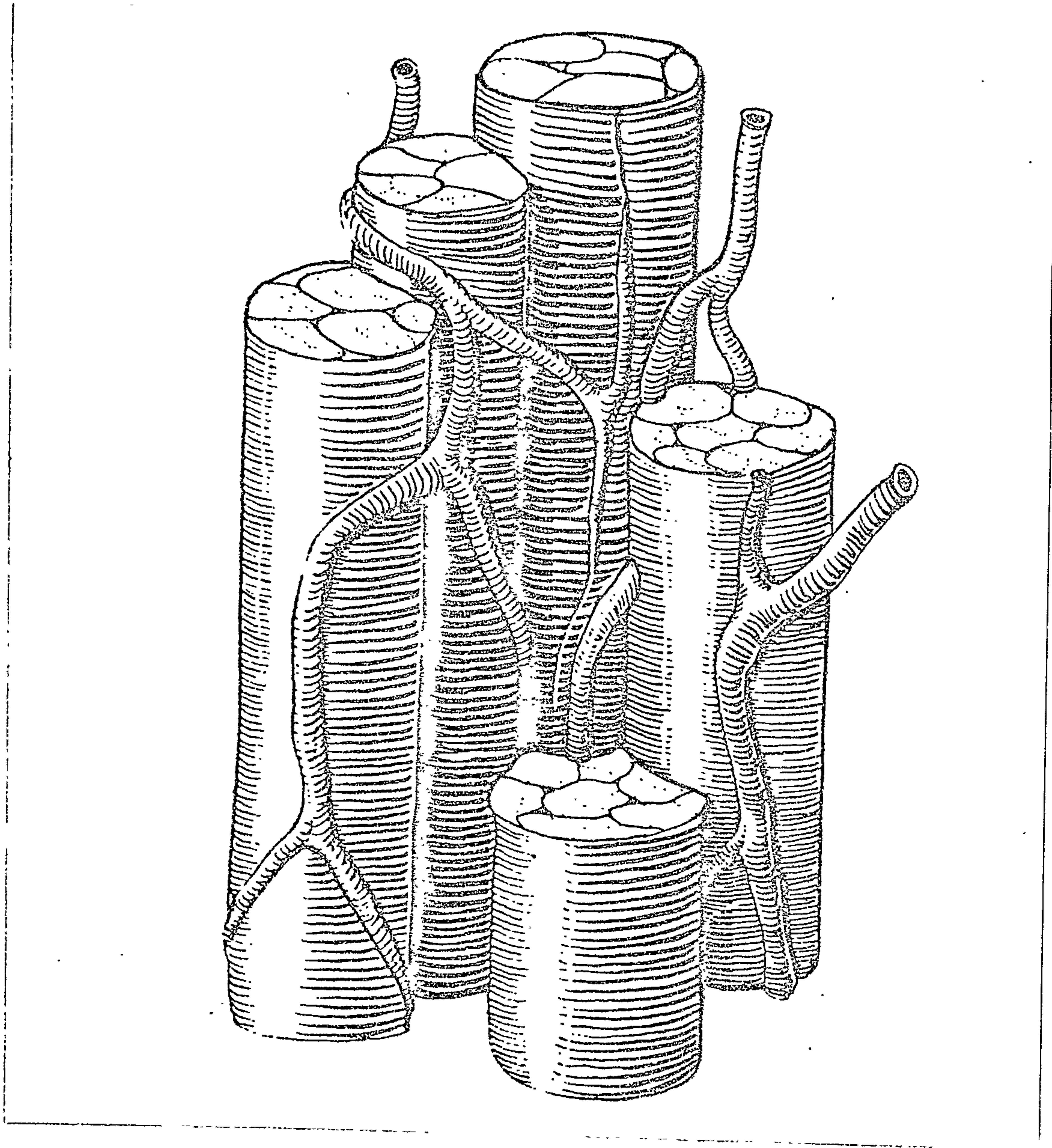


Figure 29. Diagram illustrating the distribution of the superficial and interfunicular arterioles.

to give support to and maintain the form of the endoneurial tube. In nerve injury an intact endoneurial tube is critical, for it provides a passage for the regenerating axon to proceed smoothly to completion, i.e., to reinnervate the original end organ so that the original pattern and function is fully restored (see Chapter - Regeneration, and Chapter - Nerve Injury). The majority of the collagen fibres are arranged longitudinally and the remainder obliquely. These collagen fibres are the product of the Schwann cells as there are very few fibroblasts internal to the perineurium (Causey, 1960). Interposed between the endoneurium and the Schwann cell is a thin delicate membrane, called the basement membrane of the Schwann cells, but, unlike the Schwann cells, it does not dip at the nodes of Ranvier. This layer is referred to by many names, e.g., Schwann sheath, neurilemmal sheath or inner endoneurium. During degeneration when the Schwann cells are active they separate readily from this layer to be converted into macrophages and to form the Bungner bands for the regenerating axons.

(v) BLOOD SUPPLY (Figs. 24, 29).

Peripheral nerves are abundantly vascularised throughout their length by a succession of vessels which, by their repeated division and anastomosis within the nerve, form an unbroken intraneural vascular net (Sunderland, 1945a). Furthermore, nerve fibres, if they are to survive and function normally, require an adequate and continued supply of oxygen (Porter and Wharton, 1949). The vessels that enter the nerve and terminate intraneurally are known as 'arteriae nervorum'. They supply the nerve exclusively and arise from the main vessel supplying the area and are intimately related to the nerve. The number of nutrient arteries to any nerve varies and nerves can run considerable distances without receiving a nutrient vessel, the circulation being maintained by large descending intraneural channels.

Richards (1954) noted that injured nerves may regenerate well in an ischaemic limb. From their clinical observations Bjorksten (1947) and Sunderland (1949) had also concluded that the vascular lesion does not necessarily impair the course and rate of recovery after nerve suture. As a general rule it may be

accepted that the course of spontaneous regeneration is much the same regardless of whether or not there is an associated vascular injury and the satisfactory end result after suture is not necessarily excluded by a vascular complication (Sunderland, 1968).

Causey and Stratmann (1953) maintain that for the first six to eight hours after section of a nerve the metabolic activities associated with the recovery of the nerve are more dependent on the blood supply to the fibre than its connection with the cell body. Blunt (1960) claims that the overlap and the free and extensive anastomosis linking the various vascular systems supplying the peripheral nerve trunk are such that the collateral circulatory mechanisms effectively maintain the circulation in the event of one of the regional nutrient arteries or even several arteries being interrupted.

Venules (Fig. 24) are the largest vessels seen in and leaving the nerves. Venules and arterioles do not always run together and the number of venules leaving the nerve does not always correspond to the number of arterioles entering it. However, the intra-funicular venules outnumber the arterioles. The veins of the cutaneous nerves drain into veins both superficial to and beneath the deep fascia (Sunderland, 1968).

(vi) LYMPH DRAINAGE

There is a lymphatic capillary network in the epineurium and this is drained by the lymphatic channels which accompany the arteries of the nerve trunk. These ultimately pass to regional lymph nodes. However, there are no true lymphatic capillaries in the funiculi but there are endoneurial spaces between the nerve fibres and spaces between the perineurial sheath. The relationship between the extra-funicular lymphatics and these spaces is undefined. Thus the knowledge concerning the anatomical features and central relations of these pathways, and the movement of material along them, is incomplete (Sunderland, 1968). It would seem that a further study of the lymph drainage of peripheral nerves could help throw more light on the degenerative and regenerative processes following nerve injury. This would seem to be a neglected area of research.

5. NEUROPHYSIOLOGY

From such an extensive literature dealing with this subject of neurophysiology it becomes an almost impossible task to present it in a condensed form. The author has tried to highlight those basic concepts which he considers of prime importance to help establish a clear understanding for clinical application in the consideration of peripheral sensory nerve injuries.

THE FUNCTION OF THE NERVOUS SYSTEM

The function of the nervous system is, in a word, communication. Excitability and conductivity are inherent properties of cytoplasm and reach their highest expression in the nervous tissues. 'Excitability' is the capacity to react to the various physical and chemical agents whilst 'conductivity' is the ability to transmit the impulses from one locality to another (Bloom and Fawcett, 1975). The activity of the nervous system is initiated partially by the input elements - the sense organs - and partially by endogenous activity arising in certain cells of the system. The output of the system is ultimately expressed via effector organs - muscles, glands, chromatophores, etc. (Aidley, 1971). Thus, this system co-ordinates the functions of the organs of the body so that its integrity and efficiency are maintained, i.e., data originating in sensory endings are relayed to the brain stem and cerebellum, where they are utilized in various circuits. This information is also transmitted to the thalamus and cerebral cortex where it becomes part of conscious experience resulting in immediate or delayed behavioural response.

Effective function, in mammals, never results from the conduction of a single nerve impulse, but depends on a series of impulses in each fibre being properly synchronised with those in many other fibres. For proper functioning following injury the regenerated fibre must carry impulses at the right speed and frequency and this implies that it must have the right diameter and myelination (Young, 1942). This, of course, cannot be guaranteed for all regenerated fibres and will account for a decrease in quality of sensation as discussed in the chapter on regeneration (Chapter 8).

A knowledge of the mechanism of transmission of nerve impulses in the living body, and of the biologic processes involved in this mechanism is important therefore for our clinical understanding of nerve lesions. These impulses are self-propagating and are conducted from end organs to the C.N.S. and back again to muscles or glands so that an appropriate action can occur. Experimentally the fibre can be stimulated at any accessible point on its course; the nerve impulse set up at the point of stimulation travels just as readily centrally as distally. Under normal conditions the nerve impulse is usually generated in the nerve cell and travels distally along the axon, the main exceptions being the afferent neurones (dorsal nerve roots and afferent cranial nerves). In these the impulse is set up by appropriate stimulation of sensory terminals (Samson Wright, 1965).

THE STRUCTURE OF THE NEURONE RELATING TO FUNCTION

It is important to understand the detailed structure of neurones (Chap. 4 ii) when discussing the transmission of sensation, be it pain, pressure, touch or temperature. The term nerve cell is used to describe the nerve cell and its processes, the axon and dendrites, and is the structural and functional unit of the nervous system. Neurones are morphologically and trophically independent but are anatomically and functionally interconnected at synapses via their processes to other nerve cells, to epithelia, and to muscular and glandular cells. Although all neurones conform to the general principles outlined above there is a wide range of structural diversity.

Classification of Nerve Fibres

Gasser and Erlanger (1927) 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. On this basis sensory fibres were divided in A, B and C groups with subdivisions of the A group (myelinated somatic) into Alpha (α), Beta (β), Gamma (γ), and Delta (δ) (Gasser, 1943). Bullock (1977) points out that:-

A α fibres are 12-20 μm in diameter and have a velocity of 70-120 m/sec.

A β fibres are 5-12 μm in diameter and have a velocity of 30-70 m/sec.

A γ fibres are 3-6 μm in diameter and have a velocity of 15-30 m/sec.

A δ fibres are 2-5 μm in diameter and have a velocity of 12-30 m/sec.

B fibres are less than 3 μm in diameter and have a velocity of 3-15 m/sec.

C fibres are between 0.3-1.4 μm in diameter and have a velocity of 0.6-2.2 m/sec and have little apparent myelin.

A fibres are found in both motor and sensory nerves, B in autonomic ones and C in sympathetic nerves and in dorsal spinal roots. The dorsal root C fibres play the major role in the conduction of pain impulses (Brazier, 1968).

There is a difference in the rate of conduction between A and C fibres which introduces the question of double pain and therefore a dual response associated with noxious stimulation. The dual response theory has been questioned by some e.g., Sinclair (1955), Jones (1956). Bishop and Landau (1958) found that when there was an absence of the myelinated A pathway, pain from C fibre stimulation was enhanced contrary to the views of Sinclair and Jones. In 1965 Melzack and Wall introduced the gate control theory and if this theory were accepted only a simple modulated response would be recorded centrally (Brazier 1972). Despite all the conflicting evidences according to Ganong (1971) the concept of fast and slow pain is now tenable.

Double Pain

Double pain is generally described as being due to the difference in fibre size - conduction speeds between nociceptive fibres. The first pain is mediated by myelinated mechanical nociceptors, the second is mediated about a second later by non-myelinated axons (Iggo, 1974). The initial sharp "bright pricking pain" experienced by the patient is said to be carried by the A fibres and this is followed by a less intense and dull protracted sensation "burning pain like cold pain" said to be due to the smaller diameter C fibres (Wolf, 1968). This separation time of the two responses is directly proportional to the distance from the site of impulse stimulation to the brain.

The following concepts are basic to an understanding of nervous transmission in the various fibre types.

Resting Nerve-Membrane Potential (Fig. 30)

Cell membrane mechanisms reveal that there is a link between the physico-chemical changes at cell membrane levels and transmission of touch, temperature, and pain. For an understanding of the electrical signals in the nervous system the distribution of ions across the membrane, the permeability of the ions and the factors that determine ionic permeability and distribution need to be well understood. The membrane potential of a nerve cell is that of the inside with respect to the outside. Under normal resting conditions a nerve plasma membrane is negatively charged inside with respect to the outside (i.e., polarized) and this electrical difference of about 60 - 70 mv, known as the resting nerve membrane potential, is a function of the concentration gradients of diffusible ions across the membrane (Bullock, 1977). The extra cellular fluid contains a predominance of sodium ions (Na^+), chloride ions (Cl^-) and calcium ions (Ca^{++}) while in the cytoplasm we find mainly potassium ions (K^+) and organic anions. This ionic imbalance is not due to the impermeability of the cell membrane but to a continuous interchange of all ions which are kept in the observed concentration by the mobility of the ions. The entry of sodium ions (Na^+) into the nerve cell or nerve fibre is restricted by the resting membrane whereas the principal intracellular cation potassium is freely permeable (Shepro et al., 1974).

The evolution of electrodes small enough to penetrate the neurone has made possible the direct measurement of potential difference across the membrane in the absence of current flow (Fig. 30). This is found to be about 60 mv (inside negative to outside of membrane). The resting potential between the two sides of the nerve cell or axon membrane is related to the $[\text{K}^+]$ gradient and $[\text{Na}^+]$ gradient and the relative permeabilities of these ions. Nerst's equation describes the equilibrium potentials and the resting potential lies between the potassium equilibrium potential and the sodium equilibrium potential and that position is dependent upon their relative permeabilities.

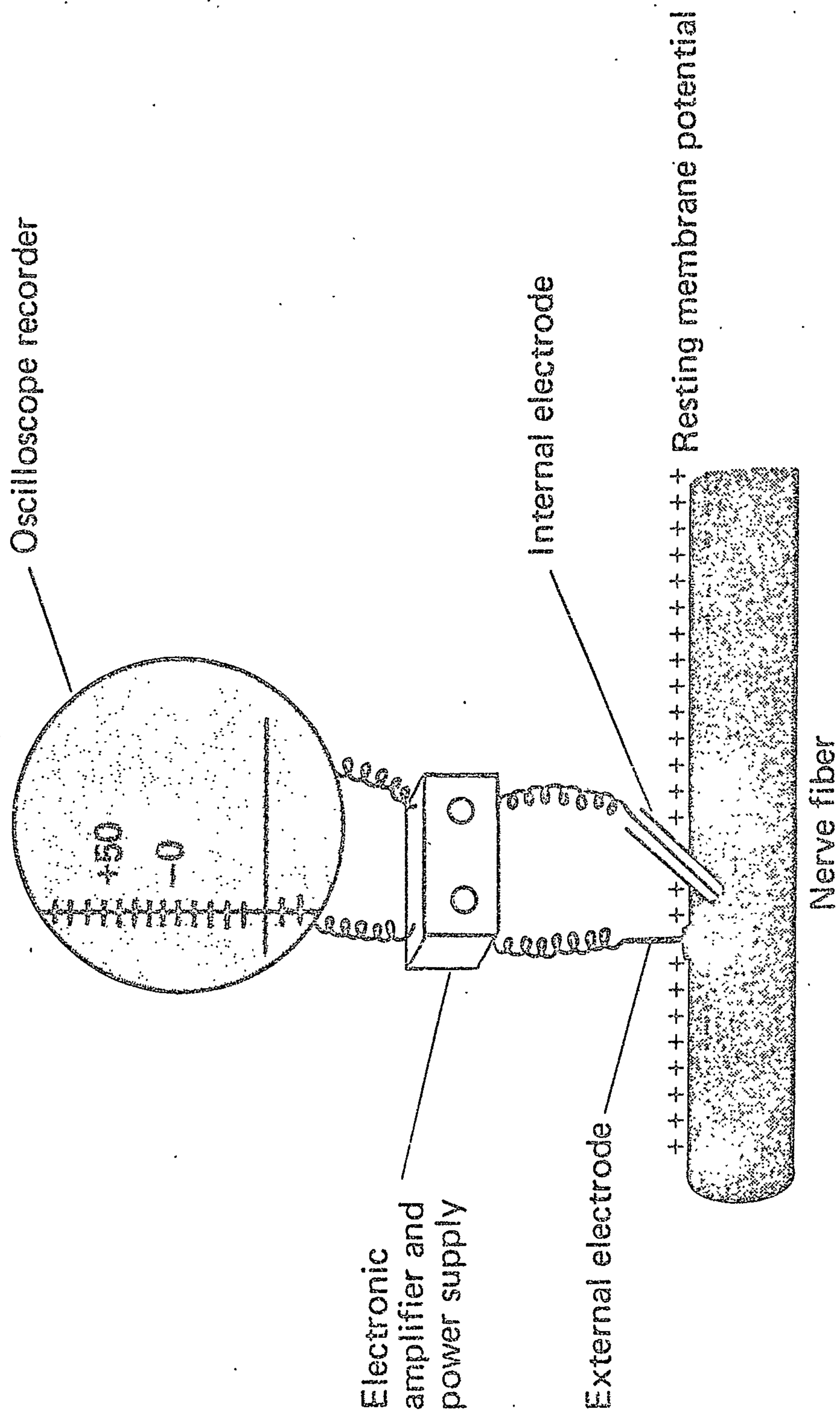


Figure 30. Demonstration of resting nerve-membrane potential using intracellular and extracellular electrodes and amplification.

Nerst's equation

$$\text{for potassium } E = \frac{RT}{2F} \ln \frac{[K^+]_o}{[K^+]_i}$$

Where E = equilibrium potential

R = gas constant

T = absolute temperature

F = Faraday constant

2 = valence of the ion species

$[K_o]$ and $[K_i]$ = outside and inside potassium concentrations.

The electro-chemical potential is the sum of the potential energies both concentration and electric and at equilibrium the ionic flux is zero. The sodium pump plays an important part in relation to the resting membrane potential i.e., re maintaining its steady state.

The Sodium Pump

The intrinsic cellular mechanism responsible for active ionic transport is known as the "sodium - potassium pump" (Eccles, 1957). The energy for the active ionic transport is supplied by the metabolism of the neurones and the rate at which the energy is released decides the magnitude of the resting potential. The inflow of Na^+ and the approximately equal efflux of K^+ associated with a nerve fibre action potential are juxtaposed by the active extrusion of Na^+ by the pump in the recovery phase and the energy for this is thought to be supplied by Adenosine triphosphate (ATP) by mechanisms of oxidative phosphorylation in the cell membrane (Dahms and Boyer, 1974). Thus the pump is responsible for the maintenance of the resting membrane potential by moving positively charged sodium ions out of the nerve cell. The level of ATP sufficient for active ionic transport is maintained by the presence of glucose under aerobic conditions (Aidley, 1971). Biological oxidation of glucose via the pyruvate-citric acid cycle yields the ATP. A change in the glucose concentration or oxygen in the blood causes a change in the resting potential of all nerve cells.

A deficiency in any one of these factors will produce derangement of the nervous system, e.g., the brain and nervous tissue, unlike other cells which will oxidise fat, can only metabolise carbohydrates and cannot store glucose. They are therefore dependent for their energy on the contemporaneous blood sugar. Hypoglycaemia produces symptoms mainly of cerebral dysfunction when glucose is not readily available. This excitability varies firstly with the electrolyte balance of the body as a whole and secondly with the metabolic processes which allow the neurone to maintain its resting potential. This fact is of basic importance when considering clinical aspects of nerve regeneration or abnormal nerve function.

Nerve Impulse (Fig. 31)

An impulse must be distinguished from a stimulus, which is an external force (either electrical, chemical, thermal or mechanical) which initiates the impulse (Brazier, 1968).

Nerve fibres signal events by transmitting electrical impulses. An alteration in the electrical state at the surface of the fibre sufficient to cause a depolarization of the electrical potential of its membrane, results in the nerve cell generating an impulse when a certain threshold value is reached. This potential change therefore results in the development and propagation of nerve impulses and represents the essential process involved in transmitting impulses along the fibre.

Action Potential

When a stimulus of sufficient intensity is applied to any part of the neurone, activity is transmitted throughout from the point of stimulation. In afferent peripheral nerves the direction of activity is towards the central nervous system and is referred to as orthodromic.

The changes in electrical potential within a nerve fibre membrane when an impulse is generated are defined as the "action" potential (Fig. 32). During an action potential the permeability of the membrane to sodium and potassium is markedly altered. A brief specific increase in cell membrane permeability to Na^+ takes place at the peak of action potential; reversal of this reaction provides a physiological explanation for "overshoot" and subsequent

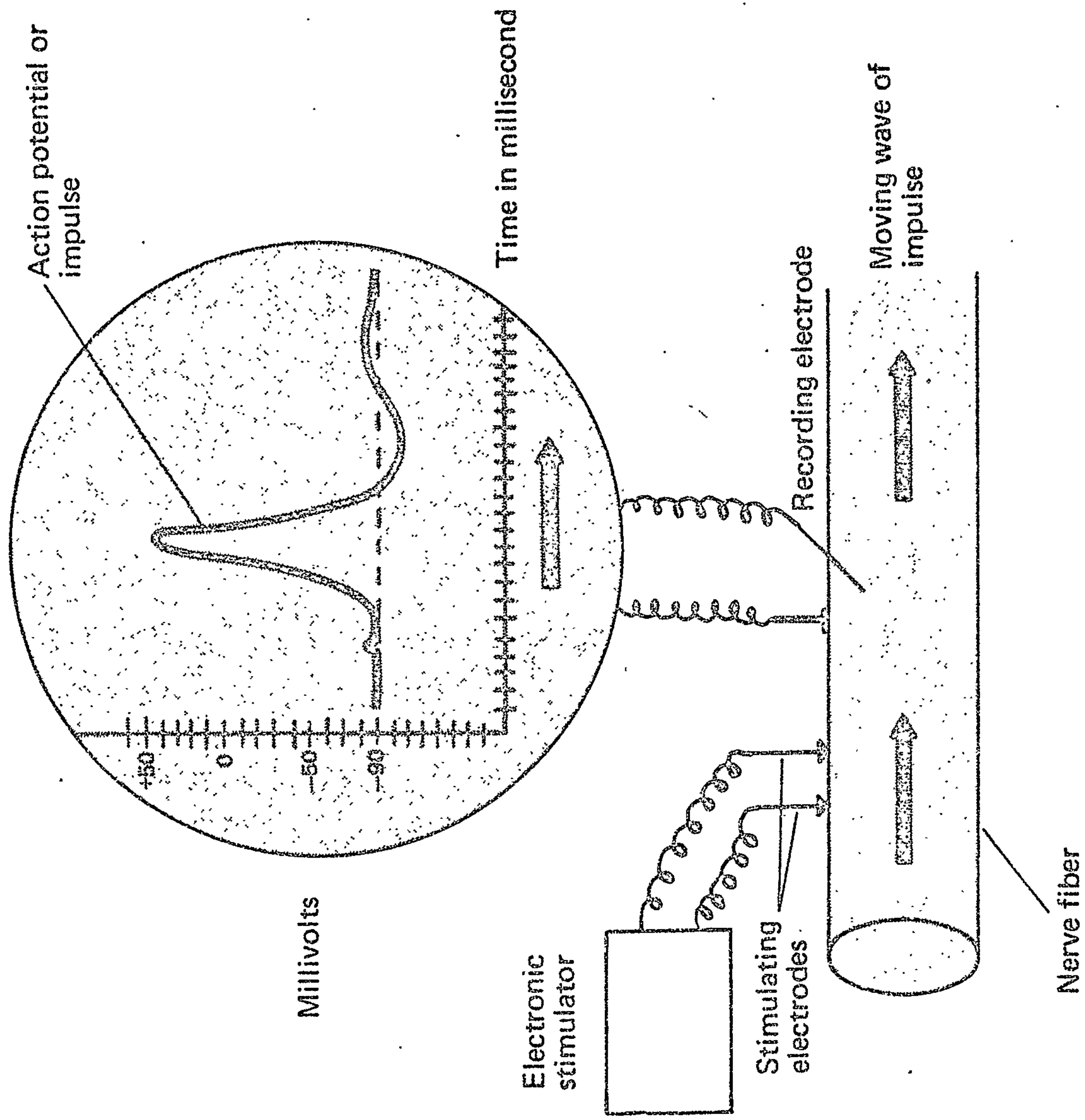


Figure 31. Initiation of a nerve impulse.

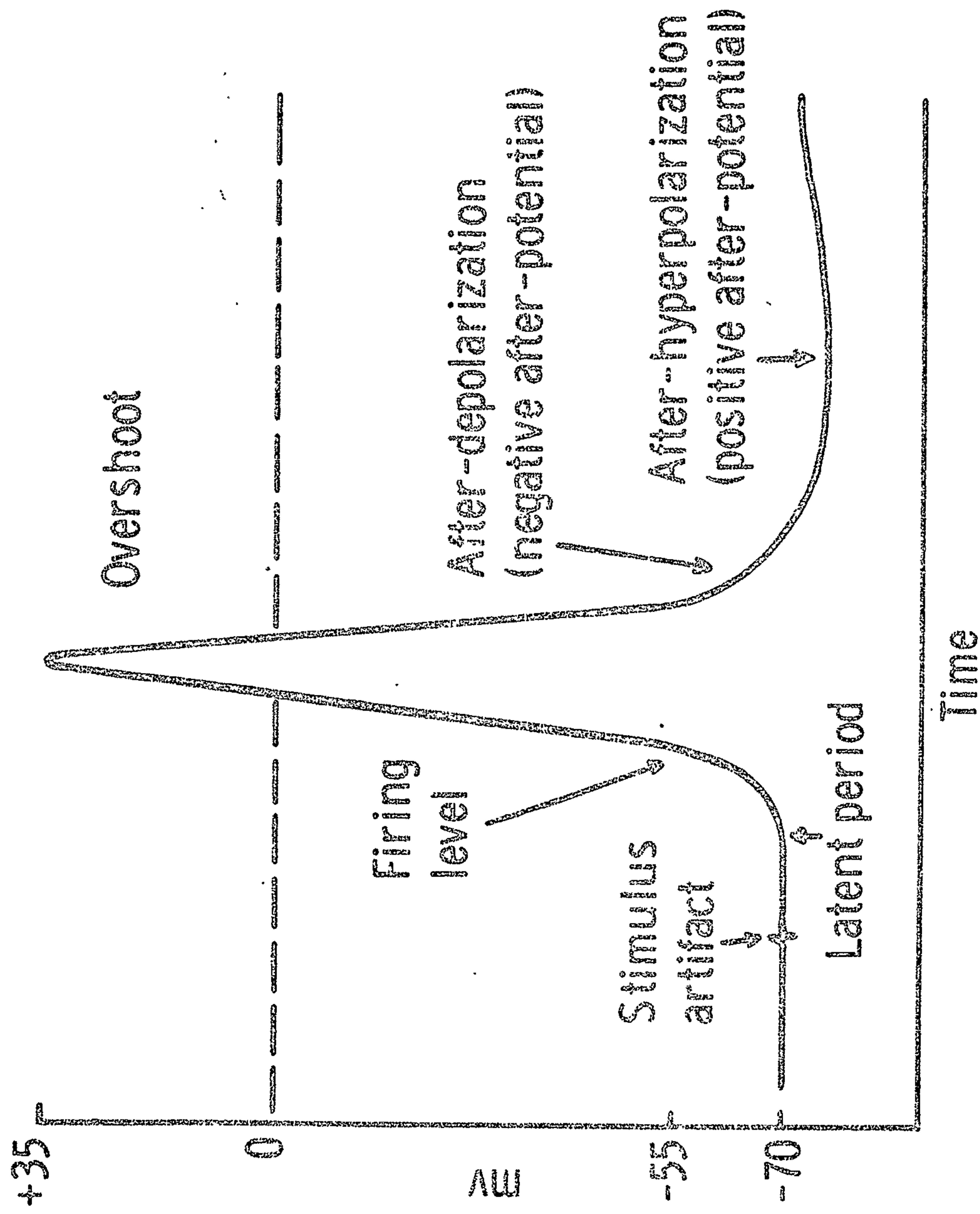


Figure 32. The electrical phenomena in nerve cells (Action potential).

repolarization concomitant with re-excitability along the nerve fibre (Brazier, 1969). Immediately after the peak action potential there is a refractory period in which the nerve will fail to respond to any kind of stimulation (Brazier, 1968). Just before equilibrium is established the cell membrane becomes hyperpolarized (positive after potential), a factor which tends to limit the firing rate and to control the rhythm of action potential. Recovery takes place by active expulsion of Na^+ across the plasma membrane.

The ratio of
$$\frac{[\text{K}^+]_i}{[\text{K}^+]_o}$$

is a major chemical factor governing the excitability of nervous tissue as well as the conductance of sensory impulses (Vaughan and Lunn, 1973). It is believed that enzymes built into the membrane structure on the cytoplasmic side of the plasma membrane may play an important role as physical blockers of the membrane to Na^+ (Elfvin, 1968). However, the presence of Na^+ inside the cell activates membrane localized ATPase (Post, 1968). The release of this from its membrane site to catalyse energy reactions may open the gateway to Na^+ thereby assisting in sodium conductance through the membrane.

Depolarization

The electrotonic state of the membrane is largely dependent on the concentration gradients of K^+ , Cl^- and Na^+ across the membrane. A transient increase in membrane permeability to Na^+ produces depolarization (excitability) where a similar change in permeability specific for Cl^- with associated K^+ leakage results in hyperpolarization (inhibition) (Brazier, 1969). Depolarization is the trigger for the following action potential but an action potential is not always the response to depolarization, e.g., the axon may be fired but not the soma or dendrites because of their higher threshold (Wall, 1974). Factors which prevent depolarization also inhibit action potential, e.g., local anaesthetics inhibit action potential because with the prevention of influx of Na^+ and subsequent depolarization of the membrane the nerve becomes incapable of firing an action potential (Kramer and Schmidt, 1968).

Impulse Initiation

A nerve cell fires when there is sufficient change in the electrical potential of its membrane. The degree of depolarization is derived from and is proportional to the summation of EPSP and IPSP (excitatory and inhibitory post-synaptic potentials) input from impinging synaptic connections. The level of depolarization becomes critical at the axon hillock where threshold is lowest and which is thought to be the site of impulse initiation from the cell (Brazier, 1969). Neuronal activity is complicated when there is a convergence of many synaptic contacts upon a single neurone which may itself also transmit impulses along many divergent synaptic pathways (Gunderfest, 1969).

All or None Theory

Provided the strength of the exciting stimulus is adequate an action potential of a maximum magnitude is set up independent of the strength, i.e., once the threshold intensity is reached a fully fledged action potential is produced and any further increases in the intensity of the stimulus produces no increment or other change in the action potential. Any stimulus below threshold strength therefore fails to elicit a propagated action potential and the property of a single nerve fibre is such that it either does not respond with an action potential or else it responds maximally (Bullock, 1977).

Action Potential Propagation

Once an action potential is initiated in a sensory nerve, the action potential propagates towards the C.N.S. The propagation is initiated when the action potential is at its peak and depends on the formation of electrotonic fields, i.e., one particular action potential does not itself travel along the membrane, rather, each action potential triggers, by local current flow, a new one at an adjacent area of the membrane. The old action potential provides the electrical stimulus that depolarizes the new membrane site to just past its threshold potential. Once this has happened the sodium activation cycle at the new membrane site takes over and an action potential occurs there. When the new site is depolarized to threshold, the action potential generated there is solely dependent upon the electro-chemical gradients and membrane permeability properties at the new site (Bullock, 1977). Therefore, the

initiation of an impulse is a chemical mechanism in so far as it is closely linked to the energy requirements of the sodium-potassium pump, where impulse propagation is largely a physical mechanism relying on electrical conduction along the nerve fibre. Therefore, conduction in nervous tissue is the consequence of the unidirectional passage of electrical currents from the active region to the inactive area ahead of the impulse (Brazier, 1968). The amplitude and velocity of the impulse are constant regardless of the strength of the original stimulus and the larger the nerve fibre the greater is the speed of conduction (Shepro et al., 1974). When the impulse reaches the synapse the electrical energy is converted to secretory activity by an unknown coupling mechanism which initiates the release from the nerve end buttons of transmitter chemicals normally stored in the vesicles apparent in the buttons (Fig. 33). This release leads to the generation of a new action potential on the post-synaptic membrane, which can then be propagated along the membrane of the post-synaptic cell (Shepro et al., 1974).

Velocity of Action Potential Propagation

The velocity with which an action potential is transmitted down the membrane depends on the diameter of the fibre and whether or not it is myelinated. The larger the diameter the faster is the action potential propagation because it offers less resistance to local current flow thereby bringing adjacent regions of the membrane to threshold faster (Shepro et al., 1974). Although great emphasis has been placed on the events occurring at the membrane surface of a nerve axon, the interior plays a significant role in the functioning of the neurone, i.e., the prime source of energy for the sodium pump is derived from the metabolic processes of the neurone cytoplasm.

