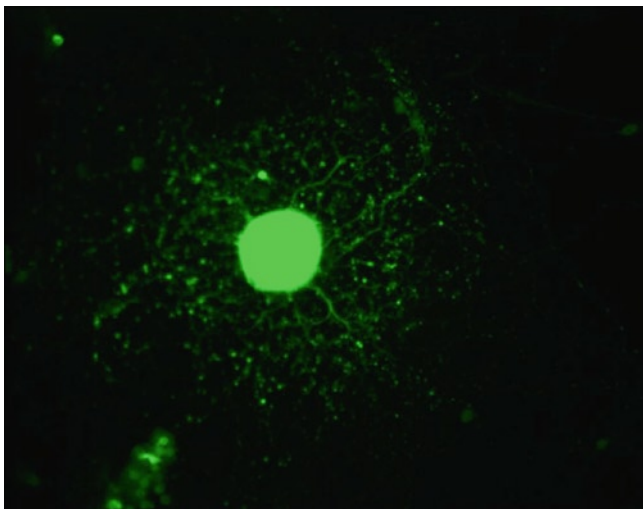


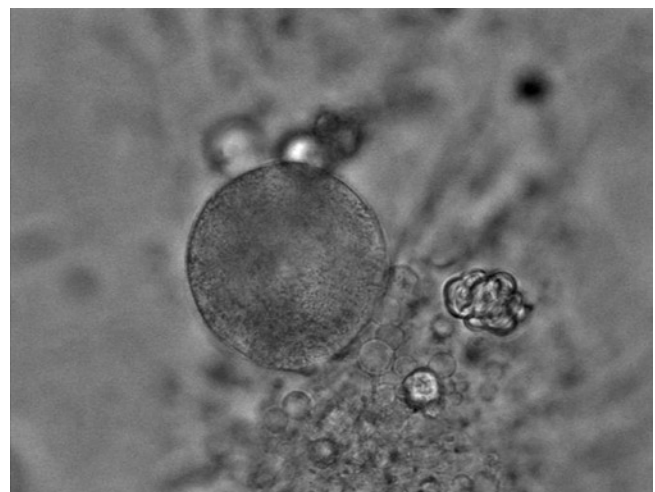
*The neurone and neurotrophins; transitional zone and roots; the Schwann cell and myelin; the connective tissue sheaths; conduction; axonal transport; blood supply; nervi nervorum; changes with aging; motor path with central and peripheral connections; sympathetic outflow; sensory path with superficial and deep peripheral connections and with central connections; the role of visceral afferents; neurotransmitters.*

The essential component of the system is the nerve cell with its dendrites and its prolongation, the axon (Figs. 2.1–2.3). Young (1945) characterized the axon as “a very long cylinder of a semi fluid nature.” It is a column of neuronal cytoplasm, the *axoplasm* enclosed by a cell membrane, the axolemma. Thomas et al. (1993a) described the axoplasm as a “fluid cytosol in which are suspended formed elements.” The most conspicuous of the latter is the cytoskeleton consisting of neurotubules, neurofilaments and matrix. In addition, there are mitochondria, axoplasmic reticulum, lamellar and multi-vesicular bodies, and membranous cisterns, tubes and vesicles. It is the cytoskeleton that provides the apparatus for axoplasmic transport. Berthold et al. (2005) describe the axolemma as a three-layered unit membrane about 8 nm thick and consider that it: “conveys signals between the neurone and its Schwann cells that control the proliferative and myelin

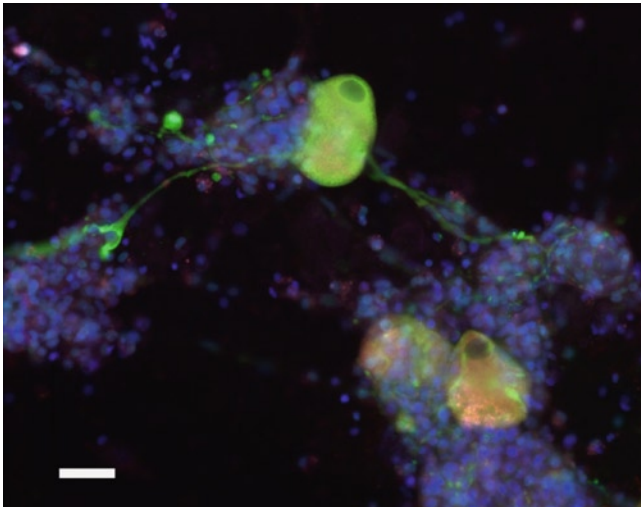
producing functions of the Schwann cells and partly regulate axon size.” The *glial cells* of the peripheral nervous system are essential for the development, maturation, survival and regeneration of the neurone. The relationship between the axon and the Schwann cell is lifelong. The myelinating and non myelinating Schwann cells are the main peripheral glial cells. There are others, which include the satellite cells surrounding cell bodies in the dorsal root and autonomic ganglia, the glia of the enteric system; the teloglia (terminal Schwann cells) at the terminals of somatic motor axons and the glia associated with sensory terminals such as the Pacinian corpuscle. Mirsky and Jessen (2005) observe: “evidence to date suggests that the molecular and morphological differences between these various cells depend on the specific location and cellular environment in which they are found and that the glial cells of the PNS retain unusual plasticity throughout



**Fig. 2.1** Cultured human dorsal root ganglion neurone immunostained for Gap 43 (growth associated protein) showing the cell body and neurites arising from the cell body, x40 (Courtesy of Dr. Uma Anand).



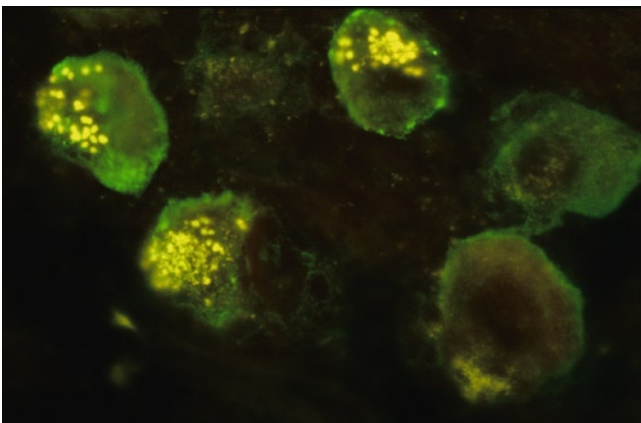
**Fig. 2.2** Phase contrast image of a single DRG neurone showing the large rounded cell body, x63 (Courtesy of Dr. Uma Anand).



**Fig. 2.3** Cultured human DRG neurones immunostained for Gap 43 (green) and for the vanilloid receptor TRPV1 (red), the nuclei of satellite cells are stained blue (DAPI). Bar=25  $\mu$ m (Courtesy of Dr. Uma Anand).

life.” King (Berthold et al. 2005) estimated that about 10% of nuclei within the endoneurium of a normal peripheral or spinal nerve root are fibroblasts, and that endogenous macrophages account for between 2% and 9%. Most of the remainder are Schwann cells. Whilst mast cells are also seen their function is not well understood.

“Neuron theory” Cajal (1954) asserts that “the neuron, a nerve cell with its processes, is the structural unit of nervous tissue, and the neurons are the only elements in the nervous system which conduct nervous impulses” (Brodal (1981b)). There is no continuity between nerve cells: the termination of the axon on a cell is no more than a contact, a contact to which Sherrington (1897) gave the name, synapse. Brodal (1981b) goes on: “not only is the neuron a structural unit; it also, in most cases, behaves as a trophic unit”; but the neurone itself requires trophic support during maturation and for survival after injury to the axon (Fig. 2.4).



**Fig. 2.4** NGF immuno reactivity in neurones in a human dorsal root ganglion which was avulsed from spinal cord six weeks earlier. Immuno reactivity, identified by green fluorescence staining, is localized to cells of the small type. The yellow intracellular granules are lipofuscin deposits which exhibit auto fluorescence. Indirect immunofluorescence method, x50 (Courtesy of Professor Praveen Anand).

## 2.1 The Neurotrophins

### 2.1.1 Nerve Growth Factor

Cajal (1928) proposed that there was no autogenous regeneration of the peripheral stump. His belief in the presence of some neurotrophic factor in the distal stump is expressed in the phrase “The penetration into the peripheral stump implies a neurotrophic action, or the exercise of electrical influence by the latter.” He named contact guidance “tactile adhesion.” Young (1942) seemed to conclude that “successful nervous regeneration must depend mainly on the chances provided for adequate numbers of outgrowing fibers to establish connections resembling their original ones.” A hint of belief in neurotrophins had, however, been given in his work with Holmes (Young and Holmes 1940). It was during the 1940s that Hamburger and his colleagues (Hamburger and Keefe 1944) showed that the removal of a limb bud from a chick embryo led to a reduction in the number and size of the neurones destined for that limb whereas addition of extra target tissue during embryonic development was followed by an increase in the number and the size of the relevant neurones. “These observations led directly to the discovery of nerve growth factor (NGF)” (Windebank and McDonald 2005).

Levi-Montalcini et al. (1954) and Cohen et al. (1954), described an agent found in mouse sarcomata which markedly promoted growth in the sympathetic and posterior root ganglia of chick embryos. They found that treatment with snake venom enhanced the activities of this agent, and that snake venom itself contained a potent growth promoting agent. The results of partial purification and characterisation of this *nerve growth factor* (NGF) were presented and suggested that the active material was a protein or bound to a protein. Levi-Montalcini and Angeletti (1968) indicated the specific action of NGF on sensory and sympathetic nerve cells: “the control exerted by the NGF on sensory and sympathetic nerve cells stands out by virtue of the magnitude of its effects, its target specificity, and the plurality of its actions.” Windebank and McDonald (2005) defined growth factors as “soluble extracellular macromolecules that influence the proliferation, growth and differentiation of target cells by a cell surface receptor mediated mechanism.” Most neurotrophins are polypeptides which are produced in tissues such as skin or muscle from whence they are transported to the neuronal cell body by the fast centripetal component of axonal transport. Three major families of growth factors are recognized.

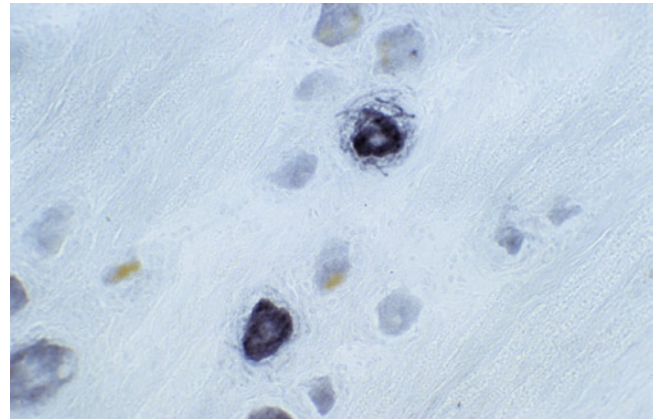
1. The classic neurotrophins include nerve growth factor (NGF), brain derived nerve factor (BDNF) and the neurotrophins 3–7 (NT3, 4, 5, 6, 7). NGF is produced by cells including keratinocytes, melanocytes, vascular and smooth muscle cells, testis and ovarian cells, and endocrine and exocrine tissue. NGF interacts with the high

affinity receptor p140 tyrosine receptor kinase (TrkA) which is expressed by sympathetic neurones and by small diameter neurones in the dorsal root ganglia. After nerve injury, cells in other tissues, including Schwann cells and fibroblasts, synthesize and release NGF. Mice experimentally engineered to be deficient in TrkA do not develop thermoceptive or nociceptive neurones. BDNF apparently supports the development of motor neurones and their survival after axotomy. After nerve transection, BDNF messenger RNA increases in muscle and the messenger RNA of one of the receptors to this nerve growth factor, tyrosine receptor kinase B (TrkB) increases in motor neurones. Neurotrophin 3(NT3) is mainly expressed in muscle spindles, Merkel cells and the Golgi tendon organs. This neurotrophin specifically binds to tyrosine receptor kinase C (TrkC). Mice which have been genetically engineered to lose this receptor lack proprioceptive organs.

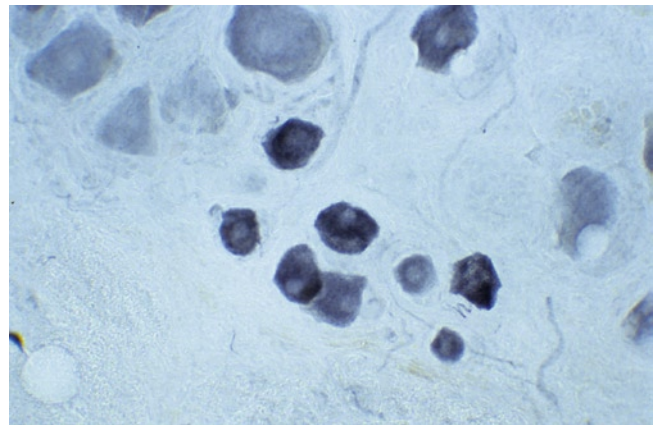
2. Other neurotrophins are synthesized by the glial cells. It is likely that these factors support the embryonic midbrain and motor neurones in the spinal cord. The glial derived nerve factor (GDNF) binds with its high affinity receptor, also the tyrosine kinase receptor c-Ret. The ciliary neurotrophic factor (CNTF) first binds to its receptor and also the leukemia inhibitory factor receptor beta (LIFR  $\beta$ ). CNTF supports neurones in the ciliary ganglion, dopaminergic neurones, retinal rods and sympathetic and motor neurones.
3. The third family include the insulin growth factor (Igf) which structurally resembles insulin and binds with the tyrosine kinase IGF-I receptor, which is itself homologous to the insulin receptor. This receptor is expressed throughout the nervous system.

Nerve growth factors are synthesized by the target organs of the nerves and are conveyed centrally to the neuronal cell bodies. This transport ceases after axotomy. The interruption of this flow contributes to cell death amongst central neurones, an effect which is more severe in the immature nervous system and after axotomy close to the neuronal cell bodies (Figs. 2.5 and 2.6).

Anand and his colleagues have extensively investigated neurotrophic factors and their receptors in the normal human nerve, and in nerves affected by diabetes, leprosy, and injury. These studies have been extended to neurones from human dorsal root ganglia, (Anand et al. 1996, Bar et al. 1998, Saldanha et al. 2000, Yiangou et al. 2000, Durrenberger et al. 2004, Chessell et al. 2005, Facer et al. 2007). More recently, Uma Anand and her colleagues have perfected methods in vitro for the study of living neurones from human dorsal root ganglia and this has permitted close study of the effects of neurotrophins and molecular mechanisms. (Anand et al. 2006, Sanchez et al. 2007, Anand et al. 2008a, Anand et al. 2008b, Anand et al. 2008c) Anand et al. (2006) summarize the effect of neurotrophin factors on the morphology and expression of some receptors in cultured human dorsal



**Fig. 2.5** Brain derived neurotrophic factor (BDNF) immunoreactivity in medium sized neuronal cell bodies and associated axons in human dorsal root ganglion 6 weeks after avulsion of spinal nerves, x40 (Courtesy of Professor Praveen Anand).

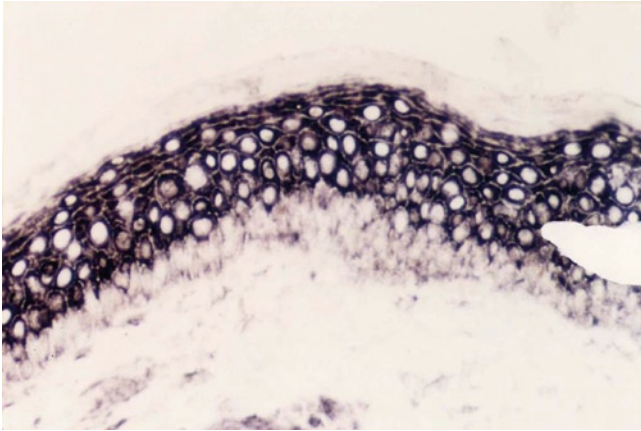


**Fig. 2.6** Glial derived nerve factor (GDNF) receptor Cret immunoreactivity in neuronal cell bodies of human dorsal root ganglion two weeks after avulsion of spinal roots, x40 (Courtesy of Professor Praveen Anand).