Rapid conduction without an extremely large increase in axon diameter is due to the sheath of myelin. In myelinated fibres it acts as a powerful electric insulator and influences propagation velocity. Regular breaks in the sheath, called Nodes of Ranvier, are exposed to the extracellular fluid where ionic exchange occurs. Action potentials do not occur along the sections of the membrane protected by the myelin and as such the action potential appears to jump from one node to the next (Fig. 34). This is called saltatory

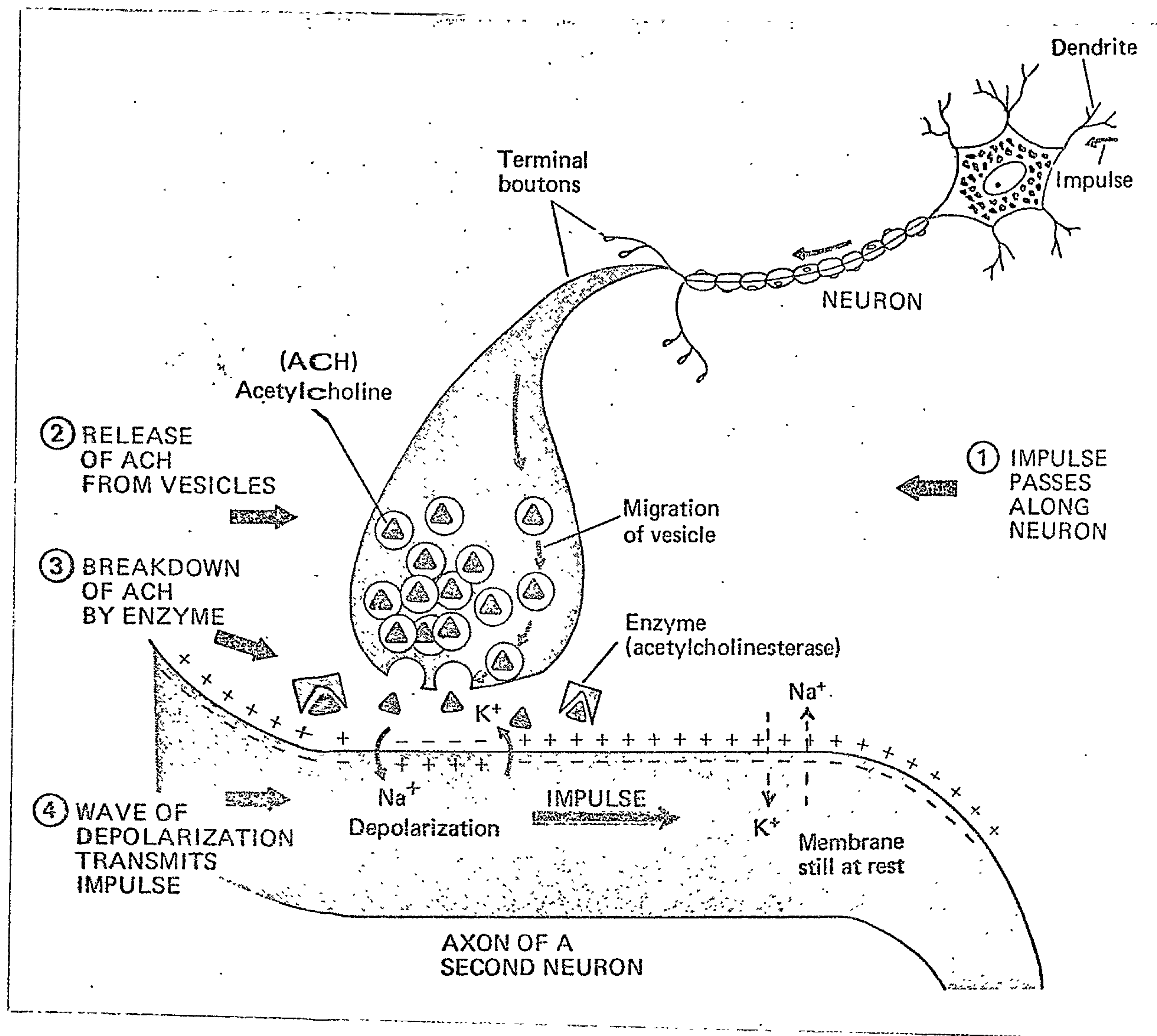
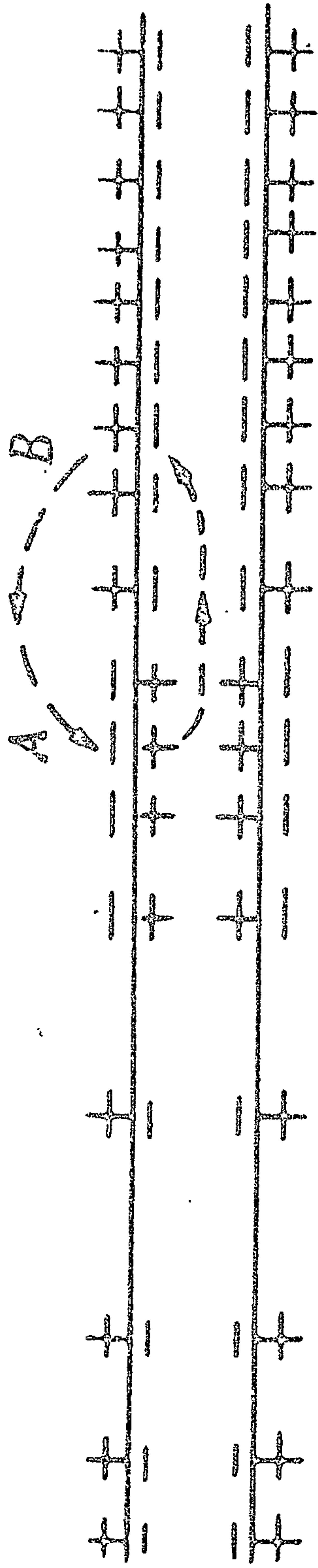
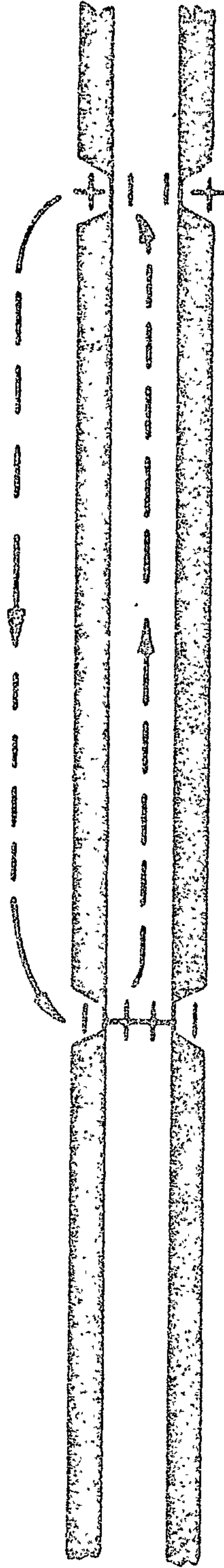


Figure 33. Release of transmitter substances (ACH) at a synaptic contact to bring about depolarization and impulse transmission. (From Shepro et al)



UNMYELINATED



MYELINATED

Figure 34. Conduction in myelinated and unmyelinated fibres.

conduction. Thus the active generation of current (which is due to the entry of Na^+) is confined to the nodes but depolarizes the whole internodal length of the fibre by local current action. Thus the myelin acts to increase the conduction velocity creating local circuits acting at a considerable distance ahead of the region activated. In addition, as the action potential is confined to the nodes, the ionic exchange is reduced and the metabolism necessary to maintain the ionic gradients is less (Bullock, 1977). In unmyelinated fibres the impulse proceeds by simple ionic interexchange along the entire length of the fibres (Fig.34). Hughes (1967) indicates the conduction velocity in very fine unmyelinated fibres to be less than 1 metre/sec whereas in large heavily myelinated fibres, it is between 5 and 100 metres/sec.

Synaptic Transmission (Fig. 33)

Synaptic transmission of impulses between nerve cells is apparently across a junction for in vertebrates there is no known continuity of nervous tissue from one neurone to another (Brazier, 1968). The impulses are propagated along a one way system of synapse involving mediation by a specific chemical transmitter substance released at nerve ending bulbs (bouton terminaux) proximal to the synapse. The modes of connection between neurones are so various that it is impossible to speak of a typical synapse. It is now recognized that both electrical and chemical interactions occur between neurones but the chemical synapse appears to be by far the most common (Bullock, 1977).

The hypothesis that neurones interact through chemical mediators is a complicated one. The process involves metabolic machinery for the synthesis and storage of the chemical in the pre-synaptic neurone, a release mechanism, specialized chemical sensitivity of the post-synaptic cell, and a mechanism whereby the chemical is inactivated. The pre-synaptic terminals are easily recognizable in the electron microscope by the high concentration of mitochondria together with minute vesicles of about 500 Å in diameter containing the chemical transmitter substance (Ham 1974).

There is a synaptic delay between depolarization of the pre-synaptic terminal and the earliest appearance of a post-synaptic response. Impulse conduction

speed is slower when multi-synaptic changes are involved due to a delay of 0.4–0.5 m/sec required for transmission from the pre-synaptic cell to the post-synaptic nerve fibre (Bullock, 1977). Synaptic latency varies with the type of tissue and its excitability, e.g., latency is greater in smooth than in voluntary muscles. When pre-synaptic stimulation ceases, specific enzymes function to deactivate the transmitter substances thereby inhibiting any further excitation of the post-synaptic cell. The hydrolytic mechanism operates by lowering the level of depolarization previously introduced by synaptic excitation (Ambache, 1967).

Two different kinds of synapses, depending on the chemical transmitters, excitatory or inhibitory, have their effects on the post-synaptic cells. During excitation the excitatory post-synaptic potential (EPSP) (Fig. 30) brings the membrane potential closer to threshold and, like the generator potential of the receptor, is a local, passively propagated potential. Its only function is to help trigger an action potential. During the inhibitory phase the inhibitors may cause an increase of the negative potential difference across the membrane of the cell, a hyperpolarization of the post-junctional membrane that prevents the neurone firing. This is called the inhibitory post-synaptic potential (IPSP) (Brazier 1968).

Transmitter Release

It is now known that Ca^{++} are essential for the release of synaptic transmitters. This release is shared to some extent by Sr^{++} and Ba^{++} . On the other hand Mg^{++} and Mn^{++} are said to antagonize this process (Bullock 1977). Experimental work carried out by Gilbert, Willie and Davison (1975) indicates that ATPase may be a "possible trigger" for the release of neurochemical transmitter substances such as acetylcholine and nor adrenaline from synaptic vesicles. Secretion of a particular neurochemical substance is triggered by the summation of EPSP's or IPSP's that impinge upon the pre-synaptic cell (Aidley, 1971). There is evidence for a quantal release of synaptic transmitters. This coincides with the finding by electron microscopists of synaptic vesicles in the terminals of pre-synaptic axons. One hypothesis for the release is that the vesicle membrane fuses with the external membrane and the contents of the

vesicle are emptied into the synaptic cleft some 200-500 Å in width (Fig 35). Once released a neurotransmitter reacts with specific molecules on the post-synaptic cell termed receptors (Bullock, 1977). The inhibitory or excitatory nature of each mediator is dependent on the uptake coupling mechanism in the post-synaptic cell which favours the movement of specific ions across the post-synaptic membrane via special ion "permselective channels" (Grundfest, 1969). Following reaction with specific receptors on the post-synaptic membrane the neurotransmitter is removed from the synaptic cleft by

- (a) enzymatic destruction
- (b) active uptake into the nerve terminals or satellite cells
- (c) diffusion into the intracellular spaces (Bullock, 1977).

Transmitter Substances

Pre-synaptic neurones influence post-synaptic neurones by releasing chemical transmitters. At synaptic junctions acetylcholine (Ach) and norepinephrine have been labelled as central transmitters (Salmoiraghi and Weight, 1967). Besides these, the excitatory and inhibitory amino acids have been implicated also (Krnjevic, 1967). Gamma aminobutyric acid (GABA) and glycine may be major central inhibitory transmitters (Aidley, 1971) while aspartic and glutamic acids have been strongly suggested as central excitatory transmitters (Duggan, 1974). There is evidence, in varying degree, that all these compounds, acetylcholine (Ach), noradrenaline (norepinephrine), dopamine, γ aminobutyric acid, glutamate, glycine, 5-hydroxy-tryptamine, histamine and even adenosine triphosphate, function as neurotransmitters as none fulfill the ideal requirements and more than one transmitter substance may act at any given time. Only the studies with Ach at vertebrate neuromuscular junctions come close to fulfilling this criterion (Bullock, 1977). This same transmitter was found to have a muscarinic and nicotinic action on post-synaptic cells.

Adrenergic and cholinergic fibres

Peripheral nerve fibres are said to be either cholinergic or adrenergic at effector cell synapses. All post-ganglionic sympathetic fibres are adrenergic except those associated with sweat glands, whereas the pre-ganglionic

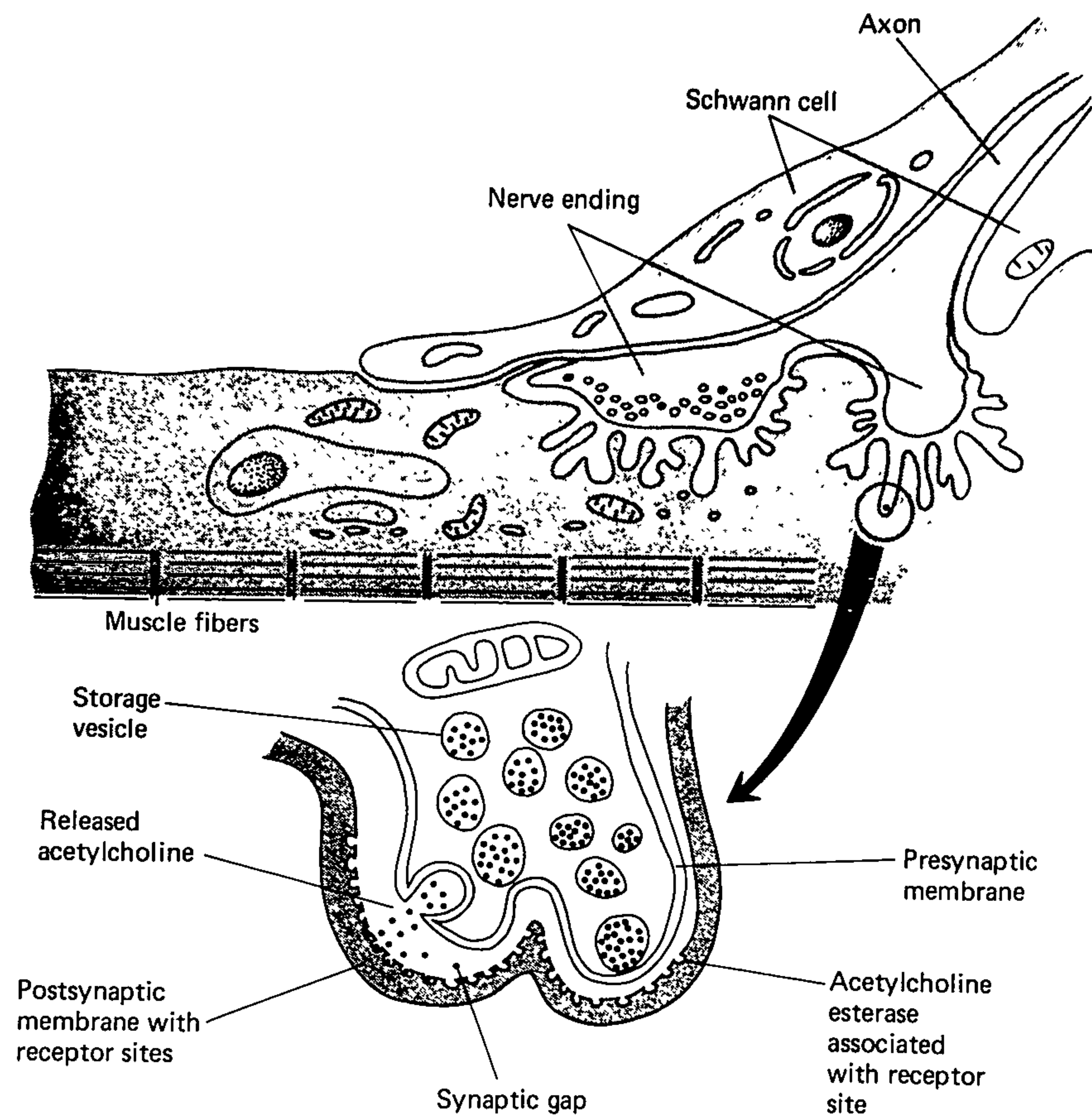


Figure 35. Release of transmitter substance (ACH) at a synaptic contact.
(From Shepro et al)

sympathetic fibres release Ach on the passage of an impulse. Both pre-ganglionic and post-ganglionic fibres of the parasympathetic system are cholinergic, as are the motor fibres to skeletal muscle (Brodal, 1972).

6. THE CLASSIFICATION OF NERVE INJURY

INTRODUCTION

It is not only convenient for the clinician but necessary for diagnosis and report writing to employ a classification as a guide in clinical work. Such a classification should be based on the effects of the injury rather than the cause thus aiding prognosis and treatment planning. Two such classifications are:-

- (i) Seddon's classification introducing the terms neurotmesis, axonotmesis and neurapraxia (Seddon, 1943).
- (ii) Sunderland's "five degrees of nerve injury". This classification is clinically more useful because it has expanded the earlier classification of Seddon considerably (Sunderland, 1951 a).

(i) SEDDON'S CLASSIFICATION

Seddon in 1943 directed attention to the unsatisfactory current classification of nerve injuries. From his wide experience of traumatic nerve injuries (particularly those from World War II) he advocated a more precise and useful classification. He introduced the terms neurotmesis, axonotmesis and neurapraxia for the three types of nerve injury leading to loss of function and claimed that this was reasonably accurate from a histological standpoint and of value clinically. The essential features of these three types of nerve injury were:-

Neurapraxia.

This is a lesion in which there is no axonal degeneration but there may be a localized degeneration of the myelin sheath. Blunt injuries and compression are the commonest causes of the condition. There is a graduation of susceptibility to injury in the various fibre types, those of large size being more vulnerable. Hence the motor and proprioceptive fibres, the largest and most generously myelinated of the peripheral nerve fibres, are chiefly affected. The clinical picture is one of complete motor paralysis and incomplete sensory loss. Recovery is spontaneous and

complete, and so rapid that it cannot be explained in terms of regeneration following Wallerian degeneration (q.v.). There is no change in the electrical excitability of the affected muscles. Subjective sensory disorders such as tingling, numbness and burning are common.

Axonotmesis.

This is a "lesion in continuity" in which the supporting structures of the nerve are more or less preserved but there is complete interruption of the axons with true Wallerian degeneration (see Chapter on Degeneration) occurring peripherally. It is usually produced by a blunt injury. The local nerve lesion, when seen some time after infliction of the injury, may be almost indistinguishable clinically from normal nerve although there may be a "fusiform neuroma" (Fig. 36) present. This fusiform swelling may arise following intrafunicular damage and fibrosis in the area (see sections on intrafunicular damage and neuromas). Such intrafunicular fibrosis will obstruct, divert or constrict regenerating fibres. Histologically there is complete interruption of the axons but the Schwann tubes, endoneurium and perineurium are intact. Clinically the symptoms are not distinguishable from neurotmesis but recovery subsequently occurs and is of good quality because the regenerating fibres are guided into their proper paths by their intact sheaths. In this type of injury an open wound is likely to produce neurotmesis but a closed one is often an axonotmesis, e.g., a mandibular fracture.

Neurotmesis.

This is a lesion of such severity that all the essential parts of the nerve trunk are destroyed locally. There is anatomical division of all or nearly all of the nerve and complete interruption of conduction of the nerve, i.e. there is paralysis and wasting of all muscles below the level of the lesion where motor nerves are involved and anaesthesia, analgesia and therm-anaesthesia within the cutaneous areas supplied by the sensory branches. Wallerian degeneration occurs peripherally. The typical gross lesion that develops at the site of injury with neurotmesis is a central neuroma, connected by more or less scar tissue with a peripheral glioma. Rapid

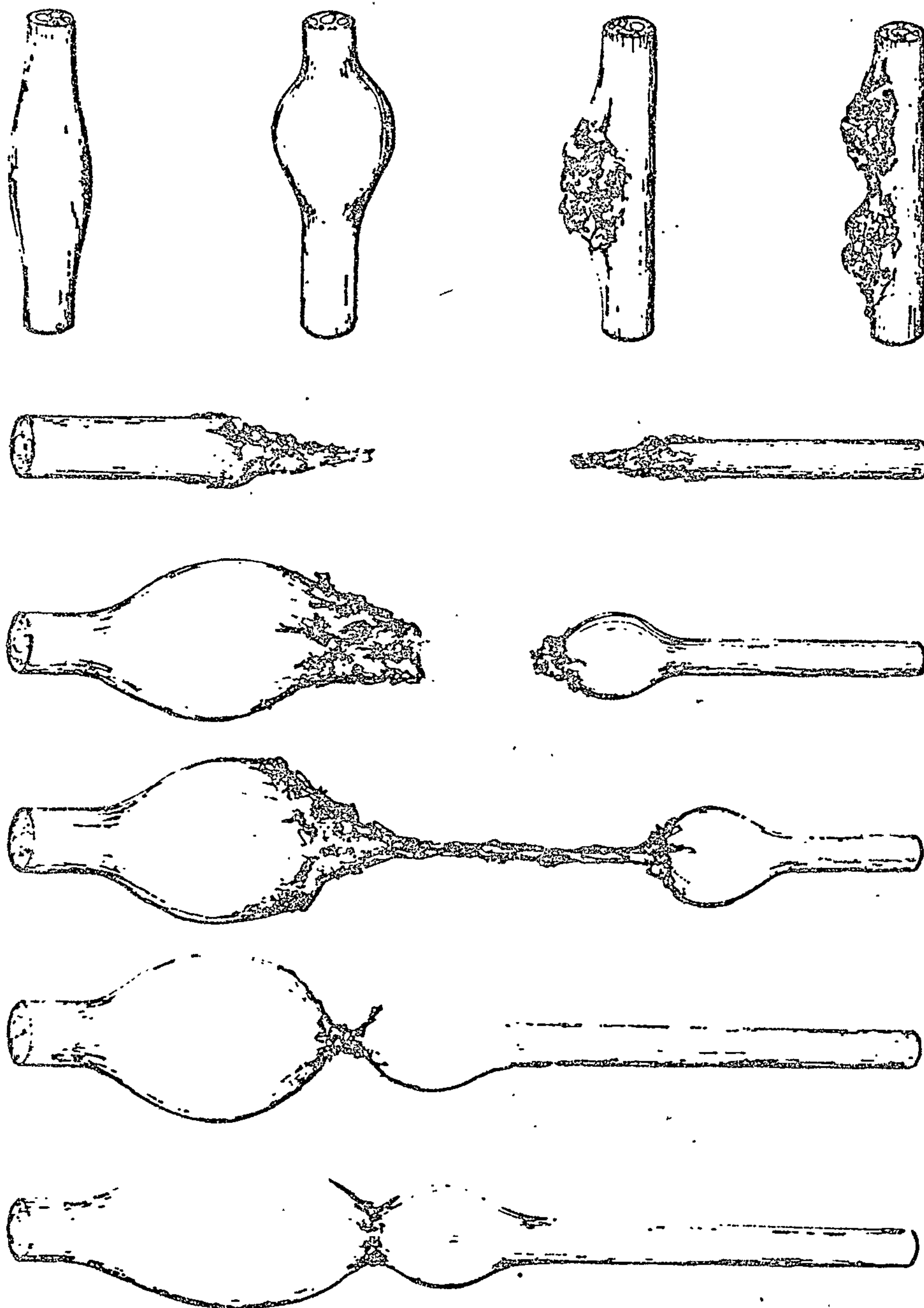


Figure 36. Common forms of neuromas ('bulbs') involving nerves in continuity and the ends of a severed nerve.
(From Nerve and Nerve Injuries, Sunderland, 1968)

recovery is therefore rare and the quality of the recovery is always imperfect.

THE LIMITATIONS OF "SEDDON'S CLASSIFICATION":

This classification is limited because it cannot account for the gradations in nerve damage which can occur between true axonotmesis and neurotmesis. Seddon himself found that when the presenting signs and symptoms indicated pure axonotmesis the nerves on surgical exploration sometimes exhibited "fusiform neuromas" and, incomplete recovery instead of full recovery occurred in these cases. He has not included in his classification injuries in which the axons and their immediate sheaths are interrupted, while the perineurium and the funiculus remain in continuity. In this type of injury regenerating axons can escape from endoneurial tubes which they originally occupied and enter foreign tubes.

It is possible to make a shrewd forecast of the consequences of a few types of injuries utilising Seddon's classification - for example, a closed fracture is likely to produce axonotmesis, a tourniquet is likely to produce neurapraxia and in the case of penetrating wounds mixed lesions may result. The weakness of the Seddon classification is that it describes only what might be called three pure colours widely separated in a spectrum containing many intermediate shades. However, this classification must be extended considerably if it is to be of much further use clinically. One must bear in mind that a collection of nerve fibres subserving many functions, differing in their vulnerability to injury and sometimes differently related in space to the line of injury, is so complex a structure that no classification can possibly portray the consequences of every grade of violence. With these weaknesses in mind Sunderland (1951 a) put forward a more useful classification for clinical purposes.

(ii) THE SUNDERLAND CLASSIFICATION

In an attempt to include all the other intermediate forms of injury Sunderland proposed a new classification based on a long-term study of 300 cases of peripheral nerve injury. It was based on the changes induced in the normal anatomy of the nerve trunk, and covered all types of traumatic injury producing

loss of function. Five degrees of injury, in ascending grades of severity were defined as:-

- i. those that affect conduction in the axon,
- ii. those that affect the continuity of the axon,
- iii. those that affect the continuity of the endoneurial tube and its contents,
- iv. those that affect the continuity of the funiculus and its contents,
- v. those that affect the continuity of the entire nerve trunk.

"The five degrees of nerve injury", could be produced by a great variety of agents, mechanical, thermal, chemical and ischaemic. Depending on the intensity and the time for which they operate the same agents may produce any one of the first four degrees of injury while mechanical deformation may be responsible for all five (Sunderland, 1968).

First Degree Injury

With this injury there is interruption of conduction at the site of the injury, although the nerve trunk and the axon are preserved. The pathological changes are minor and there is no Wallerian degeneration. Axonal continuity between neurone and end organ is also preserved. This type of injury was described by Erb (1876) and more recently by Seddon (1943) as neurapraxia and is the injury about which we know least. Experimental evidence shows that:-

- a. conductivity is restored before the histological changes associated with the cessation of conductivity (nerve block) are corrected - (Denny-Brown and Brenner, 1944a and b);
- b. cessation of conductivity may exist without any detectable modification of nerve morphology (Weiss and Davis, 1943);
- c. nerve fibres with grossly modified sheath structure may continue to function efficiently (Sunderland, 1951 b).

Therefore it may be concluded that, in first degree injury, the fundamental disturbance leading to interruption of conduction is one which involves the axon and not its sheaths. Controversy exists as to whether the nerve block is due to compression ischaemia or the proximo-distal flow of essential materials being impeded by this deformation, resulting in the

molecular structure of the axoplasm being sufficiently altered to interrupt conduction but not to threaten the survival of the axon (Weddell and Sinclair, 1947; Merrington and Nathan, 1949). This disturbance is localized, provided the causative agent ceases to act before the critical point of rapidly reversible damage is reached. The changes, whatever their nature, are fully reversible and function is rapidly and completely restored. Beyond this point axonal disintegration sets in.

Clinical Features Associated with First Degree Injury

Direct compression of a limb, e.g. tourniquet or sphygmomanometer cuff, will cause paralysis and sensory impairment within a few minutes due to ischaemia. Function is rapidly restored following release of such pressure. Ischaemia of the compressed segment of the nerve is generally held responsible for the temporary interference with conduction (Lewis et al., 1931; Merrington and Nathan, 1949).

Sensory modalities, namely touch and pain, are less severely affected and recover more rapidly than motor or proprioceptor functions (Sunderland, 1951 a). Cutaneous sensory loss in first degree injuries is usually transient and is not observed unless the patient is examined soon after the injury. Touch is affected to a greater extent than pain and recovers more slowly. If the condition of sensory nerve block is present it is only transitory and the residual sensory disturbance may be one of paraesthesia which is an indication of disturbed conduction and subsides within a few days. However, in motor nerve block muscle recovery may be delayed for periods from a few minutes to several weeks (sixty days), though only in exceptional cases is it delayed beyond the fourth week (Sunderland, 1951 a). Complete recovery inevitably follows this type of injury because axonal continuity is preserved. Any disturbance in the pattern of innervation due to loss of axons or delay of many months in the restoration of function is indicative that the injury is of a more severe nature. As axonal continuity is preserved and the disturbance responsible for the block of conduction is localized to the site of injury, a motor nerve trunk and the muscles supplied retain their electrical excitability. In other words a response can

be achieved by increasing the intensity of the stimulus. Similarly, this is the case with sensory nerves (see E.S.S. Chapter II).

Second Degree Injury

In this injury the axon is severed and there is Wallerian degeneration (see Chapter 7) of the axon distal to the site of injury and for a short distance proximal to it (one to two millimetres or to the first intact Node of Ranvier). However, the integrity of the endoneurial tube and the structures comprising the nerve trunk are preserved. Clinically the difference between first and second degree injuries is the interval of time before function is reconstituted. The time required to effect complete recovery exceeds that required after first degree injury. Seddon (1943) refers to this type of injury as axonotmesis.

Due to disintegration of the axon and the breakdown of the myelin sheath the peripheral end-organ becomes isolated from its corresponding neurone. However, the regenerating axon is confined within its own endoneurial tube and is invariably directed back to the end organ originally innervated.

Clinical Features Associated with Second Degree Injury

There is complete loss of motor, sensory and sympathetic functions in the autonomous distribution of the injured nerve (i.e., the peripheral zone that is exclusively supplied by this nerve). Due to degeneration of the nerve distal to the injury there is a lack of response to electrical stimulation.

The latent period between the infliction of the injury and the onset of recovery is much longer than a first degree injury and comprises:-

- a. A quiescent period before the axon tips commence to regenerate. This is directly related to the level of the injury, the rate of advance of the axon tips and the duration of the denervation of the affected tissues, especially muscles in motor nerve damage where muscle atrophy, and therefore delay in response, can be expected. As each of these present individual variations, the total delay is much longer than after first degree injury (Sunderland, 1951 a).

b. The time taken to regenerate a functionally efficient pathway which in turn involves:-

- (1) the re-establishment of axonal continuity,
- (2) maturation of the fibres which leads to functional efficiency as a conducting pathway,
- (3) effective union of the nerve fibres with muscle fibres and skin,
- (4) the presence of a minimum number of mature fibres for voluntary contractions

Since recovery depends on the restoration of axonal continuity the pattern of recovery differs significantly from that of first degree injury. In the latter, motor recovery occurs simultaneously over the entire field as does sensory recovery. After second degree injury the affected muscles are reinnervated in the order in which they were originally supplied so that recovery in individual muscles proceeds in serial order, i.e. the proximally supplied muscles recovering before those innervated at more distal levels (Sunderland 1951 a).

Since sensory fibres degenerate and regenerate in a similar manner to motor fibres the time taken for onset of sensory recovery will be in strict conformity with the distance which must be grown by the sensory processes. This has been my observation in the series of cases I have been investigating. The growth of the regenerating sensory dendrites can often be followed by tracing the progression of the point at which Hoffman-Tinel's sign can be elicited. This sign cannot be elicited with the inferior dental nerve because of its containment within the inferior dental canal. The progress of this sign is a reliable guide because the sensory dendrites are regenerating in their original tubes and the pattern of sensory innervation is fully reconstituted. Function is completely restored as the reinnervation is identical to that before injury. The onset of recovery is invariably delayed and therefore the time required to effect complete recovery exceeds that required after a first degree injury.

Third Degree Injury

This injury is due to more severe trauma. There is axonal disintegration with loss of endoneural continuity, Wallerian degeneration and disorganization of the internal structure of the funiculi (see Chapter 4, section iii), but the perineurium shows only minor changes and the bundles remain in continuity. In the more severe forms of this injury besides fibre disorganization, there may be intra-funicular haemorrhage, oedema, vascular stasis and ischaemia.

Intra-funicular fibrosis often develops due to these complications in retrograde neuronal degeneration. This degeneration can be fairly severe, resulting ultimately in the reduction of the number of axons available for regeneration. In addition, axon growth is considerably delayed because additional time is required for the neurone to recover from the severe retrograde disturbances. Considerable axon branching also occurs during the passage through the intra-funicular fibrosis resulting in:-

- a. some axons being diverted from their original paths;
- b. other axons being arrested;
- c. those axons that successfully penetrate the scar finding that their subsequent growth, development and function are adversely affected due to the constriction of the endoneurial tubes, and
- d. regenerating axons, though still confined within the funiculi, may no longer be confined in their own endoneurial tubes and may be free to compete for tubes below the lesion and may descend along functionally unrelated tubes (Fig. 27).

Clinical Features Associated with Third Degree Injury

There is complete loss of motor, sensory and sympathetic functions in the field served by the nerve following intra-funicular damage. The retrograde disturbances are more severe and result in the onset of recovery being delayed. The duration of denervation being longer, fibre mixing as a result of cross shunting at the site of injury (Fig.27) and reduction in the number of surviving axons contribute to the residual defect. Therefore, Hoffman-Tinel's sign ceases to be a guide to the

quality of recovery. Complete functional recovery is delayed and in some cases it is not only incomplete but may differ significantly from the original.

Fourth Degree Injury

Here the funiculi are breached or disorganised. They are no longer sharply demarcated from the epineurium in which they are embedded and with which they share the reaction. The continuity of the outer sheath of the nerve trunk is preserved although the involved segment is a tangled mass of connective tissue, Schwann cells and regenerating axons. These latter may become enlarged to form a neuroma. Scarring is more extensive as the endoneurium, perineurium and epineurium have all been damaged. Hence, large numbers of axons are blocked and others go astray during regeneration. The retrograde degeneration is more serious, resulting in a greater reduction in the number of surviving axons. Regenerating axons, instead of being confined to the funiculi, are free to enter the interfunicular spaces and become lost, or terminate blindly. The chance of these entering foreign tubes is also greatly increased. This type of injury requires excision of the involved segment and surgical repair of the nerve.

Fifth Degree Injury

The entire continuity of the nerve trunk is lost in this type of injury and there is complete loss of all functions. The nerve ends remain separated or, after sufficient time has elapsed, become joined by an attenuated strand of tissue, composed of a fibroblastic and Schwann cell framework. The retrograde neuronal effects are very severe resulting in a great reduction in the number of surviving axons. When there is tissue loss the funicular patterns of the nerve ends are distorted (Sunderland, 1951 a) and the majority of the regenerating axons emerging from the open end of the proximal stump, fail to reach the funiculi and endoneurial tubes of the distal stump due to their arrest in the intervening mass of scar tissue. In addition, shrinkage of the distal stump increases with the period of denervation thus producing a dissimilarity of the cross sectional areas of the nerve ends (Sunderland and Bradley, 1950). Early primary suturing of

the nerve ends does help recovery, but the extent and quality of restored function are still greatly reduced and some residual disability persists.

(iii) NEUROLOGICAL COMPLICATIONS OF NERVE INJURY

Introduction

Injury at any point along a sensory nerve trunk will cause various disturbances such as loss of all forms of sensation (anaesthesia), or the distortion of sensory-evoked signals giving rise to abnormal impulses in the damaged nerve fibres. These abnormal impulses reach the sensory cortex in the form of unusual and confused patterns of information resulting in abnormal sensations or distortion of localization. Normal sensory function depends on the integrity of the entire afferent system from the peripheral receptors to the cerebral cortex.

Anaesthesia and Analgesia

The condition of total local anaesthesia is observed when the affected cutaneous area or region is insensitive to all forms of sensation. In a dissociated sensory loss (dissociated anaesthesia) a particular sensory modality or modalities have been removed from the sensory system by selective nerve injury, e.g., some of the fibres in a nerve trunk innervating muscles may be damaged whereas those innervating the cutaneous area are undisturbed (Sunderland, 1968).

Anaesthesia renders the skin, joints and other structures more susceptible to trauma because:-

- (a) The patient is unaware of the part.
- (b) There is loss of protective sensory mechanisms.
- (c) The patient is more likely to ill-treat tissues and structures that are insensitive (Sunderland, 1968).

Local anaesthesia is most commonly the result of trauma to a nerve. This condition can arise surgically, accidentally or by pathological causes. It prevents conduction of a nerve impulse to the brain, and the symptom is a numb feeling in the distribution of the injured nerve. All sensory modalities are involved.

Local analgesia is the absence of sensitivity to pain whereas the inability to recognise sensations of heat and cold is known as thermanaesthesia.

Paraesthesia

Paraesthesia is best described as an altered sensation following nerve injury and this is referred to as spontaneous paraesthesia. Paraesthesia is sometimes described inaccurately as partial anaesthesia. Paraesthesia gives symptoms which are mixed - a numb feeling is often associated with a burning and prickling sensation or formication. It is often associated with recovery of sensation. The typical injury causing the symptom of paraesthesia is the first degree injury of Sunderland where there is merely an interruption of normal conduction but no anatomical discontinuity of the nerve fibre. Anaesthesia and paraesthesia may exist side by side and an anaesthetic area may revert to a paraesthetic state during nerve regeneration. The events leading to this particular state of paraesthesia must be recognised as differing from those which give rise to paraesthesia following the first degree injury.

Paraesthesia, as an experience of altered sensation to an area of tissue, can be enhanced by the application of external stimuli, e.g., pressure, tension or cold applied to that area. This is referred to as induced paraesthesia. Electrical stimulation does not evoke this experience.

Paraesthesia could be defined therefore as a subjective disturbance of sensation which is described by a patient variously as that of pins and needles, tingling, burning and aching which can be increased by the application of some external stimuli. These are the features of progressive, incomplete or recovering nerve lesions.

Hyperaesthesia

Hyperaesthesia is excessive sensitiveness to all forms of normal stimuli. The sensation elicited by the external stimulus is hyper-acute rather than different and is characteristic of partial nerve lesions. It is a fairly constant feature of cutaneous areas in which sensory recovery is occurring. In causalgia (q.v.) the hyperalgesia (excessive sensitiveness to pain) in the area of returning sensation is usually of a greater degree and

the painful areas are exquisitely hypersensitive to the lightest touch. Also, the hyperalgesia is more persistent and extends over an area much greater than the normal distribution of the injured nerve (Sunderland, 1968). Melzack and Wall (1965) indicated that the state of hyperalgesia would require two conditions; (i) enough conducting peripheral axons to generate an input to produce this condition and (ii) a marked loss of large peripheral nerve fibres. I believe these conditions occur during regeneration when there are a large number of nerve sprouts which are immature and undergoing maturation following traumatic peripheral nerve lesions.

The condition of cutaneous hyperaesthesia is also commonly associated with referred pain from diseased viscera. This is because somatic and visceral afferent fibres associated with pain converge on the same spinothalamic neurones. Somatic pain is more common than visceral pain and, when the same pathway is stimulated by activity in visceral afferents, the signal reaching the brain is no different, and the pain is projected to the same area, e.g., pain originating in the temporo-mandibular joint can be referred to an area of skin which is hyperaesthetic. Various hypotheses have been postulated for this cutaneous hypersensitivity during nerve regeneration. Protopathic fibres, by regenerating in advance of the epicritic fibres, have been said to produce this abnormality (Head, 1920). The reduction in the normal pattern of impulses reaching the C.N.S. due to reduction in peripheral innervation is stated by Weddell et al. (1948) to be interpreted as unpleasant. Antidromic impulses cause release of agents which have been blamed for sensitizing pain receptors (Lewis, 1942). Sympathetic fibres are also involved and have been implicated in producing these unpleasant sensations. These conditions can be relieved by sympathectomy (Leriche, 1947). The explanation provided by Trotter and Davis (1909) was later expanded and confirmed by Sunderland (1968) who stated that this hyper-sensitive condition was the result of disturbances in conduction in damaged and immature regenerating fibres. In addition, synaptic junctions become hypersensitive as a result of retrograde neuronal

and trans-synaptic changes induced by the nerve injury. This abnormal activity at the junctions further contributes to this hypersensitivity (Sunderland and Kelly, 1948). Sunderland (1968) also stated that, with the arrival in the skin of the immature nerve endings at the termination of regeneration, the area of skin which was previously insensitive becomes acutely and unpleasantly sensitive to pin prick and to temperature. The sensations elicited by these stimuli are abnormal, extremely unpleasant, radiate widely, defy localization and lack any qualitative features. With maturation this abnormal sensation usually settles.

Hypoaesthesia

In hypoaesthesia the individual sensory modalities are retained but diminished due to a decreased number of active fibres. This decreased sensory efficiency is quantitative rather than qualitative. The affected area is only sparsely innervated and therefore the effect of the stimulus produced is less than normal. This condition is seen in another situation, e.g., in the marginal zone of sensory overlap. Weddell et al (1941) from experiments and Livingston (1947) from clinical observation state that, following section of a peripheral nerve, sensory terminals from neighbouring uninjured nerves sprout and actively invade the denervated skin. This leads to a gradual and progressive reduction in the area of sensory loss which is observed clinically prior to, or in the absence of regeneration of the severed fibres. The rate and extent of this growth is determined by the success with which the sprouts find pathways which facilitate their growth. Some of these fibres are known to extend from the marginal zone to overlap into the autonomous zone to reinnervate receptors and so reduce the anaesthetic area. Perhaps this would partly explain the well known patient's acceptance of anaesthesia given time.

Causalgia

Although the term causalgia is universally accepted it is a brief and expressive name for a little-understood syndrome. Sunderland (1968) states that, before a condition can be labelled as causalgia, the pain must follow injury to a nerve trunk and be quite unrelated to damage to non-

neural tissues. It must also be severe in character, spontaneous and persistent but it can be aggravated by environmental and/or emotional factors. The pain should also have persisted for more than 5 weeks before the category of causalgia is applied.

Burning is the description most frequently applied to the pain in causalgia (Echlin et al., 1949) and the sufferings of the patient are often very severe, the paroxysms being described as "agonising" or "excruciating". Lewis (1942) indentified the skin as the site of burning pain and the pain was of two qualities; (a) "pricking" if of brief duration, (b) "burning" if prolonged. The causalgic pain usually occurs in the first few weeks following injury". The duration of pain varies widely from case to case (Sunderland and Kelly, 1948; Echlin et al., 1949) and some factor additional to the injury is necessary to precipitate causalgia. Many workers including Barnes (1954) maintain that most lesions with causalgia are due to perforating high velocity missiles and the stretching of the nerve in these cases is the additional factor (Puckett et al., 1946). There is no significant relationship between neuroma formation and causalgic pain. Tenderness in a neuroma should not be confused with causalgic pain arising from it (Sunderland, 1968). Speigel and Milowsky (1945) found that percussion at the site of injury did not precipitate or intensify causalgic pain, and stated that the pain was not due to continuous irritation by the scar or a foreign body. In addition, the onset of causalgia occurs well in advance of scarring, much of which is intra-funicular and the causalgic pain is unaffected by surgical neurolysis.

Neuromas

Neuromas represent the greatly altered and distorted parts of an injured nerve in which the Schwann cell-endoneurial barrier has been broken and regenerating axons have escaped to grow in a disorderly fashion in the connective tissue framework of the nerve trunk. Neuromas are of several types (Fig. 36). Neuromas on nerves in continuity arise as a result of lesions in which the perineurium is not broken. These are known as spindle neuromas. Those which result in the perineurium of some of the funiculi

being broken give rise to lateral neuromas. Other types that can occur are bulb neuromas which form at the ends of the severed nerve and amputation stump neuromas. Sunderland (1968) says lesions that do not break the endoneurium are not associated with neuroma formation and that at least a third degree injury has to be sustained for a neuroma to occur. The small spindle shaped swellings (neuromas) seen on nerves subjected to chronic friction or irritation are said to be due to the increase in connective tissue at the site of trauma and can be relieved by surgical neurolysis. In third degree injury the swelling is confined to the funiculi and the size and form of a neuroma will depend on the size and number of bundles of funiculi affected. Intra-funicular haemorrhage and associated cellular reaction contribute to the swelling and in severe third degree injuries inter-funicular tissue also contributes to the size of the neuroma.

Phantom Limb

A phantom limb is a natural and almost invariable sequel of amputation and almost all patients experience a vivid sense of the presence of the whole or part of the limb which has been lost and this sensory illusion may be retained for many years. In most cases this new situation is rapidly adapted to and the image fades and disappears. In a few cases the phantom becomes the seat of severe and unrelenting pain which may defy all attempts to terminate or relieve it (Sunderland, 1968).

Following the amputation of a limb, neuromas form at the ends of the divided nerves and these amputation stumps are often subject to repeated blows, pressure and irritation. This results in an increase in their size and sensitivity and they can often become acutely hyper-sensitive and therefore extremely painful to the slightest pressure or traction. They are therefore thought to have a possible influence on the appearance and persistence of phantom sensations (Sunderland, 1968).

7. NERVE DEGENERATION FOLLOWING TRAUMA

INTRODUCTION

Although the inclination is to divide the process of healing following nerve injury into two distinct areas, that of degeneration and regeneration, it must be borne in mind that these two processes do overlap (Fig. 37,57). While the process of degeneration is still active peripherally in the distal stump, axonal sprouting may be occurring in the proximal stump. For the purposes of clarity and discussion in this thesis these two phases of healing (degeneration and regeneration) have been dealt with separately although inevitably some overlap in discussion will occur.

THE PROCESSES OF DEGENERATION

Nerve fibres degenerate after injury, at different rates. Factors which influence this rate of degeneration are as follows:

- (i) The type of experimental animal used.
- (ii) The size and degree of myelination of the fibre, e.g. axons of large myelinated fibres degenerate more rapidly than those of small myelinated fibres and unmyelinated fibres are the most resistant of all to degeneration (Guth, 1956; Hojin et al., 1959; Ohmi, 1961 and Lee, 1963).
- (iii) Whether the fibre involved is sensory or motor, e.g. sensory fibres degenerate earlier and more rapidly than motor fibres (Gutmann and Holubar, 1950).
- (iv) Age, e.g. changes appear earlier and proceed more rapidly in young growing animals than in mature adult animals (Mannell and Rossiter, 1952).

Our knowledge of degenerative processes in human nerve is incomplete in several aspects and for this reason we are compelled to rely on animal experiments for information. Further, as observations have been made on different nerves, in different species and under different experimental conditions, published information is conflicting.

The sequelae of axon interruption and regeneration of nerve fibres following injury

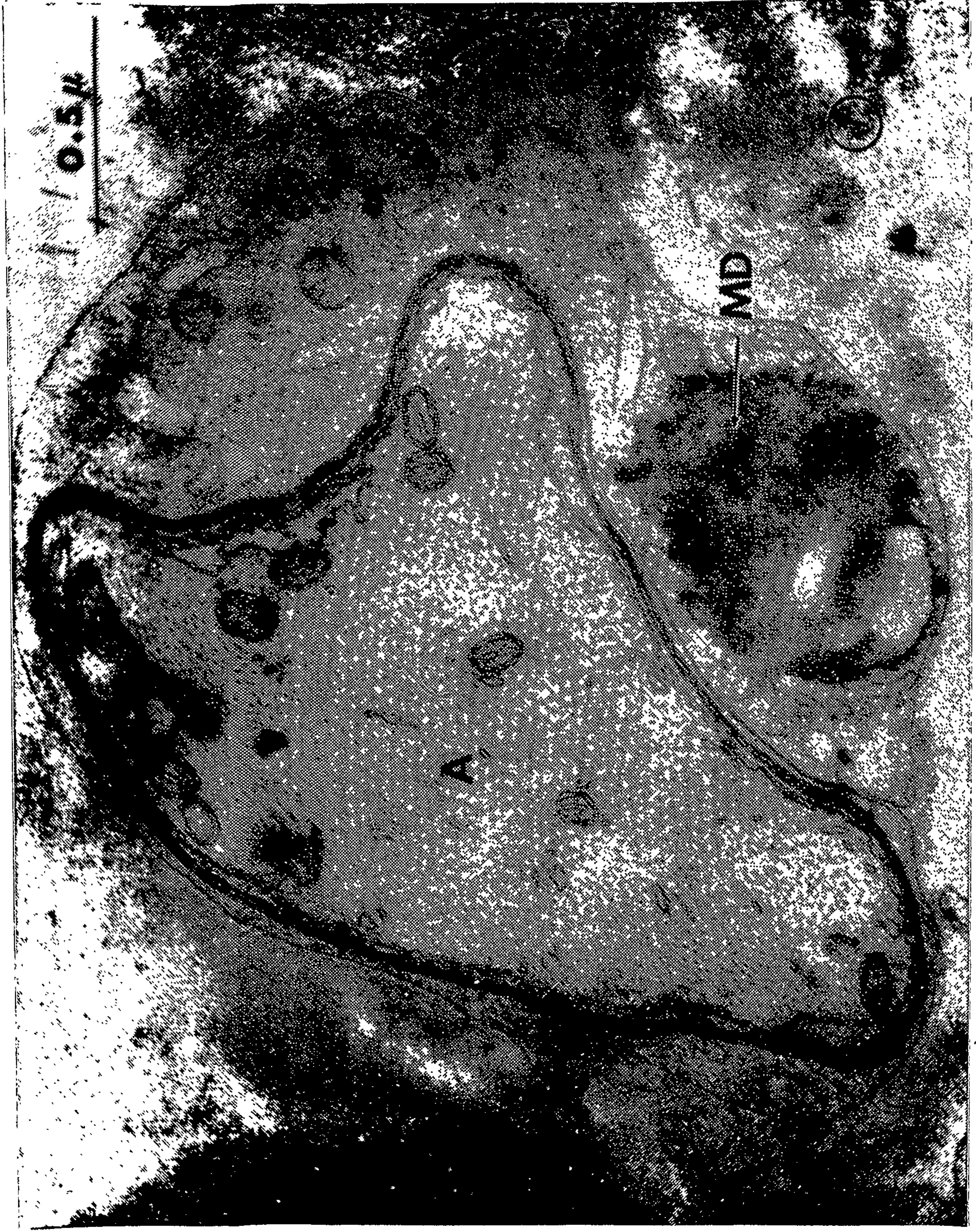


Figure 37. Electron micrograph showing the processes of regeneration and degeneration going on side by side. (From Satinsky, Pepe and Liu, 1964)

have important clinical implications. In addition, advantage is taken of Wallerian degeneration where one sees structural and chemical changes to trace specific fibre pathways in the central nervous system for research purposes (Barr, 1974).

When a peripheral nerve is cut or injured, predictable physiological and morphological changes occur in all portions of the neurone. These changes are seen at the site of injury, in the proximal and distal axonal segments, and in the centrally located cell body or perikaryon (Fig. 38). Significant connective tissue changes are also noted surrounding the site of nerve injury. The sequence of reaction in an injured nerve is similar whether it be a peripheral nerve or one in the central nervous system. Fibres of the C.N.S. may receive damage from causes such as infarction due to vascular occlusion or in a locus affected by one of the demyelinating diseases, or they may be injured due to trauma arising from accidental injuries or neuro-surgical procedures (Barr, 1974). Traumatic injury may be one of transection, crushing, local injection of toxic substances (Duncan and Jarvis, 1943) or interference with the blood supply (Denny-Brown and Brenner, 1944 a and b). The resulting injury may fall into one of the classifications that have been proposed by Seddon (1943) and Sunderland (1951 a). See Chapter 6(i) and (ii).

The early physical change of degeneration is seen as the disintegration of the axon and myelin sheath (Fig. 39) along the whole of the distal segment and in myelinated fibres up to one to two nodes of Ranvier along the proximal segment from the point of injury (Fig. 38,39). In unmyelinated fibres this occurs in only 1-2 mm of the proximal segment (Weddell and Glees, 1941). The proximal changes are referred to in various terms such as retrograde degeneration, or axon reaction or response (Barr, 1974) while the distal changes are known as Wallerian degeneration also referred to as anterograde degeneration (Fig. 38). Degeneration is therefore initially a break-up and removal of the disintegrated axon and myelin and secondarily a proliferation of the Schwann cells and their conversion into protoplasmic strands to receive the regenerating axon (Young, 1942). The pattern of degeneration following trauma differs both qualitatively and quantitatively in myelinated and unmyelinated fibres (Nathaniel and Pease, 1963 a). Two to four days after nerve section that portion of the nerve distal to the lesion becomes incapable of conduction. This gradual loss of function appears earlier in sensory cutaneous fibres than in motor fibres (Gutmann and Holubar, 1949) and signifies the commencement of the degenerative process in the distal segment.

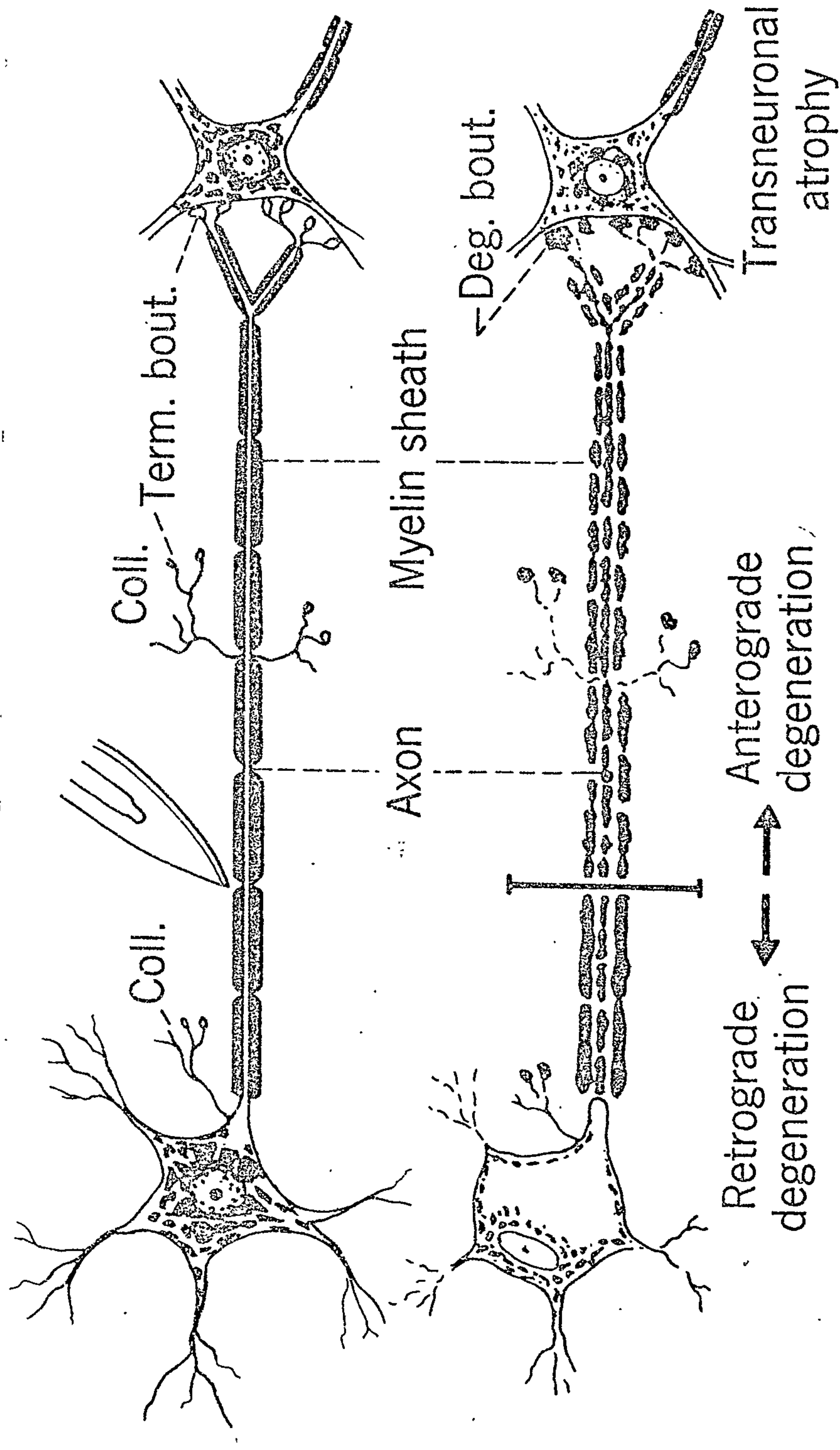


Figure 38. Diagrammatic representation of the changes in the neuron which follow transection of its axon. Above, the normal situation; below the changes as they appear some days after the lesion, central to the cut (retrograde degeneration) and peripheral to it (anterograde degeneration). Below to the right the transneuronal changes are indicated. (Brodal, 1969)



Figure 39. The axoplasm (A) has degenerated into several gross clumps. The myelin (M) is disintegrating as shown by separation into layers. The characteristic phagocytic neurilemma cytoplasm (S) surrounding the degenerating fibre contains much debris and many vacuoles. (Satinsky, Pepe and Liu, 1964)

a) AXON RESPONSE

Proximally (Retrograde traumatic degeneration)

Within one hour of cutting a peripheral nerve there is a marked swelling from the point of severance back up the nerve as far as 1 cm. The amount of swelling is greater than three times the cross-sectional area of the intact total nerve (Ducker and Hayes, 1968). The swelling consists of both intracellular and extracellular oedema, mostly consisting of a gel-like amorphous substance that contains large quantities of acid mucopolysaccharides. This persists for a week or more and subsides slowly thereafter (Oester and Davis, 1956). The term Wallerian degeneration should not be applied to any changes in the proximal trunk, since it is not true Wallerian degeneration, as Waller's original description referred only to the changes in the distal stump (Waller, 1862).

The changes in the proximal portion of the affected neurone vary according to the type of neurone and species involved. An example of species difference is the absence of axon reaction in motor cells of the spinal cord of the rat or rabbit following peripheral motor nerve section whereas a typical axon reaction occurs in those same cells of most animals including man (Barr, 1974). Further the nature of the injury influences the degree of axon reaction, i.e. there is considerably greater activity and the changes are more marked following traumatic blast injuries (including gun-shot wounds) than in a simple clean-cut injury. It is also seen that as a result of severe motor neurone injury, some cells undergo progressive degeneration and ultimately disappear. Alternatively, the proximal portion of the neurone may not be altered significantly by axon section, e.g. the cell bodies of cerebro-spinal ganglia react to section of their peripheral but not their central processes (Barr, 1974). The retrograde reaction follows a pattern similar to that occurring below the level of injury though the Schwann cell proliferation is not as great (Logan et al., 1953).

Distally (Wallerian degeneration).

Waller (1850) first described changes in the nerve fibre distal to the point of injury from light microscopic studies. These changes have since been referred to as Wallerian degeneration. His findings have been elaborated and reviewed by Cajal (1928), Nageotte (1932), Young (1942), Guth (1956) and many others.

Wallerian degeneration is initiated by injury to a nerve either with or without interruption of endoneurial continuity. This degeneration occurs along the whole length of the fibre below the level of the injury and follows a centrifugal course (Causey and Stratmann, 1953) (Figs 38,40).

Two important responses of the neurone to injury are Wallerian degeneration and the morphological changes which occur in the perikaryon of the neurone (Fig. 38). These responses have been said to exemplify the 'neurone doctrine' and illustrate the trophic influence of the nerve cell body over the axon and its other processes (Bloom and Fawcett, 1975). The severed axon does not survive long when separated from the cell body, as it is dependent on the nucleus for the synthesis of cytoplasmic proteins which are carried distally in the axon by cytoplasmic flow to replace proteins that have been degraded as part of the metabolic activity of the neurone (Barr, 1974). Therefore, distal to the site of injury there is complete degeneration of the terminal arborizations, myelin sheath and the axon following severance (Bloom and Fawcett, 1975) (Figs. 38, 40).

A series of changes is observed in the distal axon during Wallerian degeneration. As early as 12 hours following injury and within 24 hours the axon becomes swollen and irregular with fragmentation of the neuro-filaments. In the period 48 to 72 hours, twisted fragments of the axon are seen dispersed along the fibre distal to the site of injury (Weddell and Glees, 1941). The ability of the fibre to conduct nerve impulses ceases with the loss of axonal continuity while complete failure of conduction even of an electrical stimulus occurs within 3-5

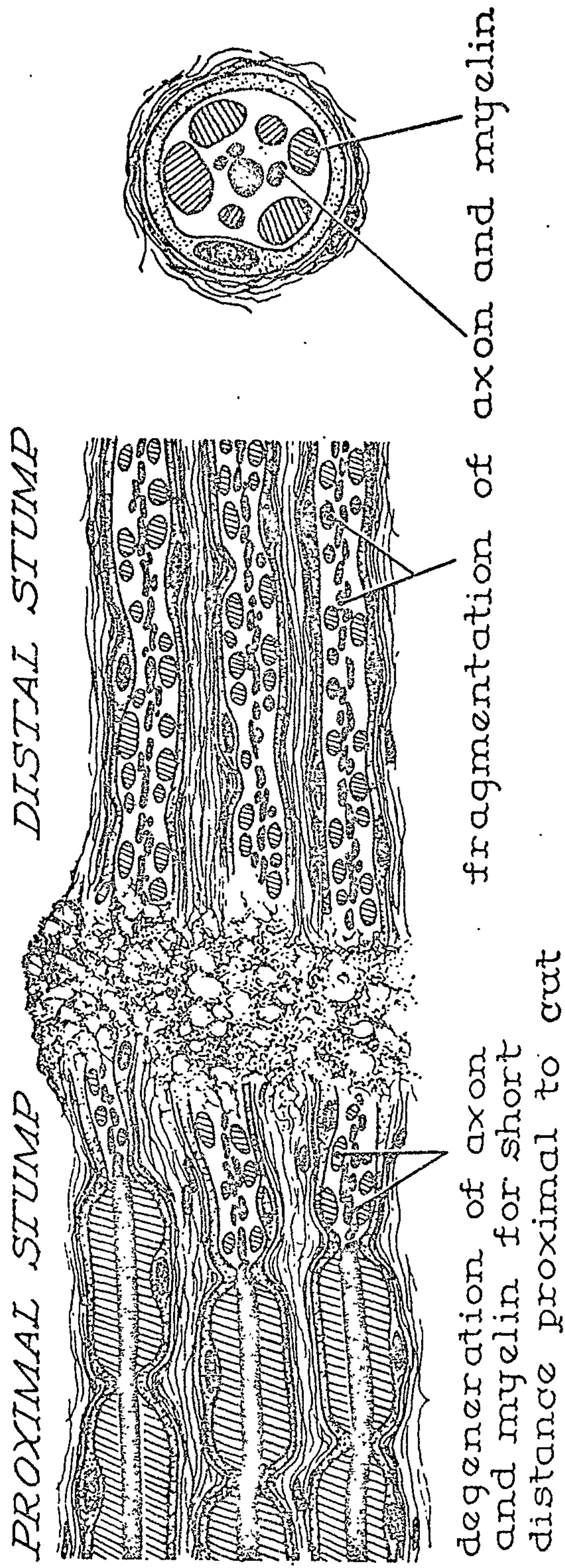


Figure 40. Diagram showing changes at the site of an injury and in the regions proximal and distal to it. (From Ham, 1974)

days (Erlanger and Schoepfle, 1946; Landau, 1953). It is assumed that the neurilemma cells (Schwann cells) in these circumstances are responsible for the conduction of the impulse during the later stages (Hughes, 1967).

Erlanger and Schoepfle (1946) and Gilliat (1961) pointed out that nerves undergoing Wallerian degeneration maintain essentially normal conduction velocity until very late in the degenerative processes, while nerves undergoing degeneration as a result of degenerative disease exhibit a greatly diminished conduction velocity fairly early in the degenerative process. Simon and his co-workers (1969) claimed that Wallerian degeneration is an atrophic process and that macrophages slowly digest the myelin sheath but probably leave a protective layer of myelin around the axon until a very late stage in the degenerative process. However, in degeneration as a result of disease the myelin sheath could be disrupted down to the axon at irregular intervals while not necessarily affecting the major portion of the myelin. Also the chemical structure of the myelin may become abnormal which could affect its electrical resistance. Under certain conditions these two possibilities could allow a "leakage" of current which might result in a decrease in conduction velocity. If this reasoning is correct the process of Wallerian degeneration and that of a disease state proceed by entirely different mechanisms and hence Wallerian degeneration would provide a relatively poor model for the study of degeneration of nervous tissue in many pathological conditions.

Barr (1974) stated that muscular contraction on electrical stimulation of a degenerating motor nerve ceases abruptly 2-3 days after the nerve is severed. The degeneration includes the neural component of sensory and motor endings. The sheath and other non-nervous components of the endings remain intact for a considerable time and are reinnervated under favourable circumstances. Lee (1963) says that all traces of the axon of myelinated fibres distal to the site of injury are lost by the 2nd week, but remnants have been reported in non-myelinated fibres up to

28 days after injury but not beyond the 35th day.

There have been numerous studies on the ultrastructural changes occurring in Wallerian degeneration. However, there is little agreement on the interpretation of the findings. In addition, no attempt has been made to solve some of the problems which have not been answered by light microscopy, e.g.

- (i) whether the earliest changes occur in the axoplasmic organelles (Vial, 1958; Webster, 1962) or in the membrane system (mesaxon and myelin lamellae) (Nageotte, 1932; Engstorm and Wersall, 1958);
- (ii) whether large or small myelinated fibres (Young, 1942; Hojin et al., 1959) or unmyelinated fibres (Ohmi, 1961) are more vulnerable to Wallerian degeneration;
- (iii) and whether Schwann cells do (Guth, 1956; Ohmi, 1961) or do not (Terry and Harkin, 1959) behave like macrophages.

Wallerian degeneration in sectioned sciatic nerves of rats and rabbits was studied by Lee (1963) by means of the electron microscope. No differences were observed in the degeneration of the nerves between these two species of animals. He found that the axons, whether myelinated or unmyelinated, contained four kinds of organelles - endoplasmic reticulum, mitochondria, neurofilaments and dense particles but the last two were sparse (Fig. 41). The slender mitochondria and the neurofilaments were arranged parallel to the long axis of the nerve fibre.

Lee (1963) made an attempt to explain the different views of previous authors. He failed to observe any signs of degeneration in the first 12 hours following nerve section but by the 19th hour he noticed simultaneous changes in the endoplasmic reticulum, mitochondria and neurofilaments of the axon. These changes had been described earlier (Causey and Hauffman, 1955; Hojin et al., 1959; Ohmi, 1961) and involved swelling of the endoplasmic reticulum and mitochondria and aggregation of the neurofilaments. However, no fragmentation of

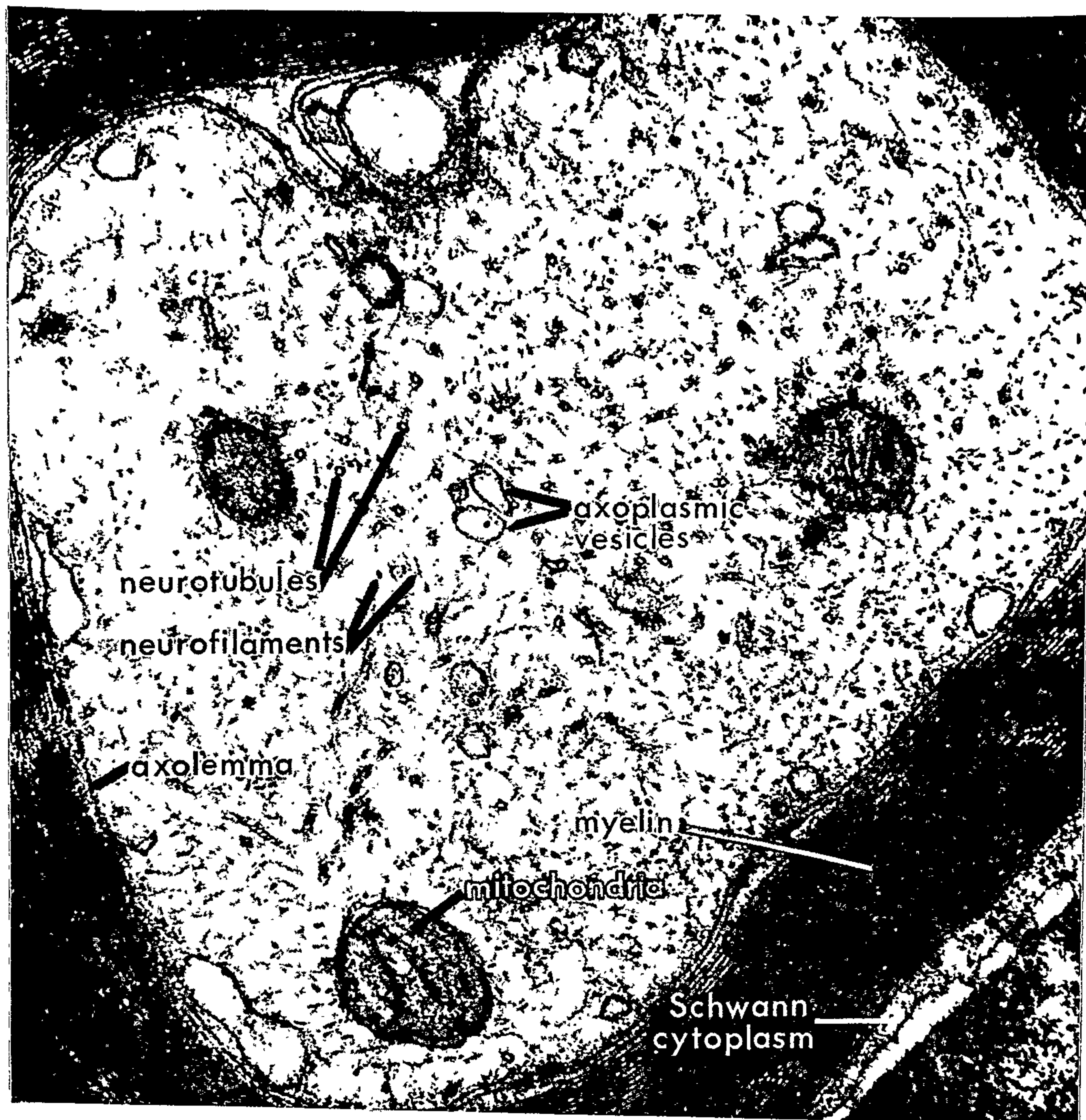


Figure 41. Electron micrograph of a cross-section of an axon showing various organelles. (From Ham, 1974)

these organelles was seen before the second day of Wallerian degeneration, which is contrary to the findings of Vial (1958) and Terry and Harkin (1959). He claimed the early disturbance of the colloidal medium (Noback and Reily, 1956) as a reasonable cause for the disturbance and aggregation of the neurofilaments.

Changes in the mitochondria (namely, swelling) were attributed to one of two mechanisms:

- (a) channels may exist between the axoplasm and the intramitochondrial substance as found in the mitochondria of other tissue cells (Chandra, 1962) and any disturbance in the axoplasm could spread directly into the mitochondria through these channels;
- (b) the sequelae of the trauma may affect the osmotic equilibrium outside and inside the mitochondria, resulting in their swelling.

If the second mechanism (b) is valid this could also apply to the endoplasmic reticulum. However, this is yet to be confirmed. Lee observed an increase in mitochondria and dense bodies or particles two days after neurotomy. This had been observed by Causey and Hauffman (1955), Engstrom and Wersall (1958), Vial (1958) and Terry and Harkin (1959), but no explanation was offered for this increase in the case of sectioned nerves. Webster (1962), who confirmed this increase in particles in crushed nerves, suggested that the migration and proliferation of axonal mitochondria might be responsible for the increase.

Hudson and his collaborators (1961) and Smith (1961) had reported definite increases in mitochondria in the cell body following nerve section and there was evidence (Hudson et al., 1961) of a significant correlation between the average increase in the number of dense bodies and that of mitochondria. They assumed that the mitochondria might be derived from the dense bodies. Hay (1960), Webster (1962) and many other investigators have claimed that the neuronal mitochondria are formed in the cell body and migrate into the axon. This could explain

the mitochondrial increase in crushed nerves or in a damaged nerve fibre where there is cytoplasmic continuity with its cell body, but cannot explain the mitochondrial increase in the distal stump severed from its perikaryon. Lee (1963) noticed large dense bodies the size of microbodies in various stages of differentiation into mitochondrion-like structures in the axoplasm of severed nerves and in the cytoplasm of Schwann cells. He believed that the numerical increase of mitochondria in the distal stump may be due to local proliferation of dense bodies and to their subsequent differentiation and that these dense bodies may serve as an intermediate stage in the formation of mitochondria.