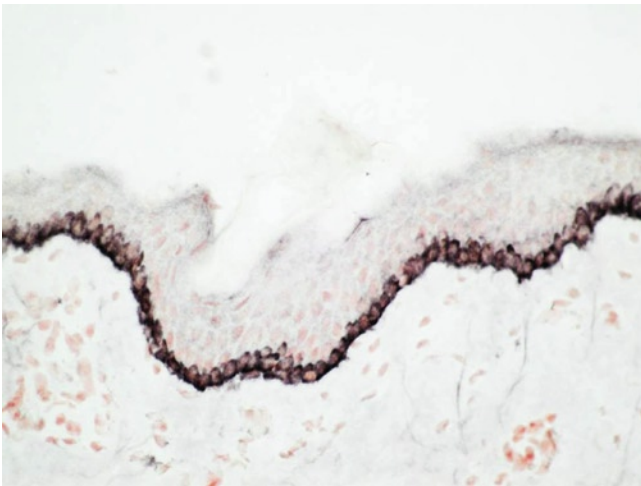
root ganglion sensory neurones: the factors NGF, NT3 and GDNF are produced by peripheral target tissues such as epidermal keratinocytes and affect the phenotype of cultured sensory neurones. In the mature nervous system neurotrophins switch from providing trophic support for neuronal survival to maintenance of a specific neuronal phenotype thereby facilitating modality specific sensory function. For example GDNF and NGF regulate the normal function of two distinct classes of nociceptors via their receptors Ret and TrkA respectively. The levels of these factors are altered by injury. Administration of NGF induces thermal and mechanical hyperalgesia, it is upregulated by inflammation and plays a key role in the pathophysiology of nociception (Figs. 2.7–2.10).

Evidently, important questions regarding the role of neurotrophic factors both in regeneration of peripheral nerves and in causation of pain and cutaneous hyperaesthesia and

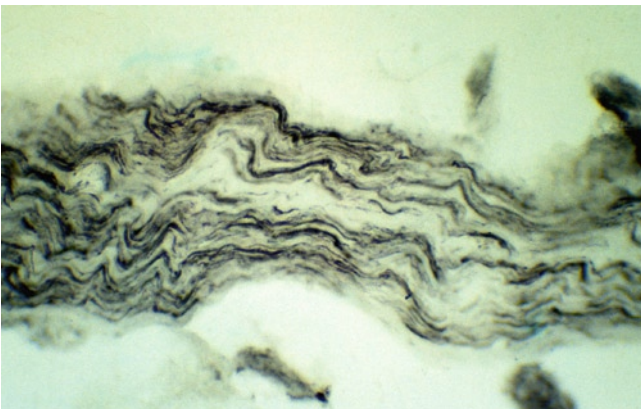




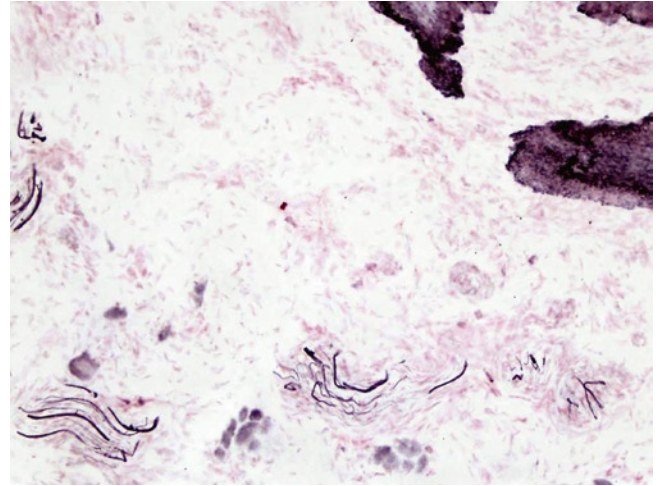
**Fig. 2.7** Neurotrophin 3 (NT3) immunostaining in suprabasal epithelial cells of human glabrous arm skin, x40 (Courtesy of Professor Praveen Anand).



**Fig. 2.8** Nerve growth factor (NGF) immunostaining of basal epithelial cells in human glabrous arm skin, x40 (Courtesy of Professor Praveen Anand).



**Fig. 2.9** GDNF immunoreactivity in Schwann cells of healthy human sural nerve, x150 (Courtesy of Professor Praveen Anand).



**Fig. 2.10** Subepithelial fascicles of NGF positive axons in the tongue of patient with burning mouth syndrome (BMS), x40 (Courtesy of Professor Praveen Anand).

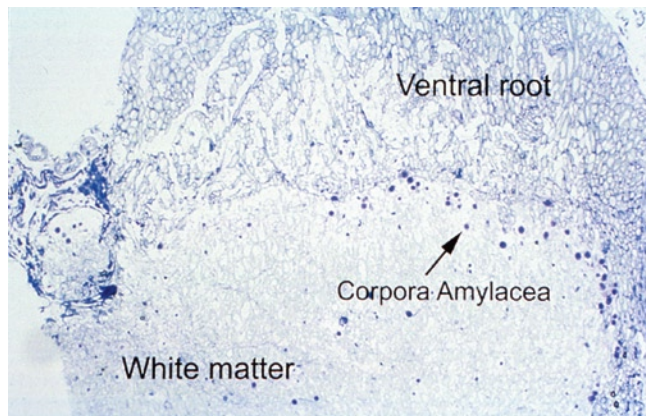
hyperalgesia are raised by the continuing work in this field. Although trials using factors for the treatment of amyotrophic lateral sclerosis and diabetic neuropathy failed, their therapeutic roles continue to be explored and developed.

## 2.2 The Peripheral Nerve Fibres

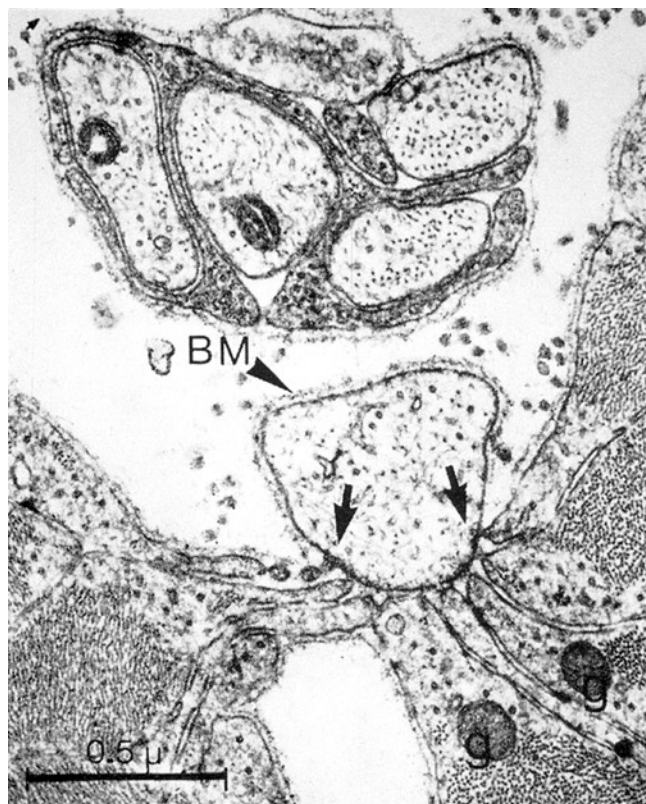
In the central nervous system the neurones are supported in a network of oligodendrocyte and astrocyte processes, with very little extracellular space. The structure of peripheral nervous tissue is one of nerve fibres (axons – Schwann cell units) suspended in a collagen rich extra cellular space (Berthold et al. 1984, 1993). The transition from central to peripheral nervous structures takes place in the rootlets or less often in the roots of the spinal nerves. This is the *transitional region or transitional zone (TZ)*. The development of the transitional region in dorsal rootlets was described by Carlstedt in 1981. The extension of CNS structure into the base of the rootlet is cone-shaped. Thus, “each transitional region can be subdivided into an axial CNS compartment and a surrounding PNS compartment” (Berthold et al. 1993) (Figs. 2.11 and 2.12). The myelin sheath distal to the transitional zone is formed by the transitional Schwann cell and that central to it by the transitional oligodendrocyte. The basal lamina of the axon remains continuous through the TZ. Some myelinated nerve fibres become nonmyelinated centrally. Fraher (2005) states that during development: “the CNS-PNS interface oscillates and continually changes its form and position as the two tissue classes establish their mutually exclusive territories.” The astrocyte barrier, which is at first flush with the glia limitans becomes pushed



peripherally by the central tissue process. Myelination is delayed in the transitional zone and that in the proximal rootlet segment lags behind the rest of the root. The ventral root

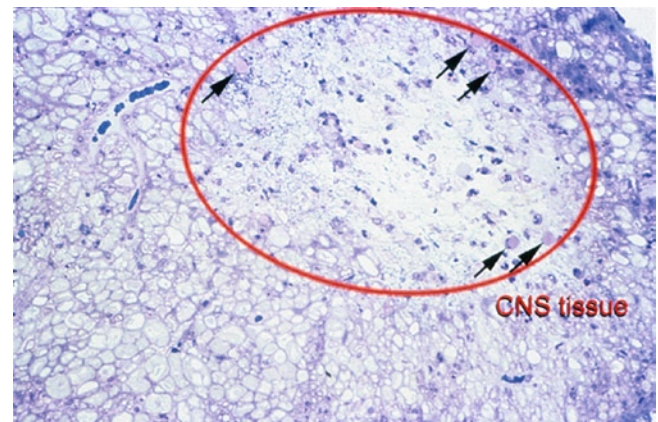


**Fig. 2.11** Morphology of the normal human spinal cord. A transverse light microscopic section at C7 showing a ventral root. A single large root in transition is demonstrated with central islands of autolysed glia. Numerous corpora amylacea are seen on the central side of the transitional zone. Toluidine blue, x100 (Courtesy of Editor Journal of Bone and Joint Surgery [British]).

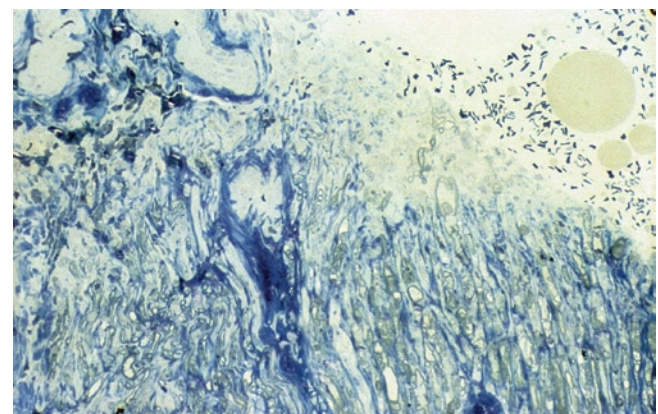


**Fig. 2.12** Normal anatomy of the transitional zone. Schwann cell processes are seen above, astrocyte processes lie closely to an unmyelinated axon (arrows) which is surrounded by a basal lamina (arrow head). Electron microscopy by Michael Kayser, Institute of Orthopaedics (Courtesy Michael Schenker).

of the rat has a rich blood supply unlike the dorsal root; in the cat the blood vessels do not accompany the axons in the dorsal root, instead they deviate from the endoneurial space and join vessels on the surface of the cord. Fraher suggests that this arrangement causes the dorsal roots to be more susceptible to ischemia than ventral roots. His findings that the mechanical arrangements lead to rupture at the rootlet rather than in the transitional zone has been confirmed in the human by Schenker (Schenker and Birch 2001) who examined biopsies of the tips of avulsed roots in 12 patients by light and by transmission electron microscopy. Of the ten biopsies taken within 4 weeks of injury the level of rupture was central to the TZ in two of the roots and peripheral to it in the remaining eight (Figs. 2.13 and 2.14). Schenker also studied the corpora amylacea (CA), round homogeneously staining



**Fig. 2.13** Transverse section of the tip of an avulsed dorsal root at C6 4 days after injury showing a central avulsion. The tissue in the centre of the section is CNS tissue in which glial cells show post traumatic lytic changes. Corpora amylacea are indicated by arrows. Toluidine blue, x100 (Courtesy of Editor Journal of Bone and Joint Surgery [British]).



**Fig. 2.14** Avulsed ventral root of C6 4 days after injury showing a peripheral intradural rupture. The nerve tissue at the site of the rupture showed no CNS features. The tip is covered by organized blood clot and erythrocytes which interweave with fibrin strands. The myelinated fibres show early signs of Wallerian degeneration. Toluidine blue, x200.

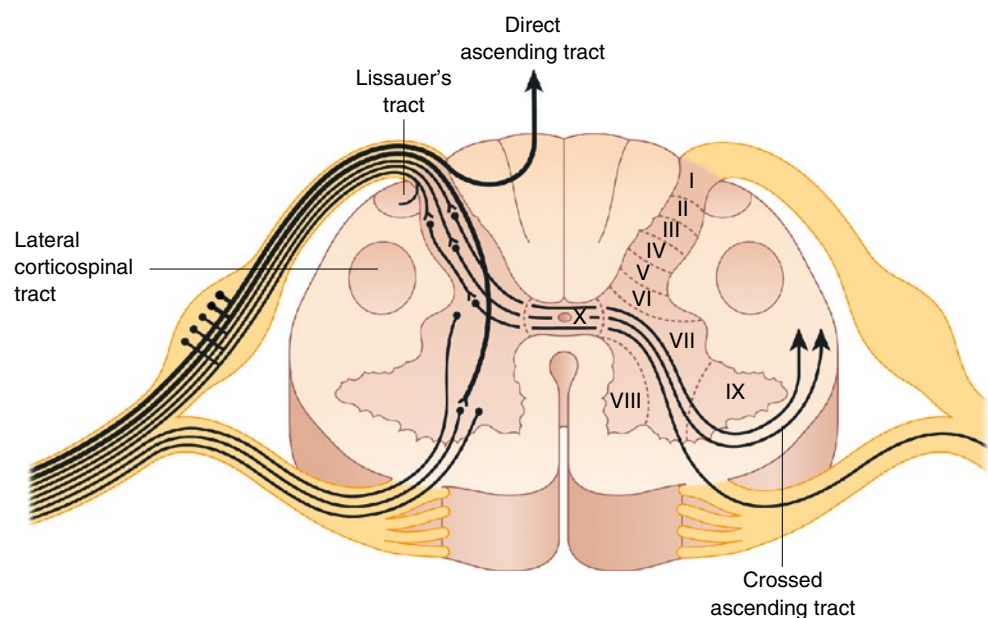
bodies 15–50  $\mu\text{m}$  in diameter, which are found in the subpial zone of the spinal cord in post mortem material. The CA mark the watershed between the central and the peripheral nervous systems. The basal lamina surrounding the Schwann cell – axon unit extends into the spinal cord and cannot be used as a reliable indicator of peripheral nervous tissue.

Most of the fibres of the ventral roots have their cells in the ventral horn of the grey matter. They can, perhaps, be regarded as outposts of the peripheral system in the central system. The fibres of the dorsal roots have their cells in the dorsal root ganglion: possibly, outposts of the central in the peripheral nervous system? These neurones are “unipolar in form with a single axon and no true dendrites” (Thomas et al. 1993b). Each axon bifurcates into peripherally and centrally directed axons after leaving the cell body at a variable distance from the cell. The centrally directed branch is of smaller caliber than the peripheral one. The central processes enter the spinal cord along the posterolateral sulcus. In the cord the fibres bifurcate into ascending and descending branches. The branches of the smaller fibres in the lateral part of the root reach the dorsal horn of the grey matter, where both soon terminate having traversed between three and five segments. The branches of the larger fibres in the medial part of the root, mostly myelinated, similarly bifurcate after entering the white matter just medial to the dorsal horn. Some ascending fibres reach as high as the gracile and cuneate nuclei in the caudal part of the medulla. Other fibres of this group have short ascending and descending branches which enter the grey matter of the dorsal horn to establish synapses with nerve cells in its different laminae (Fig. 2.15).

Sherrington (1894) showed that ventral roots of cats and monkeys contained intact myelinated nerve fibres after

transection of both the ventral and dorsal roots and he concluded that some afferents reached the spinal cord the “wrong way” through the ventral roots. Unmyelinated afferent fibres certainly enter the spinal cord in the ventral roots (Coggeshall et al. 1974). They may be concerned with the transmission of painful impulses (Clifton et al. 1976) though White and Sweet (1969) failed to produce pain in man by stimulation of ventral roots. On the other hand, Brindley (1986) described three paraplegic patients who experienced pain whilst stimulating the ventral roots of S2 and S3 or of S3 and S4 to induce micturition by an implanted stimulator. Brindley says: “the Bell-Magendie law is certainly nearly true, but on published evidence it seems likely that it is not exactly true,” pointing out that pain could be evoked by antidromic impulses in efferent fibres.

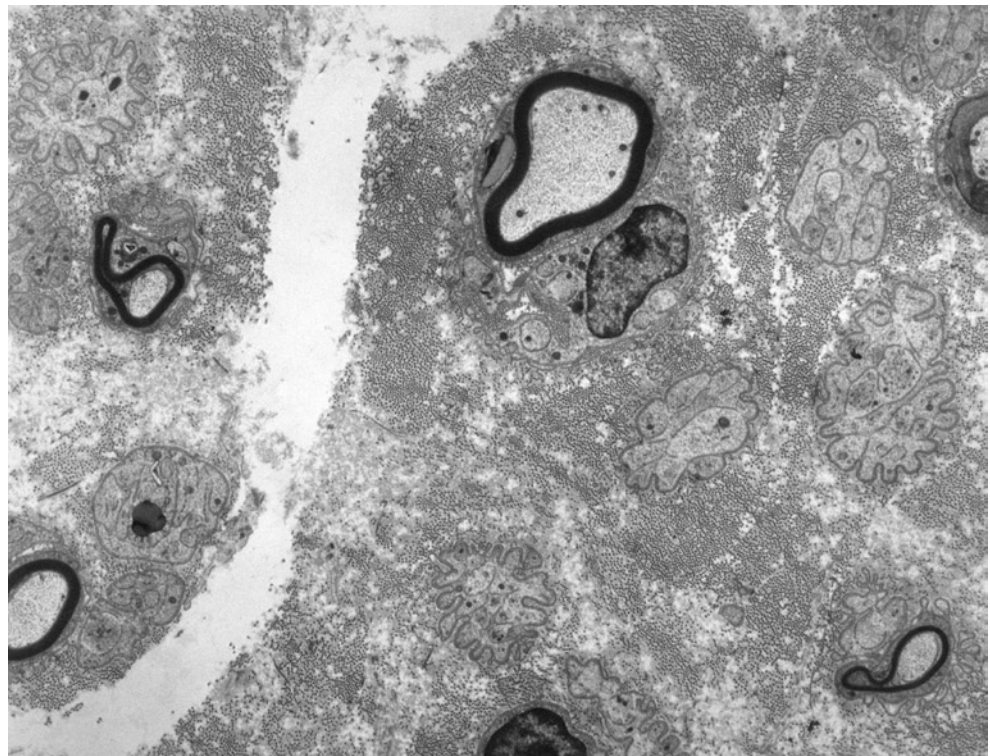
We were able to take advantage of the opportunity offered by intradural damage to nerves of the brachial plexus to demonstrate the presence of afferent fibres in the ventral roots of man. Stephen Gschmeissner examined by electron microscopy the ventral root of the eighth cervical nerve avulsed with its dorsal root and found with it at operation for exploration of the plexus in the posterior triangle of the neck. He found several surviving small myelinated and unmyelinated axons (Fig. 2.16). Clearly, the cell bodies of these axons must have been in the nerve or in the dorsal root ganglion; the fibres must have belonged to the afferent system. These findings were confirmed by Schenker (Schenker and Birch 2000) who examined biopsies from the tip of the avulsed rootlets in nine patients. The tips of the dorsal and of the ventral rootlets of 5 spinal nerves were examined within 8 days of injury, the other patients were operated at intervals ranging between 4 and 50 weeks from injury. Schenker found intact myelinated fibres in all ventral root specimens. The majority of those



**Fig. 2.15** The paths of the afferent fibres entering and efferent fibres leaving the spinal cord. Note (right) the laminae of the grey matter.



**Fig. 2.16** Afferent and efferent fibres in the ventral root. Large healthy myelinated axons in the ventral root of the 8th cervical nerve avulsed from the spinal cord 6 weeks previously. The myelinated efferent fibres have undergone Wallerian degeneration and there is much collagenisation (Electron microscopic study by Mr. Stephen Gshmeissner, x5000).

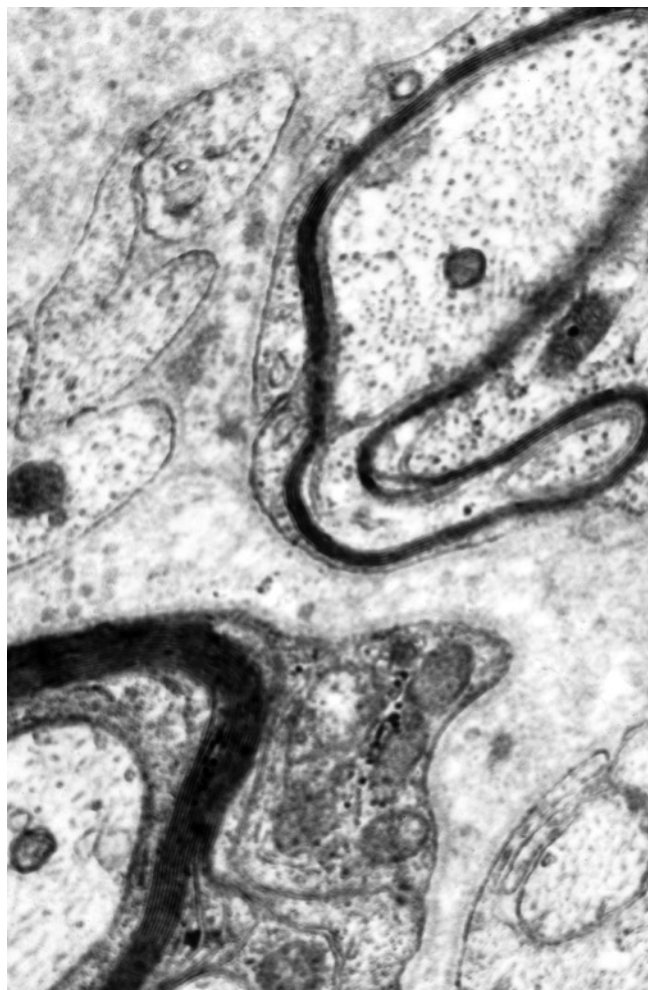


identified in the later biopsies were regenerating, perhaps signifying collateral sprouting from the intact cell bodies of the adjacent avulsed dorsal root ganglion. There were a small number of intact fibres in the early specimens and Schenker suggests that: “it is therefore likely that these few fibers of the ventral root represent afferent fibers in continuity with the cell body in the DRG.” Less than 5% of the central processes of all dorsal afferents survive the traction injury and it was assumed that “wrong way” ventral afferents do just the same so that the few surviving ventral root afferents that were observed may represent only a very small proportion of the population. Based on this assumption Schenker proposed that the proportion of afferent fibres in the ventral root of man is similar to that found by Loeb (1976) who, by microelectrode recordings in cats, calculated that 3.9% of all afferent fibres reached the cord through the ventral root (Fig. 2.17).

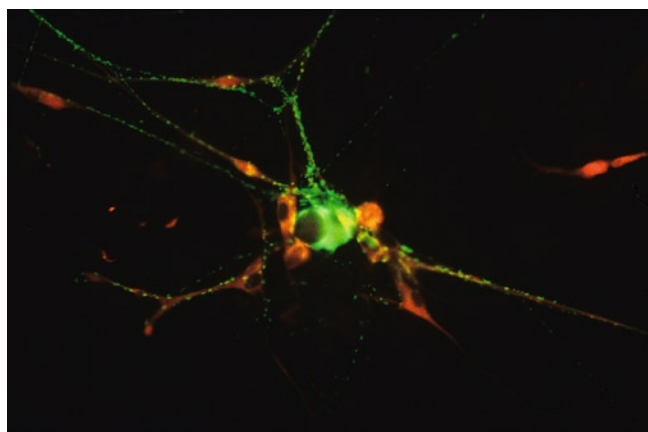
In the peripheral nervous system the axons are closely associated with the Schwann cells (Schwann 1839). Sanders (1942) established the central role of Schwann cells in regeneration through grafts: “autografts remain alive and myelin fragmentation and Schwann multiplication go on very much as in a normal peripheral stump.” Sanders rejected methods of repair which do not enrich the environment with Schwann cells. Schwann cells arise from the neural crest, from the same cells that differentiate into peripheral neurones; they provide essential trophic support to the neurone during development and also during regeneration. Our present understanding of the part played by these cells in repair owes a

great deal to the work of Susan Hall of Guy’s Hospital, and now editor of Gray’s Anatomy. (Hall 1997, 1999, 2001, 2005, Li et al. 1998) (Fig. 2.18).

Mirsky and Jessen (2005) described how two important growth factors, neuregulin 1 and endothelin regulate early Schwann cell development. The Schwann cell separated from its axon survives for rather longer in the mature than in the immature nervous system. The most important component of the basal lamina is laminin which interacts with receptors in the plasma membrane of the Schwann cell which include the integrins and alphadystroglycan. Laboratory mice which have been genetically engineered to produce defective laminin or a defective receptor for laminin, develop profound nerve pathology and muscle dystrophy (Uziyel et al. 2000). Schwann cells provide another important protein, the tumor suppressor protein, Merlin (schwannomin), which links membrane proteins to the actin cytoskeleton in epithelia and other cell types. Mutations in the gene controlling Merlin lead to an increased frequency of schwannomas. In leprosy, components of the cell wall of *M. leprae* interact with laminin 2, the major isoform of laminin, and this interferes with the normal interaction between laminin and alphadystroglycan leading to demyelination and to axonal degeneration. During myelination Schwann cells radically transform their phenotype in response to signals from the larger axons; as Mirsky and Jessen (2005) say: “this response represents one of the most striking examples of cell-cell interaction that is known.”



**Fig. 2.17** Rupture of the ventral root of C5 peripheral to the transitional zone examined 5 months after avulsion. Two thinly myelinated axons are seen. x 17,000 (Electron microscopic study by Mr. Michael Kayser, Institute of Orthopaedics. By courtesy editor Journal of Anatomy).



**Fig. 2.18** In vitro cultures of mouse DRG neurones and Schwann cells. The Schwann cells are immunostained for S100 (red) the neurones for nerve growth factor (green), x50 (Courtesy of Professor Susan Standring).

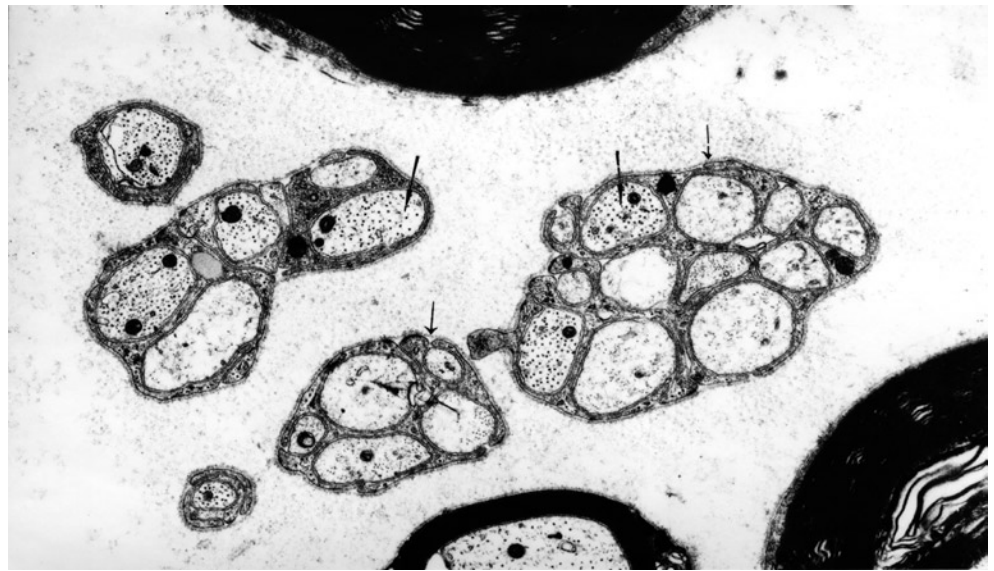


**Fig. 2.19** A large myelinated nerve fibre within the posterior root of a 7<sup>th</sup> cervical nerve which had been avulsed from the spinal cord six weeks previously. The axoplasm contains neurofilaments and a few microtubules. The Schwann cell cytoplasm it is enveloped by a well defined basal lamina. There are processes from fibroblasts from within the endoneurium, x16,200.

Scherer and Arroyo (2002) provide an extensive review of the molecular organisation of myelinated axons. The larger axons are enwrapped along their length by a continuous series of contiguous Schwann cells into which they are invaginated. The *nodes of Ranvier* represent the points of contiguity of adjacent Schwann cells (Fig. 2.19). The fibre is contained within a basal lamina. The basal lamina separates nerve fibres from the endoneurial space and it runs without interruption from the central nervous system to the termination of the axon. Thomas (1963) defined this structure in an electron microscope study. Schwann cells are surrounded by a basal lamina approximately 250 Å in thickness which is separated from the plasma membrane of the Schwann cell by a gap of 250 Å. The endoneurium is organized in two layers which surround the basal lamina. The inner layer is composed of collagen fibres of smaller diameter than those in the outer layer which run longitudinally, circularly and obliquely. This layer is inflected at the nodes with the basement membrane. The outer layer consists solely of longitudinal collagen fibres and it is not inflected at the node. Bunge et al. (1986) considered the basal lamina essential in the linkage



**Fig. 2.20** Clusters of unmyelinated axons (long arrows), enveloped by Schwann cell cytoplasm. Short arrows indicate basal lamina, x26,220.



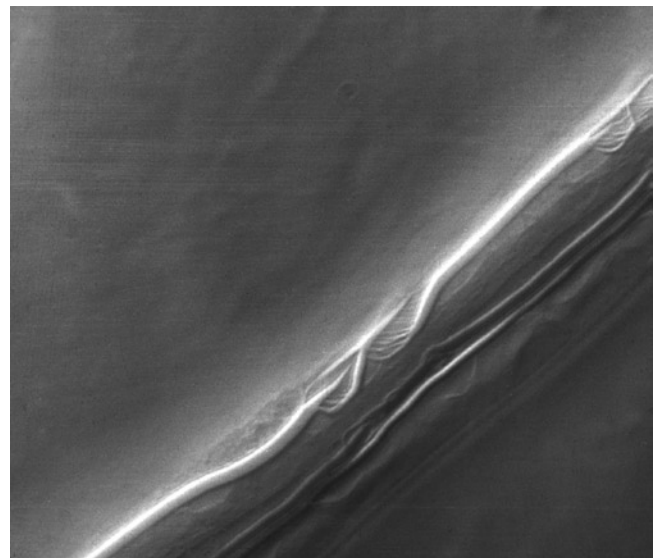
between the Schwann cell and the axon and with the extracellular matrix. The smaller fibres are contained in bundles by columns of Schwann cells. Eames and Gamble (1970) showed the ensheathing arrangement of successive Schwann cells which overlapped and interdigitated:

the Schwann cells of unmyelinated axons in these nerves give off multiple cytoplasmic processes, which form close relationships with axons, with other processes, and with bundles of collagen. A ramifying “network” system of Schwann processes is thereby present throughout the endoneurium.

Eames and Gamble recognize areas of specialisation of the Schwann membranes which consisted of “a short length of increased plasma membrane thickness and electron density.” Later studies using scanning electron microscopy and freeze fracture replication have generally confirmed these earlier observations (Stolinski and Breathnach 1982). It is at times very difficult to distinguish between a nonmyelinated axon and a Schwann cell process in histological sections of regenerating peripheral nerves! (Fig. 2.20).

The diameter of the axon is one important factor which determines whether the Schwann cells will lay down a myelin sheath around it. Webster (1993) proposes that the sheath is laid down in spiral layers by the Schwann cell, or part of its surface, moving around the axon (Webster 1993). The multilamellar sheath has a high lipid content and some protein components. Suter and Martini (2005) say that the major component of the protein components of myelin is Po myelin protein zero (MPZ), which accounts for 50–60% of all myelin protein. Peripheral myelin protein 22 (PMP 22) comprises from 2% to 5% of myelin proteins and mutations of the controlling gene lead to inherited myelin disorders. Suter and Martini comment that mutation of this gene was: “the first identified culprit gene for inherited neuropathies of Charcot-Marie Tooth (CMT) type.” Myelin basic protein

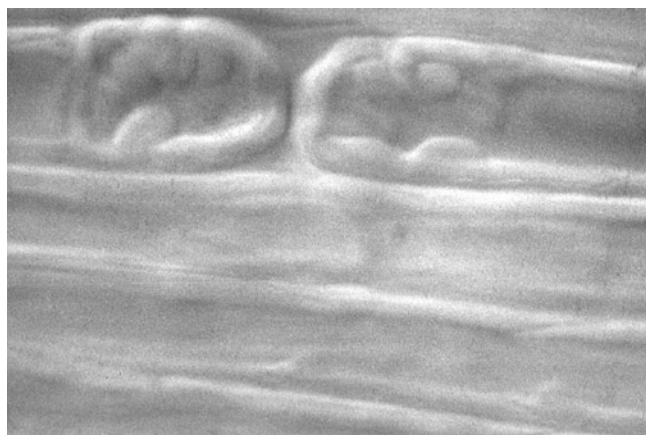
(MBP) accounts for 5–15% of myelinated proteins. The myelin associated glycoprotein (MAG), which forms no more than 0.1% of the myelin proteins, may play a pivotal role during myelination because of its early expression and because of its location to the axon-Schwann cell interface. Mice genetically engineered to be deficient in MAG showed extensive axonopathy and degeneration of myelin in motor fibres. The myelin sheath is traversed by cytoplasmic channels – the incisures of Schmidt-Lanterman (Hall and Williams 1970) (Fig. 2.21). The meeting points of consecutive Schwann cells are the nodes of Ranvier. These are short, about 1 micron in length and the axon here is constricted,



**Fig. 2.21** A widened Schmidt-Lanterman incisure in a teased mouse sciatic nerve. Normal saline in vitro, x100 (Courtesy of Professor Susan Standing).