Lee noticed also that the axons of unmyelinated fibres disintegrated much later than those of myelinated fibres. Axons of unmyelinated fibres were observed in the distal stump at seven days by Hojin and his co-workers (1959), at fifteen days by Taxi (1959) and at 28 days by Lee (1963) following neurotomy, when all the axons of myelinated fibres had disappeared. This observation is in agreement with the physiological findings of Rosenblueth and del Pozo (1943) but in contrast to the light microscopic findings of Nageotte (1932) and Guth (1956) and to the electron microscopic observations by Ohmi (1961), who found that the axons of unmyelinated fibres disintegrated earlier than those of myelinated fibres. Lee (1963) believed the longer survival of unmyelinated fibres to be due to the more intimate relationship of these fibres to the cytoplasm of the Schwann cells whose metabolism is independent by comparison to the other neural elements (Guth, 1956), i.e. during proliferation Schwann cells undergo chemical alterations and this proliferation of Schwann cells is neither regulated nor accelerated by outgrowing neurites or central impulses. Lee (1963) claimed that by the 14th day the myelinated fibres were devoid of axons (substantiated by Sunderland, 1968) and that the myelin sheaths had collapsed and fragmented. However, during this period of Wallerian degeneration the axons of unmyelinated fibres were still preserved although starting

to show degenerative signs. The changes occurring in the myelin and Schwann cells are discussed under the sections dealing with demyelination and Schwann cells.

a) CELLULAR RESPONSE

Central cell

There is a typical reaction which occurs in the central cell. The cell body swells, becomes round and the cell boundaries between the dendrites assume an abnormal ballooning (normally concave) (Bloom and Fawcett, 1975). The nucleus which is centrally placed assumes an eccentric position moving away from the axon hillock (Figs. 42,43). The swelling is due partly to uptake of water and partly to an increase in organic material (Brattgard et al., 1957). The orderly array of the granular endoplasmic reticulum is disrupted and there is loss of ribosomes from the outer surface of the cisternae and an increase in the number of free ribosomes in the cytoplasmic matrix. Numerous coarse neurofilaments make their appearance and swarms of dark vesicles (apparently from the Golgi apparatus) are seen suggesting a role in resynthesis of the granular endoplasmic reticulum. These reactions reach a maximum 10-20 days after axon injury and are more marked when the injury is close to the cell body. The end result of these reactions may be cell necrosis, a full recovery or the persistence of a residual defect that reduces the efficiency of the nerve (Fig. 44). The changing histologic picture of the affected cell body reflects changes in the biochemistry of the cell. This is discussed also under chromatolysis.

Demyelination

Geren (1956) demonstrated by electron microscopy that the myelin in the peripheral nervous system was a tightly wrapped spiral extension of Schwann cell plasma membrane and was thus an integral part of it (see Chapter 8). A classical and convenient way of studying demyelination is to follow the course of Wallerian degeneration. Excellent reviews



Figure 42. Normal cell body showing Nissl bodies and centrally placed nucleus. (From Ham 1974)



Figure 43. Central cell body showing typical response to injury - eccentric nucleus and chromatolysis.
(From Ham, 1974)

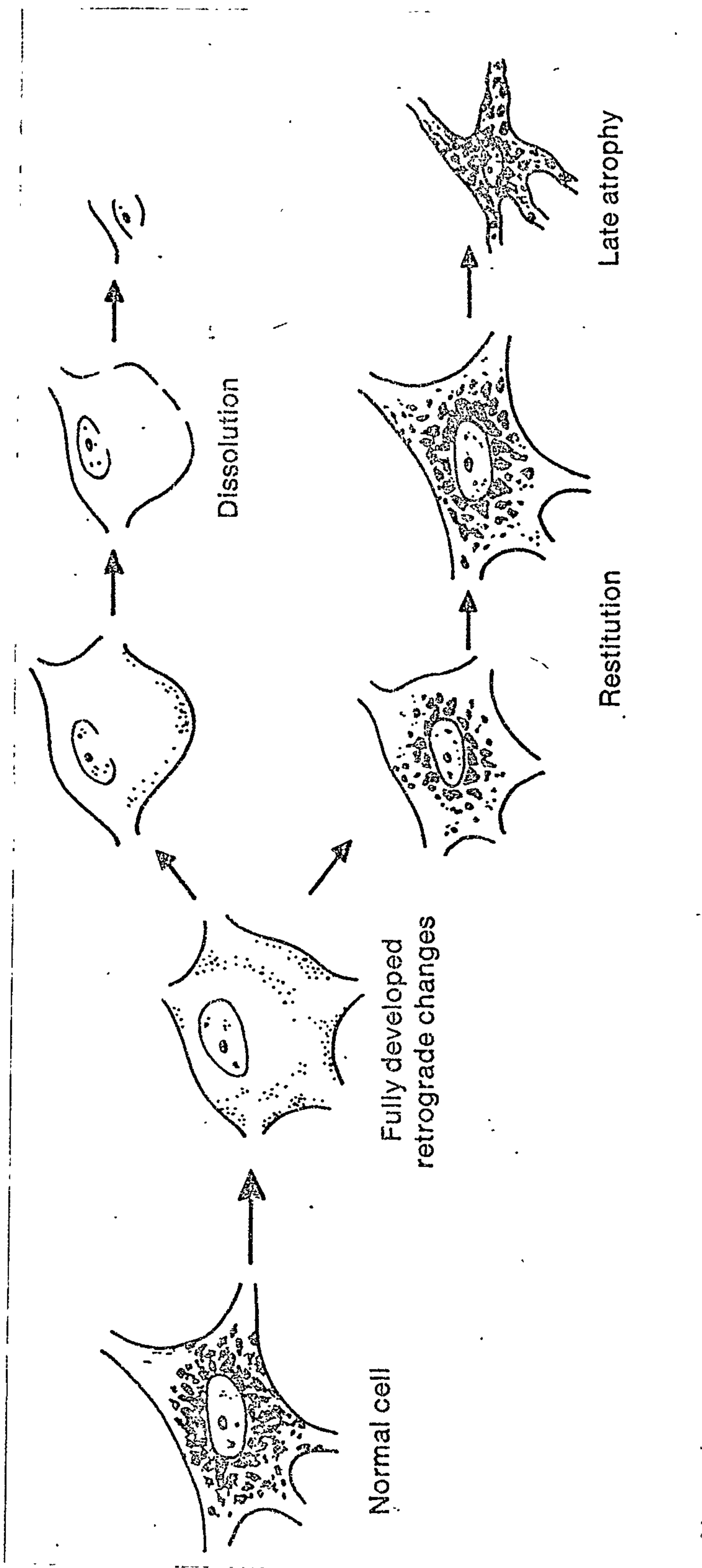


Figure 44. Possible pathways of nerve cell response to injury. Atrophy will be an end-result if function is not re-established.
(Adapted from Brodal, 1969)

dealing with this topic include those of Cajal (1928), Young (1942), Weiss (1944 a) and Guth (1956).

According to Nathaniel and Pease (1963 a) a gradual laminar disintegration of the myelin without any preferred site of initiation occurs following axon damage in myelinated fibres. This causes the lamellae to separate creating spaces of considerable size (Fig. 45). This observation is supported by Lee (1963). Simon (1966) further enlarged by saying that the myelin is broken down in an orderly, sequential manner, starting with myelin that was laid down last and progressing towards myelin laid down early in the period of myelination.

The breakdown of the myelin is faster in the fibres of smaller diameter and the large myelinated fibres degenerate most rapidly of all. The myelin is seen first retracting from the axon at the nodes, leaving a greater area of naked axon. The retraction occurs at the nodes nearest the lesion and secondarily spreads peripherally (Causey and Palmer, 1953). These changes are followed by the fragmentation and degeneration of the myelin into lipid droplets (Cajal, 1928; Weddell and Glees, 1941).

Barr (1974) found that short ellipsoidal segments of degenerate myelin appear in the first few days following nerve injury. Sunderland (1968) confirmed this and stated that this occurs within 28-96 hours. Gradually complete disintegration of the myelin occurs and the resulting particles of degenerating myelin disappear over a period of several weeks.

From light microscopic studies Guth (1956) concluded that there were no remnants of myelin sheaths after the fourteenth day of Wallerian degeneration. This is in contrast to findings of electron microscopy by Lee (1963) where free and phagocytosed myelin fragments were noticed 28-35 days following neurotomy.

The break-up of the myelin into globules and the removal of the latter is associated with the activity of the macrophages. Myelin globules

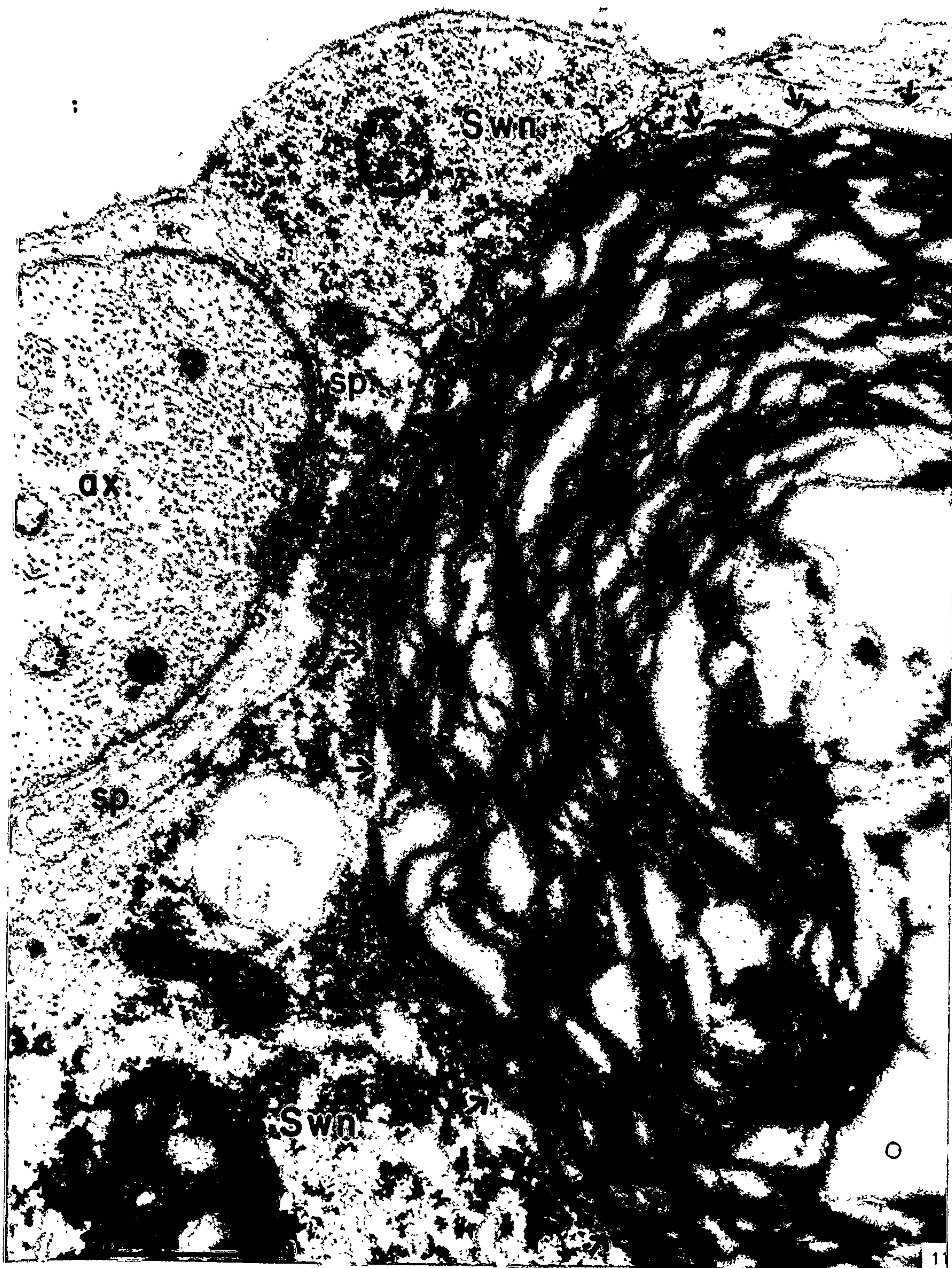


Figure 45. Lamellar disintegration of the myelin sheath (arrowed). Note Schwann cells (Swn), Axon (Ax), space (sp). (From Nathaniel and Pease, 1963)

have been reported in the Schwann cell cytoplasm (Fig. 46) as early as the second or third day (Ohmi, 1961) but Lee (1963) could find no fragmentation of the myelin before the seventh day. The segmentation of the myelin follows as a mechanical result of the collapse of the neurone due to disintegration of the axon. These physical changes are completed by about the eighth day when chemical disintegration commences and complex lipids are broken down into simpler fats. Setterfield and Sutton (1935) claimed that the chemical breakdown of myelin involves its conversion into isotropic granules of triglycerides which begins as early as the 18th hour and is completed by the 6th day.

Several workers (Johnson et al., 1950; Kline et al., 1959; Simon et al., 1969) have reported that cholesterol esters were not found in normal nerve and that the cholesterol in normal nerves remained fairly constant. However, due to chemical changes during the process of degeneration the amount of cholesterol ester increased.

These chemical changes can be assumed to be due to the activity of enzyme systems derived from a cell type which may be present in small numbers in normal nerves but would be present in great numbers during the active stages of Wallerian degeneration. Both the macrophages and the Schwann cells meet these requirements (Sunderland, 1968) and either or both could provide the source for these enzyme systems.

must vary because free and phagocytosed myelin remnants have been reported as being present three months (Barton, 1962) after neurotomy. The breakdown products of the axon and myelin are finally removed by phagocytes, the origin of which is still often questioned (see under Schwann Cell).

Schwann Cell

Investing the myelin and intimately related to it, is a single layer of flattened Schwann cells. Schwann cell activity is greatest during Wallerian degeneration (Sunderland, 1968) and proliferation of Schwann



Figure 46. Transverse section of a Schwann cell showing myelin fragmenting into many separate globular masses of varying size and complexity within the cell cytoplasm.
bm - basement membrane; ax - regenerating axons;
mg - myelin globules.
(From Nathaniel and Pease, 1963)

cells is due either to a chemical mediator liberated when myelin and axon disintegrate or physical factors introduced when the axons collapse. The degree of proliferation is proportional to the amount of fragmentation and the larger the fibre the greater is the cellular proliferation (Causey, 1960; Barr, 1974). Following injury to the nerve it is seen that the nuclei of the Schwann cells multiply (Bloom and Fawcett 1975). These cells also enlarge and develop prominent nucleoli and the presence of mitotic figures indicates cell multiplication which brings about a filling of the endoneurial tube (Causey, 1960) due to their containment within the endoneurium.

Schwann cell proliferation is a process wholly independent of axonal regeneration and this ceases when re-innervation has been completed. Studies on the rabbit (Abercrombie et al., 1946 b) and the cat (Logan et al., 1953) have shown that on sectioning the sciatic nerve, cellular proliferation did not occur in the first three days but by the 25th day it was eight times the normal amount. By the 225th day it had dropped to five times the normal.

Guth (1956) claimed that the proliferation of Schwann cells occurs between the 4th and 7th day after the sectioning of rabbit cutaneous nerves and by the 14th day all remains of the axon and the myelin sheath have disappeared due presumably to migration and phagocytosis by Schwann cells (further discussed later). This proliferation and migration of the Schwann cells is thought to be responsible for the phagocytosis of degenerating debris and certainly forms the bands of Von Bungner. It is not strictly restricted to the distal stump but occurs in both the proximal and distal segments and thus bridges the gap between the proximal and distal stumps of the nerve fibre (Fig. 47). However, Schwann cell activity in the distal stump is greater (Logan et al., 1953). Denny-Brown (1946a) believed, on the basis of staining properties, that the proliferated cells in the space between the cut ends of the nerve are fibroblastic rather than of Schwann cell origin. However, unmyelinated fibres do not show this early cellular

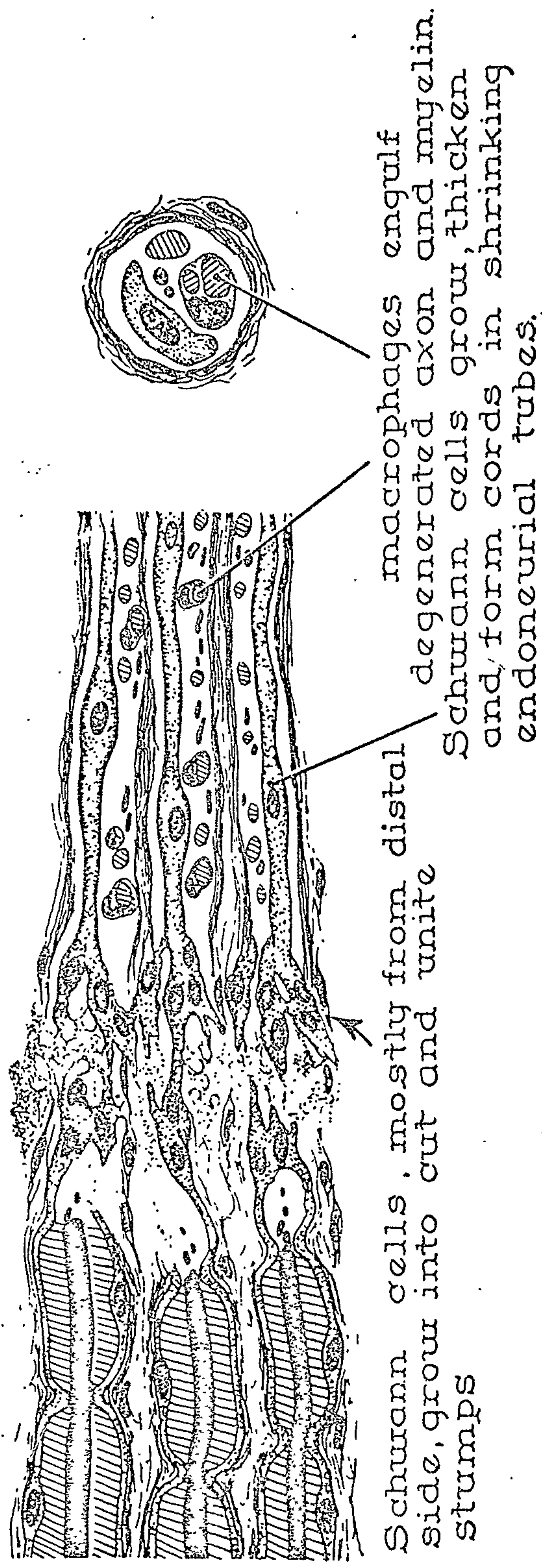


Figure 47. Schwann cells bridging gap and re-establishing continuity between proximal and distal stumps. (From Ham, 1974)

increase after sectioning (Joseph, 1950) and Logan and his co-workers (1953) indicated that regions further away from the lesion show slower and smaller increases in cellular population.

When resorption of the debris is completed, Schwann cell multiplication ceases and the cytoplasm of the proliferated and hypertrophied Schwann cells decreases in volume. During this period they also proceed to form Schwann bands (bands of Von Bungner; neurilemma bands or cords) intimately covered by endoneurium (Weddell and Glees, 1941).

The formation of the bands of Von Bungner preserves the architecture of the nerve and in essence these bands keep the tube patent for the regenerating fibres.

During proliferation, the Schwann cells also undergo chemical alterations. The cytoplasm and nucleoplasm increase in volume and large RNA containing regions appear in the nucleus indicating increased protein synthesis. Following transection of the rat sciatic nerve, Schwann cells become metachromatic in a matter of three to four days and the gradual increase in intensity of this was found to parallel the rate of increase of cytoplasm. This increase appears at the same time chromatolysis and protein depletion are occurring in the cell body but ceases by the time protein synthetic activity commences in the perikaryon (Hyden and Rexed, 1943).

Nathaniel and Pease (1963 a) used electron microscopic studies to show that the major changes in the cytoplasm of the Schwann cell during degeneration are an increase in the amount of cytoplasm and mitochondria and an elaboration of an abundant endoplasmic reticulum with free and attached ribosomes (Fig. 48). This increase in rough endoplasmic reticulum suggests that there is an acceleration of enzyme production so that digestion of axon and myelin debris is enhanced. They further stated that the number of Schwann cells associated with myelinated and unmyelinated fibres was about equal. They showed that as early as 24 hours following injury, there was a modest increase



Figure 48. Hypertrophied Schwann cell. Note rich development of endoplasmic reticulum (e.r.) with conspicuous ribosomes. (From Nathaniel and Pease, 1963)

in the ribosomes of the Schwann cells of both myelinated and unmyelinated fibres but no other detectable morphological changes were observed either in the axon or myelin. Ninety-six hours following such injury there was a generalized hypertrophy of the Schwann cells associated with a considerable increase in the number of ribosomes which were distinguished by their density and common occurrence as rosettes. This hypertrophy, protein density and increased concentration of ribosomes reached a maximum in about a week. All this was maintained at these high levels as long as there was degenerating myelin to be digested. The other organelles of the Schwann cells appeared not to be notably affected e.g. mitochondria, Golgi system. Mitotic figures were seen at four days following injury to the nerve (Fig. 49). The early degenerative changes in the unmyelinated fibres did not differ significantly from those which occurred in the myelinated fibres.

Lee (1963) in his investigation found no mitotic figures in any of the Schwann cells and that changes in the organelles of the Schwann cells began later and proceeded more slowly than those in the axoplasm and myelin sheaths. The changes in the Schwann cell organelles became apparent in both myelinated and unmyelinated fibres two days after neurotomy, and were very marked after 12 to 14 days and many persisted longer than thirty-five days. The ultimate fate of these cells in the distal stump of the sectioned nerve is still uncertain. Some assume that they finally degenerate, others that they survive for more than a year, while still others claim that they are transformed into macrophages (Nageotte, 1932; Terry and Harkin, 1959). However, Lee (1963), whose investigations lasted only thirty-five days, observed that during Wallerian degeneration the Schwann cells underwent various modes of changes; a few degenerated, some acted temporarily as phagocytes, the rest survived up to thirty-five days and then gradually changed into a cell type indistinguishable from the macrophage.

The life history of the phagocytic cell which is active following nerve



Figure 49. A mitotic figure seen in a Schwann cell containing degenerating myelin four days following injury.
(From Nathaniel and Pease, 1963)

injury, has been studied in some detail but as yet its source is not well known. There is conflicting opinion as to the precursor of this phagocytic cell. Raymond Cajal (1928) believed it to be a blood leucocyte. Weiss and Wang (1945) from tissue culture studies reported that Schwann cells are the major source of phagocytes. Besides migrating and organising to form neurilemma bands they apparently proliferate and change into macrophages. Their studies indicate that tissue cultured Schwann cells are capable of ingesting ink particles as well as their own myelin fragments and this supports the theory that one of the roles of these cells is to behave as common macrophages following injury. They therefore concluded that the bulk of the phagocytic role is carried out by the proliferated Schwann cells in association with fibroblasts which have been converted into macrophages. Their function as macrophages is further confirmed by Ohmi (1961). He observed under the electron microscope the presence of large amounts of myelin debris in the cytoplasm of the Schwann cells following nerve injury (Fig. 50). Later studies of Nathaniel and Pease (1963 a) also confirmed Ohmi's observations and they further elaborated that the Schwann cells are the predominant cellular elements seen in normal adult peripheral nerves.

Although this role of the Schwann cell has been questioned by some, the balance of evidence does point to their transformation into macrophages during degeneration (Lee, 1963; Satinsky et al., 1964). It has been described as a pluripotential role (Satinsky et al., 1964). During degeneration, due to cytoplasmic changes, macrophages of Schwann cell origin are almost indistinguishable from other macrophages. The difference between these two types of cells is related to the basement membrane found to surround those of Schwann cell origin but not the connective tissue cell type (Nathaniel and Pease, 1963 a) (Fig. 51). The phagocytosis of myelin breakdown products and the remyelination process seem to occur from within the same Schwann cell (Fig. 50). However, this phagocytic role of the Schwann cell is not



Figure 50. Schwann cell indicating presence of myelin debris (M) in its cytoplasm. Note remyelination and mesaxon (m). (Satinsky, Pepe and Liu, 1964)

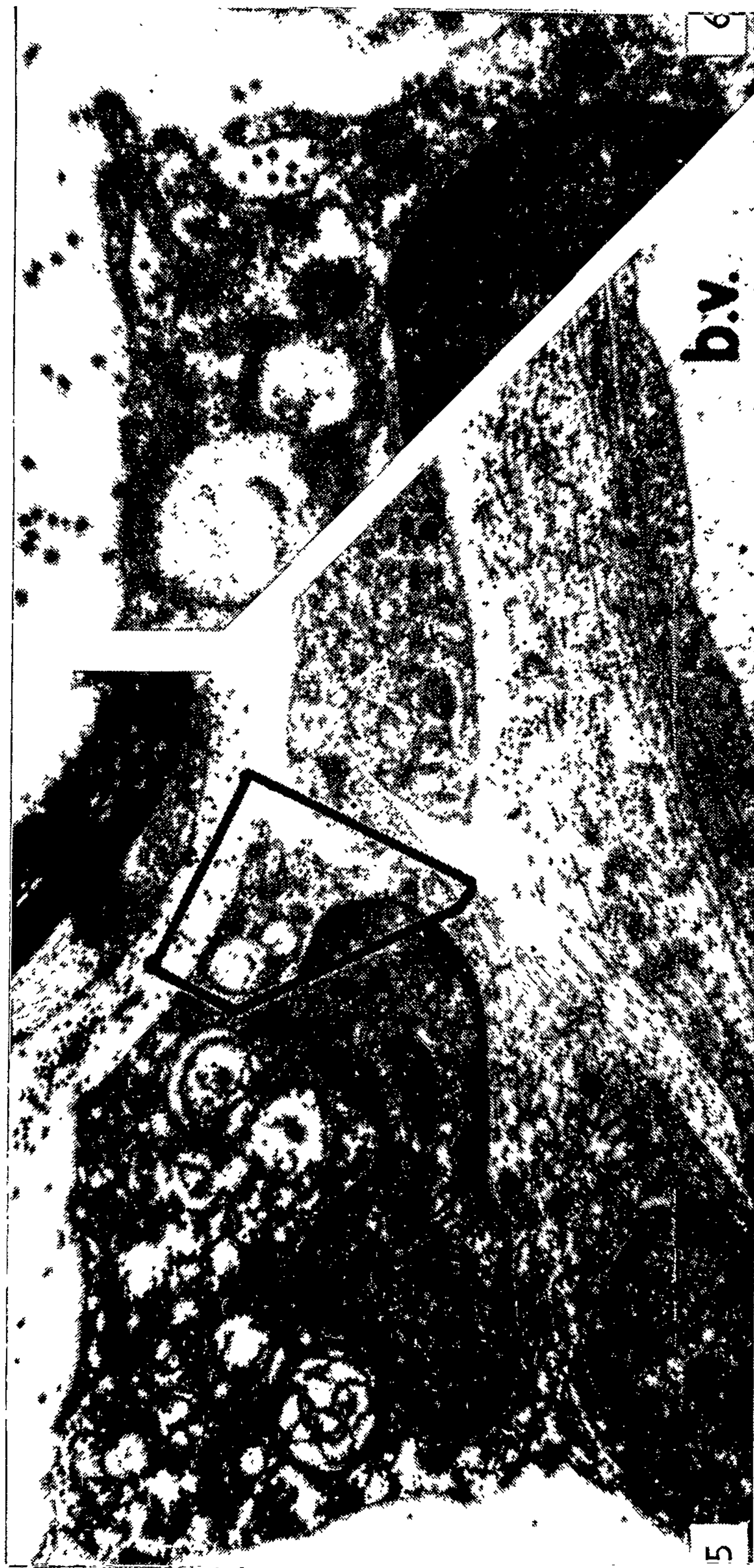


Figure 51. Photomicrograph of connective tissue macrophage associated with a blood vessel (b.v.). Note the enlargement which shows pseudopods and lack of basement membrane thus distinguishing it from a macrophage of Schwann cell origin. (From Nathaniel and Pease, 1963)

seen in the intact nerve and seems to be triggered during degeneration. Some workers assumed that the fragments of axon and myelin are ingested by tissue macrophages and macrophages of haematogenous origin. Nathaniel and Pease (1963 a) and Barr (1974) claimed that the elimination of myelin is in essence an autodigestive process on the part of the Schwann cells. They metabolise their own breakdown products of myelin. These workers said that histiocytes or invading haematogenous cells play no part in the phagocytosis of myelin as they are never found in appreciable quantities in the endoneurium. It takes Schwann cells at least several weeks, sometimes up to 3 months, to autodigest their own damaged myelin. By the time the myelin sheaths on regenerated axons have reached full thickness, which requires about 3 months, almost all degenerating masses have disappeared. This does not prevent the regeneration of new fibres and by the second week new myelin is being formed (Nathaniel and Pease, 1963 a). In addition reinnervation of the regenerating axons may serve to hasten the process of autodigestion of myelin (Nathaniel and Pease, 1963 a). However, Causey (1960) from his studies pointed out that 85% of the cell population of peripheral nerves are Schwann cells while only 10% are endothelial and the remaining few are fibroblasts, histiocytes, etc. Macrophage activity commences about the 3rd day following trauma to a nerve and removal of debris from the degenerating material is completed by the 4th week (Sunderland, 1968). Young and his co-workers (1940) stated that macrophages enter the endoneurial tube and on completion of their role depart leaving the Schwann cells as the sole occupants of the endoneurial tube. Beside the phagocytic properties they possess, in nerve injury when the axon is severed, the Schwann cells and fibroblasts proliferate out into the gap and bridge the defect between the two segments of the sectioned nerve at a rate not exceeding 0.3 mm per day. This occurs from both the proximal and distal endoneurial tubes and results in the continuity of the tube being re-established. Finally, all that remains following the removal of the

debris of degeneration is the central core of Schwann tissue enclosed in a sheath of endoneurium awaiting the arrival of regenerating fibres (Sunderland, 1968).

My own conclusions from observation of the electrical skin stimulation tests indicate that the current required to obtain a response is less when the test is carried out within 24 hours of the injury. This clinical impression arises from results in a limited number of cases but was quite distinct despite adverse clinical problems which would all amount to an expectation of a higher reading. For example the lips were oedematous and patients reaction to pain was depressed due to sedation and G.A. The stimulus required to obtain a response is greater in the subsequent 24-48 hours or 72 hours and therefore false readings are likely to be eliminated. This observation would tie in with Sunderland (1968) who states that the changes in the axon occur within 24 hours whilst changes in the myelin sheath are evident 28 to 96 hours following injury. This might be the contributing factor why conduction does not cease immediately following injury. On the question of the function of Schwann cells as macrophages, Professor Sunderland (1979) believes that the number of fibroblasts in the endoneurium is scanty and could not account for the large number of macrophages found during degeneration. He believes that the Schwann cells act as macrophages and contribute significantly to the removal of the debris. This and the presence of a large number of macrophages further indicate that mitotic activity occurs in Schwann cells (confirmed by a number of authors) although Lee (1963) did not observe any mitotic figures.

8. NERVE REGENERATION FOLLOWING TRAUMA

INTRODUCTION

Following the degenerative phases described in the previous chapter, processes of regeneration can now be separately described. These include all those processes which go on to restore the capacity for effective function in nerve tissue.

i) THE PROCESS OF REGENERATION

Regeneration commences at the distal tip of the proximal axon adjacent to the site of injury and is a very active process. The aim of this activity is to replace that section of the nerve which has degenerated distally in order to restore the original anatomical features and physiological properties of the nerve fibre (Young, 1942).

The quality and extent to which regeneration occurs is greatly dependent on the degree the proximal and distal templates for reinnervation are preserved, i.e. the state of the endoneurial tube following injury (Hubbard, 1972).

Regeneration results from an amoeboid extension of the distal tip of the proximal stump of the severed axon (Lewis, 1945). The axoplasm for this growth is the result of protein synthesis in the nerve cell body. The protein formed is passed distally towards the fibre tip in a continual proximo-distal axoplasmic flow (Hyden, 1943). From his experiments constricting nerve fibres with clips and cuffs, Weiss (1943 b) has shown that there is damming of the axoplasm central to the constriction due to pressure which is exerted from the cell body. Following the release of the clip or cuff there is a flow of material proximo-distally. It has also been shown under the microscope that large masses of this viscous material are present on either side of the crushed region. There is also an accumulation of tissue fluid in the endoneurium at the axon tip which serves as a superior growth medium for the outgrowing Schwann cells and nerve sprouts. Weiss (1943 b) claims that this medium possesses anti-fibrotic properties.

The regenerative process for all nerves after injury follows an established pattern (Fig. 52), but the period taken for the completion of this process varies

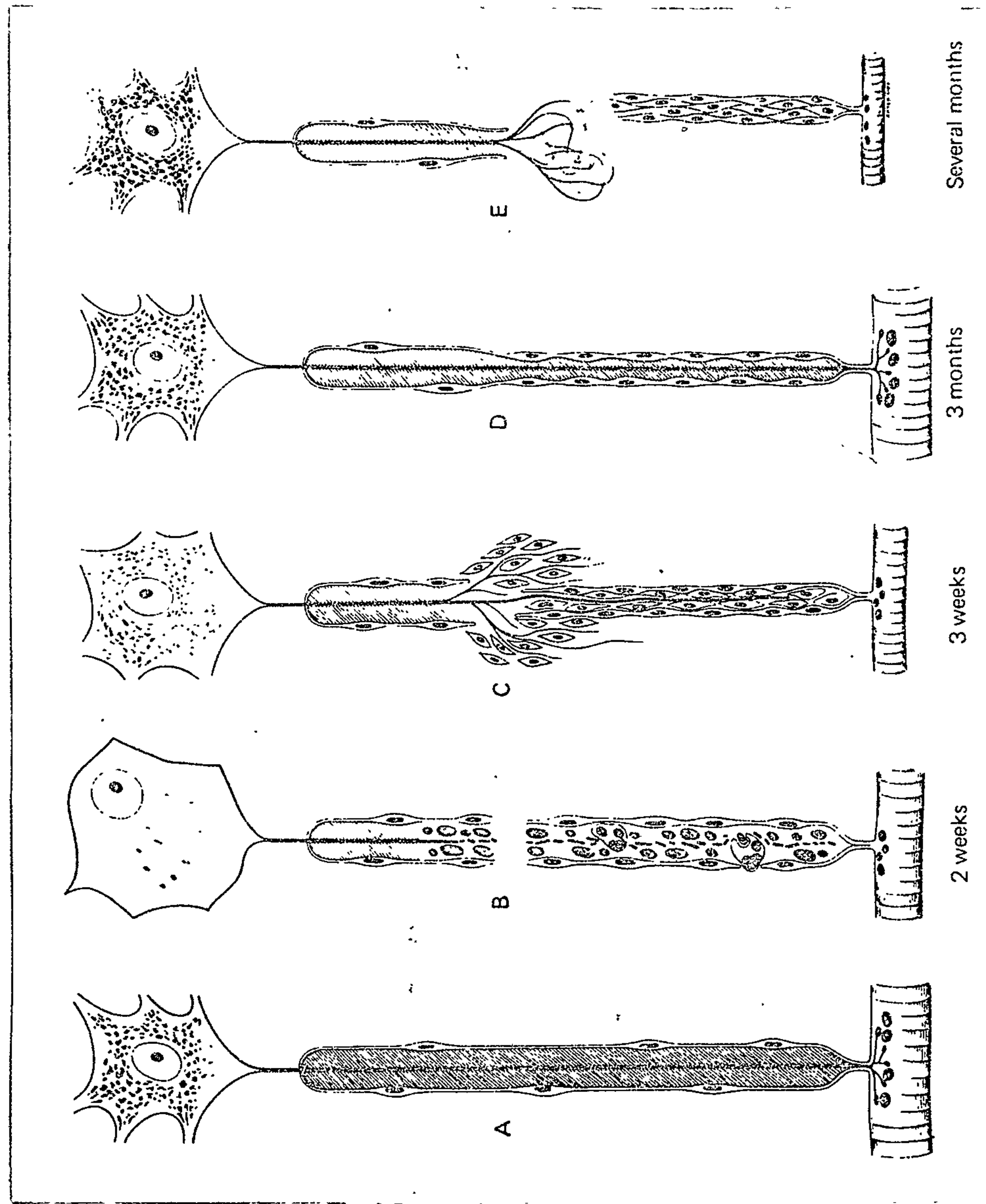


Figure 52. Stages in the regeneration of an injured nerve. Note failure of regeneration due to an amputation neuroma. (From Junquera et al)

considerably. The regenerative process may be delayed or arrested at any stage during, or after, the restoration of axonal continuity with the periphery. This introduces wide variations in the interval between injury and recovery and therefore it is impossible to predict with any certainty the precise time course of regeneration in any individual patient. A whole series of processes occurs before functional recovery is achieved and an understanding of the rates at which each of these processes occurs is of great significance. According to Young (1942), the steps in regeneration of all nerves are:-

- (a) Closure of the gap between the severed stumps mainly by some outgrowth of Schwann cells from the distal stump and to some degree from the central (proximal) stump.
- (b) Retrograde degeneration of the cut central end of the nerve fibre and the sending out of many fine branches.
- (c) The progress of the tips of the axons from the central stump across the scar to the peripheral (distal) stump.
- (d) Break-up of the axons and myelin in the peripheral stump and removal of them by macrophages.
- (e) Multiplication of the nuclei of the Schwann cells and increase in the volume of their cytoplasm to make the Schwann bands (bands of V. Bungner) which eventually fill the old sheaths.
 "Bungner bands" may be defined as cords of reactive Schwann cells which have become arranged into a syncytial structure replacing axon-Schwann cell units following Wallerian degeneration. Schwann cell multiplication is one aspect of their development and these bands are established as a preparatory step for the reception of new regenerating axons (Nathaniel and Pease, 1963 b).
- (f) Progress of the axon tips along the peripheral stump, their arrival at the end organ and union with it.
- (g) Increase in the diameter of the fibres originally laid down, their myelination and maturation before they can conduct impulses and produce effective function (Pumphrey and Young, 1938).