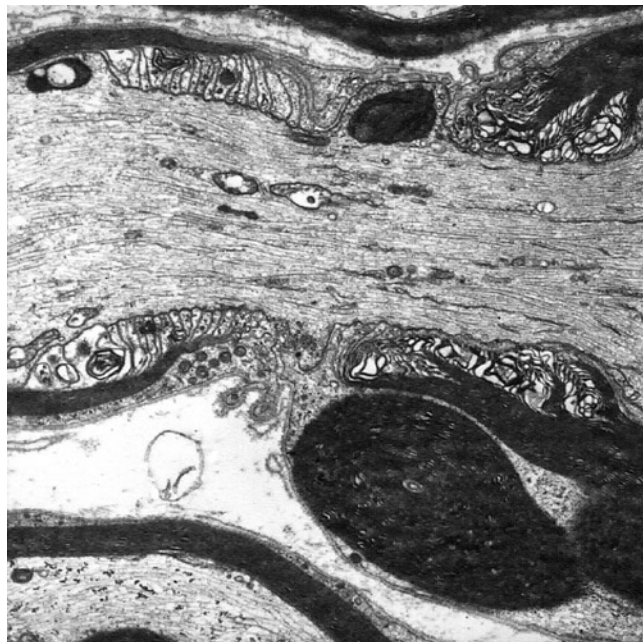
free of myelin but enveloped by projections of Schwann cytoplasm. The node is bordered by an adjacent paranode, which is dilated and which contains an increasing amount of mitochondrial rich Schwann cell cytoplasm outside a more or less crenated myelin sheath. Berthold et al. (2005) characterize the node thus: “these parts of the myelinated nerve fibers, the paranode-node-paranode (PMP) regions, constitute, structurally as well as functionally, the most spectacular parts of a myelinated nerve fiber.” The PMP regions are responsible for the generating and propagation of the action potential and they are the centers for activity in the early phases of Wallerian degeneration and collateral sprouting (Figs. 2.22–2.24).

The axon-myelin sheath–Schwann cell complexes are arranged in bundles otherwise known as fascicles or funiculi. In so small a nerve as the fourth cranial there may be as many as 3,400 fibres. In the roots inside the spinal canal endoneurial collagen is scanty in contrast with the abundant content in the nerves outside the foramen (Gamble 1964; Eames and Gamble 1964). The surgeon who has had dealings with nerves inside and outside the spinal canal will appreciate the distinction: the spinal roots and rootlets are fine and fragile and very susceptible to trauma; the peripheral nerves are strong and have much greater resistance to handling. Outside the intervertebral foramina the three supporting structures, epi, peri, and endoneurium are clearly established. The *epineurium*, in effect the prolongation of the dural sleeve of the nerve roots, is composed of longitudinally directed collagen fibres, fibroblasts and fat cells. (Gamble and Eames 1964). The *perineurium*, which ensheaths the bundles, is composed of flattened cell processes alternating with layers of collagen. It provides a barrier to diffusion (Thomas 1963). The perineurium is strong; the intrafascicular pressure can be raised to more than 300 mmHg before it ruptures (Selander and Sjostrand 1978). The contents of the perineurium are under tension so that when it is cut they are extruded, rather like

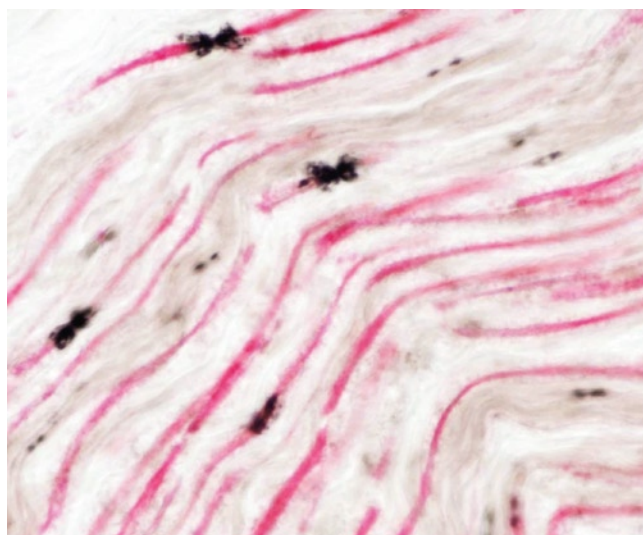


**Fig. 2.22** Node of Ranvier, mouse sciatic nerve in vivo, oblique incident illumination, x400 (Courtesy of Professor Susan Standing).

toothpaste. This is most clearly seen on the day of injury in nerves which have been transected or ruptured and it is one of the indications that the level of section of the stump is adequate. The outflow rapidly diminishes over the course of several days. In the *endoneurium*, supporting the fibres



**Fig. 2.23** Longitudinal section through a node of Ranvier, showing a remyelinated heminode (*left*) adjacent to a normal heminode (*right*). Compare the complexity of the paranodal fingers of the normal myelin sheath with the simple arrangement of the paranodal loops of the thinner, remyelinated sheath, x5,000 (Courtesy of Professor Susan Standing).



**Fig. 2.24** Double immunostaining of sural nerve showing nodes of Ranvier (*black*) stained with antibodies to junction adhesion molecule (JAM – c) and axons (*red*) stained with antibodies to neurofilaments, x40 (Courtesy of Professor Praveen Anand).

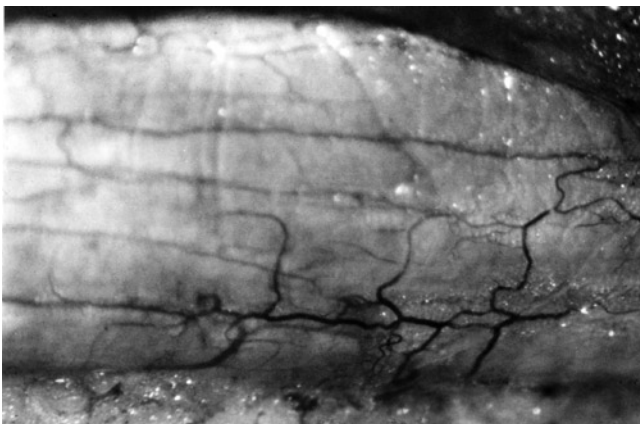


themselves, there is a return to longitudinal direction of cells and fibres; there are abundant collagen fibrils (Thomas 1963; Gamble and Eames 1964). Stolinski (1995) describes the epineurium as an outer layer of alveolar connective tissue and a more compact inner layer containing collagen and elastic fibres which are arranged in a wavy pattern. Perineurial cells are also arranged in a wavy manner and Stolinski suggested that the spiral bands of Fonata represent the wavy or zig zag organisation of nerve fibres. These arrangements provide a degree of protection to the nerve against traction. The nerve can be stretched by as much as 20% before the wavy arrangement is converted into a linear array. Tillett and her colleagues (2004) offer the concept of a distinct core and sheath in the rat sciatic nerve, and proposed that the interactions between the core and the sheath involve physical connections rather than a viscous fluid interface. The anatomical features of this interface were characterized using transmission electron microscopy and it appeared that the sheath was derived from the epineurium and most of the perineurium, whilst the core consisted of the endoneurium and a small proportion of perineurium: the plane of cleavage involved the innermost perineurial cell layer.

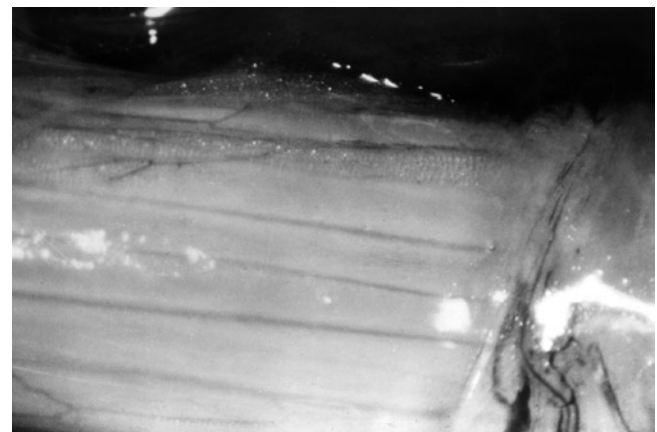
A normal peripheral nerve trunk exposed at operation is enveloped in a well defined translucent envelope. This is the external epineurium (Fig. 2.25). Normal nerve trunks are easily distinguished from other longitudinal structures by the appearance of white spiral bands on their surface, the spiral bands of Fontana (Clarke and Bearn 1972, Stolinski 1995). The individual bundles or fascicles are seen within. These are enclosed by the perineurium with some condensation of the innermost epineurium forming a white, opaque layer (Fig. 2.26). The tissues surrounding the bundle form the epineurium, rather loose in texture, and rich in blood vessels which pass longitudinally along the axis of the nerve. However, the observer will see adventitial material outside the epineurium which is more clearly defined in some nerves

than in others and in different locations within the limb. There are, for example, translucent connective tissue arcades accompanying the median nerve in the forearm where it passes between the superficial and the deep flexor muscles of the fingers. Such vessels provide an alternative collateral pathway to the part; they also supply the nerve trunk so permitting the use, for example, of the ulnar nerve as a free vascularized graft. This tissue plane not only conveys vessels to the nerve but it also permits gliding of that nerve across joints and against the adjacent tissues. Thomas (1963) has estimated that 45% of nuclei seen in transverse sections of nerves are those of fibroblasts. Sunderland (1968) mapped the arrangement of bundles along the course of nerve trunks, showing branching, fusion and changes in number. He further showed that the cross-sectional area of the nerve occupied by connective tissue was variable, ranging from 60% to 85% (Fig. 2.27).

These findings, especially those concerning re-arrangement of bundles, have been used to cast doubt on the feasibility of achieving accurate co-aptation of the ends of divided nerves. However topographical organisation is one essential quality of the nervous system and this is shown by the considerable topographical segregation of neurones involved in the somatic afferent pathways in the dorsal root ganglia, dorsal horn of the spinal cord, the thalamus and the sensory cortex. Perhaps predictably injury anywhere in the nervous system provokes considerable reorganisation. Sunderland himself recognized that there was a degree of topographical segregation of nerve fibres according to function over considerable lengths of the median and ulnar nerves. Microneurographic studies (Torebjörk and Ochoa 1980) confirmed these findings. Specific organisation (aggregation) of sensory and motor fibres occurs in the median nerve in the arm, so it does in all peripheral nerves. This segregation permits transfers such as that of Oberlin et al. (1995), in which one bundle of the ulnar nerve

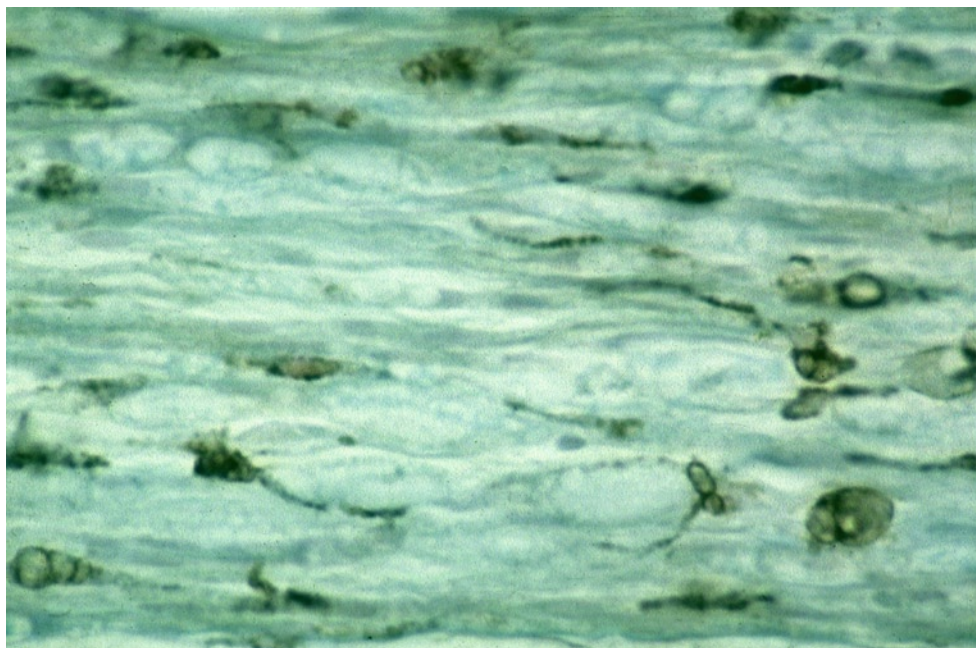


**Fig. 2.25** The extrinsic epineurial vessels of the ulnar nerve, x40.



**Fig. 2.26** The bundles and epineurial vessels of the ulnar nerve after displacing the adventitia, x40.

**Fig. 2.27** Sural nerve undergoing Wallerian degeneration 4 days after a proximally sited crush lesion showing macrophages stained positively for ED1,  $\times 100$  (Courtesy of Professor Susan Standring).



is anastomosed to the nerve to the biceps. Stimulation of individual bundles, whose number ranges from 6 to 12, permits separation of those passing to the flexor muscles of the wrist and fingers from those passing to the small muscles of the hand. The ability to “map” the stump of a divided nerve allied to the ease of matching individual bundles by their size and disposition is but one of the great advantages of urgent repair of nerves (Fig. 2.28).

### 2.2.1 Conduction

The special property of the nerve fibre is that of conducting a signal in the form of a propagated action potential (Landon 1985). Rasminsky (1985) opens the subject thus: “Nerve fibres are specialized processes of nerve cells that have the unique property to propagate action potentials, the currency of information in the nervous system.” The action potential is a brief, self propagating reversal of membrane polarity and it depends on an initial influx of sodium ions which cause a reversal of polarity to about +40 mV followed by a rapid return towards the resting potential as potassium ions flow out. In the unmyelinated fibre, a wave of depolarisation spreads continuously along the axon, attenuated by the large capacitance of the axolemma, which limits the velocity of conduction to about 1 m/s. Standring (2008) likens this to:

a flame moving along a fuse. Just as each segment of the fuse is ignited by its upstream neighbor, each segment of axon membrane is driven to threshold by the depolarization of neighboring membrane. Sodium channels within the newly depolarized segment

open and positively charged sodium ions enter, driving the local potential inside the axon towards positive values. This inward current in turn depolarizes the neighboring, downstream, non depolarized membrane, and the cyclic propagation of the action potential is completed.

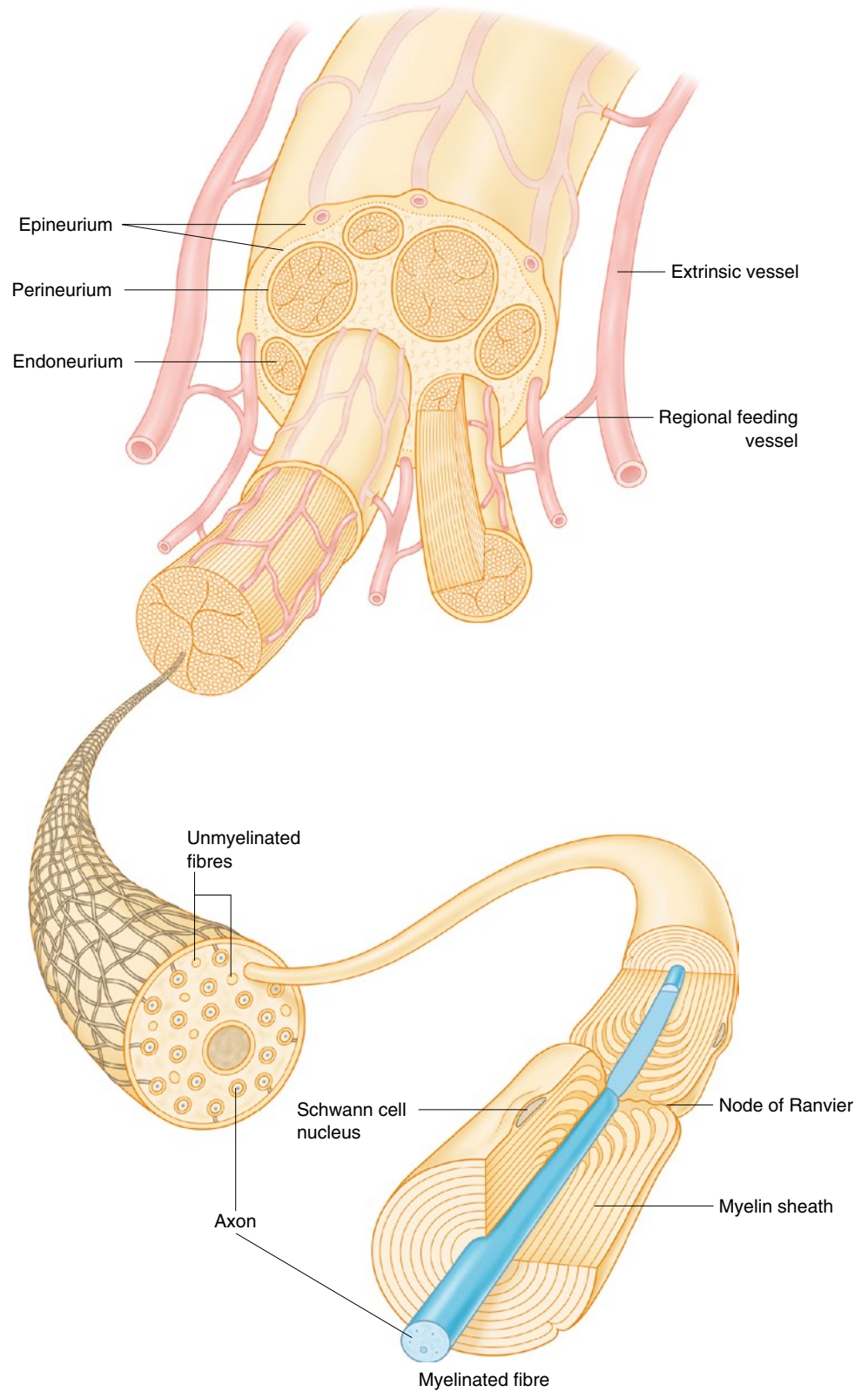
The action potential is evoked by a stimulus which exceeds threshold by the all or nothing law of Adrian (1928); the cell body, on the other hand, responds in a graduated manner to stimuli transmitted across synapses which either inhibit or facilitate by raising or lowering the threshold respectively.