The principles of growth of the axons regenerating after injury are similar to those of the growth of young axons (Ranson and Clark, 1959). During regeneration the growth of the axon tip to the end organ is one of the most dramatic of the phases in the process of regeneration but this does not imply that the re-established muscle function and sensation are of pre-accident quality (Young, 1942). The nature and severity of the injury have a direct bearing on this quality of returning sensation as discussed under classification of nerve injuries. Seddon (1943) and Sunderland (1968) have described a number of stages in the process of nerve regeneration in a somewhat more condensed form. Significant factors contributing to the time lapse of the process of regeneration can be considered as follows:

An Initial Delay at the Site of the Lesion.

During the initial delay following injury the neurone recovers before any axonal growth commences to reach the injured zone. The time required for the neurone to recover sufficiently before regeneration commences depends on the severity of the injury and its proximity to the cell body. Bowden and Scholl (1950) claimed that there is a delay of 2 to 15 days in injuries in which the endoneurial wall is undamaged, but this varies up to several months in severe injuries where the endoneurial tube and nerve have been torn and severely stretched, or where infection or concomitant bone injury is associated.

The Scar Delay.

This is the time taken for the growing axon to traverse the injured zone. The extent of the injured zone and the density of the scar tissue determine the time taken for the regenerating axon to reach the distal tube. Dense scar tissue would encourage neuroma formation and reduce the quality of restored function.

The period during which the axons extend distally to reach the end organ.

During this process the axon crosses the zone of injury, enters the endoneurial tube, approaches the appropriate end organ and re-establishes the original pattern of innervation. The distance to be covered and the rate of advance

determine the time taken by the regenerating axons to reach the afferent receptors.

The time that elapses between the arrival of the fibres in muscle or skin and the re-establishment of function.

This last phase is most complex because of the time required for "maturation" of the fibres and for clinical recovery to become manifest (Seddon et al., 1943).

a) AXON RESPONSE TO INJURY AND NERVE SPROUTING.

Two to three days following severance of a nerve, signs of healing occur at the open end of the neurone. After a week there is a vigorous sprouting of the axons. In traumatic injuries due to blasts, this axonal sprouting may be seen one, two or three centimetres proximal to the point of severance (Haymaker, 1948) but in a clean operative sectioning of the nerve this distance is only a few millimetres retrograde to the last intact node of Ranvier (Ducker, 1972). Axon branching or sprouting 6 mm proximal to the point of injury has been described by Shawe (1955). He stated further that in the initial stages the advancing axon and its sprouts are confined to the endoneurial tube and his investigations showed that the larger axons formed more sprouts than the small ones. The progress of the axon tip distally is the resultant of the combined action of forces originating from the central cell due to the changes occurring there (see chromatolysis).

Davenport and his co-workers (1937) said that up to three, but rarely four, of these axon sprouts acquire a myelin sheath in a single endoneurial tube and according to Weddell (1942) one sprout ultimately dominates the growth pattern and the other axon sprouts fail to survive (Fig. 52 c and d, 56). This concept is supported by Denny-Brown and Brenner (1944c) who found that "regeneration of fibres in intact Schwann tubes involved an initial production of a large number of fibres (sprouts) by the parent axis cylinder. Early maturation of one of these, presumably that which penetrated furthest, was followed by progressive resorption of the remainder".

Nathaniel and Pease (1963 b) from electron microscopic studies found multiple axons in the Schwann cells during regeneration of a nerve fibre (Fig. 53). They noticed that the Schwann cells associated with the unmyelinated fibres do not hypertrophy as is the case with those that are to be myelinated. They further observed, as others had, that in a myelinating Schwann cell one axon sprout tends to be favoured, usually the one that is thickest, and becomes myelinated while the others are suppressed and later resorbed. Following completed regeneration they could not observe multiple myelinated axons in single endoneurial tubes and they stated that most of the axons which eventually become re-myelinated are associated with Schwann cells that originally had hosted axons of the same size. Initially the regenerating axons are seen singly or in groups between the basement membrane investment (see section on Schwann cells) and the Schwann cells without being embedded in the latter. Later, gutters are formed in the Schwann cells' cytoplasm and the axons become embedded (Nathaniel and Pease, 1963 b) (Fig. 19). The events described above indicate the importance of the Schwann cells as a guiding and orienting structure for the regenerating axon.

Studies on regenerating nerves in the cat show that the new nerve fibre begins as a fine axon growth which gradually increases in diameter and myelination, and that the conduction velocity and threshold of excitability are related to these two morphological features (Berry et al., 1946). Holmes and Young (1942) found that the increase in axonal diameter is rapid - 1.2μ at 15 days, 2.3μ at 25 days and 7μ at 100 days.

b) CELLULAR RESPONSE

Within hours after injury there is an increase in metabolic activity in the central cell, the Schwann cells, the perineurial epithelial cells and in the epineurium. Cellular proliferation of nearly all these elements occurs in both the proximal and distal stumps (Ducker and Hayes, 1968). The cellular population of the nerve distal to the site of injury shows a substantial increase mainly as a result of local cellular proliferation. The

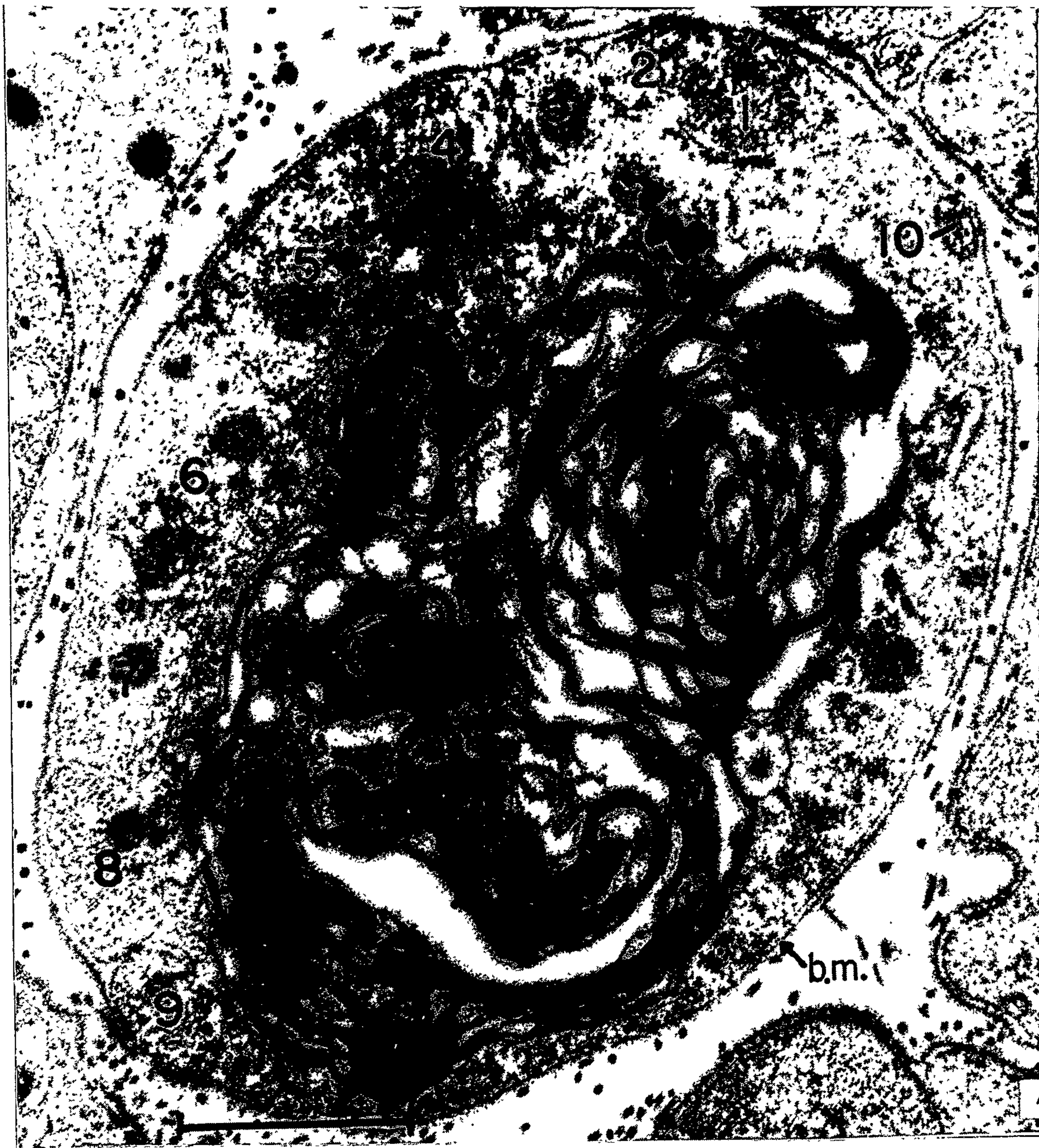


Figure 53. Multiple regenerating axons (1 to 10) in a single Schwann cell.

b.m. - basement membrane

(From Nathaniel and Pease, 1963)

increase is predominantly Schwann cells and is greatest in nerves containing a high proportion of large myelinated fibres (Thomas, 1948) and least in unmyelinated axons (Abercrombie et al., 1959). It is uncertain whether the increase (Abercrombie and Johnson, 1946a) is dependent upon a chemical stimulus provided by the degenerating axons or on the size of the vacant space created by fibre degeneration (Joseph, 1950).

Central Cell Body Reaction

While Wallerian degeneration is occurring peripherally the fundamental response in the central cell following nerve injury is known as chromatolysis. This takes place throughout the cell body including the axon hillock. Between 24-48 hours after interruption of the axon the coarse clumps of Nissl material become dispersed into fine granules. This process gradually spreads throughout the perikaryon or central cell body and is often referred to as retrograde chromatolysis (Bloom and Fawcett, 1975) (Fig. 38).

Morphologic changes in the central cell

Morphologic changes in the central nerve cell body vary according to the type of neurone and the species affected, e.g. there is no change in the motor cells of the rat and rabbit following peripheral nerve section whereas a typical reaction occurs in sensory as well as motor cells in most animals including man (Barr and Hamilton, 1948).

In peripheral nerve injury the central cell begins to progressively enlarge at about the third or fourth day. This enlargement reaches a peak between the fourth and twentieth days and persists as long as there is active regeneration (Fig 52 b, c). Following conduction maturation, the enlarged cell returns slowly to normal size (Fig. 52 d). The entire nerve is dependent on the central cell for its substrates and no significant protein is synthesised along the course of the axon (Droz, 1969).

Metabolic Changes in the Central Cell

Metabolic alterations to the central cell are associated with all peripheral nerve lesions. Changes seen in the metabolic system are the same for all neurones be they motor or sensory.

Sanders (1948) stated that the properties of the axon and the axoplasm proximal to the injury provide the environment for the initial regenerative process to occur. Bodian and Dziewiatkowski (1950) were of the opinion that the metabolic changes in the nerve fibre proximal to the injury are primarily responsible for axon regeneration rather than the readjustments occurring further centrally in the nerve cell. It is now well established that the central trophic centre (the central cell body) contains the organelles and nucleus that control the metabolism of the entire neurone (Fig. 54). The manufactured proteins are said to be transported to the periphery from the central cell in the axoplasm during the normal metabolic state and this passage is termed "axoplasmic transport" (Droz and Leblond, 1963). It is now generally accepted that, for the continuous growth and myelination, the regenerating axon is dependent on the parent cell.

Sunderland (1968) suggested that the forces that act to propel the axon tip distally come from changes that occur centrally in the cell. Similarly, the activity of the growth cone localized at the axon tip which causes an elongation of the axoplasm is brought about by impulses which come from the cell centre (see also axon response). The nutrients supplied to the nerve trunk or axon are transported down the axon by two processes. A slow component is mediated by peristalsis in the nerve trunk membrane and during the passage of the nutrients down the axon, proteins are partly consumed to replace the catabolised enzymes in the membrane (Turner, 1943). A significant fraction of this slow component of nutrients reaches the terminal segments of the axon and the synaptic region (Fernandez and Davison, 1969). The fast component is mediated by the microtubules

(Fig. 12, 55) in which the molecules move 100 times faster than the slow component (peristalsis) of 1 mm per day (Ochs et al., 1969). Metabolic activity in the central cell reaches two peaks when the nerve is injured; once soon after the injury and then again at the time of reinnervation following regeneration, i.e., when new sensory end organ attachments and new myoneural junctions are formed (Ducker, 1972).

Chromatolysis

This is a morphological term used to describe a sequence of changes (Nissl, 1892) occurring in the cell bodies (perikaryon) of neurones after injury to their peripherally directed axons (Fig. 43). Chromatolysis is always seen to be associated with peripheral nerve regeneration and this central cell activity is initiated by peripheral nerve injury (Engh and Schofield, 1972). Nissl (1892) interpreted chromatolysis as a primary cellular irritation resulting from axon injury. Gersh and Bodian (1943) termed these changes of chromatolysis as 'retrograde degeneration', i.e., disappearance of the prominent basophilic staining Nissl granules (now known to be clusters of ribosomes), early cellular swelling, migration of the nucleus to the periphery of the cell and decrease in ribonucleoprotein. This early and rapid depletion of Nissl material is related to disturbances in the cell control mechanism due to the loss of large amounts of cell cytoplasm (axoplasm) and to the increased growth requirements created by the early sprouting of the regenerating axon (Bodian, 1947). However, several workers (Brattgard et al., 1957; Edstrom, 1959; Hyden, 1960) disagreed with the degenerative concept and suggested that chromolytic neurones are hyperactive and regenerative and the chromatolysis represents a re-distribution rather than an actual reduction in the amount of ribonucleoprotein and they demonstrated increased total cellular ribonucleic acid. Using autoradiographic evidence Engh and his collaborators (1971) reported that in peripheral axon injuries there is initially a decreased

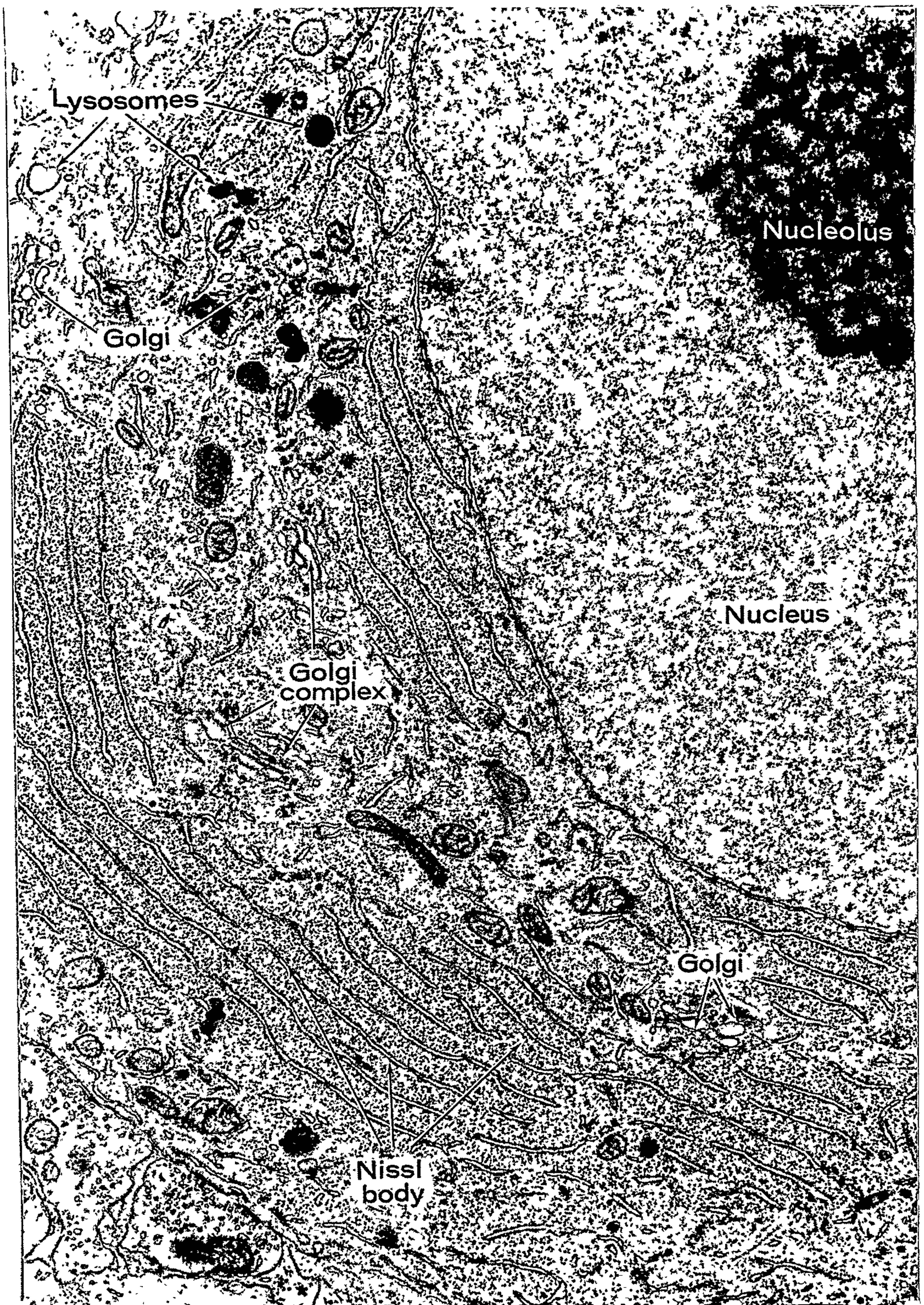


Figure 54. Electron micrograph showing portion of the perikaryon of a typical neurone illustrating the principle organelles concerned with cell metabolism. (Bloom and Fawcett, 1975)



Figure 55. Electron micrograph showing collagen deposits adjacent to Schwann cells. Inset shows part of an axon with numerous neurofilaments and micro-tubules. (From Junquera et al)

perikaryal synthetic activity and that this continues until successful peripheral axon regeneration is evident. Further, this decreased protein synthesis persists if successful peripheral regeneration does not occur. Centrally produced axonal cytoplasm is normally used along the entire length of the peripheral nerve and at its terminal endings. Axoplasmic function includes maintenance of the activity of peripheral nerve regeneration, maintenance of specialised end organ function and a trophic influence on non-nervous tissue. When the axon is cut, the last two functions are eliminated and therefore the demand for centrally synthesized axonal cytoplasm is reduced. Normal, and sometimes greater than normal, perikaryal cytoplasm production is observed with a return of normal perikaryal morphology, and this is characteristic of the maturation phase of peripheral nerve regeneration and occurs only if peripheral axon regrowth is successful (Engh and Schofield, 1972).

Chromatolytic changes obviously represent evidence of neuronal involvement, but the converse is not necessarily true (see Neurapraxia). There is no explanation for chromatolysis occurring in some cells following section of nerve trunks, and its absence in others of the same functional group (Smith, 1961).

Barr and Hamilton (1948) noticed that the rate of chromatolysis and cell recovery varies greatly in the same functional group. The greater the violence to the axon the more intense is the retrograde reaction (chromatolysis) and the intensity of the reaction varies inversely with the distance of the site of injury from the cell body (Bodian, 1947). Thus chromatolysis is greater after lesions close to the parent cell than after damage more peripherally. This is related to the amount of cytoplasm (axoplasm) amputated from the cell.

The number of cells that perish following nerve division varies

(Cavanaugh, 1951) and recovery of the neurone following chromatolysis depends on the union of the central and distal stumps of the severed nerve. If union does not occur, the central cell may die. Central cell reaction is more severe and rapid in sensory than in motor nerve damage (Cavanaugh, 1951). It has been shown experimentally that retrograde disturbance or chromatolysis extends beyond the cell originally involved by inducing trans-synaptic effects in related neurones (Matthews et al., 1960). During chromatolysis there is a depression, with possible failure, of synaptic transmission. There are also abnormalities in the pattern of synaptic activity and unfavourable effects on the integrative function of the neurones (Eccles et al., 1959).

Schwann Cell

Schwann cells are epithelial in character but ectodermal in origin and are extraordinarily specialised. These cells assume a phagocytic role at injury (see Degeneration) but later resume their original function of axis cylinder envelopment and myelin formation. It is confidently stated in the article by Nathaniel and Pease (1963 c) that the basement membrane is manufactured by the Schwann cells and that collagen fibrillogenesis goes on simultaneously within the basement membrane during regeneration.

The Schwann cell is held responsible for collagen production (Nathaniel and Pease, 1963 c). This is because of the presence of collagen adjacent to the Schwann cell (Fig. 55) and at remote distances from the nearest fibroblast. This collagen is deposited between the Schwann cells and their own basement membrane. These collagen fibres gradually disappear when normal axon-Schwann cell relationship is regained leaving only the basement membrane. Electron microscopic studies equate the neurilemma with the basement membrane envelope of the Schwann cell. They further

show that these envelopes guide and limit the movements of these active Schwann cells which play a key role in the organization and orderly development of the Bungner bands which are the result of Schwann cell multiplication following injury. Following reinnervation, the Schwann cells become quiescent with no evidence of duplication of the basement membrane. Schwann cells also have the ability to induce collagen production by fibroblasts (Barton, 1962). Nathaniel and Pease (1963 b) found mitotic figures indicating Schwann cell multiplication four days after the lesion. However, these mitotic figures were not common. In that study, it was thought that the most active proliferative period was missed and that the multiplication was limited to the time the Bungner bands were being established as a preparatory step for the reception of new axons (Rexed and Fredricksson, 1956). Schwann cells also possess substantial mobility during the early phases of regeneration and there is considerable overlapping of Schwann cells along the course of a single band at that point of time. This is only a transitory phase as hardly any overlapping of Schwann cells is seen at three months when regeneration is essentially complete (Nathaniel and Pease, 1963 b).

The Schwann cell is thought to be responsible for the myelination of the sprouts from myelinated fibres. New myelin has been observed in regenerating nerves as early as 22 days after the original injury (Clark and Clark, 1947).

Majno and Karnosky (1957) claimed that lipogenesis increases in the distal stump during the period from 22 hours to a few months following nerve severance. This early increase in lipid synthesis is consistent with the early appearance of a highly developed endoplasmic reticulum. Therefore, the high level of lipid synthesis may reflect new myelin formation. This leads to a consideration of the process known as myelination.

Remyelination following nerve injury

The concept of myelination of a nerve fibre has been discussed previously and is similar to that during embryonic development (see Chapter 4 ii). Remyelination is a similar process and occurs in two stages. First, there is the formation of a thin coat of lipid followed by a thickening of the sheath. Behind the bare axon tip further changes occur to restore the original architecture of the regenerating nerve fibre.

Remyelination proceeds centrifugally (peripherally) down the fibre and the process is not unduly delayed in comparison with the advance of the axon tip. Rexed and Swensson (quoted by Guth 1956) say a thin myelin sheath is detected at 6 to 7 days after injury from 15 to 20 days after crushing (Quilliam, 1958), and from the eleventh day on according to Glimsted and Wohlfort (Wohlfort 1961). In transected nerves myelination does not commence until the second month (Glimsted and Wohlfort, 1960). Growth in the diameter of the axon continues after the appearance of the myelin sheath (Cajal, 1928), until the original dimensions are restored. The final stage of this process is delayed if a functional relationship is not re-established (Gutmann and Sanders, 1943). Studies by Berry and his colleagues (1944) and Berry and Hinsey (1946) indicate that the new fibre begins as a fine axon growth which gradually increases in diameter and myelination and that these two morphological features influence conduction properties. Sanders and Whitteridge (1946) from histological examination of the proximal and distal fibres following regeneration after a crush injury found that the conduction velocity correlated more closely with myelin thickness than axon diameter. Residual defects occur following regeneration subsequent to nerve section and crushing and normal conduction velocity is never fully regained (Cragg and Thomas, 1964; Jacobson and Guth, 1965). Cragg and Thomas (1964) in seeking for an explanation for the reduction in

conduction velocity found the distal residual reduction in fibre diameter to be insufficient to account for the whole reduction in conduction velocity. They finally concluded that the full explanation remained unknown with some factor or factors other than fibre diameter contributing to the reduction.

As discussed earlier, re-myelination is the function of the Schwann cell and one Schwann cell is associated with one myelin segment in a myelinated fibre and in this way the nodal arrangement is restored. However, there is a departure from the original condition in that the internodes are now all of approximately the same length (Vizoso and Young, 1948).

Fibroblasts

Denny-Brown (1946) said that following severance of the nerve, fibroblasts from the endoneurium and perineurium proliferate from the severed ends of the fibre forming outgrowths to bridge the gap. The end result of this reaction is scar tissue formation which is composed of a disorganized matrix of Schwann cells and fibroblasts. This role of the fibroblasts in nerve regeneration can sometimes be an inhibitory one (see section on Scar tissue). Besides contributing to the formation of scar tissue they assume the role of macrophages but only to a minor extent during degeneration and assist the Schwann cells in phagocytosis of the myelin and axon debris. However, the cells remain morphologically distinguishable from the macrophages of Schwann cell origin (Weiss and Wang, 1945) (Fig. 51) (also see section on Schwann cells). Fibroblastic activity is maximal 2-5 days after transection of a nerve (Abercrombie and Johnson, 1942).

ii) FACTORS INFLUENCING REGENERATION

The health of the central cell

In the study of primary nerve suture it was found that axon buds begin to advance cross the injured zone at two or three weeks at the latest and by four weeks are across the anastomosis. At six weeks a sizeable number are found in the distal segment (Kline et al., 1964). The onset of this budding and regeneration occurs concomitantly with the anabolic hypertrophic phase of the cell body (see section Central Cell).

The guidance of Schwann cells

The regenerating axon starts as an amoeboid extension and is dependent on contact guidance of the adjacent supportive cellular structure namely the proliferating Schwann cells which form the new neurilemma bands, bands of Von Bungner (q.v.), along which the axon travels (Guth, 1956). Following injury to the nerve the Schwann cells become mobile and form a syncytium which results in the formation of the bands of Von Bungner. Electron microscopic studies show that this orderly arrangement of the Schwann cells is brought about by the presence of the basement membrane (see section Schwann cells). During regeneration the growing fibre tip lies against this cord of Schwann cells and uses them to guide it distally for reinnervation with an end organ.

Species differences

A comprehensive study of the response of various species to nerve injury undertaken by Kline and his collaborators (1964) found that species differences in response to crushing are minimal. However, there is a greater delay in the advance of the axon across the surgical repair or suture of the nerve following nerve severance in man and higher primates than for other mammals such as cats and dogs. In addition, this delay is found to be greater for proximal lesions than distal ones.

Presence of local inflammation

In blast and contaminated wounds, because of a local inflammatory response and increased scar formation, a further delay can occur before the axon buds and crosses a repair site (Ducker 1972).

Proximal and Distal regeneration

The rate of regeneration of nerve tissue is commonly stated as being 1 mm per day or 1 inch per month. This is a reasonable rule of thumb guide for clinical purposes. However, the progress of regeneration is known to begin slowly but once the neurone has bridged the injured zone and entered the distal stump the progress increases to 3 mm per day. There is a further delay during reinnervation with the end organ and/or muscle (see section Rate of Regeneration).

The age of the patient

The age of the patient and the nature of the injury also influence regeneration considerably. There are no statistical studies to validate the claim that the younger the patient the better the regeneration of the peripheral nerves following injury. However, Moyer and his co-workers (1953) found the rate of regeneration in nerve fibres was maximal in early life. Certainly most surgeons are of this opinion. It is assumed that the growth hormone in children may play a significant role in this process of regeneration (Ducker, 1972).

The maintenance of neuroectodermal and mesenchymal elements

As the debris is cleared from the injured area all that is left behind is the mesenchymal and neuroectodermal scar. This scar is the result of the response to injury by the cells of the supportive structures and is directly proportional to the wounding agent, i.e., the tissue response is less marked in a clean operative injury than in a battle casualty (Haymaker, 1948). This response to the injury of the supportive

structures is immediate and thick collagen is laid down starting three weeks after injury. The neuroectodermal and mesenchymal elements are seen to be partly dependent on the nerve fibres to maintain their anatomic and metabolic existence (Ducker, 1972).

Remyelination

With the penetration of the new axon into the distal segment metabolic activity of the Schwann cells increases preparatory to the laying down of new myelin. However, this new myelination is never as good as the original construction (see section on Remyelination) and this fact along with nerve size and endoneurial tube size (see section on Endoneurial Tube) accounts for the slower conducting times after repair or severe injury of nerves (Ducker, 1972).

Scar Tissue

On leaving the proximal stump the regenerating axon enters a new environment in the form of scar tissue which lies between the ends of the severed nerve fibre. This scar tissue must be traversed if the axon is to reach the distal section of the endoneurial tube. The bridging scar tissue is not a suitable medium for the growth of the axon as is the endoneurial tube. Varying in density, arrangement and amount, this scar tissue usually delays, and may obstruct and/or misdirect the axon in its passage distally. Despite the range of variation which would account for individual and species differences, the scar delay in any individual case will be longer if the nerve has been severed or sutured as compared with a simple crush injury (Sunderland, 1968). The resistance which the axon meets in its passage through the scar tissue distally, gives rise to the formation of multiple sprouts at the axon tip (Shawe, 1955). As has been previously stated a single regenerating axon may give rise to as many as 50 sprouts. Several of these may reach, enter and descend into the distal endoneurial tube (Weddell, 1942) but only one sprout will survive to reach the end organ (Fig. 56).

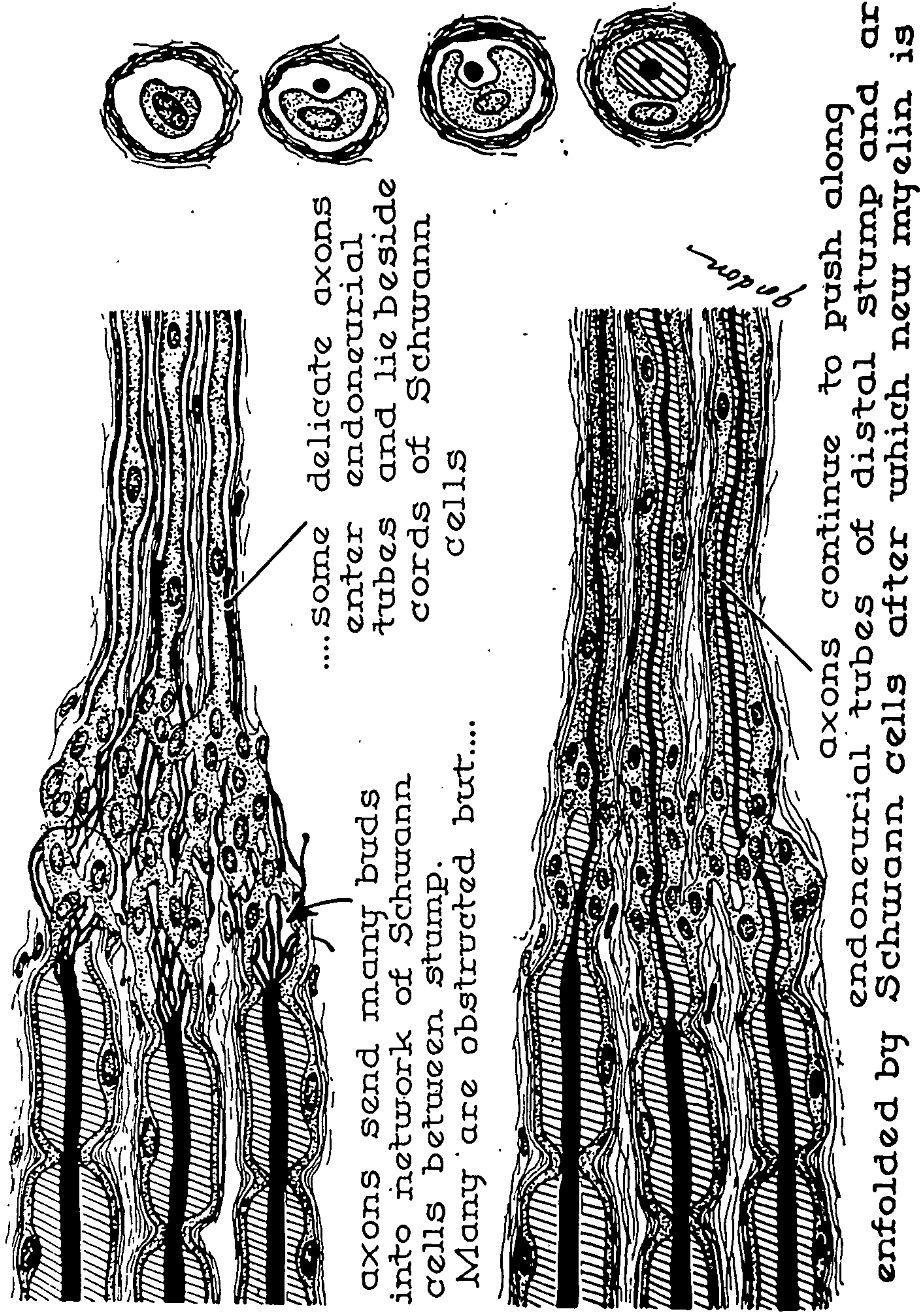


Figure 56. Diagram showing regenerating sprouts penetrating scar tissue and entering distal endoneurial tubes. (From Ham, 1974)

Further scar tissue may cause the regenerating fibres to be misdirected, enter a foreign tube and innervate the end organ whose function is unrelated to the new fibre (Sunderland, 1968), thus seriously affecting the restoration of normal function (Evans and Murray, 1954).

The regenerating proximal axon may end blindly in the scar tissue and fail to reach the distal section, or its entry may be unduly delayed by the bridging scar tissue. However, on freshening the axon during repair or suture at the site of injury, regeneration can again commence and, from experiments, this capacity for the central stump to sprout is retained for nearly a year from the original injury (Sunderland, 1949). There is much clinical evidence that in human nerves this capacity is retained for several years (Sunderland, 1968).

The Endoneurial Tube

The condition of the endoneurial tube distal to the point of injury is critical in determining the course and consequence of regeneration.

Provided the endoneurium is preserved, regeneration, although delayed, proceeds to completion and the original pattern of innervation is established. However, destruction or sectioning of the endoneurial tubes may result in disorganization of the endoneurium to an extent that regeneration is seriously affected and recovery is incomplete or negligible (Sunderland, 1968) (see section on Classification of Nerve Injuries).

Whilst regenerating, the axon tip is initially within the endoneurial tube. The branching of the axon usually occurs when the injured zone is reached (Fig. 56), but this is not a feature of regeneration with intact endoneurial tubes.

Following severance or severe damage to a peripheral nerve the endoneurial tube of the distal segment persists for months after the

disappearance of its axon and awaits the arrival of regenerating axons. Any undue delay in the regeneration of the nerve (due to severity of the injury and amount of scar tissue present) or delay in nerve repair results in the shrinkage of the endoneurial tube and downgrades the prognosis (Hudson et al., 1970). Hammond and Hinsey (1945) had indicated that after a seven month period when regeneration was not allowed to take place, the inner diameter of the tube diminished thus preventing the growth of regenerating axons to their original diameter.

Abercrombie and Johnson (1946 b) stated from their studies that the collagen in the distal segment of the denervated tube doubled in 200 days and that new collagen was formed at the external surfaces of the basement membrane of the Schwann cell. According to their studies, prolonged denervation causes the Schwann cells to become thin, the collagen denser and the tube narrower. Despite these morphological changes these peripheral channels will receive regenerating axons and guide them to the periphery (Sunderland, 1950 a). Abercrombie and Johnson (1946 b) further indicated that this collagenisation hinders the expansion of these tubes following reinnervation and therefore the restoration of normal fibre diameter is prevented. The collagen formation is attributed to the Schwann cells as histologically there is little or no fibroblastic activity inside the denervated funiculus (Barton, 1962).

Another view was expressed by Sunderland (1968) who stated that the progressive reduction in the calibre of the endoneurial tube with increased periods of denervation is due to its shrinkage and not to the thickening of the tube wall at the expense of the lumen. He believes that the shrinkage is caused by the loss of intracellular pressure transmitted along the normal axon when the axon and myelin degenerate and are removed. Further the study of the cross-sectional

area of the funiculi under these conditions reveals a progressive decrease corresponding in time and degree to the reduction in the lumen of the endoneurial tubes. Therefore, if the reduction in calibre were due solely to the thickening of the endoneurium, then the funicular area would remain unchanged.

According to Sunderland and Bradley (1950), three months after severance, the largest tubes that are available for regenerating axons will rarely exceed $3\ \mu$ in diameter. From clinical studies Sunderland (1950 b) has shown that the endoneurial tube retains the capacity to transmit regenerating axons peripherally for at least 12 months and during regeneration the new axon has the capacity to inflate the tube into which it has grown (Sunderland, 1968).

Lubinska (1952 a) claimed that degeneration must reach a certain stage before regenerating axons will grow into denervated tubes and that regenerating axons will not grow into innervated endoneurial tubes. However, evidence also shows that neither the debris (see chapter on degeneration), nor the reaction associated with the removal of the products of degeneration in the endoneurial tube (see section on Schwann cells) offer any significant obstruction to the advance of the axon (Sunderland, 1968). In other words, regeneration and degeneration occur side by side (Figs. 37, 57).

iii) RATE OF REGENERATION

General

Knowledge of the expected rate of recovery in the various types of nerve injury is important when the decision for operative or conservative treatment is being considered. It has been seen that regenerating nerve fibres pass through several phases before full functional recovery is established. Nerve fibres comprising a nerve trunk differ greatly in length because of the positioning of their terminal end organs. At a given level the rates of advance of fibres equidistant from the parent cell differ because some are approaching their termination and here axon



Figure 57. Two Schwann cells containing much degenerating myelin whilst within the rectangle a regenerating axon is undergoing myelination.
(From Nathaniel and Pease, 1963)

growth is slowest. Therefore at a given level regenerating axons will be advancing at different rates in different fibres. Other factors contributing to the rates being different are variations in the onset of regeneration, the regenerative power of recovering neurones (severity and level of injury) (see d. and e.), amount of scar tissue that the regenerating axon has to traverse, species differences, duration of denervation and the state of the peripheral tissues, in particular, the endoneurial tube. Also, due to the asymmetry in the scar at the site of the injury, when regeneration begins the rate of advancement of the axons is not uniform as some have very little scar tissue to penetrate (Seddon et al., 1943), others have more. On reaching the distal segment they find their way into the neurilemmal tubes when the growth rate accelerates to several millimetres per day.

With reference to regeneration rates in man, Sunderland (1947) suggests that:-

- a. the axon growth tip advances more rapidly than does the process of functional restitution;
- b. the regeneration rate and the process of maturation progressively diminish with time over longer lengths and should not be regarded as constant;
- c. the closer the lesion is to the cell body the faster is the initial rate.
More distally the growth rate is slowed and corresponds to the initial rate of axon growth after a lesion performed at that level. This is said to be due to the reduction in the pressure operating centrally from the cell body and is said to decline as the distance of the actively growing tip from the cell lengthens;
- d. both initial and final regeneration rate are greater after crushing than after sectioning of the nerve;
- e. the level of the initial lesion and the length of nerve over which the regeneration rate is calculated must be taken into consideration in the estimation of the days for recovery;
- f. the initial delay in man is far greater than in animals (Sunderland, 1946 a).

Another factor which has a bearing on the rate of regeneration in injured nerves

is the nature of the lesion, e.g., neurapraxia, axonotmesis, and neurotmesis (Sunderland and Bradley, 1952 a) (see section Nerve injuries). Fibres of different sizes and functions regenerate at different rates. The sensory rate is based on regeneration of touch and pain fibres and, is found to be faster than for motor fibres. This is because the sensory fibres are unmyelinated or more finely myelinated than the motor fibres and so require less time to achieve functional completion (Thulin, 1960). Age, as we have seen, also influences the rate of regeneration.

Methods of measuring rates of recovery

Measuring the rates of recovery of function is a complex and difficult procedure because there must be a distinction between the rate of advance of the axon tip and the rate of return of function of the regenerating nerve fibres. These problems in measurement are due to our ignorance of the rate of maturation of nerve fibres, the degree of maturation required for the restoration of particular functions and the rate of reversal of atrophic changes in the end organ (Seddon, 1954).

(a) Histological Method

Rates obtained histologically from experiments on animals have given readings varying between 1.1 mm/day in the rhesus monkey after section and suture (Davenport et al., 1939) and 5 mm/day in the rabbit (Weddell 1942) following a crush injury. These were based on the identification of the regenerating axon tips in the nerve below the lesion.

(b) Electrophysiological Method

Studies on rat nerve fibres by Jacobson and Guth (1965) gave readings which indicate that the rate of regeneration accelerates exponentially from an initial 0.3 mm/day immediately post-operatively to 3 mm/day eighteen days following a crush injury. These workers exposed the sciatic nerves of rats and crushed them with a haemostat. The point of trauma was marked with 7.0 silk through the epineurium and the wound was

closed. The nerves were removed immediately post-operatively, and at 4, 7, 11, 18, 21, 28 and 56 days and tested for regeneration. At the time of testing, the removed sciatic nerve was immersed in mineral oil at 37°C in a chamber. This contained sixty six parallel electrodes at 1 mm intervals and the electrodes were connected to an oscilloscope. The proximal nerve end was stimulated with single shocks and the compound action potentials elicited by the stimulation were recorded successively millimetre by millimetre down the nerve. Immediately post-operatively, action potentials could be recorded no further than 2 mm proximal to the lesion. By 4 days, potentials were observed up to 2 mm distal to the lesion. By the twenty-eighth post-operative day the nerve fibres had regenerated into the leg muscles. Although the amplitude of the action potentials increased steadily it was only 20% of normal by 56 days and the conduction velocity increased steadily to 75% of normal by 28 days and did not change during the ensuing 28 days. Erlanger and Schoepfle (1946) from similar types of studies on dogs reported a 4.6 mm/day rate of regeneration.

(c) The Pinch Method

The Pinch method has been used on rabbit nerve and has revealed that the average rate of regeneration following a crush injury to be 4.5 mm/day (Guttmann et al., 1942) or 3.5 mm/day (Konorski and Lubinska, 1946). The Pinch method consists of exposing the nerve under light anaesthesia and pinching it with fine forceps at 1 mm intervals from below upwards to the zone of injury until a reflex response is elicited. The presence of axon tips at that point is then revealed histologically. When the distance in mm advanced by the regenerating nerve is plotted against the time taken to reach that point, it is found that, in most cases, it fits a straight line (Guttmann et al., 1942). Bowden and Sholl (1954) have shown that over longer lengths this rate of recovery declines progressively. The usefulness of the Pinch method has obvious limitations in its application to man. The number of human histological examinations akin to those carried out on

animals by Gutmann is only a total of eight. This is too small a number to give values of any significance. These human experiments of Seddon and his co-workers (1943) were all carried out on regenerating nerves in limbs that were to be amputated. There appear to be no other reports in the literature since 1943 which would add to these findings. Thus the number of cases has to be increased considerably to give data of statistical value and so it would appear that the exact rates of human nerve regeneration are yet to be accurately established.

(iv) Clinical Methods

Clinical methods consist of the Hoffman-Tinel test (Tinel, 1917), to a lesser degree, the examination of muscle biopsies (Bowden and Gutmann, 1944) (described later) and observation of the rate of shrinkage of anaesthetic/paraesthetic areas.

The Hoffman Tinel test.

This test is used to detect regeneration in sensory nerve fibres. The nerve trunk is gently percussed percutaneously from below upwards (distal to proximal) until a tingling sensation is first elicited in the cutaneous distribution of the injured nerve. This indicates the most distal point of growth of the regenerating sensory process. On successive examinations one can determine again the most distal point at which the sign is elicited and thus calculate the rate of growth of the regenerating sensory fibres. This is still a popular method of estimating the regeneration rate of the nerve and is generally taken as an indication of the progress of the axon tip. Tinel himself gave this rate as 1-2 mm per day. The basis for both tests, the muscle biopsy test and the Hoffman-Tinel test, is in the increased mechanical excitability of regenerating fibres (Konorski and Lubinska, 1946).

Tinel's sign, though of limited clinical significance, is a useful method for the study of sensory recovery. The rate of motor recovery is obtained by recording the time at which the first sign of voluntary contraction

becomes evident against the distance from the site of injury. The variables that affect clinical estimates of the rate of recovery are:-

- (a) After axonotmesis: The extent of the damage to supporting structures namely endoneurium and perineurium within the trunk of the nerve; and
- (b) After suture:
 - (1) the interval between the injury and repair of the nerve;
 - (2) the state of the stumps at the suture line; and
 - (3) the damage inflicted by post-operative stretching

In both axonotmesis and neurotmesis before functional recovery is established in man the regenerating fibres pass through three phases - first, retrograde degeneration, secondly, scar delay and thirdly, the delay during the processes leading to the recovery of function (maturation). Due to the differences in the rate of recovery it is preferable to consider the lapse of time between the injury or suture and the first sign of voluntary activity in the different muscles or return of sensation. One concludes that the rate of outgrowth of the axon tip and the rate of recovery of function are more rapid after a simple crush injury than after a suture of the nerve or an extensive lesion in continuity (e.g., 4th degree injury) (Seddon, 1954). The initial delay and the delay before functional recovery are also shorter after a simple crush injury than after nerve suture.

Muscle biopsy

In motor nerve injuries, a muscle biopsy can be made. This can be thought of as a form of nerve biopsy. The characteristic change in muscle fibres following denervation is one of shrinkage of the fibres and subsequent atrophy if no reinnervation occurs. One also finds signs of Wallerian degeneration and the presence of empty nerve trunks and terminal branches. Bowden and Gutmann (1944), from examination of biopsy specimens from denervated muscles and muscles in the process

of reinnervation, calculated that the average rate of regeneration of axons was about 3 mm/day after second degree injuries.

Rate of shrinkage of abnormal sensation

Another measure of the rate of sensory regeneration may be obtained by observing the rate of shrinkage of an anaesthetic area after nerve injury. This was found to be 1.98 mm/day following a crush injury and 1.57 mm/day following suture (Gutmann and Guttman, 1942). It was also shown by this technique that proximal lesions gave slower rates of recovery than more distal ones owing to the more scattered arrival of new fibres in the case of the proximal lesions (Gutman and Guttman, 1942). A similar finding has been reported using the Tinel sign method.

In animals, by plotting the distance against time, a rate curve can be obtained for regenerating fibres and this was found to be linear on the basis of available evidence (Guth, 1956), thus confirming Gutmann's earlier finding.

In man, due to deceleration, the rate curve is not linear and this difference between the two is due to species variation and/or length of the regeneration path. Experiments conducted on rabbits showed that the average velocity of fibre growth was 3-4 mm/day and the initial delay in the scar was 5-8 days, whilst the final delay, prior to the onset of functional recovery, occupied 20 days (Konorsky and Lyubinskaya, 1944). In man the initial rate of regeneration can be as high as 8 mm/day with a gradual deceleration to a value of 0.5 mm/day distally (Sunderland and Bradley, 1952 a). The initial and final delays occupy an average of 13-16 weeks and are considerably greater in man than in lower animals. Following crush injuries both in man and in lower forms, the regeneration rate is faster and the delays are shorter than after complete (surgical) transection. Based on such experimental and clinical data the rate of regeneration of peripheral nerves in man is

universally accepted for clinical purposes as being on average about 1 mm per day (Seddon et al., 1943). For all practical purposes the rate of regeneration is regarded as constant and this regeneration advances at a uniform rate over the moderate ranges of time and distance over which the process was recorded (Gutmann et al., 1942). Thus the figures provided by Seddon and his co-workers (1943) and Napier (1949) are useful rough approximations of the rates of regeneration. The question seems to remain unanswered as to whether the regeneration progresses at a uniform rate once the initial delay at the site of the lesion is past.

The distances involved in the regeneration of a nerve in man are very much greater in comparison to the animals used in the various studies and will therefore have some bearing on interpretation of the results. The rate of advance of Tinel's sign gives an indication of the rate of outgrowth of the axon tips and, from the numerous observations of Konorski and Lubinska (1946), Sunderland (1946) and Napier (1949), the evidence shows that the rate of advance of axon tips decreases with time and distance in man. Since there is considerable variation between individual cases it is not possible to find a definite and reliable figure for the rate of recovery.

(iv) MATURATION OF REGENERATED NERVE FIBRES

Maturation is that process leading to the restoration of normal fibre diameter and normal electrical properties of the nerve. Connection of the fibre with the periphery is of utmost importance in maturation. However, inadequate peripheral connections and/or undersized endoneurial tubes (see section on endoneurial tubes) prevent full genetic expression resulting in a restriction of fibre diameter (Sanders and Young, 1946; Aitken et al., 1947).

Correlation of maximum conduction velocity and fibre diameter in normal nerves has been well-established (Berry et al., 1944; Berry and Hinsey, 1946). Regenerated fibres never attain a fibre diameter of more than 80% of normal

(Berry and Hinsey, 1946) and therefore maximum conduction velocity will also be only 80% of normal (Berry et al., 1944) following second degree or greater injury. Thus it may be concluded that the growth of the axon and the restoration of the axonal conduction pathway (on which depends the functional efficiency of the new fibre) occur as two separate but related events during repair. The complex morphological changes that constitute maturation advance at a slower rate than does the axon tip and continue long after the axon has been reconstituted.

In man, the diameter and degree of myelination of the fibres are two morphological features that are known to influence conduction properties even if some details of this relationship remain obscure (Sunderland, 1968). It is therefore assumed that as function is fully restored, the morphology of the reconstructed fibre is identical with that before the injury. This is because there is an absence of confirmatory evidence from histological studies of nerves in man which would relate morphological features to functional efficiency.

9. SURGICAL REPAIR OF NERVES

In the past century we have gained much in our knowledge of neuro-anatomy, nerve physiology and axon regeneration and have developed refined surgical techniques. Despite these advantages the record in re-establishing normal function in the damaged nerve is still rather poor.

Indications for surgical repair of nerve lesions are the loss of sensibility and muscular activity. Another indication is that a painful neuroma can best be avoided by satisfactory peripheral nerve repair. Even if no useful sensibility is achieved the symptoms of the neuroma will be much diminished (Edshage, 1968).

Nerve suture is still a field of surgery where results often fall short of goals. Moberg (1966) emphasizes that regeneration of sensibility should always be in terms of "functional recovery" and not "academic recovery". By academic recovery he means the kind of sensibility registered by needle and cotton wool test. He regards the most useful tests for examination of sensibility as the two point discrimination test of Weber and the pin pick test both of which give reliable information about the quality of the regenerated sensibility (see chapter 10). Another test is the ninhydrin test which relates to perspiration of the skin. Normal innervated skin perspires and this contains amino acids which turn purple when in contact with ninhydrin. Denervated skin is dry due to loss of sudomotor function (Onne, 1962).

Brown (1972) indicated that the factors which influence successful repair of damaged nerves are:-

- (a) Type of nerve - unmixed sensory or motor nerves are simpler to repair than mixed and the results are generally better.
- (b) Age of the patient - younger patients have a more satisfactory response to nerve repair than the older patients, e.g., their extremities are shorter and therefore the distance to be covered in repair is shorter. The young patient has a greater capacity for sensory re-education and adaptation.
- (c) Level of injury - the axon, as a part of the nerve cell, forms a percentage of the total mass of that cell and the more proximal the injury, the higher

the percentage of the cell that is impaired. Proximal lesions present a greater challenge to the regeneration capability of the nerve cell as the challenge is present for a longer period of time. During this period the degenerative changes distal to the lesion are continuing and progressive. Therefore, the degree of damage to be reversed is greater for the proximal lesion.

- (d) Associated injury - nerve repair cannot be effected or is made difficult when there is skin loss, infection, vascular insufficiency or joint stiffness. Wound healing, skin coverage, control of infection and mobilization of joints must be achieved before the nerve can be successfully repaired.
- (e) Surgical Technique - the degree of technical excellence with which the injured nerve is handled and sutured is an important factor if the repair is to be successful. The matching of severed fascicles becomes increasingly difficult as the length of the segmented deficit increases due to the twisting and plexiform course of the fascicles. The maximum defect which can be made up surgically, termed 'the critical gap', rarely exceeds 10 cm in any nerve under ideal circumstances.
- (f) Time factor - when should the repair be undertaken for it to be successful? Delays in repair are common in severe injuries as the treatment of other tissue damage must precede nerve repair. Notwithstanding the above, it is still widely believed that the earlier the nerve suture is done, all other factors permitting, the better the chances of motor and sensory return. A contrary opinion to this theory is also held by some surgeons. Thus the premise that it is never too late to attempt a nerve repair and the doctrine that the sooner the nerve repair is done, the better the chances of success, though seemingly contradictory, are not irreconcilable and both principles can be useful to the surgeon at times. The controversy as to whether primary or secondary repair is to be carried out when peripheral nerves are interrupted remains unresolved, but there is impressive evidence to support both techniques. However, it is agreed that secondary repair under favourable conditions will give better results than a primary repair under unfavourable circumstances.

(i) PRIMARY NERVE SUTURE

This is undertaken when the nerve injury is a clean sharply incised wound with no element of crush and minimal contamination. Also the severed ends should be clearly visible and able to be mobilized without extension of the wound and this should be done within 12 hours of the injury and carried out by skilled personnel with all proper facilities, e.g., microscope, etc. If any of these conditions cannot be well met primary nerve suture should not be done. Even when these criteria are met Zachary and Holmes (1946) and Nicholson and Seddon (1957) have opposed primary nerve suture and have regarded early secondary suture as the choice of operation for all cases of nerve severance.

Sunderland (1949), from his observations, believes that primary suture is of great advantage when the nerve is cut cleanly, no preparatory trimming of the nerve ends is required with minimal loss of nerve substance and union can be established without tension at the suture line. With delay, nerve ends become lost in scar tissue and become difficult to identify at a later date. Primary suture further reduces the time for which the peripheral tissues are denervated and the period for which the patient is incapacitated. Primary suture obviates the need for further surgery but should a second operation be necessary, technically it is made easier because the first suture prevents the retraction and shortening of the nerve ends and reduces the amount of tissue to be resected and also therefore, reduces the gap to be closed. Sunderland (1968) further says primary repair, provided it is prompt and technically sound, gives excellent results in the young. Recovery, though imperfect in the adult, is as good or superior to that obtained after early secondary suture.

Stacy (1979) from his records on osteotomies (sagittal split) carried out, informs me that on two occasions, once in 1968 and the other in 1974, he had the misfortune to transect the inferior dental nerve (I.D.N.). In the early case the I.D.N. was transected in the canal. The segments were merely repositioned accurately in the I.D. canal without any primary suture. Full sensation had returned to the lip in eleven weeks. In the latter case the I.D.N. was transected 5 mm above its entry to the mandibular foramen, i.e., in the pterygomandibular space. Primary suture was achieved. First signs of

returning sensation in the vermilion border were noticed at 6 $\frac{1}{2}$ weeks. During the period of 2 $\frac{1}{2}$ years the sensation improved and at the last visit only "a small area of pins and needles sensation was present centrally" towards the midline. The ages of these patients were 21 and 18 years.

(ii) SECONDARY REPAIR

Secondary repair is indicated in cases of nerve severance where the wounds are such that the nerve ends are ragged and contused (e.g., gunshot) or when a segment of variable length has vanished, and when there is an acute inflammatory reaction with infection which is nearly always present. Other factors indicating a need for secondary repair are the condition of the epineurium, which may be soft and friable due to marked oedematous swelling, and the destruction of soft tissue or skin which may need grafting before repair of the nerve can be attempted. Control of infection and adequate healing of damaged structures and the restoration of lost tissue make secondary repair the treatment of choice under these conditions (Sunderland, 1968). Primary suture, if undertaken under these conditions, often fails (White, 1960). A delay of about three weeks before nerve repair clearly defines the nerve trunk in relation to the surrounding tissues representing the nerve bed, and allows one to make an accurate evaluation for mobilization or transplantation procedures to overcome nerve gaps. This delay allows the epineurium to become thicker and stronger facilitating suturing and the repair can be planned and carried out in an unhurried manner as an elective procedure. Two less convincing arguments have been put forward for deferring repair. Zachary and Holmes (1946) and Seddon (1960) claim that at about the third week the Schwann cell activity is greatest and the condition of the endoneurial tubes in the distal stump is at an optimal level for regeneration. In addition the products of Wallerian degeneration would have been cleared thus preventing any obstruction to the regenerating axons.

Nerve Grafting

Because of nerve injuries produced by automobile accidents, gunshot wounds and other severe injuries the problem confronting the surgeon today is what to do when faced with a large deficit in a peripheral nerve.

Nerve grafting would be the ideal procedure to use to bridge the defect if a ready source of nerve grafts was available which could be accepted by the patient's tissues. Various techniques have been developed to allow closure of large defects, such as stretching the nerve ends, cable grafting, plastic tubes and vein (Hirasawa and Marmor, 1967), artery and nerve grafts. The history of nerve graft goes back to 1870 (Phillipeau and Vulpian) who demonstrated that nerve fibres can grow through a nerve graft. Since then nerve repair by homografts and heterografts has been tried in man but has failed. However, autografts to repair the facial nerve (Ballance and Duel, 1932) and digital nerves (Boyes and Bunnell, 1939) in man have not been rejected by the patient and have been successful, and the sural nerve has been the donor nerve (Marmor, 1972).

With the introduction of surgical microscopes and the development of newer nerve operative micro-surgical techniques the technical problems of nerve grafting can now be looked upon as solved. Favourable results are being achieved even in the grafting of long nerve transplants (Hausamen et al., 1973).

In the three years prior to 1974, Hausamen et al. (1974) used free autologous nerve grafting to successfully bridge defects of the facial and accessory nerves, inferior alveolar and lingual nerves following maxillo-facial trauma or following radical management of benign or malignant tumours.

Lathrop (1949, 1964), Maxwell (1954), Stricker (1973), have all shown the importance of nerve transplant for bridging defects of the facial nerve. Hausamen et al. (1974) used the sural nerve for reconstruction of the entire facial nerve plexus, firstly because of its length, and secondly, because of its method of branching at the level of the outer malleolus. The other nerve that can be used is the greater auricular nerve. The full rehabilitation of facial nerve function required six months to a year, depending on the length of the bridged defect. They also used the sural nerve for the reconstruction of the inferior alveolar nerve in mandibular reconstruction and when the donor nerve was thin a double bent transplant was used. They embedded it at a distance from the bone graft and below

the submandibular gland which is a well vascularized soft tissue bed. This was done because the nerve graft must rely on diffusion for its viability and the natural bed, the bone transplant, is not yet vascularized and therefore unsuitable as a host site (Hausmen et al., 1973). In the repair of the lingual nerve (Hausamen et al., 1974) the greater auricular nerve was the donor for the autologous transplant. These authors believe that reconstruction of nerve defects of the lingual and inferior alveolar nerve by autologous transplants should be restricted to young patients as the ability for the nerve to regenerate is reduced in older patients. The success of full nerve grafting is dependent on the exact approximation of the nerve stump at the site of anastomosis and the rapid revascularization of the transplant. Cutaneous nerves are more suitable as donors than thick nerve trunks which degenerate because of central nutritional deficiency. This is because revascularization of the transplant occurs initially at the stump ends and sometimes directly from the graft bed. In the meantime, its viability is maintained by diffusion. Hausamen et al. (1974) state finally that because of their encouraging results surgeons should encourage further acceptance of modern neuroplasty within their speciality and not limit repair of traumatic and tumour induced defects to the reconstruction of bone and soft tissue. Surgeons should include the restoration of nerve function in the planning of plastic repair.

(iii) EXPERIMENTAL RESEARCH

In the case of mandibular fractures nerve regeneration in the mandibular canal frequently occurs without surgical aid other than accurate reduction because the canal acts as a guide to nerve growth and union (De Bats and Phillips, 1944). Hence, after injury of the mandibular nerve, sensation frequently returns rapidly. However, if the bony canal is obstructed by displaced bone or a displaced fragment of a tooth or if fractures of the mandible are not properly reduced, the severed nerve always results in permanent numbness of the lip (Thoma, 1969). Merrill (1966) performed crush, and crush-and-compression injuries on the exposed inferior dental nerves in dogs. By applying a

vitalometer to the lower canine teeth, under minimal general anaesthesia, he found that initial signs of nerve function occurred in 17.6 days in crush injuries alone whereas on the side where the nerve was crushed and then compressed by displaced cortical bone it took 25.1 days on average. In addition, six months after the latter injury the canal was still partly obstructed and relatively large neuromas had formed due to severance of some of the nerve fibres within the trunk. There was also a marked decline in the number of axons regenerating. The mean number was 905 compared with a normal number of 1250 fibres per nerve trunk.

Several methods have been used in the repair of inferior dental nerves to improve regeneration. Some of these are early decompression (Thoma, 1969), micropore adhesive tape to guide the nerve and promote repair (Merrill, 1967), tantalum foil to prevent scar tissue and new bone impingement during the healing of bone (Woodhall and Lyons, 1946), millipore filter sleeves (Freedman et al., 1970) and nerve grafts (already discussed). All have considerable merit and the results all show some degree of successful regeneration. Whether one method is superior to another is debatable. The decompression technique involves the freeing of the nerve, eliminating the cause of the compression (usually bone), removal if necessary of the pathologic or injured part of the nerve, repairing the mandibular canal or creating a channel in the bone into which the nerve ends are placed (Thoma, 1969). When using tantalum foil the above technique is carried out but in addition the nerve ends are wrapped in tantalum foil (Woodhall and Lyons, 1946) and placed back in the canal. The use of tantalum foil has been largely discontinued with the advent of micropore tape which is less reactive. Merrill (1967) in his experiments to repair the inferior dental nerve in dogs used micropore adhesive tapes. His findings showed early decompression to be superior to bridging with micropore in crush injuries. To improve regeneration in six week old severance lesions which were also complicated by bony obstruction, it was found that bridging with micropore tubes was superior to decompression alone and to no treatment. However, the original population of axons was never regained following repair. The result of this study supported Freeman's conclusions that micropore adhesive tape is a

simple, effective and relatively non-reactive material for use in the repair of injured nerves. Freeman (1965) used micropore tape to repair delicate branches of the facial nerve and as an adjunct to the anastomosis of the larger digital, forearm and infraorbital nerves.

Millipore filters have recently been used in experiments on dogs by Freedman et al. (1970) to bridge defects of 1.2 cm in the inferior dental nerves without grafting. The sleeves facilitated regeneration of the severed nerve tissue by preventing displacement of the nerve ends and the interposition of other tissue. However, the results of sensory testing were not conclusive in that the authors were unable to bring all dogs to the same level of anaesthesia at each testing session. Further there was the possibility that the denervated areas could be reinnervated by collaterals from the long buccal nerve thus possibly complicating the final readings. Nerve fibre counts exhibited a 30 percent or greater axon regeneration as compared to pre-operative values on the experimental side. On the control side where the nerve was similarly cut but with no millipore sleeve inserted axon regrowth was less than 5 percent of the pre-operative values. This is attributable to the efficacy of the millipore sleeve.

10. CLINICAL TESTS TO ASSESS NEURAL FUNCTION

Sensations are subjective responses and are generated in free and specialized nerve endings in the tissues of the body. These reach the sensory cortex via synaptic relays and are here translated into a sensory experience. The primary sensory modalities for the skin are touch, pressure, pain, temperature.

Two hypotheses have been advanced for the manner in which different stimuli are distinguished by the sensory apparatus of the skin (Sunderland, 1968). One theory states that there are structural differences in the receptor end organs which are significant in relation to function and each sensory modality is assigned to a morphologically distinct receptor or group of receptors. These features impart specificity to the system, each receptor giving rise, on stimulation, to only one specific sensation. The second hypothesis denies any specific relationship as both histologically and physiologically they have failed to equate the four recognized modalities of cutaneous sensibility with four structurally distinct types of nerve endings in the skin (Lele and Weddell, 1959). According to the second theory the different types of sensation are attributed to variations in the spatio-temporal pattern of excitation in the sensory nerve fibres (Sinclair, 1955). However, according to Sunderland (1968) the pattern of excitation as well as some measure of receptor specificity both play a part in distinguishing one type of sensation from another. Sensory receptors vary in their arrangement, distribution and threshold to stimulation and are stimulated not singly but in varying numbers and combinations and at different intensities and intervals.

Standardising all aspects of sensory testing is difficult, because sensory response may fail to be identified in the same way at successive examinations due to the ever-changing background to sensory perception. Therefore, the testing of sensation has to be kept within the bounds of practicability due to the many variables operating such as:-

- (a) Attitude and co-operation of the patient,
- (b) The ability of the operator to make the patient comfortable, relaxed and attentive and aware of the nature of the test. The tests should be made in conditions free of confusing interruptions.

TYPES OF TESTS PRESENTLY USED TO ASSESS SENSATION(i) PIN PRICK (Fig. 58)

This is elicited by pricking the skin with a sharp needle and varies from a feeling of touch to one of sharpness and finally pain. This sensory modality shows characteristic changes following denervation and during regeneration. The sensibility to pricking, registered as sharpness or pain, can be measured by means of an algesimeter. This is a calibrated cylinder with a fine steel rod attached to a spring and the tension or compression put on the spring exerts a corresponding pressure on the needle point applied to the skin. One then records the force applied at the needle point when pain or sharpness is felt.

(ii) LIGHT TOUCH

The object of this test is to stimulate only cutaneous receptors without deforming subjacent tissues. This technique is used for verifying the absence of tactile sensation. A wisp of cotton wool or nylon thread is used to lightly stroke the area while the eyes are closed. Von Frey's hair test is a quantitative method of testing this sensation. In this test bristles of varying thicknesses are applied to the skin until they bend and that bristle which elicits a threshold sensation is recorded. The light touch test is often used as a quick screening test for gross sensibility.

(iii) PRESSURE

The initial sensation due to pressure to one of touch which is replaced by pressure when increased sufficiently and there is no sharp line of demarcation between the two. Sensibility to touch is a function of the receptors in the superficial layers of the skin whilst sensation of pressure is dependent on the receptor activity in the subcutaneous and deeper tissues. The test is made by pressing a blunt object on the surface of the skin.

(iv) THERMAL (Figs. 59 and 60)

Due to fluctuations in skin temperature and difficulty in maintaining a constant temperature of the test object throughout the examination, the patient's ability to distinguish between hot (Fig. 59) and cold (Fig. 60)



Figure 58. Pin prick test.

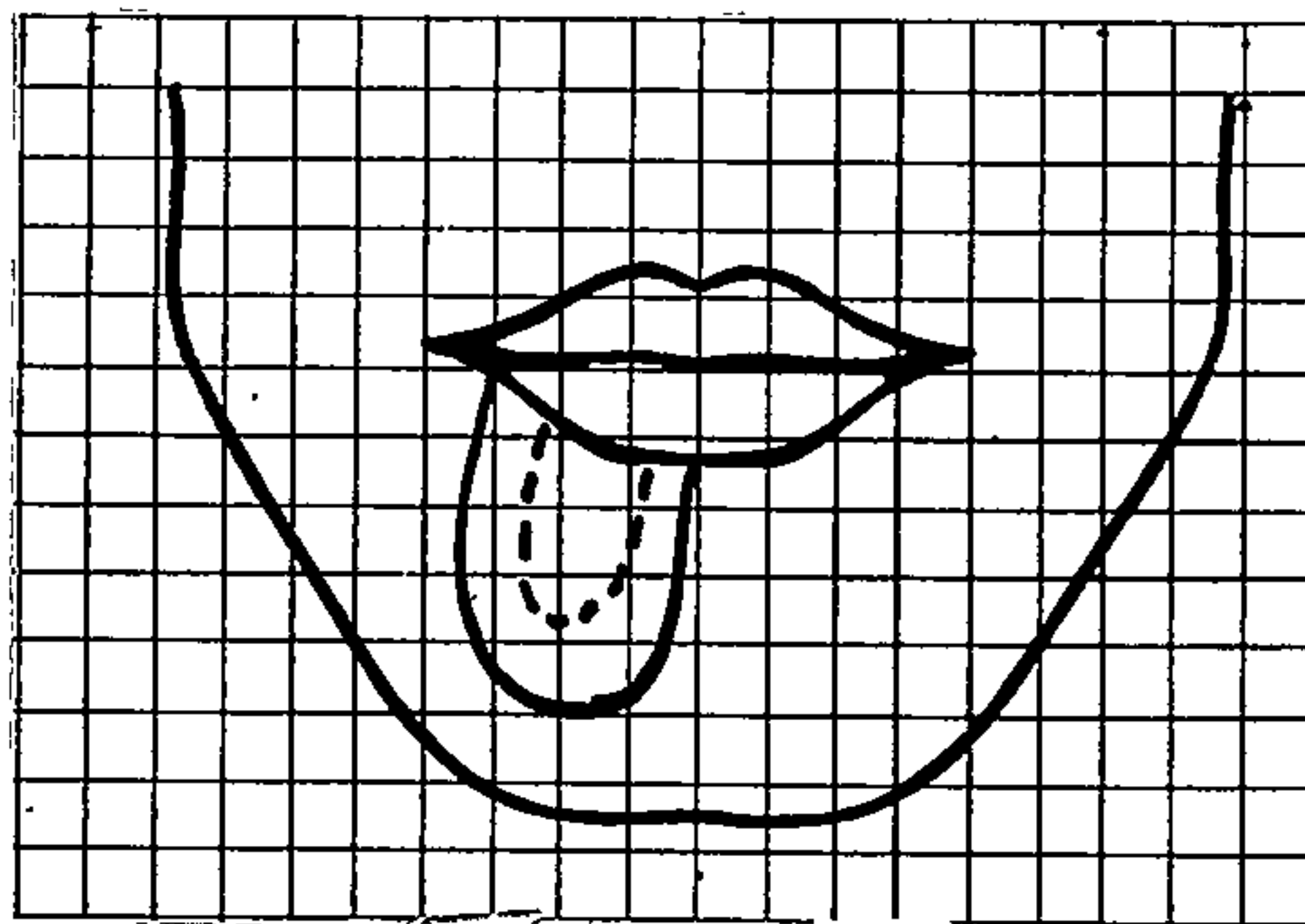


Figure 58A. Illustration showing the recording of the extent of anaesthesia on a graph of the lip/chin area using the pin prick test. Continuous line shows the extent of the area of anaesthesia initially. Dotted line indicates a reduction of the area of anaesthesia during regeneration in subsequent weeks.