In the myelinated fibre the myelin sheath acts as a capacitor and limits radial resistance at the internode, so that most of the current flows axially along the fibre. It is, says Bostock (1993) “powered by inward ‘kicks’ of inward membrane current at the nodes of Ranvier.” This method of “saltatory” conduction was so named by Tasaki and Takeuchi (1941; 1942), and further confirmed by Huxley and Stämpfli (1949). The myelin sheath thus enables the fibre to conduct rapidly without the necessity for a very large increase in axonal diameter. The caliber of unmyelinated axons varies from 0.4 to 1.25  $\mu\text{m}$  (Gasser 1955); that of myelinated fibres from 2 to 22  $\mu\text{m}$  (Ranson 1915; Greenfield and Carmichael 1935; Sunderland et al. 1949). The largest, fastest conducting elements are the myelinated fibres of around 20  $\mu\text{m}$  diameter concerned with somatic afferent and efferent activity; the smallest and slowest conducting are the fibres of around 1  $\mu\text{m}$  diameter that subserve autonomic activity and delayed pain sensibility (Galbraith and Myers 1991).

Conduction velocity ranges from about 0.7 m/s in small unmyelinated fibres to about 80 m/s in the largest



**Fig. 2.28** Fascicular arrangement of nerve fibres and their supporting structures, the vascular systems of the peripheral nerve.



myelinated fibres. Omer (1980) gives a range of 40–75 m/s in large myelinated fibres. The electrical changes associated with the wave of depolarisation can be measured through electrodes placed on the skin over the nerve, on the nerve, in the nerve or in individual fibres. These reactions form the basis for electrophysiological examination and for microneurography.

### 2.2.2 The Basis of the Action Potential: Ion Channels

Hodgkin and Huxley (1939) made the first intracellular measurements of the resting potential across the cell membrane in the unmyelinated giant axon of the squid. In 1952 Hodgkin and Huxley described the cycle of depolarisation and repolarisation which underlies the high speed transmission of nerve action potentials and showed that the reversal of polarity was brought about by the influx and efflux of sodium and potassium ions across the axon membrane through individual parallel pathways which are controlled by independent gating particles or charges. Conduction of an action potential was blocked by pressure or by cold (Hodgkin 1937a, 1937b) Chiu (2005) defines the ion pathways, now known as channels: “voltage gated ion channels are like membrane lodged proteins that mediate rapid ion flux ( $10^6$  ions/s) across cell membranes.” Chiu describes some of the methods that have been developed to define these entities. The patch clamp technique permitted study of the electrical events associated with the opening and the closing of a single ion channel. Later came the cloning of ion channels which permitted the recognition of 50 potassium channel genes and 10 sodium channel genes (by 2005). Later still the pore structure of potassium channels was studied by x-ray crystallography at a resolution of between 2.4 and 3.2 Å. Scholz, Reid, Vogel and Bostock (1993) were amongst the first to study, by patch clamping, sodium and potassium channels in the human nerve. The voltage-gated sodium ion channels are uniformly distributed along the membrane of nonmyelinated axons but they are densely concentrated at the nodes of Ranvier in the myelinated nerve axons. The potassium channels, on the other hand, are concentrated in the membrane at the juxta paranode. Ion channel function is energy dependent, it is ATP driven and this function is curtailed or altogether blocked by anoxia. Distortion of the myelin sheath adjacent to the node of Ranvier may unmask the potassium ion channels to such an extent that prolonged conduction block ensues. Evidently, demyelination is bound to lead to decrease of conduction velocity (McDonald 1963; McDonald and

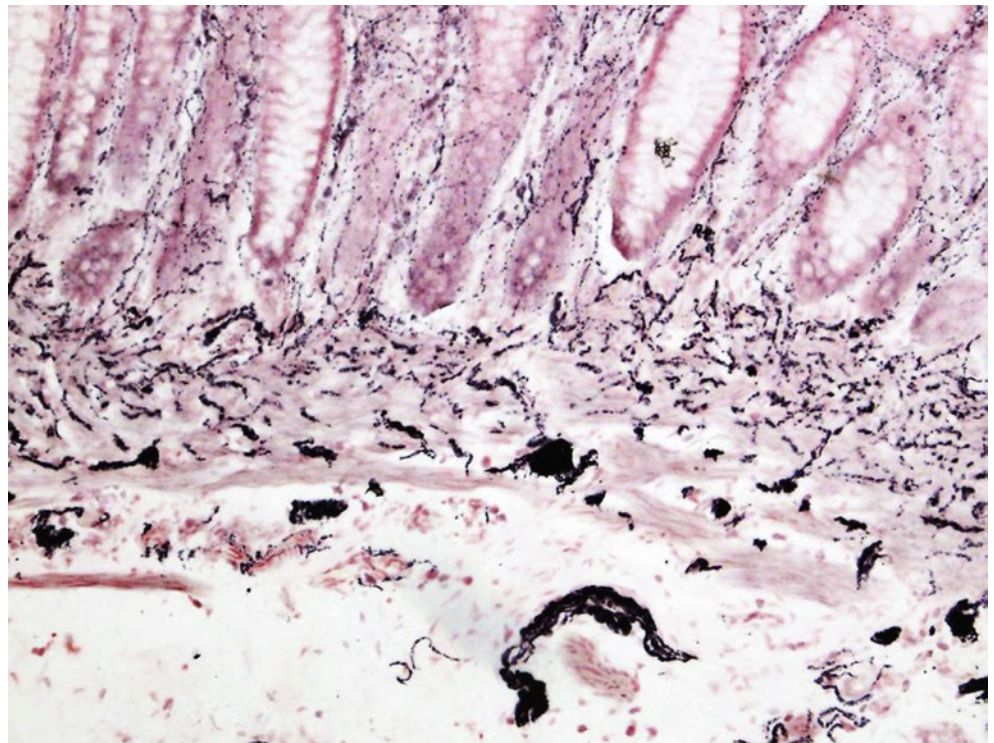
Sears 1970) and eventually to conduction block. These facts will not escape the attention of the clinician faced with an ischaemic limb or with a deepening nerve lesion caused by expanding haematoma or entrapment. Once again we are indebted to Praveen Anand and his colleagues who have provided us with illustrations of sodium and potassium channels in the normal and in the injured nerve. Their extensive studies on the behavior of the ion channels in the injured nerve and in painful lesions of nerves are described in Chaps. 3 and 12. One of their observations reveals an important difference between the immature and the mature peripheral nerve in the human. Two voltage-gated sodium channels, Nav 1.8 and Nav 1.9 play a key role in neuropathic pain. The sodium channel Nav 1.9 could not be demonstrated in the nerves of infants (Yiangou et al. 2000) (Figs. 2.29 and 2.30).



**Fig. 2.29** Sodium channel staining normal sural nerve, x40 (Courtesy of Professor Praveen Anand).



**Fig. 2.30** Nerve fibres within the mucosa and submucous plexus in human rectum stained with antibody to Protein Gene Product 9.5 (PGP9.5), a pan neuronal marker, x10 (Courtesy of Professor Praveen Anand).



### 2.2.3 Axonal Transport

The axon functions as part of the neurone as a whole in transporting materials to and from the cell body. Lasek (1982) goes further than this:

neurones exhibit a remarkable form of locomotion when they extend axons over great distances without moving the cell body. This capacity of neurones to extend axons independently of the movement of the perikaryon is one of the distinctive properties of the neuronal linkage because it distinguishes neurones from other migratory cell types.

Lasek (1982) further proposes that the unusual feature of neurones – their ability to translocate the axonal skeleton independently of the perikaryon – is accomplished by the continuous addition of cytoskeletal proteins at the proximal end of the cytoskeleton in the perikaryon. So, the neurone is able to extend its process “without towing the cell body along.” Ochs and Brimijoin (1993) define axonal transport as: “a system of intra cellular motility enabling nerve cells to deliver essential proteins and membrane components to the periphery, and to receive from these chemical signals and materials for disposal.” Two forms of transport, fast and slow, are recognized (Brimijoin 2005). The former may be orthograde (centrifugal) or retrograde (centripetal).

The fast retrograde (centripetal) component conveys material to the cell body in microvesicles at the rate of 150–300 mm/day. The fast orthograde (centrifugal) component

transports proteins, peptides, and neurotransmitters from the cell body at a rate of 200–400 mm/day. All systems are ATP dependant, and the microtubules are critical for fast axonal transport.

Landon (1985) puts it this way: fast transport “is concerned with the orthograde transport of particular constituents of the axoplasm and materials such as some transmitter synthesizing enzymes, glycoproteins and membrane components, and the retrograde transport of membranous prelysosomal structures, and extra cellular materials such as nerve growth factor ingested at the axon terminal.” The process is sensitive to temperature; it is sensitive to deprivation of oxygen.

Slow transport is uni-directional, orthograde (centrifugal). Rates of transport are from 1 to 4 mm daily; it is concerned with the transport of the neurotubule-neurofilament network of the cytoskeleton. Brimijoin recognizes two distant components:

1. Slow component A (SCa averaging about 1 mm/day)
2. Slow component B (SCb averaging 2–10 mm/day)

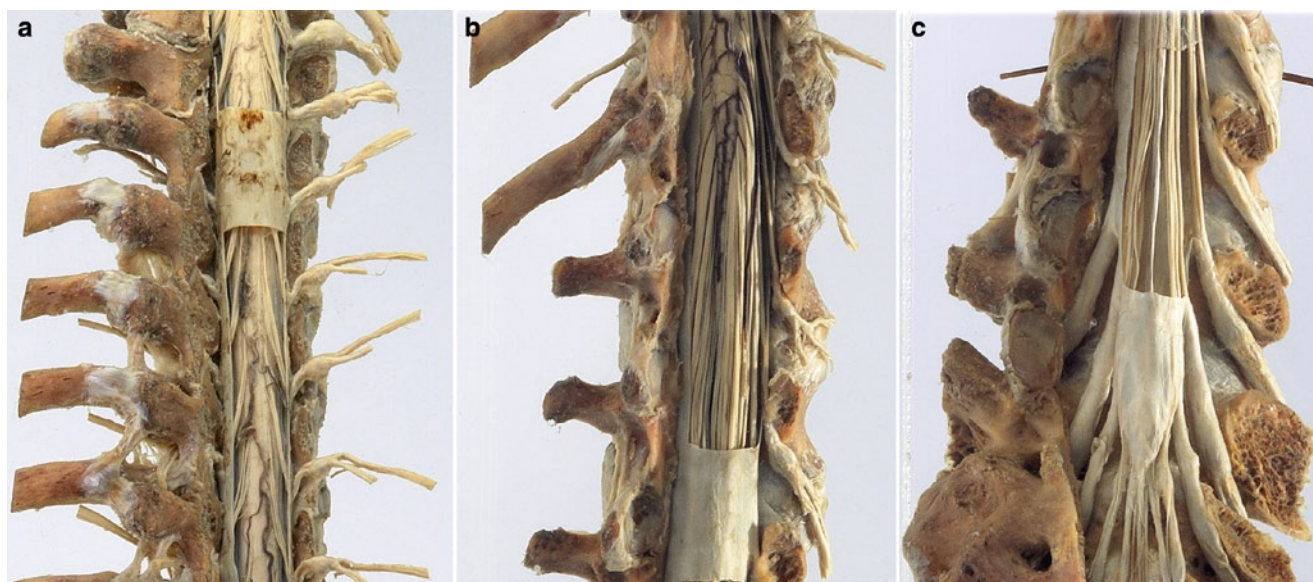
The rate of transport of the SCa component is of course about the same as the rate of peripheral regeneration after axotomy. The significance of axonal transport in disorders of peripheral nerves is plain: interference with the centrifugal process is likely to lead to defect or cessation of conduction; interference with the centripetal process will ultimately lead to degeneration of the nerve cell.

### 2.2.4 The Blood Supply of Nerves

Nerves have a very good blood supply: they need it. The surgeon notes the segmental blood supply from without and the axial vessels within the nerve. There are indeed (Lundborg 1979,1988) *intrinsic* epineurial perineurial and endoneurial plexuses, and *extrinsic* regional vessels in the “paraneurium.” These form “separate but extensively interconnected micro-vascular systems” providing a wide margin of safety. As McManis and colleagues (1993) remark: “these anastomotic vessels confer a resistance to ischemia in peripheral nerves so that nerve suffers functional or structural changes only when there is widespread vascular or microvascular damage.” Dyck et al. (2005) show that arterioles and small arteries are detectable only in the epi- and perineurium, and that these vessels may range in diameter from 50 to 400  $\mu\text{m}$ . The arteries penetrating the perineurium are small, only rarely do they exceed 15  $\mu\text{m}$  in diameter and small arteries are rarely detectable within the endoneurium. Lymphatics have not been detected within the perineurium. The endothelial junctions of the endoneurial vessels are tight, unlike those in the epineurium (Low 1976). Some nerves are better supplied than others. Kadiyala and his colleagues (2005) showed that the common peroneal nerve at the knee has far fewer extrinsic vessels than the tibial nerve at that level. Seddon (1975) commented on the extent to which it was permissible to mobilize the nerve in order to facilitate suture. His rather sanguine views of the effect on the blood supply are not confirmed by the later injection studies of Bell and Weddell (1984); indeed, later clinical experience has shown that it is preferable to bridge a gap by interposition than by mobilisation.

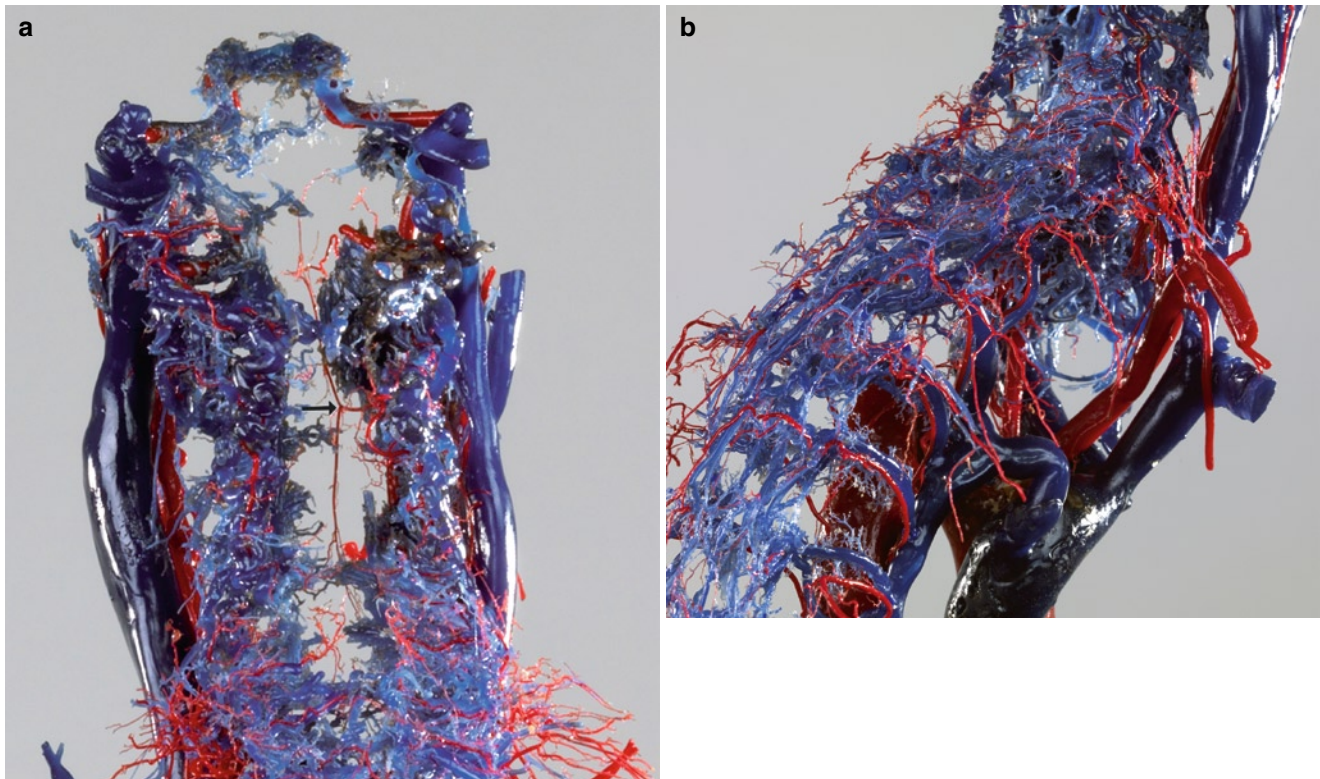
Weerasuriya (2005) proposed the concept of a “blood-nerve interface” instead of the “blood-nerve barrier.” Weerasuriya comments: “the structure of the perineurium combines features of the dura mater in terms of mechanical strength and the arachnoid with respect to impermeance.” Endoneurial fluid is in contact with the cerebro-spinal fluid through the subarachnoid angle. Flow is proximal to distal, the hydrostatic pressure of cerebro-spinal fluid is 10 mmHg, it is 3.5 mmHg in the dorsal root ganglion and it drops to between 1 and 2 mmHg within the peripheral nerves. Endoneurial hydrostatic pressure (EHP) rises in the aged nerve and it is possible that external pressure increases EHP by obstructing flow. This may be one factor underlying the effect of entrapment or compression. Hill and Hall (1999) suggest that the aggregation of Renaut bodies at sites of potential entrapment represents a response to local injury to the endoneurial capillaries.

The blood supply to the roots of the spinal nerves is much less robust (Figs. 2.31a–c and 2.32). Two distinguished Cambridge anatomists, Woollam and Millen (1958), considered that: “man has just as much nervous system as he can supply with oxygen and no more.” The most important spinal vessel, the anterior spinal artery, was studied in the fetus and in the guinea pig and rat. Relatively few radicular arteries survived into adult life, the average number of those so doing was eight. Two of these seemed to be particularly important: a cervical vessel, arising from the vertebral artery and entering into and sustaining the anterior spinal artery at C6, C7 or C8, and the artery of Adamkiewicz 1881a,b, in the upper lumbar region. Figure 1 in Woollam and Millen’s paper shows, in a 24 week human fetus, that the radicular vessel adjacent to



**Fig. 2.31** The dorsal vessels to the spinal cord and cauda equina: (a) upper thoracic segment (b) thoraco lumbar junction, (c) cauda equina.





**Fig. 2.32** Resin cast of the blood vessels of the neck, seen from the front (a) and from the side (b). The arteries are shown red, the veins blue showing the segmental arrangement of vessels. The anterior spinal artery is shown (arrow) with an important segmental feeder vessel.

the seventh cervical nerve was the major supplier for the anterior spinal artery (Fig. 2.33). Dommissie (1974, 1975) confirmed that the number of radicular arteries (which he termed the medullary feeders) reinforcing the anterior longitudinal arterial channel was eight and that those reinforcing the dorsal arterial columns were 17. Only 8% of those passing to the cervical spinal cord arose from the vertebral artery. The pattern was variable: “but the principle of a rich supply for the cervical and lumbar enlargements was confirmed” (Dommissie 1975). In the 6 drawings from cadaver dissections a total of 12 vessels are described, 4 of these at the level C6, C7 and 4 more at C4. The anterior spinal artery is the most important of the longitudinal channels. Its central branches, which are end arteries, supply about two-thirds of the cross-sectional area of the cord. The rest of the dorsal grey and the white columns are supplied by branches arising from the dorsal arterial system. Occlusion of the anterior spinal artery leads to the catastrophe of infarction of the anterior cord, the anterior spinal cord syndrome. The significance of damage to major feeder arteries is emphasized by the work of Svensson (2005) who addressed the risk of severe cord lesion after aortic surgery. Svensson achieved a rate of paralysis of 3.8% on patients most at risk, those with complex thoraco-abdominal aneurysms, by a number of measures which included: “sequential segmental repair with repositioning and moving the clamp upon the grafts sequentially downwards

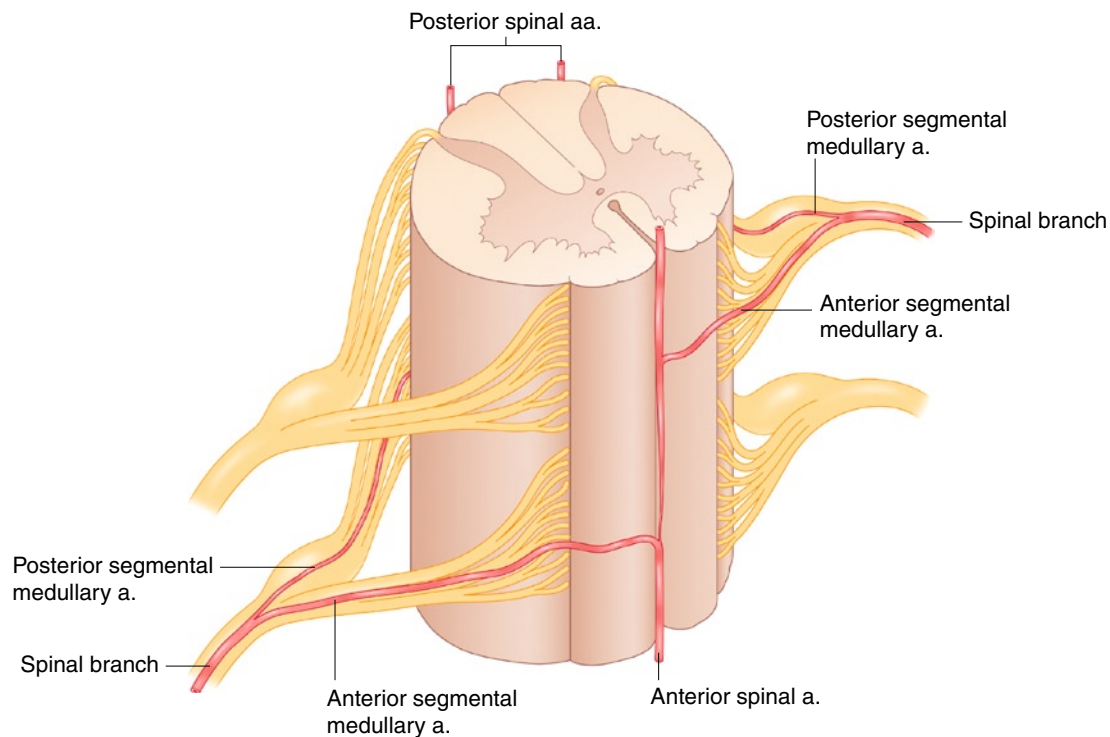
and reattaching intercostal and lumbar arteries.” Disruption of the radicular arteries entering the spinal canal with the spinal nerves which form the brachial plexus probably underlies the partial Brown Séquard syndromes which are seen in cases of avulsion. Occlusion of flow through those vessels by tamponade explains the catastrophe of spinal cord infarction or even death complicating spinal nerve or interscalene block.

### 2.2.5 The *Nervi Nervorum*

Curiously but perhaps predictably, nerves have their own nerve supply in the shape of the *nervi nervorum*, derived from their own fibres. There are free endings in the epi-, peri- and endoneurium, and some encapsulated endings of Pacinian type in the endoneurium. (Hromada 1963). These are probably one factor underlying the exquisite sensitivity of nerves trapped in fibrosis after operations for “entrapment” neuropathy.

### 2.2.6 Changes in Nerves with Ageing

Corbin and Gardner (1937) examined the dorsal and ventral roots of the eighth and ninth thoracic spinal nerves of 34



**Fig. 2.33** The segmental medullary (radicular) arteries and the anterior spinal artery in the lower cervical cord (after Woollam and Millen 1958).

cadavers whose ages ranged from 1 day to 89 years. The highest number of myelinated fibres, found in persons in their second and third decades, was 187% larger than that found in the nerves of a 1 day old infant. They found that after the third decade there was a gradual loss of myelinated fibres, up to 32% for the person of 89 years. Cottrell (1940) examined the median, femoral, sciatic and common peroneal nerves of 30 persons coming to necropsy at ages ranging from 3 h to 81 years. She found changes in the vessels and the connective tissue, with “alteration and loss of the nerve fibers.” Ochoa and Mair (1969) examined portions of the sural nerves of seven volunteers aged 5–59, and were the first to show that active destruction of unmyelinated fibres started early in life, whereas loss of myelinated fibres was found only in the 59-year-old.

Tohgi and colleagues (1977) examined the sural nerves of 79 persons coming to necropsy after “acute death,” whose ages ranged from 1 week to 88 years. The average density of small myelinated fibres decreased rapidly from the age of 1 week (26,300/mm<sup>2</sup>) to the second decade (9,560/mm<sup>2</sup>), and continued to decrease gradually with age, to reach at the eighth decade an average of 74% of that at the second decade. There seems to be an error in the printing of the figure for the eighth decade. Large myelinated fibres appeared first in an infant aged 3 months. Their density increased rapidly, to reach at 3 years the level found in the young adult. The average of the

third decade was 6,480/mm<sup>2</sup>; at the ninth decade it was 3,480/mm<sup>2</sup>. In this extensive study there is mention of the ageing changes in the vasa nervorum and the perineurium. Jacobs and Love (1985) made a qualitative and quantitative study of 27 sural nerves obtained within 24 h of death from human subjects without history of disease or of ingestion of drugs known to affect peripheral nerve. Densities of myelinated and unmyelinated fibres decreased from birth to the end of the eighth decade, because of increasing size and separation of fibres during the first decade, and an increase in endoneurial collagen in the older persons. Also, the slope of the internodal length-fibre diameter increased progressively during the first decade, but then remained virtually constant until the age of 60. Then, degeneration, regeneration, demyelination and remyelination caused increasing variation in internodal length. Thomas et al. (1993b), summarising previous findings, refer to “mild peripheral neuropathy” of older humans.

Norris and colleagues (1953) examined age changes in the maximum conduction velocity of motor fibres of the ulnar nerves of 175 ambulatory male patients, employees and staff members of the Baltimore City Hospitals. There was steady reduction in conduction velocity from the third to the ninth decade. They canvassed possible causes for this regression. Taylor (1984) studied the effects of age on conduction and amplitude in motor and sensory fibres of adult nerves. He indicated that tables of normal data of the rise and



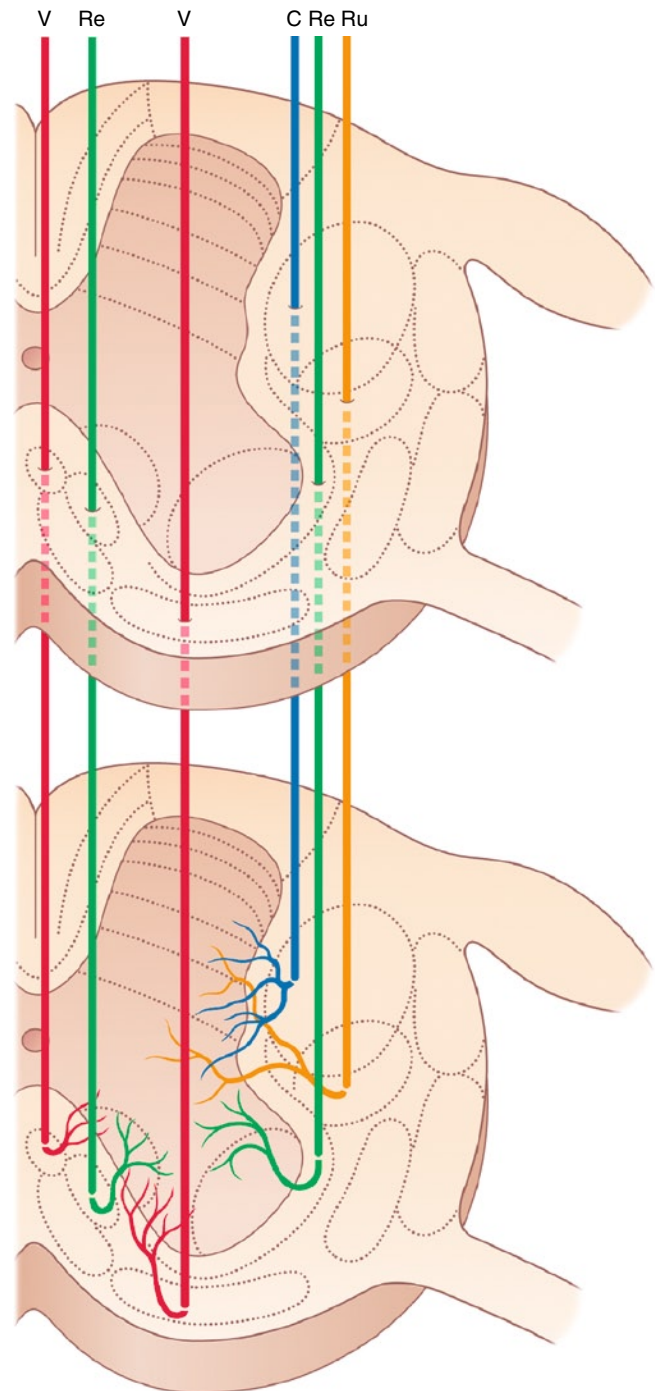
fall of conduction and amplitude could be constructed for use in clinical investigation. Kimura (1993) stated that: “nerve conduction velocities are roughly half the adult value in full-term infants, but increase rapidly, reflecting the process of myelination, to the adult value at age 3–5 years.” He noted the slow decline of conduction velocity after the fourth decade, and drew attention to the contemporaneous increase of the latencies of the F wave and somatosensory evoked potentials. Cowen et al. (2005) describe the greater vulnerability with increasing age of large, long, myelinated nerve fibres, and of larger sensory neurones. There also appears to be selective vulnerability of some autonomic neurones, notably within the enteric system. Evidence is provided to support the proposal that “interactions between sensory neurones and their receptor targets are crucial initiators of an age related nervous deterioration.”

These changes must evidently concern clinicians treating the very young and the rather old: in the former, they may have a bearing on diagnosis; in the latter, they may be relevant to the susceptibility of a nerve or nerves to damage by pressure or traction.

### 2.3 The Somatic Motor System

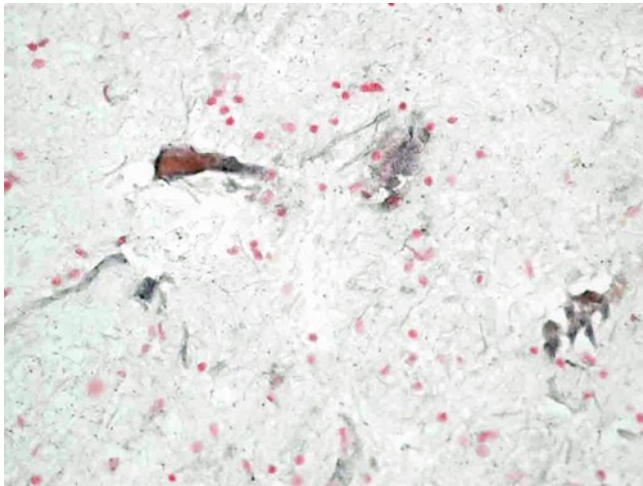
The motor pathway begins in the neurones in the pre-central gyrus of the cerebral cortex. Their axons pass by the *internal capsule* to the mid-brain and to the *pyramids* of the medulla. From each side most fibres cross the mid line at the decussation of the pyramids to descend in the lateral part of the white matter of the cord as the lateral corticospinal tract. At various segmental levels impulses from this tract activate, through internuncial neurones, the motor cells in the anterior part of the grey matter (Fig. 2.34). “Extrapyramidal” tracts from the red nucleus, the vestibular nuclei and the reticular formation also influence the activity of the ventral horn neurones. Brodal (1981c) prefers to discard the designation “extrapyramidal,” on the grounds that “those cortical regions which give rise to fibers in the pyramidal tract also give rise to fibers to a number of nuclei which project further caudally....”