Figure 59. Testing for heat.



Figure 60. Testing for cold.

and the time taken to identify correctly the nature of the stimulus are simply recorded. Copper rods are used for these tests. The test should be limited to a short series of applications as temperature loss from the test object occurs rapidly. Due to conduction and convection phenomena at the skin surface and fluctuations in skin temperature one must be satisfied with recording whether or not the patient can distinguish between hot and cold and the time taken to identify correctly the nature of the stimulus.

(v)

TWO-POINT DISCRIMINATION (Fig. 61)

This is a measure of the capacity of the cutaneous innervation to resolve two points applied simultaneously to the skin surface by a pair of compass points. The points are first separated by a distance which enables the patient to decide without doubt or difficulty that he has been touched simultaneously by two points. The points which are blunt to prevent painful stimuli are then progressively brought closer together at successive applications until eventually they can no longer be recognized as two separate contacts. The shortest distance by which two touch stimuli must be separated to be recognized as such is the two-point threshold.

(vi)

ELECTRICAL STIMULATION (see Chap. II, Method and Materials)

Levant (1967) appears to be the only author in the literature to have used a device similar to that used in this study to electrically stimulate an area of skin in order to assess the integrity and sensory function of an injured nerve. Levant investigated 10 patients who had mandibular body osteotomies. He correlated the electrical stimulation response with the various phases of altered clinical sensation. He concluded that where the onset of formication was delayed beyond an average time there was a corresponding delay in return to normality. The investigation reported in this thesis has been extended beyond the work of Levant to cover the whole of the process of nerve regeneration from the clinical aspect.



Figure 61. Two-point discrimination test.

11. A CLINICAL INVESTIGATION OF I.D.N. REGENERATION FOLLOWING TRAUMA

1. AIMS

A study of the regeneration of the I.D.N. has been undertaken using an electrical skin stimulation (E.S.S.) test in the peripheral innervation of the nerve - namely the lip/chin area. The main aims of this study were to -

- a) assess the value of the E.S.S. as a predictor of the time of recovery of the I.D.N. following injury;
- b) compare the E.S.S. method with those methods presently used in clinical practice to estimate the prognosis following I.D.N. injury.

2. METHOD AND MATERIALS

a) Patients

i) Controls

In unilateral trauma of the I.D.N. where mental anaesthesia/paraesthesia was present, E.S.S. readings together with data of the other clinical tests were taken of the uninjured side. These were used as the control for comparison with the data from the injured side in each case. A separate control group was established for bilateral cases. Prior to the commencement of the experimental series, 100 E.S.S. and 100 two-point discrimination readings were obtained from left and right sides of 50 normal individuals of both sexes. Ages varied from 16 years to 60 years and those with a previous history of trauma or pathology to the I.D.N. were omitted. The averages of the normal values so obtained were used as controls in bilateral I.D.N. involvement (due to M.V.A. or P.V.) with resultant mental anaesthesia/paraesthesia.

In patients undergoing osteotomies the control readings of the various tests were obtained one day prior to surgery. These were used as base-lines for subsequent post-operative readings.

ii) Experimental

A total of 68 I.D.N. injuries were studied:-

35 were due to osteotomies

17 were due to physical violence (P.V.)

16 were due to motor vehicle accidents (M.V.A.)

Twelve injuries were omitted from the statistical analysis as they required a current strength of over 300 μ a before there was any response by the patient. The micro-ammeter was calibrated to only 300 μ a .

b) Tests employed

In addition to the E.S.S. test the common tests currently being used to assess the condition of mental anaesthesia/paraesthesia were applied in each case so that comparisons could be drawn especially with respect to accuracy of prognosis. The tests employed in each case were:

- i) the two-point discrimination test (Fig. 61) (Chapter 10);
- ii) the thermal tests (Figs. 59 and 60) - one for warmth and the other for cold (Chapter 10);
- iii) the pin prick test (Fig. 58). In this test the area of distribution of anaesthesia/paraesthesia was plotted on graph paper on which was outlined the lip/chin area (Fig. 58A). In subsequent weeks, it was observed that the area of anaesthesia/paraesthesia was either reduced or remained static. The reduction indicated a gradual return of normal sensation and regeneration;
- iv) the E.S.S. test. The apparatus (Fig. 62 and 62A) measures the threshold of sensitivity and permits measurements of response to graded nerve stimulation in the lip/chin area supplied by the mental nerve (the terminal branch of the I.D.N.) to be carefully recorded. A known variable current was applied to a minute area (approximately 0.1 to 0.2 mm) of the skin via electrodes. Depending on the degree of injury to the nerve and the level of current, a small painful sensation was induced at the point of

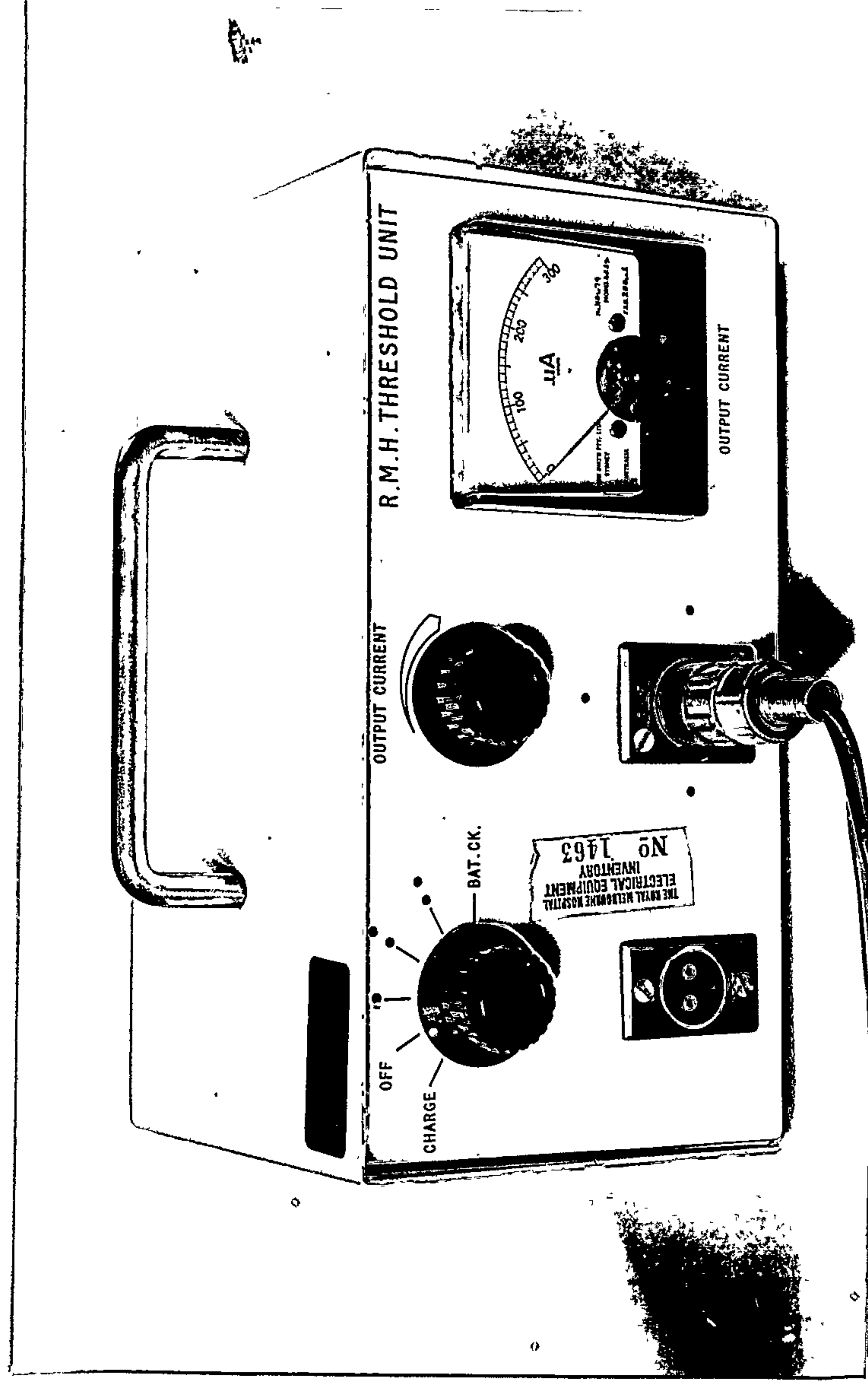


Figure 62. The threshold unit with micro-ammeter as used in the study.

application of the electrodes (Fig. 63).

The pain was one of burning or tingling and could be repeatedly reproduced. This current represents the threshold of stimulation of the nerve at that point of time. A micro-ammeter (0 - 300 μ a) (Fig. 62) measures the current output to either of right or left electrodes and the electrical return to the instrument is carried via a copper rod in the hand of the patient (Fig. 64). A perspex appliance in which the electrodes are held is contoured so that in subsequent weeks almost identical positions could be located (Fig. 65). The brass electrodes used were rhodium plated to prevent tarnishing thereby eliminating false readings which were evident during preliminary experiments.

Readings were taken of the affected and non-affected areas as soon as possible after injury or surgery. However, in some cases oedema and the psychological state of the patient prevented early assessment of the degree of injury to the nerve. In these instances initial readings were delayed until the patient was fully aware of the nature of the tests being conducted and oedema had subsided. This was essential for accurate and reliable data. Subsequent readings were taken on the third day after the initial readings and at intervals of one week for the first fortnight, then fortnightly for a month and finally monthly until normal sensation returned. Clinically, the criteria for return of normal sensation were:

- a) when the electrical readings on the affected side of unilateral injuries coincided with or were very close to those of the control side;
- b) when in bilateral cases the readings approximated the figure obtained from the separate control group;

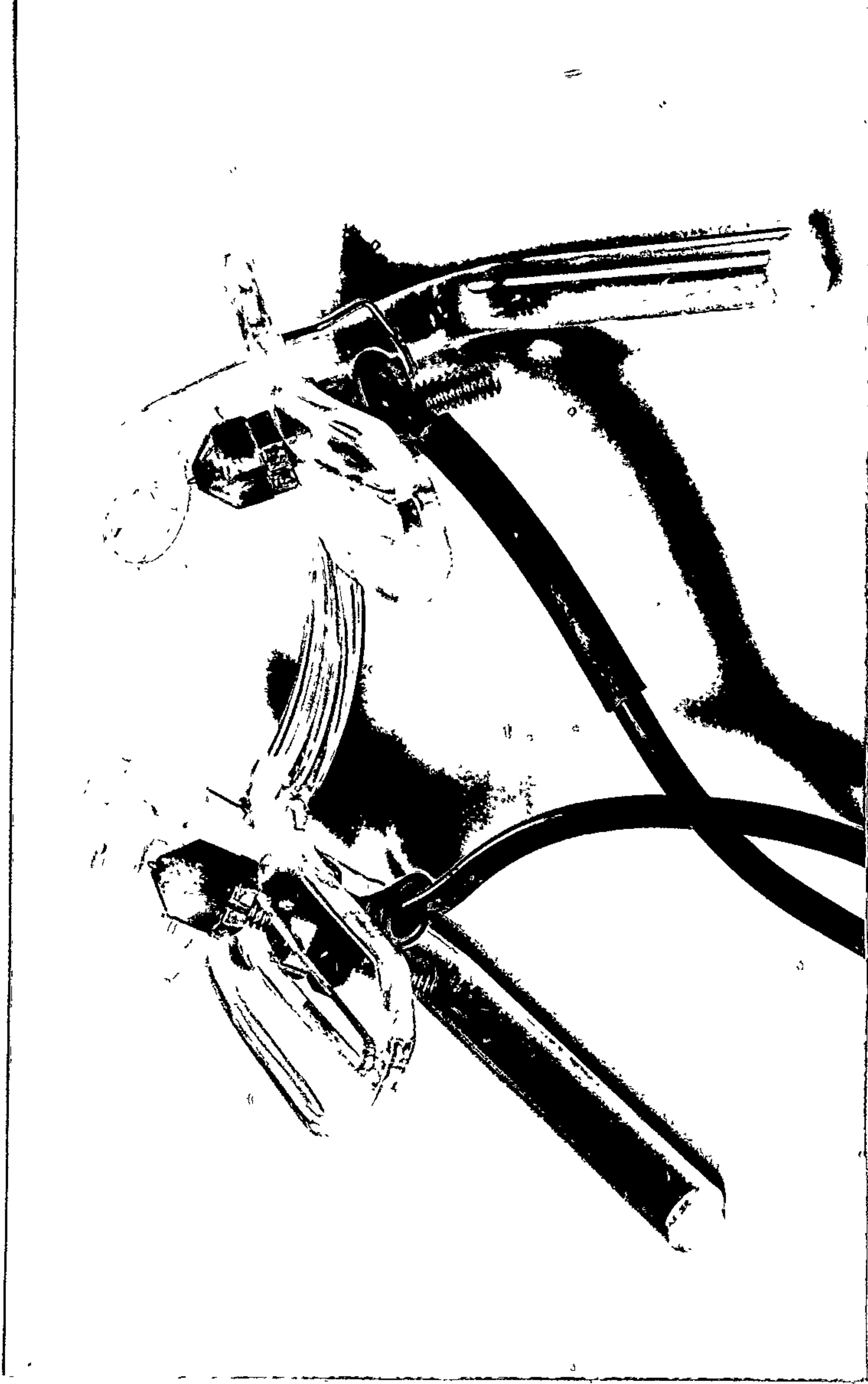


Figure 63. Detail of electrode appliance.



Figure 64. Overall view of apparatus in use.

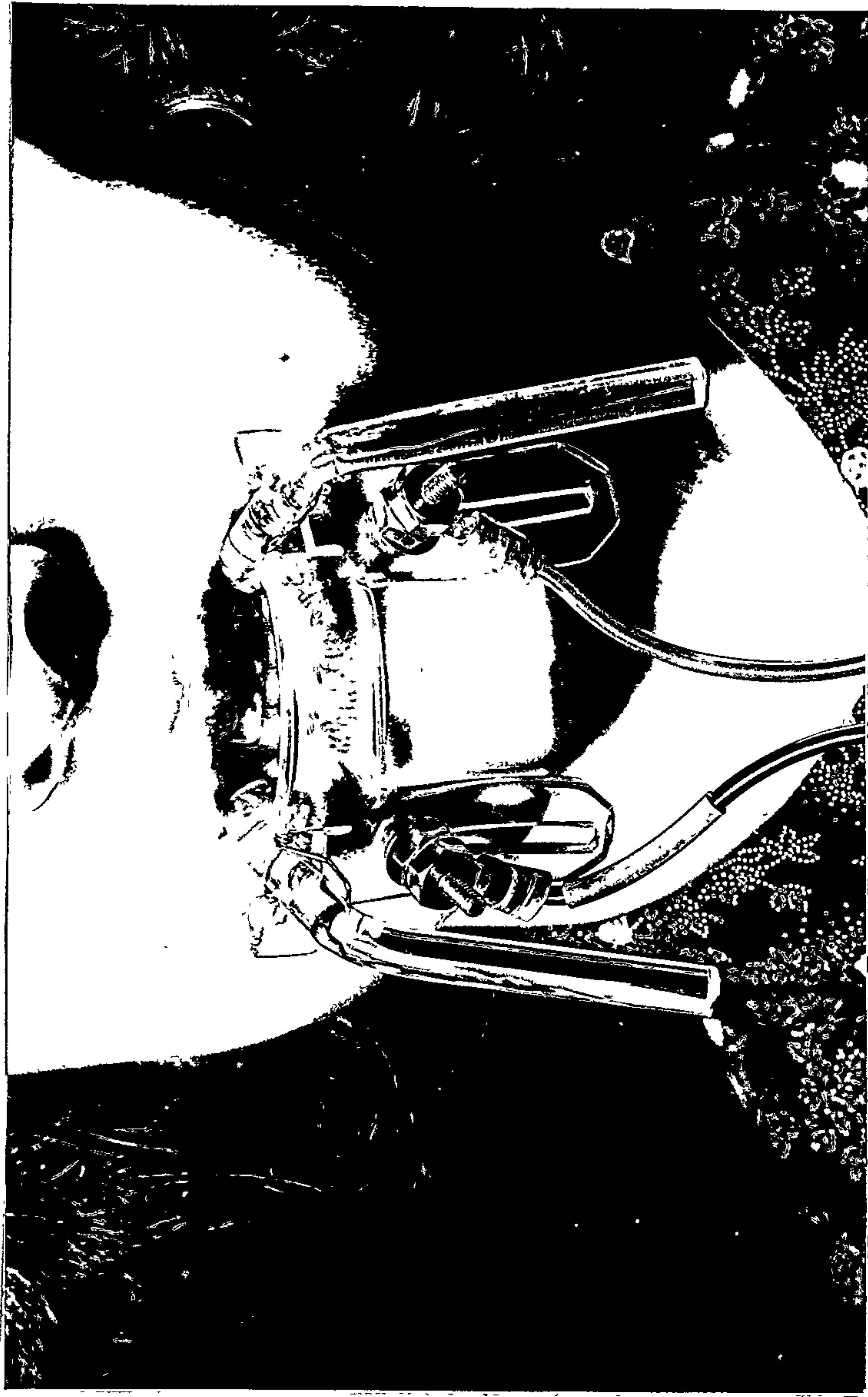


Figure 65. The perspex electrode appliance in position.

c) when in the opinion of the patient sensation seemed normal.

Unfortunately in some cases after the initial four weeks following commencement of treatment, the intervals between readings varied. This was due to:

- a) failure of patients to keep regular out-patient appointments;
- b) economic and time factors which prevented country and interstate patients from keeping regular appointments.

3. RESULTS

i) Control group

For those patients with unilateral inferior dental nerve injury in which the contralateral side was used as a control, these findings are reported in conjunction with the experimental results (e.g. see table 2 - right hand side results).

The mean value for E.S.S. recorded on 50 normal individuals, both right and left sides was 32.91 ± 3.77 (S.D.) μ a. The range of readings was from 30 to 50 μ a.

The mean value for the two point readings for the same control group was 3.17 ± 0.38 (S.D.) mm. The range of readings was from 2.5 to 4 mm.

ii) Experimental group

The record of a typical patient is shown on table 2.

This patient was in the unilateral physical violence category and was treated by open reduction.

The right hand side (control) showed normal readings of 30 μ a for the E.S.S. and 3 mm for the two point test.

On the day of injury the left side (injured) had readings of 210 μ a for the E.S.S. test and 10 mm for the two point test. The E.S.S. finding had returned to a normal value of 30 μ a in 28 weeks whilst the two point test normal value of 3 mm was achieved after 20 weeks.

NAME: JURGEN INT: K

DATE OF OP: 04.08.78

SEX: M

AGE: 21

TYPE OF TRAUMA: P.V.

	E.S.S.		2 Point		Thermal		Pin Prick		Remarks
	Reading (µa)		Reading (mm)		Cold	Hot			
	R	L	R	L	R	L	R	L	
Day of Injury	30	210	3	10	++	+	++	-	++
3rd Day Post Op.									
1st Week Post Op.	30	195	3	9	++	+	++	-	++
2nd "	"	30	170	7	++	+	++	+	++
4th "	"	30	100	4.5	++	+	++	+	++
6th "	"	30	90	4.5	++	+	++	+	++
8th "	"	"							
10th "	"	30	70	3.5	++	+	++	+	++
12th "	"	"							
16th "	"	30	50	3	3.5	++	++	++	++
20th "	"	30	40	3	3	++	++	++	++
24th "	"	30	35	3	3	++	++	++	++
28th "	"	30	30	3	3	++	++	++	++
32nd "	"	"							
36th "	"	"							
40th "	"	"							
44th "	"	"							

++ = Normal

-- = No Response

+ = Below Normal

- = Area of numbness getting smaller.

Open Reductions

Unilateral Fracture

Left Labial Skin dry

The hot, cold and pin prick tests had all returned to "normal" after 16 weeks.

Similar records were made for all 68 patients.

At the end of 40 weeks, 94.45% of the injured I.D.N's showed significant improvement. Only two inferior dental nerve injuries due to osteotomy and one due to M.V.A. totally failed to respond to all clinical tests.

The shortest periods for full functional return of all sensations were:

Osteotomies	4 weeks
P.V.	2 weeks
M.V.A.	2 weeks

The longest periods for the return of full sensation were:

Osteotomies	40 weeks
P.V.	16 weeks
M.V.A.	32 weeks

If the total recovery is defined as the preoperative value in case of bilateral osteotomy, the value for the opposing side in the case of unilateral osteotomy, M.V.A. or P.V., the results of E.S.S. readings showed that 44.5% of osteotomies, 72% of P.V. and 42% of M.V.A. recovered fully.

However, when the readings of the various tests reached about 85% of the control figures, nearly all patients indicated that their sensation had returned to normal or near normal, pre-accident or pre-operative quality. Using a similar criterion for normality viz., 45 μ a for E.S.S. and 4 mm for the 2 point test (see statistical analysis), the results are more encouraging as 89% of the injured I.D.N. due to osteotomy, 100% due to P.V. and 94% due to M.V.A. reached these levels.

As a result of the surgical experience obtained during this series, a slight surgical modification was used for the last four patients (bilateral osteotomies). The cut for the sagittal split technique was not extended forward beyond the distal of the lower 7, whereas in all of the previous cases the cut was well forward e.g., the mesial of the lower 6. It was noticed that in these latter cases (osteotomies), the E.S.S. readings and two point measurements were significantly lower post-operatively and the time taken for the return to pre-operative sensitivity in the lip/chin area was much shorter. The I.D.N. occupies a more buccal position in the region of the first and second molars during its passage to the mental foramen. The good results obtained in this latter series could be due to the modified surgical technique, where a smaller section of the I.D.N. as well as fewer fibres were exposed or subjected to any significant degree of trauma (see chapter 6 (iii)).

The incidence of dry skin (sometimes scaly) in the distribution of the mental nerve, the presence of vesicles in the lower lip/chin area and the complaint by patients of numbness in the chin and anterior part of the neck were some of the common conditions observed in this study (table 3). During the regenerative phase of the I.D.N. the condition of the skin was seen to return to normal. (see Fig. 66)

TABLE 3

	<u>M.V.A.</u>		<u>P.V.</u>		<u>Osteotomy</u>	
	Number	Total	Number	Total	Number	Total
	Affected	Number	Affected	Number	Affected	Number
Dry Skin	11	12	9	16	19	28
Vesicles	4	12	-	16	11	28
Numbness	10	12	7	16	18	28
(Chin & Neck)						



Figure 66. Photograph of osteotomy patient demonstrating vesicles post-operatively in lower lip/chin area.

As the table indicates, these manifestations did not occur in every case. All were from patients with E.S.S. readings greater than 100 μ a and all cases with an E.S.S. reading greater than 300 μ a produced all of these conditions. However, these latter have not been included in the statistical analysis (see below). This effect indicates that a certain degree of trauma may have to be inflicted to the I.D.N. before any of these conditions present themselves.

With the thermal tests, it was noticed that the return of sensitivity to cold was faster than that for heat. The times for the return of sensitivity to pin prick tests were similar to those for the hot thermal test.

(iii) Analysis of results

Observations of the E.S.S. and two point discrimination tests were analysed for their ability to predict the rate of recovery of the three groups of patients (table 4).

TABLE 4

	<u>Bilateral</u>	<u>Left Side</u>	<u>Right Side</u>	<u>Total</u>
Osteotomy	8 x 2	9	3	28
		<u>Open</u>	<u>Closed</u>	
		<u>Reduction</u>	<u>Reduction</u>	
Physical Violence (PV)		6	10	16
Motor Vehicle Accident (MVA)		8	4	12
				56

As the scale of the electrical stimulator ranged from zero to 300 μ a, patients who had an E.S.S. reading greater than 300 μ a after surgery or trauma were omitted from the analysis.

The E.S.S. and 2 point readings taken one week after surgery or trauma were used in the analysis as readings taken earlier than this appeared to be somewhat irregular and unreliable. Recovery was defined as 45 μ a for E.S.S. ($\ln 45 = 3.807$) and 4 mm for 2 point ($\ln 4 = 1.386$). These values were chosen as the majority of cases recovered to these levels which also represented almost the entire range of normal (no surgery or trauma) values. The mean value for the normal (non-injured) side was 32.43 ± 3.90 (S.D.) μ a for E.S.S. and 3.20 ± 0.36 (S.D.) mm for the two point discrimination test. These figures differed only slightly from the control figures for 50 normal subjects (see above). Hence, the mean plus 3 standard deviations would be 44.13 μ a for E.S.S. and 4.28 mm for two point test. These figures should include almost the total normal (poisson) population and approximate the figures used.

The osteotomy operations were of three types viz., bilateral, right hand side and left hand side. Eight patients who had bilateral osteotomies were used twice in the analysis, once for the right and once for the left hand side.

Natural logarithms of E.S.S. and two point were used in the calculations as this was appropriate for reflecting the anticipated, and observed, exponential nature of nerve regeneration (see appendix 1).

The summary of the results used in the analysis is included in tables 5a, 5b and 5c. These show the category of injury, readings (in natural logarithms) at one week after surgery or injury and the time to recovery.

Typical results for E.S.S. and two point tests recorded on a bilateral osteotomy patient are shown in figures 67 (a) and 67 (b) using linear co-ordinates.

Figure 68 shows the nerve regeneration of one patient in which the "normal" value was reached at approximately 9 weeks. A logarithmic scale is used for E.S.S.

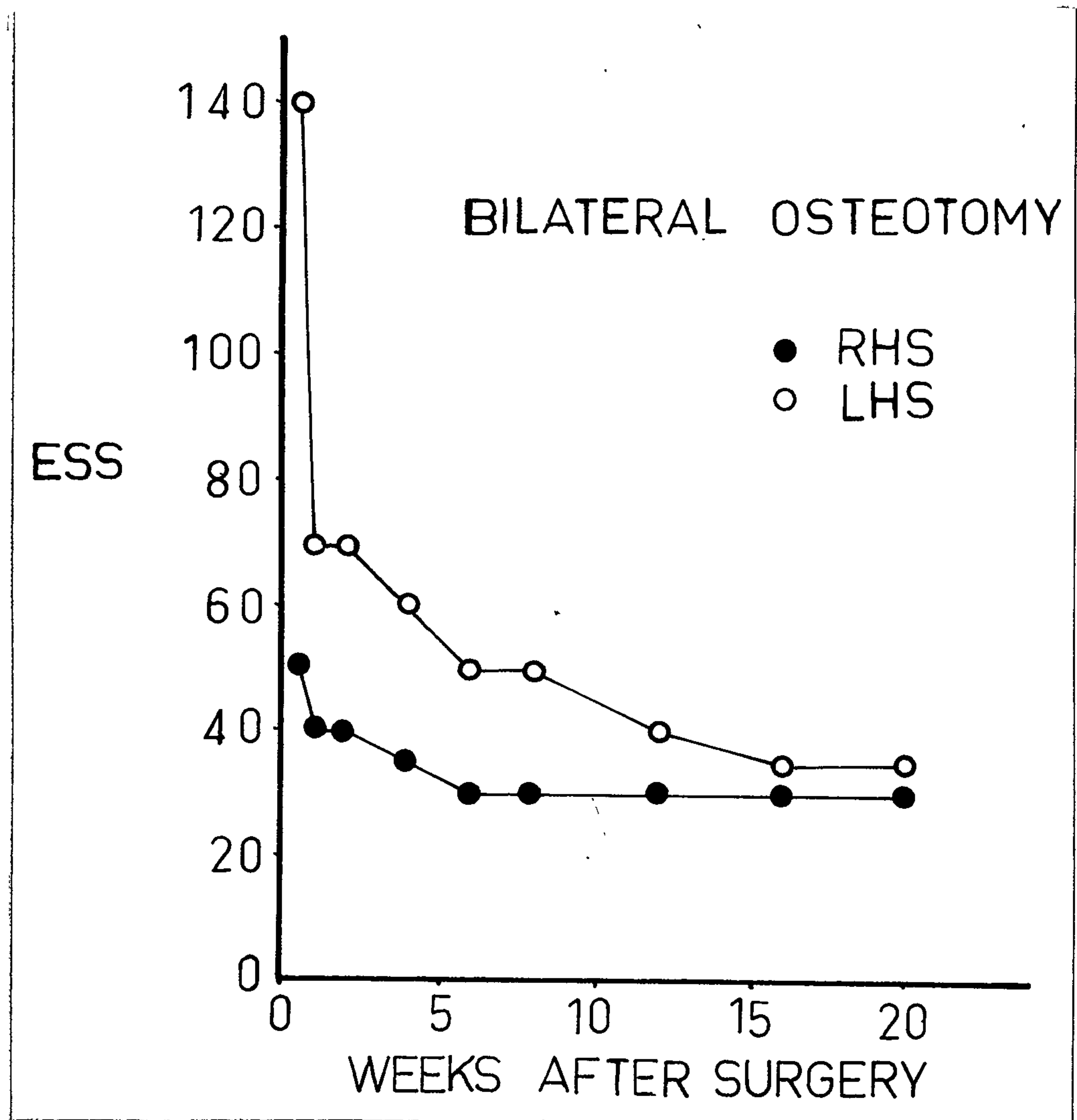


Figure 67A. Graph of ESS (in μa) readings of a bilateral osteotomy patient using linear co-ordinates.

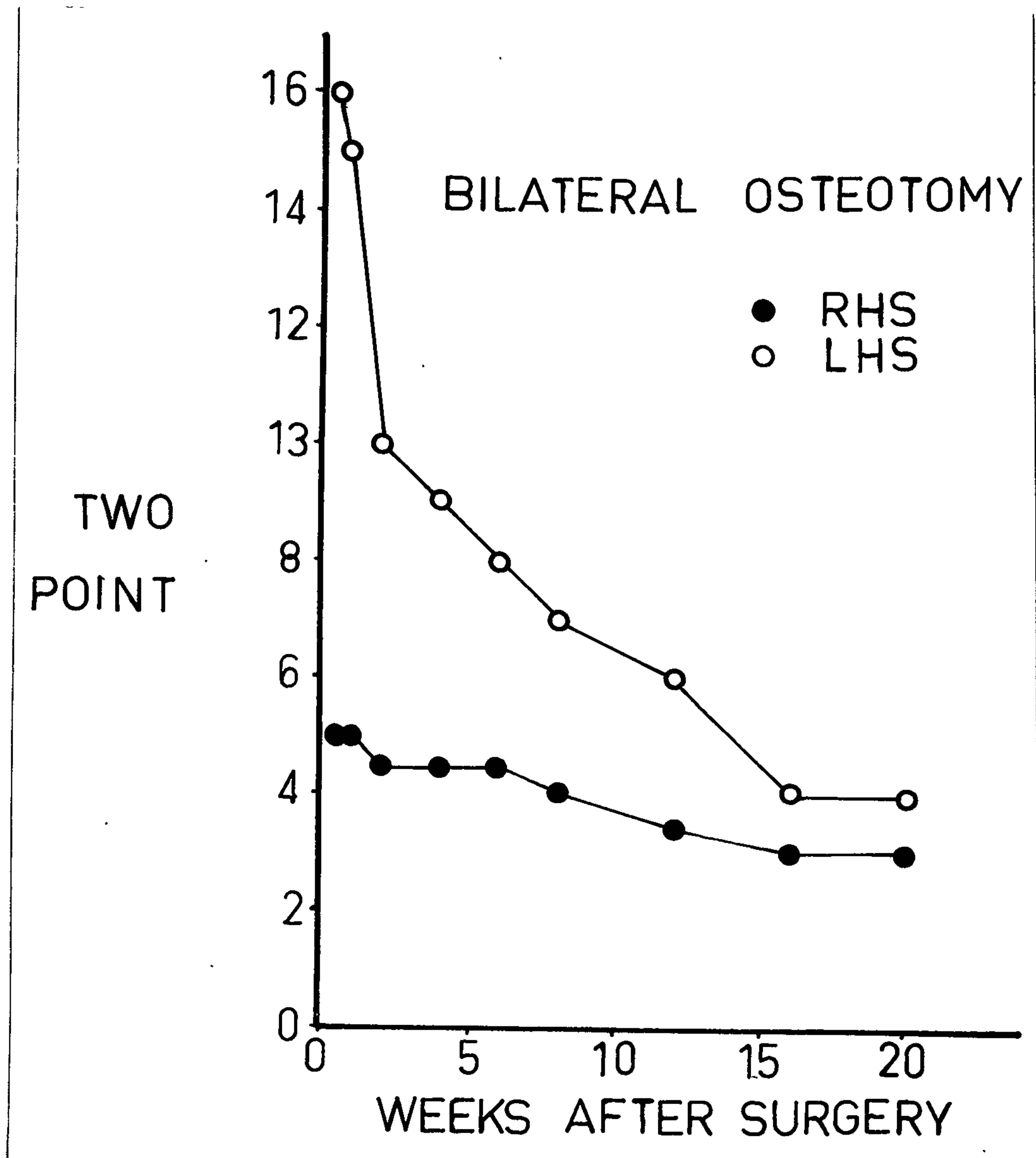


Figure 67B. Graph of 2 point measurements (in mm) of the same bilateral osteotomy patient shown in Figure 67A, using linear co-ordinates.