The cell bodies of the motor neurones are in Lamina IX (Rexed 1954) of the ventral horn of the grey matter. There are large (alpha) and small (gamma) cells (Fig. 2.35). They are acted on by primary sensory fibres and by fibres descending from the cortex and from nuclei in the brain stem. The axons from the large cells are destined for the extrafusal fibres. By correlating the distribution of paralysis with the sites of loss of cells in the ventral horn, Sharrard (1955) was able to show how the cells were grouped in the grey matter. Broadly, the medial group supply the muscles of the trunk and neck; the lateral group supply the muscles of the limbs.



**Fig. 2.34** The major descending tracts in the spinal cord and their overlapping zones of termination in the grey matter. C corticospinal, V vestibulospinal, Re reticulospinal, Ru rubrospinal.

Thus, cells of the latter group are present chiefly in the cervical and lumbar enlargements, whereas those of the medial group are found throughout the length of the cord. Nathan and Smith (1958) studied the spinal cord in patients who had earlier undergone cordotomy, and defined the descending



**Fig. 2.35** Motor neurone cell bodies in the ventral horn of human spinal cord stained with antibodies to TRPV 4, a novel ion channel, x40 (Courtesy of Professor Praveen Anand).

pathways for the control of the bladder: “in man, the majority of descending fibers concerned with micturition lie in the lateral column, on an equatorial plane passing through the central canal. This location remains the same in the cervical, thoracic, lumbar and sacral segments.”

The distribution of nerves within the muscles of the upper limb has been described by Lim and his colleagues (2004). The staining technique of Sihler was used which renders muscle translucent and stains the myelin in the nerves a dark blue. The intramuscular distribution of the nerves was then mapped by photographing the superficial and deep surfaces of the muscle using a back light technique. In flat, triangular or trapezoid muscles (class 1) the main nerve runs perpendicular to the muscle fibres giving off side branches that run parallel with them. The spindle shaped or fusiform muscles (class 2) were subdivided into unipennate or bipennate muscles. In the bipennate muscles the aponeurosis of the tendon splits the muscle into two compartments and in these the primary nerve divided into two secondary branches passing each side of the tendon. In muscles with more than one head of origin (class 3) the pattern of innervation is more complex. The pattern of innervation is determined by three factors: “the shape of the muscle, its position and orientation in relation to the passage of the nerve, and the muscle tendon morphology.” These findings support the idea of transfer of part of a muscle and they emphasize the requirement for the repair of intramuscular nerves in lacerated muscles.

Contact with, and transmission to muscle is effected through the motor end-plates (see Fig. 2.42). There are two components of each end plate: neural and muscular. They are separated by a cleft of about 30 nm. The muscular *sole-plate* contains a number of muscle cell nuclei; it is not itself

contractile. There are two types of neural endings: the *en plaque* terminal on extrafusal (alpha nerve fibre) muscle fibre, and the *plate* endings on intrafusal (gamma nerve fibre) muscle fibres. Transmission at *en plaque* endings initiates action potentials which are rapidly conducted to all parts of the muscle fibres, whereas transmission at plate endings of “trail” and “en grappe” types excites the fibres at several points. Acetylcholine released at the nerve ending interacts with receptors to produce depolarisation of the muscle membrane and trigger the action potential in the muscle.

The ventral roots from the first thoracic to the second lumbar segments of the spinal cord contain also the efferent pre-ganglionic fibres of the sympathetic nervous system: those of the second to fourth sacral nerves contain the efferent pelvic parasympathetic outflow.

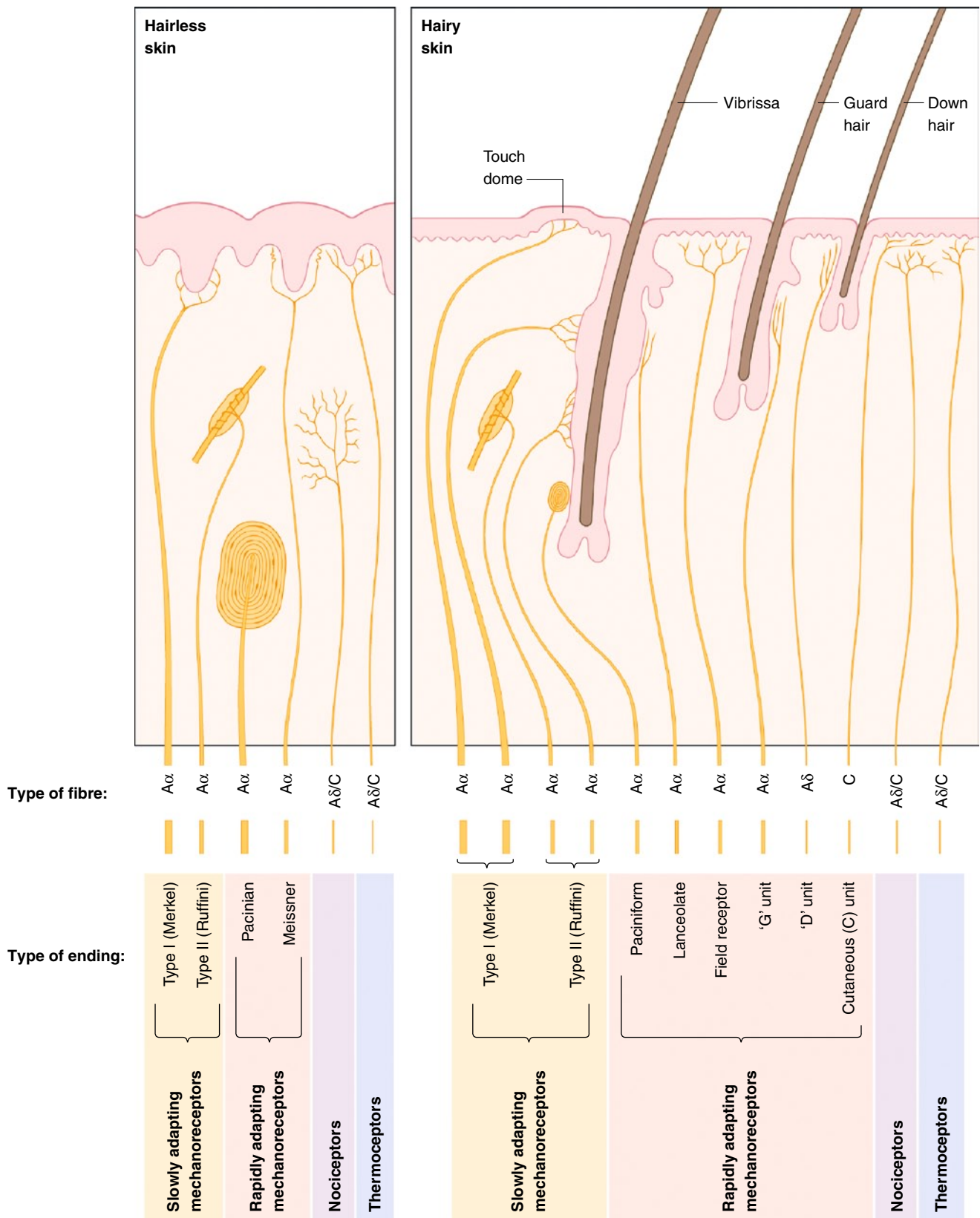
## 2.4 The Somatic Sensory System

The afferent pathways of the peripheral nervous system considerably exceed the efferent pathways in numbers and in complexity of organisation. By no means all lead to conscious sensation. Amongst the somatic afferents the Golgi organs and the muscle spindles are examples; the whole array of the visceral afferents is one more.

### 2.4.1 Cutaneous Sensibility

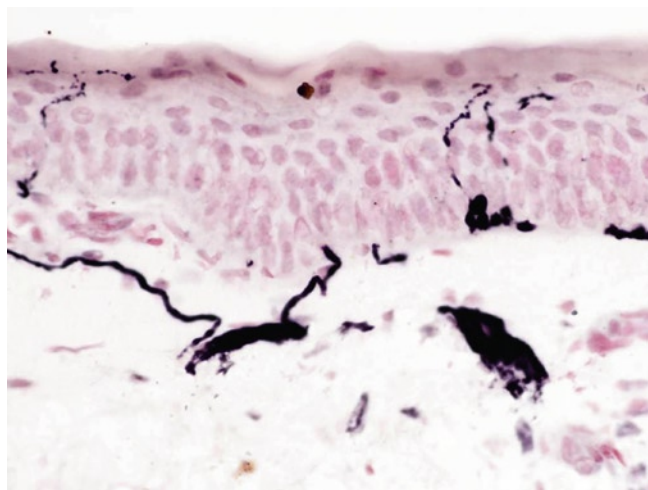
The long debate about the mechanism of cutaneous sensibility begun by Blix (1884) and Goldscheider (1884) and continued by von Frey (1894, 1896), Head et al. (1905), Head and Sherrin (1905), Head (1920), Adrian and Zotterman (1926), Adrian (1928), Zotterman (1939), Weddell (1941), Sinclair (1955) and many others is now drawing to its close: as Iggo (1985) remarks “the long-standing argument of ‘specificity’ versus ‘pattern’ in the operation of cutaneous receptors has been settled in favor of the ‘specificity’ hypothesis.” Iggo also states that: “it is now clear that no cutaneous receptors have an absolute specificity; they have a high degree of selective sensitivity, that is, a much reduced threshold to one form of stimulation” (Fig. 2.36). Adrian pioneered methods in Cambridge in the 1920s (Adrian and Zotterman 1926) which enabled electrophysiological studies of single afferent units. This led to work with microelectrodes and with intraneural microstimulation done by, among others, Hallin and Torebjörk (1973), Torebjörk and Ochoa (1980), Vallbo and Hulliger (1981) Hagbarth et al. (1993), and Torebjörk Schmelz (2005). However, as Wall



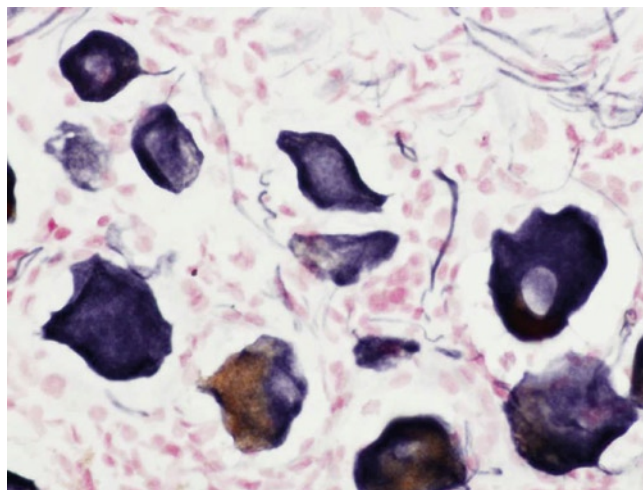


**Fig. 2.36** Cutaneous sensory receptors: glabrous skin (*left*) and hairy skin (*right*).

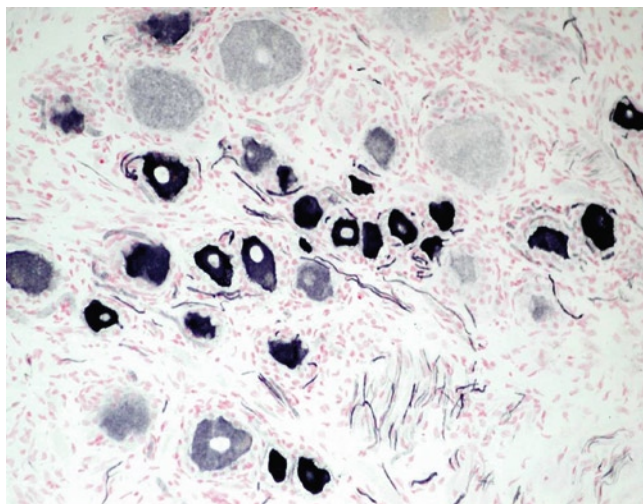
(1961) pointed out: “specific modality and patterning theories are supplementary. The recognition of receptor specialisation for transduction of particular kinds and ranges of cutaneous stimulation does not preclude acceptance of the concept that information is coded in a pattern of impulses.” Mountcastle (1980) assigns to the specialized receptors a role as transducers responsible for amplification. He points out that in areas of skin subjected to sensory testing and later marked and excised, histological examination has shown only free nerve endings. No specialized mechanosensor transducers transmitting through unmyelinated fibres have been identified yet; the same is not so for nociceptors and most thermoreceptors, where the transient receptor potential (TRP) channels have been identified as transducing specific ranges of temperature. All these receptors seem to be represented in fine branching unmyelinated nerve endings in the cell layers of the epidermis (Fig. 2.37). The basis of stereognosis is a combination of stimuli from skin, tendons, muscles and joints relaying sensory information centrally where comparison is made from memories of movement. The role of movement is vital: a blindfolded person cannot identify the nature of a material if it is simply placed on the finger. Identification is aided if the material is drawn across the finger tip. Recognition is, however, immediate if the subject is allowed to create temporal and spatial patterns by feeling the texture between the moving finger and thumb (Melzack and Wall 1962). The fibres of afferent neurones are classed by their conduction velocity. Afferent fibres from the skin are divided into A- $\alpha\beta$ , A- $\delta$  and C; muscle afferents are classed I, II, III and IV (Light and Perl 1993, Lawson 2005). There is some correlation between fibre diameter and the characteristics of the soma within the dorsal root ganglion. These are classed as large light (neurofilament rich) and small dark (neurofilament poor) neurones.



**Fig. 2.37** PGP9.5 immunoreactive somatic nerves in skin of patient with small fibre neuropathy, x 40 (Courtesy of Professor Praveen Anand).



**Fig. 2.38** Small diameter nociceptor cell bodies from a human dorsal root ganglion 2 weeks after avulsion stained with antibodies for prostaglandin receptor sub type EP1, x40 (Courtesy of Professor Praveen Anand).



**Fig. 2.39** Small diameter nociceptor cell bodies and axons in the human dorsal root ganglion immunoreactive for the heat and capsaicin receptor TRPV1 2 weeks after avulsion injury, x20 (Courtesy of Professor Praveen Anand).

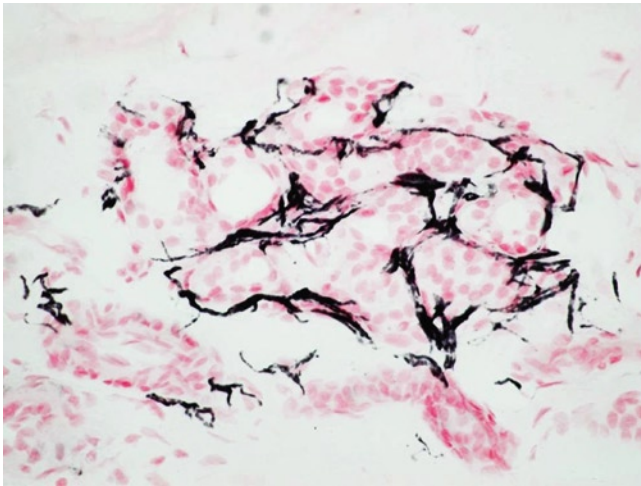
The neurones of C-fibres are small; those with A $\delta$  fibres are small to medium size; those with A- $\alpha\beta$  fibres are medium to large (Lawson 2005) (Figs. 2.38 and 2.39).

#### 2.4.2 The Skin

The introduction of immunohistochemical staining of nerve antigens has provided new insights into innervation of the skin (Kennedy et al. 2005). Kennedy says:

bundles of nerves enter the skin deep in the dermis and course towards the skin surface, giving off axons to innervate the associated end organs. Unmyelinated nerve fibers comprise the vast





**Fig. 2.40** PGP9.5 immunoreactive autonomic nerve fibres surrounding sweat glands in the skin of a patient with small fibre neuropathy, x40 (Courtesy of Professor Praveen Anand).

majority of cutaneous innervation to the above dermal structures. The few myelinated nerve fibers terminate at hair follicles, Meissner corpuscles and Merkel complexes. The vertically orientated nerve bundles form a horizontal sub epidermal neural plexus. Epidermal nerve fibers branch from this plexus and, while penetrating the dermal-epidermal basement membrane to enter the epidermis, they lose their Schwann cells ensheathment and collagen collar.

The sweat glands are carpeted by a dense pattern of autonomic nerves (Fig. 2.40). Fine unmyelinated nerve endings form a network covering larger arteries in the deep dermis. The density of innervation of the epidermis is greatest in the proximal segment of the limb. There is little change between the 20th and 80th year.

### 2.4.3 Cutaneous Sensory Receptors

Three types of cutaneous receptor are defined: low threshold mechano-sensors; thermoreceptors; nociceptors.