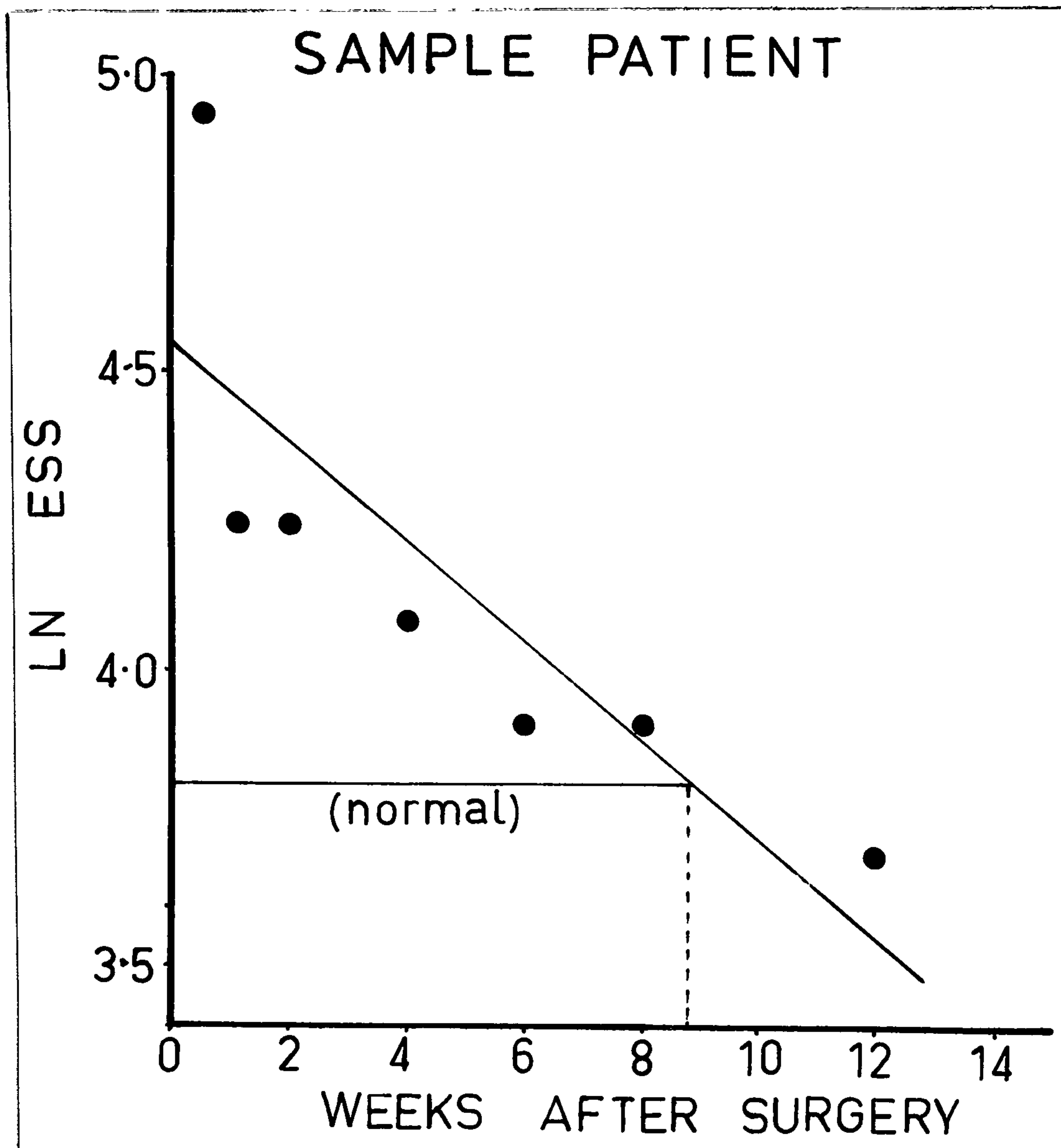


Figure 68. Graph of sample patient attaining "normal" ESS value at approximately 9 weeks. (Note logarithmic scale).

Figure 69 (A) shows the time for recovery plotted against the ln E.S.S. value at one week for all osteotomy patients.

Similarly, figure 69 (B) shows the time for recovery plotted against the ln two point value at one week for these same osteotomy patients.

Although there is a high correlation between E.S.S. and two point (correlation coefficient = 0.6149) E.S.S. is a better predictor of time of recovery than the two point test.

Correlation coefficient ln E.S.S. versus time to recovery
= 0.8542

Correlation coefficient ln two point versus time to recovery
= 0.6097.

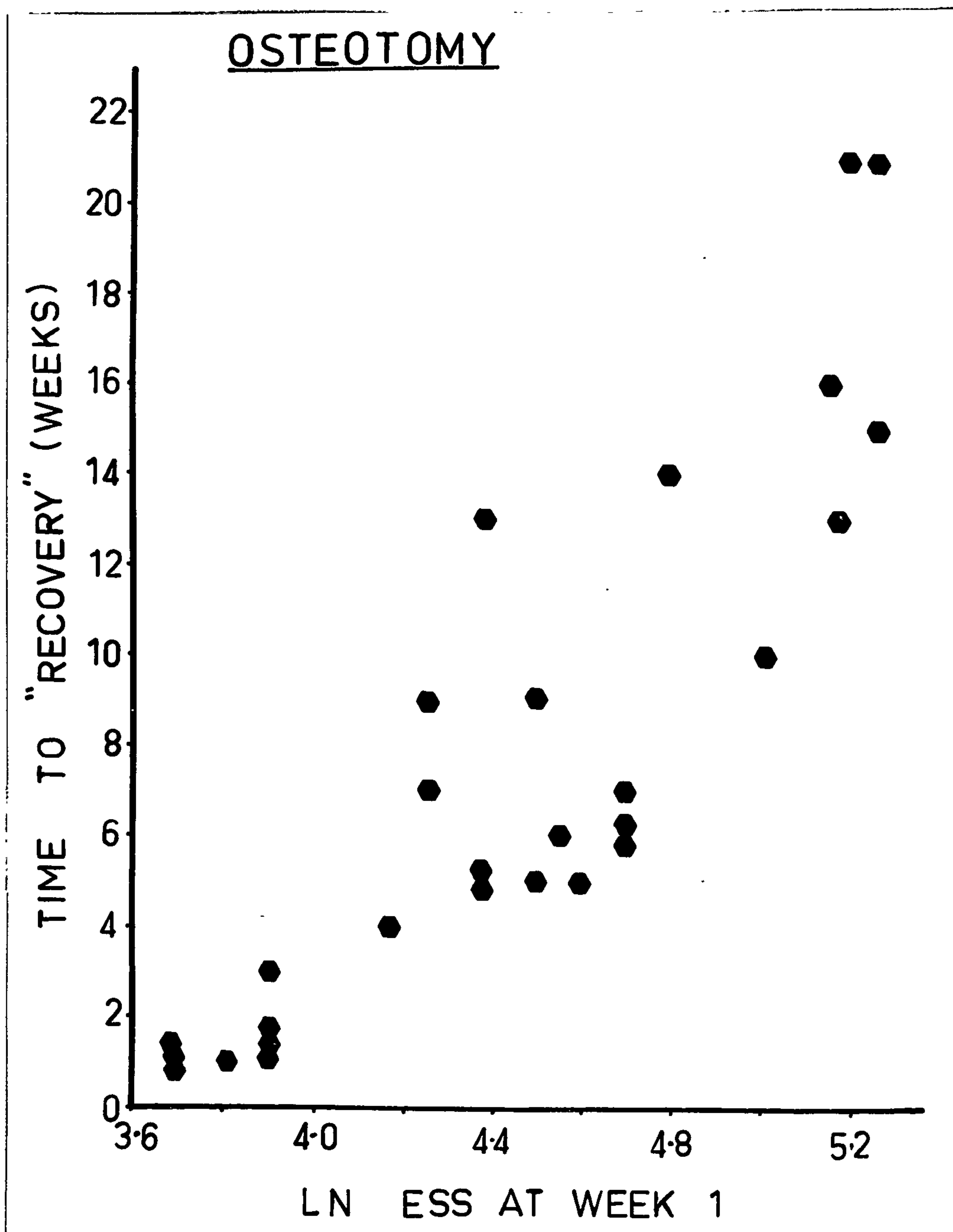


Figure 69A. Graph showing time for recovery plotted against Ln ESS at one week for all osteotomy patients.

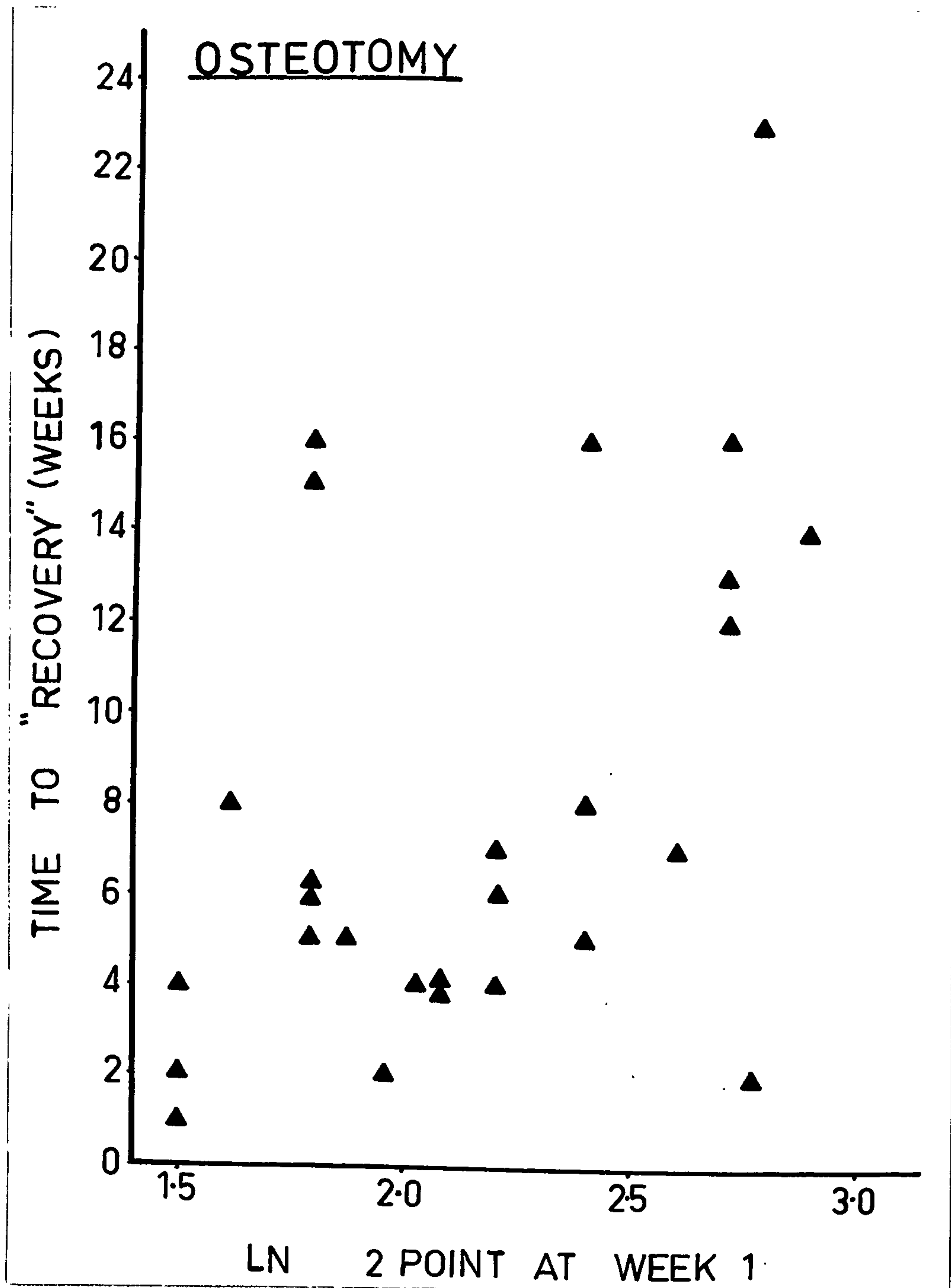


Figure 69B. Graph showing time for recovery plotted against Ln 2 point value at one week for all osteotomy patients. Note the spread of results compared with Figure 69A.

TABLE 5 (a)

Patient Number	Cause of Injury	Side	y Time (Wks) To Recovery	x In ESS At Week 1	y Time (Wks) To Recovery	x In 2-PT At Week 1
1	Osteotomy	R	1.5	3.91	4	2.02
1	"	L	6.0	4.70	4	2.02
2	"	R	1.5	3.91	5	2.40
2	"	L	1.5	3.91	2	1.95
3	"	R	5.0	4.38	8	2.40
3	"	L	1.0	3.69	2	1.50
4	"	R	5.0	4.38	12	2.71
5	"	L	5.0	4.50	4	2.08
6	"	L	7.0	4.70	7	2.20
7	"	R	1.0	3.69	1	1.50
7	"	L	4.0	4.17	5	1.79
8	"	R	6.0	4.70	4	2.08
8	"	L	13.0	5.16	7	2.60
9	"	R	10.0	5.01	6	1.79
11	"	L	6.0	4.55	5	1.87
2	"	L	7.0	4.25	4	1.50
13	"	L	21.0	5.25	16	2.40
14	"	L	9.0	4.50	2	2.77
15	"	L	21.0	5.19	13	2.71
17	"	R	15.0	5.25	-	-
17	"	L	14.0	4.79	-	-
18	"	R	1.0	3.69	8	1.61
18	"	L	9.0	4.25	16	2.71
19	"	L	1.0	3.81	16	1.79
20	"	L	16.0	5.14	-	-
21	"	R	5.0	4.60	6	2.20
22	"	R	3.0	3.91	6	1.79
22	"	L	13.0	4.38	15	1.79

TABLE 5(b)

Patient Number	Cause of Injury	Side	y	x	y	x
			Time (Wks)	In ESS	Time (Wks)	In 2-PT
			To	At	To	At
			Recovery	Week 1	Recovery	Week 1
39	M.V.A.	Closed	4	4.25	5	1.87
40	"	Open	3	4.25	2	1.50
41	"	Open-R	7	4.61	8	1.79
41	"	Open-L	8	4.65	9	1.95
45	"	Open	14	4.55	14	2.30
46	"	Open	12	4.98	20	2.48
47	"	Open	14	5.16	15	2.83
48	"	Closed	10	4.38	16	2.14
49	"	Open	1	3.91	2	1.70
50	"	Closed	4	4.17	8	1.79
51	"	Closed	19	5.19	-	-
52	"	Open	12	4.70	12	2.48

TABLE 5(c)

Patient Number	Cause of Injury	Side	y	x	y	x
			Time (Wks)	ln ESS	Time (Wks)	ln 2-PT
			To Recovery	At Week 1	To Recovery	At Week 1
23	P.V.	Closed	7	4.87	10	3.00
24	"	Closed	10	4.87	13	2.71
25	"	Open	4	4.38	6	2.08
26	"	Open	4	4.38	10	2.14
27	"	Open	1.5	3.91	8	1.61
28	"	Open	8	4.17	6	1.79
29	"	Open	3	4.17	2	1.61
30	"	Closed	8	5.35	6	2.30
(Not used in analysis)						
31	"	Closed	7	4.87	10	2.48
32	"	Open-L	1	3.81	8	1.87
32	"	Closed-R	5	3.91	9	1.87
33	"	Closed	9	4.38	3	1.61
34	"	Open	18	5.27	8	2.20
35	"	Closed	1	3.91	1	1.39
36	"	Closed	6	4.50	4	1.95
37	"	Closed	8	4.60	6	2.44
38	"	Open	3	4.38	4	1.70

In practical terms, the prediction of the time of recovery based upon the natural logarithm of E.S.S. (ln E.S.S.) is likely to be more precise than a prediction based on the natural logarithm of two point test results (ln two point).

An analysis of variance was carried out to ascertain which of the features (patient subdivisions) were significant e.g., open or closed reductions or cause of injury viz., osteotomy, P.V. or M.V.A.

For the physical violence and motor vehicle accident patients statistical comparisons were made between open and closed reduction operations. No significant differences were found. See appendix 2 for details of analysis.

For further analyses, the open and closed reductions were combined.

Next, using regression lines, for recovery time against ln E.S.S. taken one week after the operation, comparisons were made between physical violence, motor vehicle accident and osteotomy patients. No significant differences were found. See appendix 3 for analysis details. An example of the analysis used is shown in appendix 4. Here open and closed reductions in the P.V. and M.V.A. groups are compared.

The separate regression lines for open and closed reductions were calculated first to ascertain whether or not there was a significant regression for each. Then the slopes of the two lines were compared. As they were the "same", a single slope was used for open and closed reductions and the intercepts with the y-axis calculated. These were not significantly different from each other so one equation could be used to fit both sets of data. This equation is:

$$\hat{y} = -38.08 + 10.14 x$$

where x is ln E.S.S. at week 1.

If $x = 4.605$ (E.S.S. = 100), $\hat{y} = 8.71$ which is the predicted recovery time. Subsequent to the initial analysis, one patient (No.30) was found to be an "outlier" on the graphs and was not used further in the analysis. Hence, the prediction equation based on the ln E.S.S. for the combined data becomes -

$$\hat{y} = -37.83 + 10.14 x$$

where x is $\ln$ E.S.S.

This is shown in figure 70 with the 66.7% limits.

Example: If $\ln$ E.S.S. is about 4.6 (E.S.S. 100) the recovery time is 8.8 (+8.0) weeks.

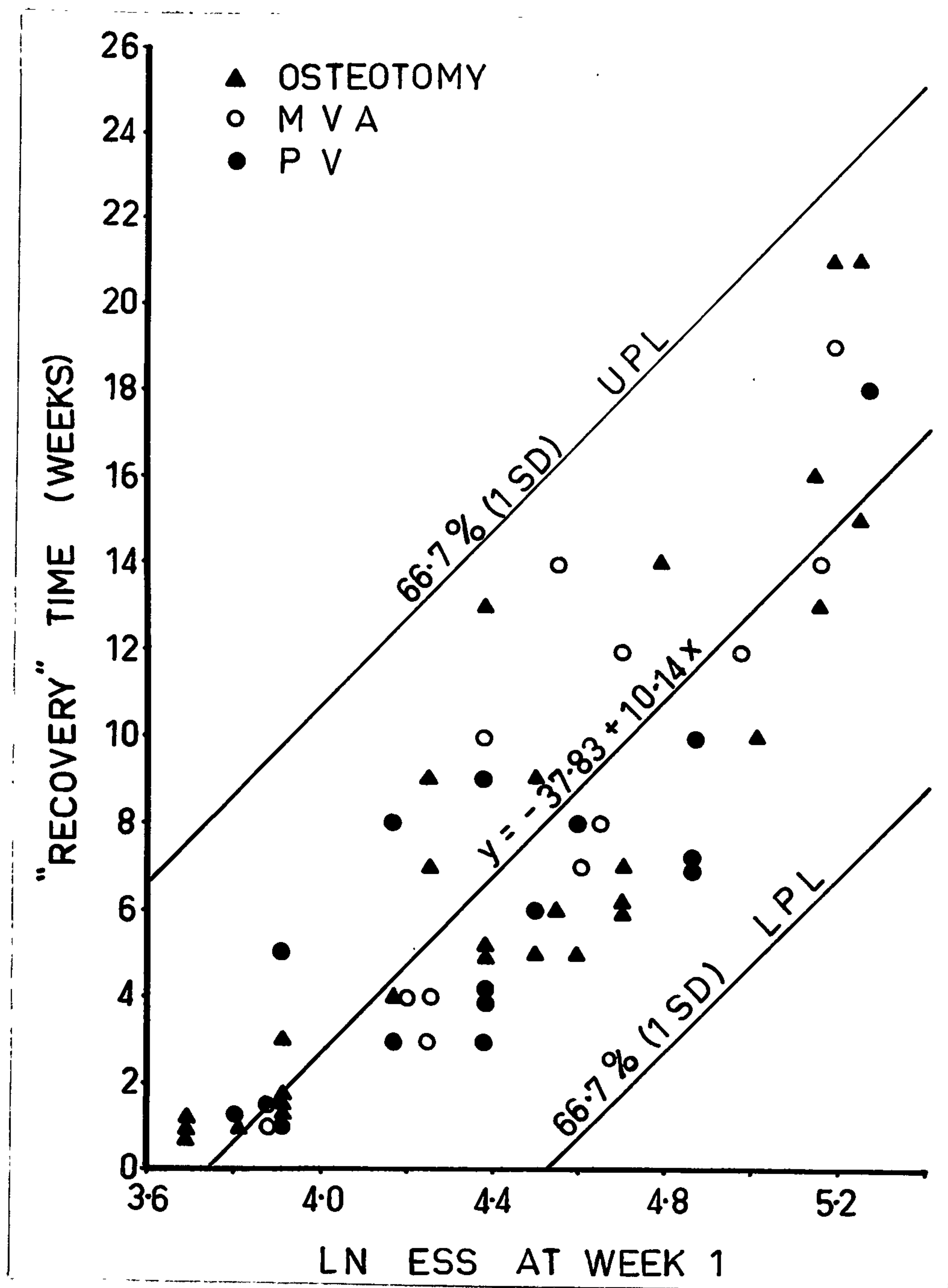


Figure 70. Graph showing regression lines for prediction of time to recovery based on Ln ESS taken one week following trauma to the inferior dental nerve.

Example: Ln ESS of 4.6 (ESS,100) the recovery time would be 8.8 ± 8.0 weeks

12. DISCUSSION

Clinicians agree that the present methods for determining the extent of nerve damage following injury are inadequate. In fact, there has been no test, in general use, to predict the time for return of full sensation following I.D.N. injury. At best, if patient follow up has been carried out accurately, some idea of the prognosis and rate of recovery can be gleaned from the observations of a reducing area of anaesthesia/paraesthesia. These are carefully mapped at regular intervals using a pin prick skin test. This is an exacting and time consuming test which is difficult to interpret due to the absence of reference data for normals. Hence, a prognosis cannot be given with any degree of certainty. The present E.S.S. test gives consistent and reliable results which permit an accurate prognosis. This facility has not been available to the clinician previously.

In addition, a more accurate means of assessment would aid in the understanding of the difficulties patients experience when speaking, drinking or carrying out other normal functions. Obviously, better patient counselling and advice would result.

The electrical stimulation test described here enables a quantitative estimate of functional loss due to nerve injury. This, in turn, permits a more accurate prediction of recovery time which gives comfort to the patient and which has obvious medico-legal implications in those patients in whom recovery is not complete.

This technique was described by Levant in 1967. However, his preliminary investigation included only 10 cases, all of whom were subjected to mandibular osteotomy. Hence, it was not possible to apply adequate statistics and he did not investigate the value of the technique as a predictor of recovery time. In addition, he did not examine the differences between osteotomy, P.V. and M.V.A. patients or between open and closed reductions. In general, the results of this investigation confirm and extend the findings of Levant. There appear to be no other reports of similar electrical devices which permit a quantitative assessment of sensitivity.

If used intelligently, the E.S.S. test measurements taken one week after nerve injury enable the surgeon to make accurate predictions of the rate of recovery of sensation. These predictions will be more accurate than those based upon other tests such as the two point or thermal tests. As a result, the patients may be given increased hope and confidence as they monitor and compare their own functional improvement with the prediction. In fact, no other author has presented a quantitative method (accurate or otherwise) for predicting the recovery time based on these other tests (i.e., the thermal and two point tests).

The ease of use of the E.S.S. device makes it a valuable addition to the surgeon's armamentarium. However, the accuracy of the prediction of recovery time still leaves room for improvement. A further study with larger numbers of patients may improve this accuracy. However, because of the differences in the extent of nerve injury and the limited knowledge of methods of treatment of nerve injury, it is probable that the spread of results and the resulting inaccuracy of prediction are at least partially the result of patient variability.

In this study, more than 94% of patients showed a significant improvement in sensation over a 40 week period. Fortunately, nerve regeneration in bony canals can occur without surgical aid because the canal acts as a guide for growth and reunion (De Bats and Phillips 1944). Hence, after injury to the mandibular nerve, sensation may return spontaneously. However, if the bony canal is obstructed by a displaced bone or fragment of tooth, nerve compression results and possible permanent numbness of the lip. This would be indicated by a lack of improvement as recorded with the stimulator over a determined period of time. Hence, the instrument described here would aid in decision making regarding surgical intervention. At present, where anaesthesia/paraesthesia appears permanent or where sensation has returned only partly, most oral surgeons are conservative in regard to any surgical intervention in these type of cases.

An interesting and unexpected finding in this study was that fractures due to trauma which needed surgical intervention for reduction and stabilization of the fragments,

did not show any significant increase in recovery time. Most oral surgeons would tend to agree that open reduction causes a greater degree of trauma to the I.D.N. Hence a slower recovery would be expected.

One obvious improvement to the E.S.S. apparatus would be to increase the range of stimulation above 300 μ a. This would permit measurement and possible prediction in the case of the more serious nerve injuries (at present greater than 300 μ a) and may also enable an immediate recognition of those patients in which recovery will not occur.

The observation that 35 of the 56 cases of I.D.N. injury were associated with a feeling of numbness in the area of the mental prominence and in the anterior part of the neck is interesting in relation to the innervation of these areas. In addition, a slower rate of return of sensation to these areas in comparison to the lip area supplied by the mental nerve was observed in these patients.

Neurapraxia of the anterior cutaneous nerve of the neck (C2) due to hyperextension of the neck during surgery is the cause of the analgesia in the submental area according to Killey et al (1968). However, Peebles (cited by Roberts and Harris 1973) attributes this condition to direct digital pressure applied to the nerve during operation.

The mental branch of the I.D.N. is known to innervate the skin and mucous membrane of the lower lip and the skin of the chin. There is no evidence of innervation by this nerve to the anterior part of the neck. Hence, there appears to be an alternative innervation to this area.

The mylohyoid nerve supplies the mylohyoid muscle and the anterior belly of the digastric and has generally been considered to be a motor nerve. There is now convincing evidence that it contains both motor and sensory components (Sicher and De Brul 1970) and the sensory component is said to continue beyond these muscles by way of the cutaneous branches to the skin area around the mental prominence. The sensory component, although frequently asymmetrical, appears to supply the skin area

around the mental prominence and in about 10% of cases a twig of this branch enters the mandible in the mental region to supply the lower incisor teeth (Sicher and De Brul 1970). Studies of dry mandibles by Shiller and Wisewall (1970) and Sutton (1974) have confirmed the presence of lingual bilateral foramens. The hypothesis that the mylohyoid nerve participates in innervation of posterior teeth (Frommer 1972) is further evidence to support that the mylohyoid nerve is a mixed nerve.

Roberts and Harris (1973) have presented clinical evidence of an alternative sensory innervation to the mental prominence. They injected lignocaine one cm deep to the lingual mucosal reflection adjacent to the lower third molar to anaesthetise the mylohyoid nerve. However, lower labial sensation remained normal whilst the area of skin overlying the chin was found to be insensitive.

Frommer and his collaborators (1970) studied the mylohyoid nerve and found that 20% of fibres were of diameter zero to 6 μm . As the nerve progressed distally from its point of origin, there was a reduction in the number of fibres of smaller diameter. Fibres of diameter 4 μm or less are unmyelinated or lightly myelinated and are associated with pain sensation (Bloom and Fawcett, 1968). Hence, this reduction in the number of fibres of smaller diameter distally may indicate that in addition to innervation of some lower teeth these fibres may be implicated in the sensory supply to the mental prominence and the anterior part of the neck.

In fractures at the angle of the mandible with gross displacement and in osteotomies involving lingual retraction or deep lingual periosteal stripping during surgery, trauma to the mylohyoid nerve could occur. The mylohyoid nerve lies in close relationship to the lingual aspect of the roots of the lower third molar (Roberts and Harris 1973). Therefore, the sensory fibres of the mylohyoid nerve must have been severely traumatized to produce the sensation of numbness. In addition, when these procedures are used for the removal of impacted third molars with a lingual split technique, a similar injury may result. (Roberts and Harris, 1973; Stacy, 1977).

There appears little knowledge about the origin of the vesicles and dry skin which occur in association with the disruption of the nerve supply to the lip/chin area (Fig. 71). However, the appearance of dry skin is due at least in part to the local sympathetic innervation, for Jacob and Francone (1974) have claimed that rapid regeneration is a feature of sympathetic fibres and a return of sensory function is initially recognized by an improvement in the colour of the skin and evidence of vasomotor activity.

Professor K. Bradley (Personal Communication) found that where he had traumatized the second division of the trigeminal nerve at its origin he often noticed a crop of vesicles erupt in the distribution of the second division, e.g., in the upper lip/cheek area. Similarly, trauma to the I.D.N. could produce this same effect in the distribution of the mental nerve. However, the possibility that these vesicles represent a manifestation of a viral (herpes) nerve infection cannot be excluded.

In considering those patients in which there was no improvement, there were really only three inferior dental nerve injuries in this category and in each case the clinical assessment indicated that little repair or improvement could be expected. All registered close to the 300 μ a. when tested for sensitivity immediately after surgery and all showed total anaesthesia even after 40 weeks.

In one of the two inferior dental nerve injuries due to osteotomy the inferior dental nerves bundle on both sides of the mandible was placed very much buccally and during the surgical procedure the nerve fibres on one side were severely traumatized with many nerve fibres being cut. On the other side the nerve was actually severed and the cut ends sutured together.

In the second osteotomy case, the inferior dental nerve was once again in a buccal position due to the anatomy of this particular patient. Again, a large number of fibres in this inferior dental nerve bundle were damaged and torn, although the inferior dental nerve bundle was not completely severed. This type of anatomical positioning of the inferior dental nerve bundle i.e. being so extremely buccal, is a rare finding.

Examination of the patient involved in a motor vehicle accident and who showed no recovery, indicated that there was gross comminution of the angle of the mandible and severe displacement of the bone fragments which would have resulted in considerable stretching of the inferior dental nerve and possibly even direct damage to fibres caused by the broken bone fragments.

Hence, in each case the damage was very severe and the lack of improvement in sensitivity was not unexpected. When fibres are severed the growing tips of the fibres may be prohibited from entering the endoneurial tubes due to fibrosis or actual destruction of these tubes. As a result, fibres are unable to reach their terminations and neural connections are not re-established. It is also possible that some severed fibres may have also extended into the fracture sites and hence failed to reach the endoneurial tubes (See Chapter 6).

CONCLUSIONS

1. Splitting of the funiculi of the human cadaver I.D.N. resulted in a greater number of bundles distally at the mental foramen. In addition, there may be an increase in the total number of fibres.
2. The E.S.S. test was found to give consistent results which can be used to assess prognosis of patients with trauma to the I.D.N. Predictions can be made according to the following equation -

$$\hat{y} = -37.83 + 10.14x$$

where x is the natural logarithm of the E.S.S. reading at one week following injury or surgery and $\hat{y}$ is the predicted recovery time (weeks).

This clinical advance will greatly improve

- (a) patient management and treatment planning
- (b) patient reassurance
- (c) medico-legal documentation

3. The E.S.S. test was found to be a better predictor of recovery time than the two point test and the other tests studied, viz., pin-prick, thermal.
4. Normal values were established for both the E.S.S. and two point tests.

E.S.S.

100 normals.

32.91 ± 3.77 (S.D.) μ .a.

68 controls

32.43 ± 3.90 (S.D.) μ .a.

(Pre-operative or non affected sides.)

Two Point	3.17
100 normals	~~32.17~~ ± 0.38 (S.D.) m.m.
68 controls	3.20 ± 0.36 (S.D.) m.m.
(Pre-operative or non affected sides.)	

5. The majority (94.45%) of injured I.D.N's showed significant improvement within 40 weeks. If the criteria of normality is 45 μ a, then 89% of osteotomies, 94% of motor vehicle accidents and 100% of physical violence patients returned to normal within this period.
6. There were no significant differences between the recovery rates for the three groups studied, viz., osteotomy, physical violence and motor vehicle accident patients.
7. There was no significant difference between the recovery rates for injury patients treated with either open or closed reduction procedures.
8. The post-surgical E.S.S. readings were found to be lower when the modified surgical technique was introduced for the last few osteotomy cases. There was also an earlier return of normal sensation, presumably as a result of fewer nerve fibres undergoing trauma. Numbers were insufficient for statistical analysis.
9. The return of sensitivity for cold appeared to be faster than that for heat.
10. Vesicles and eruptions were observed in the skin of the lip/chin area following significant I.D.N. damage (E.S.S. greater than 100 μ a.) and appear to be associated with the loss of the sensory supply.
11. Dry (and sometimes scaly) skin in the lip/chin area was frequently found following I.D.N. trauma and may be related to disruption of the local sympathetic supply.

12. A frequent finding in patients with I.D.N. damage (osteotomy, physical violence and motor vehicle accident) was the occurrence of anaesthesia/paraesthesia of the mental prominence and anterior part of the neck. It would appear that the mylohyoid nerve is involved in the sensory innervation of this region.

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APPENDIX 1Reason for taking logarithms of ESS and Two - Point

From Fig. (67a) we see that the relationship between ESS (for example) and time is of the form:-

$$Y_t = Y_0 e^{-Bt}$$

where Y_0 = ESS at time zero (i.e. day 3 or week 1)

Y_t = ESS at time t

We want the value of t for which

$$Y_t = C$$

(where C corresponds to the "recovered" value of 45 for ESS)

i.e.

$$Y_0 e^{-Bt} = C$$

$$\therefore \ln(Y_0) - Bt = \ln C$$

$$\therefore t = \frac{\ln(Y_0) - \ln C}{B}$$

That is, it is to be expected that there is a linear relationship between t and $\ln(Y_0)$.

APPENDIX 2

COMPARISONS OF PV AND MVA FOR OPEN AND CLOSED REDUCTIONS
Recovery Time on LN ESS

<u>OPEN</u>	<u>ANALYSIS OF VARIANCE</u>				
	<u>d.f.</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>P</u>
Combine regression	1	230.31	230.31		
Difference of regressions	1	4.69	4.69	1	NS
Combined residual	11	117.31	10.665		
within groups	13	352.31			
Overall regression	1	208.39	208.39	19.54	0.01
Difference of positions	1	26.94	26.94	2.53	
Difference of regressions	1	4.69	4.69	1	NS
Combined residual	11	117.31	10.665		
TOTAL	14	357.33			
<u>Closed</u>	<u>Analysis of Variance</u>				
	<u>d.f.</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>P</u>
Combined regression ¹	1	49.79	49.79		
Difference of regression	1	19.17	19.17	3.75	0.10
Combined residual	10	51.02	5.102		
Total within groups	12	219.98			
Overall regression	1	197.89	197.89	38.79	0.01
Difference of positions	1	4.72	4.72	1	NS
Difference of regressions	1	19.17	19.17		
Combined residual	10	51.02	5.102		
TOTAL	13	272.80			

d.f = degrees of freedom

SS = sum of squares

MS = mean square

F = variance ratio

P = probability level

N.S = not significant

APPENDIX 3COMPARISON OF OSTEOTOMY, PV AND MVARecovery Time On LN (log) ESS

<u>ANALYSIS OF VARIANCE</u>					
	<u>d.f.</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>P</u>
Combined regression	1	1140.38	1140.38		
Difference of regression	2	14.39	7.195	1	NS
Combined residual	50	393.62	7.872		
Total within groups	53	1548.39			
Overall regression	1	1186.46	1186.46	150.70	0.01
Difference of positions	2	17.39	8.695	1.10	NS
Difference of regressions	2	14.39	7.195		
Combined residual	50	393.62	7.872		
TOTAL		55	1611.86		

APPENDIX 4COMPARISON OF OPEN AND CLOSED REDUCTIONPV AND MVA COMBINEDRECOVERY TIME ON LN ESS ONE WEEK AFTER OPERATION

	<u>OPEN</u>	<u>CLOSED</u>	<u>TOTAL</u>
n	14	14	28
Mean x	4.634	4.307	4.471
$(x - \bar{x})^2$	2.3953	1.4565	3.8518
Mean y	8.357	6.179	7.268
$(y - \bar{y})^2$	357.21	272.80	630.01
$(x - \bar{x})(y - \bar{y})$	24.71	16.98	41.69
a (intercept)	-39.45	-44.02	
b (slope)	10.32	11.66	
r (correlation)	0.845	0.852	

ANALYSES OF VARIANCEOPEN

	<u>d.f.</u>	<u>S.S.</u>	<u>M.S.</u>	<u>F</u>	<u>P</u>
Regression	1	254.91	254.91	29.90	0.01
Residual	12	102.30	8.525		
Total	13	357.21			

CLOSED

Regression	1	197.88	197.88	31.69	0.01
Residual	12	74.92	6.243		
Total	13	272.80			

COMPARISON OF REGRESSIONS

	<u>d.f.</u>	<u>S.S.</u>	<u>M.S.</u>	<u>F</u>	<u>P</u>
Combined regression	1	451.17	451.17		
Difference of regressions	1	1.62	1.62	1	NS
Combined residual	24	177.22	7.384		
Total with groups	26	630.01			
Overall regression	1	473.49	473.49	64.12	0.01
Difference of positions	1	10.91	10.91	1.48	NS
Difference of regressions	1	1.62	1.62		
Combined residual	24	177.22	7.384		
Total	27	663.24			