#### 2.4.3.1 Low Threshold Mechanosensors

The distinction is made between slowly adapting receptors responding to sustained displacement such as continuous pressure; rapidly adapting receptors responding to the beginning or withdrawal of a stimulus or by a moving stimulus, and receptors responding to brief mechanical disturbances such as vibration and tapping.

The first group includes the Merkel cells; the second includes the Meissner corpuscles and the third, the Pacinian corpuscles. Most are innervated by large and medium sized fibres conducting at rates of from 20 to 90 m/s. A few

morphologically unidentified receptors responding to very slow displacement of hair or skin are innervated by small slowly conducting C fibres. The principal mechano-sensor in hairy skin is the hair follicle receptor; in hairless (glabrous) skin the two principal types are the Meissner corpuscle, rapidly adapting, and the Merkel receptor, slowly adapting. Beneath the skin the rapidly adapting organ is the Pacinian corpuscle; the slowly reacting organ is the Ruffini's corpuscle which is found in deep dermal layers and is characterized by large diffuse receptive fields. The Ruffini corpuscles provide information about finger position by responding to stretching of the skin (Lundborg 2004b). Stark et al. (1998) studied the distribution of Pacinian corpuscles in the hand: the total number identified was around 300 and most were located in the pulp skin of the fingers.

#### 2.4.3.2 Thermoreceptors

So long ago as 1884 Blix postulated that there were two types of thermoreceptor in the human skin: one for cooling and one for warming. Cooling receptors are served by unmyelinated and fine myelinated fibres, usually serving receptor fields about 100 mm in diameter (Light and Perl 1993). They are very sensitive to decrease in skin temperature from the normal or "neutral" level of 30–35°C. Fowler and colleagues (1988) indicate a conduction velocity of up to 2.1 m/s. Davis and Pope (2002) found that the sensation of cooling is replaced by an ache below 17.5°C and by pain below 14°C.

Warming receptors, less common than cooling receptors, have receptive fields of less than a millimetre in diameter. Warm sense is a function of unmyelinated fibres within the epidermis; as we have seen the TRP channels transduce specific ranges of temperature. Temperatures above 43°C induce firing in C-fibre polymodal receptors. Temperatures above 53°C evoke responses in fast conducting myelinated mechano-heat fibres (Light and Perl 1993, Lawson 2005).

#### 2.4.3.3 Nociceptors

The term is applied to primary afferent units which "uniquely signal stimuli intense enough to threaten physical damage to the tissue" (Light and Perl 1993). Some respond to intense mechanical stimuli; some to strong thermal stimulation, and some are polymodal. Impulses travel in myelinated fibres in the Aδ to Aαβ ranges and in unmyelinated C fibres.

Nociceptor fibres are widely distributed in the skin, muscle, joints, the epineurium of trunk nerves and the wall of blood vessels as an extensive plexus of free nerve endings. These pass to fine myelinated and non myelinated fibres and also to the largest (Aαβ) fibres (Light and Perl 1993, Lawson 2005). Aδ nociceptors are high threshold mechano-sensors.

Some respond to damaging heat. They conduct impulses from receptive fields of about 5 mm<sup>2</sup> at about 20 ms. Many of the C-fibres are polymodal, responding to a range of noxious stimuli including histamine and other chemicals, heat, cutting and crushing. C-fibres are responsible for the triple response of Lewis and they are the basis of the axon reflex. They are less than 2 µm in diameter and conduct at between 0.5 and 2 m/s from fields which range from 1 to 10 mm<sup>2</sup>. Microneurography has clarified the physiological characteristics of the nociceptors in humans. Sharp, well localized pain follows stimulation of Aδ afferents. Stimulation of single C-afferents induces dull, burning, poor localized and delayed pain (Torebjörk and Ochoa 1980). Head (with Rivers and Sherrin in 1905) observed two types of pain after the division and suture of his own superficial radial and lateral cutaneous nerves of the forearm. There was epicritic pain which was sharp and localized and protopathic pain which was dull, burning, delayed and unpleasant. It is tempting to relate these two pain types to the now proven characteristics of the two main groups of nociceptors. The reader can experience the two modalities of pain by stimulating the skin on the front of the wrist with a sharp pin. First, and almost immediately, a sharp, well localized pain is experienced. A little later the delayed response—slightly unpleasant, a little longer lasting and a little diffuse—is felt. The A-β and A-δ nociceptors have punctate superficial receptive fields and respond to noxious mechanical or noxious mechanical and thermal stimuli (Mechano-heat units) (Lawson 2005).

#### 2.4.4 Deep Sensibility

Sensation is conveyed from muscles, ligaments and tendons from specialized receptors and from free nerve endings in those structures. The receptor organs are: in muscle, muscle *spindles and free nerve endings*; in tendons, the *Golgi organs*, and in capsules and ligaments various endings, some similar to Ruffini endings, Pacinian corpuscles and Golgi organs. There are also plexuses of unmyelinated fibres (Fig. 2.41).

Joints are innervated by a network of rapidly conducting myelinated fibres some of which are associated with encapsulated mechanosensors and by high threshold, slowly conducting fibres many of which are perhaps nociceptors (Takebayashi et al. 1997, Petrie et al. 1997, Hogervorst and Brand 1998, Chen et al. 2000). Takebayashi et al. (2006) recognized sympathetic afferents innervating the lumbar intervertebral discs. Tomita et al. (2007) investigated the distribution of nerve endings in the human dorsal radio-carpal ligament by fluorescence immunohistochemistry, with confocal laser microscopy and by Kontron image analysis “to rebuild” the endings, so providing data about morphological characteristics as well as incidence, density and distribution.

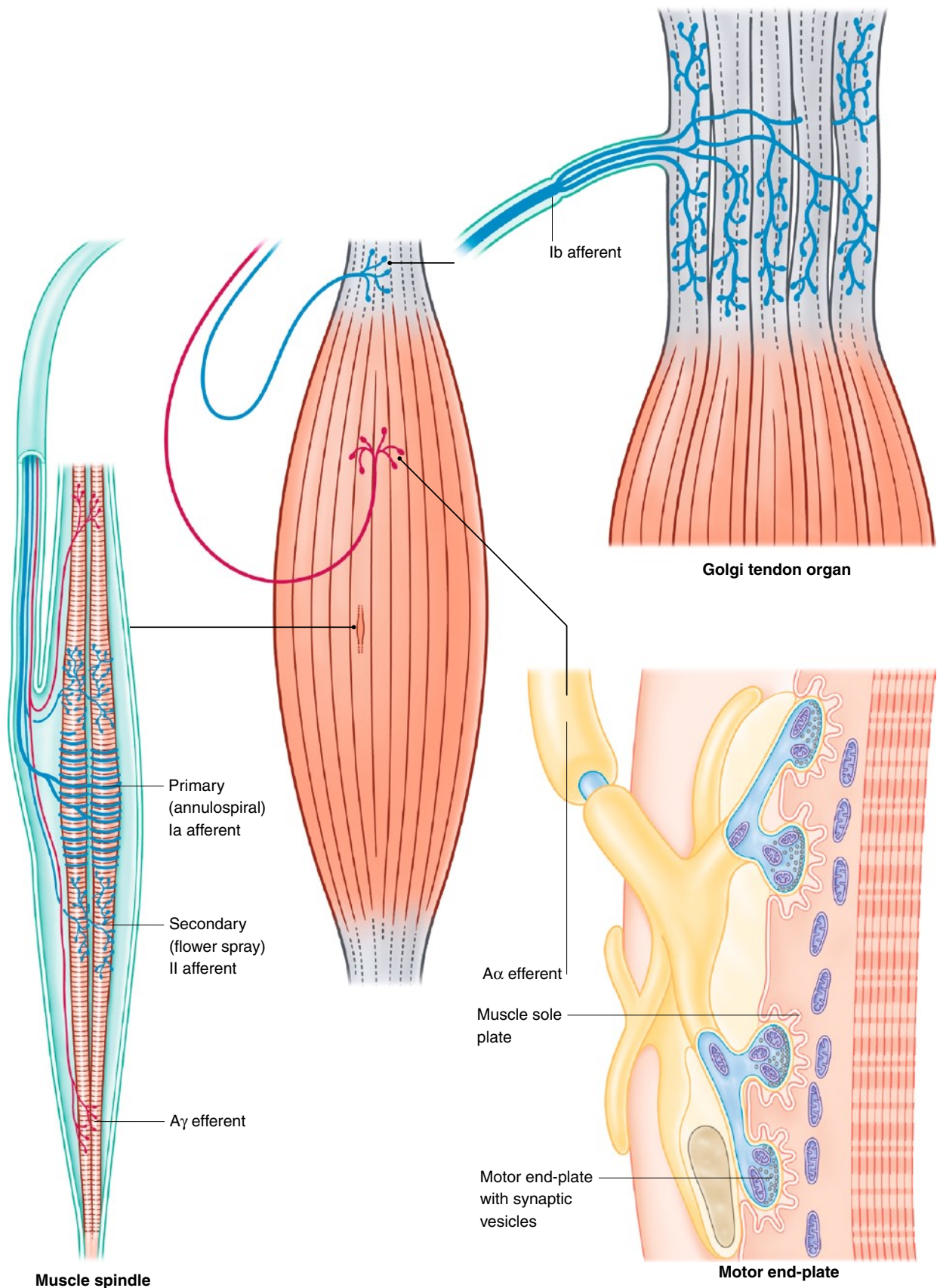
#### 2.4.5 The Muscle Spindles

It is over a 100 years since Sherrington (1894) demonstrated by ventral root section that “in a muscular nerve-trunk from one-third to one-half of the myelinated fibers are from cells of the spinal root-ganglion.” The size of these fibres was from 1.5 to 20 µm; they were not the largest fibres in the nerve; the largest came from the ventral root. On the other hand, the largest of these fibres were larger than any fibres in the cutaneous nerves. “It was shown that about two-thirds of all the afferent fibers measure above 7 µm. Of these I imagine that considerably more than one-half may be apportioned to the muscle spindles, the majority of the rest belonging to Golgi’s tendon organs.” Sherrington found too that “the smallest myelinated fibers in the muscular nerve are for the most part, perhaps entirely, root ganglion fibers.” Sherrington further showed that there were “recurrent” (afferent) fibres in the ventral roots. He identified the special end-organs of the afferent fibres in the muscle-spindles (*muskel-spindel*) of Kühne (1864). Ruffini (1897), in his observations on sensory nerve endings in muscles, defined the “sensorial” end organs of muscle as (1) the muscle spindles; (2) the tendon organs (Golgi organs) and (3) the Pacinian corpuscles. He concluded: “in my opinion it is upon these three levels of sense organ that physiology must turn its attention if it will resolve the problem of the muscular sense.” Batten (1897) further examined the muscle spindle and its behavior in various pathological conditions including injury to the brachial plexus. Horsley (1897) noted their “preservation in conditions of extreme muscular atrophy.”

Since Sherrington’s time, a very great deal of work has been done on the structure and function of the muscle spindles (Banks et al. 1982; Boyd 1962, 1966, Boyd and Smith 1984; Goodwin and colleagues 1972; Cooper and Daniel 1963; Matthews 1981). Their behavior after nerve injury and on their regeneration is described in Chaps. 3 and 4.

Boyd and Smith (1984) state that “The whole human body must contain about 20,000 spindles, each of them a marvel of micro-engineering.” Most spindles lie deep in muscle near branches of its nerve or blood vessels. Each contains small muscle fibres (intrafusal fibres) within a cellular and connective tissue capsule. Banks (2005) says: “there are two principle kinds of encapsulated sense organs in skeletal muscle.... the tendon organ, which senses the force of contraction and the muscle spindle which responds to muscle length.” Both have a copious innervation by large afferent fibres and the muscle spindle and the Golgi tendon organ account for nearly all group 1 afferent axons from muscles. There are three types of specialized intrafusal muscle fibres: the *nuclear bag* fibres (bag 1, bag 2), with a central accumulation of nuclei, and *nuclear chain fibres*, smaller and with a single row of nuclei. The spindles vary in length from a few millimeters to a centimeter. Each spindle receives up to 25 terminal branches





**Fig. 2.41** The afferent and efferent innervation of skeletal muscle.

of motor and sensory axons, together with autonomic innervation. The motor axons are the  $\beta$  and  $\gamma$  axons of the ventral root; the sensory axons are myelinated fibres of groups I and II. The combination of motor and sensory innervation is reflected in the complexity of the function of the spindles. The conception of a servo action is evidently too simple; rather, it is evident that the spindles play several roles in the “feedback” mechanism for regulating muscle contraction and for appreciation of body position. Stacey (1969) reckoned that in a “motor” nerve of the cat the distribution of fibres was one-third myelinated motor, one-third myelinated sensory and one-third unmyelinated sensory. Banks (2005) studied the nerve to the soleus muscle of the cat. The nerve contains 180 myelinated sensory and 270 myelinated motor fibres. Most of the myelinated afferents arose from 56 spindles and 45 tendon organs. There were 115 fusimotor gamma efferent fibres, which means that the 25,000 extrafusal skeletal muscle fibres are innervated by only one-third of the total of myelinated nerve fibres. The human longissimus capitis is the most densely spindled muscle and the density of muscle spindles is 25 times more in the lumbrical muscles than in the gastrocnemius (Cooper and Daniel 1963).

The other afferent endings in skeletal muscle are free endings innervated by unmyelinated and small myelinated fibres. Iggo (1961) found that these responded to sustained pressure but not to stretch or contraction. They responded to hypertonic saline, but that stimulus was sufficient to excite the spindles too. Other studies of these organs and their afferent fibres were made by Mense and Schmidt (1974) and by Mense (1977) who studied the response to chemical noxious stimulation by single fibre recording. Pomeranz and colleagues (1968) traced fine myelinated afferents from viscera, muscle and skin to Lamina V of the dorsal horn of the spinal cord.

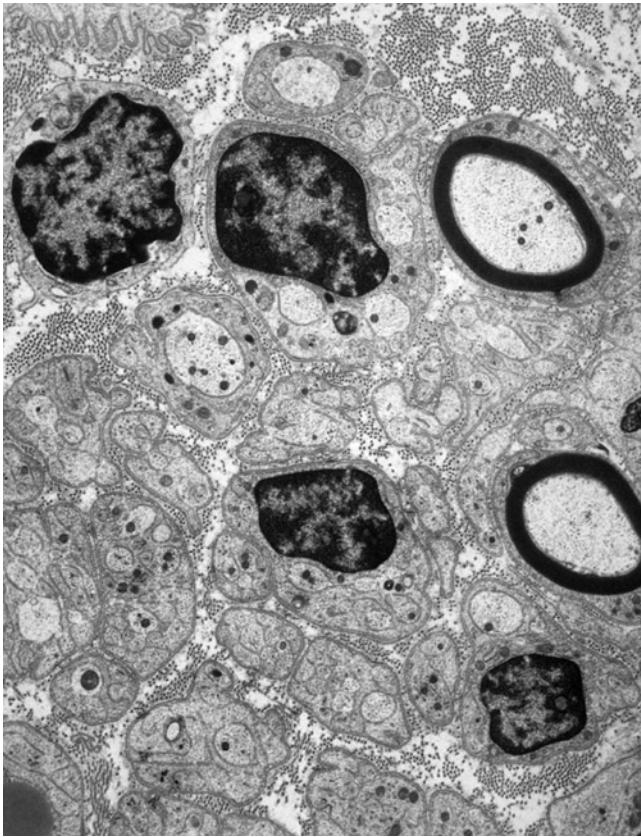
#### 2.4.6 The Golgi Tendon Organs

Scott (2005) characterizes the second of the two encapsulated mechano-sensors in muscle. The Golgi organ senses length of muscle and impulses project from it to the cerebellum and cortex. Stimulation of the fibres from the Golgi apparatus in hand muscles causes cortical potentials and “illusions of muscle stretch.” The Golgi organ is about 0.1 mm in diameter and between 0.2 and 1.5 mm in length. It contains collagen strands which continue into muscle fibres at one end and into the tendon at the other. There are between 3 and 50 of these organelles in each muscle, and Scott says that the ratio of Golgi organs to spindles is less than 0.3. The myelinated afferent fibre is a little smaller than the largest afferent from the muscle spindle, and in the cat it conducts at the rate of 60–110 m/s. The terminals interweave amongst the collagen strands as sprays or spirals. The capsule contains capsular cells which

are continuous with the Schwann cells. The receptor is slowly adapting; it responds to the whole range of muscle contraction and the firing rate is proportionate to active tension. In humans the fibres are silent at physiological rest and there are progressive steps in the firing rate with increasing steps in muscle contraction. Recovery is virtually complete after a crush lesion inducing axonotmesis, it is very much worse after repair of divided nerves. The poor recovery of the two main encapsulated mechano-sensors in muscle after repair of divided nerves may account for the common complaints of weakness, lack of stamina, and poor coordination and also for the failure of musculotendinous transfer using reinnervated muscles. As MacQuillan (2006) says: “the normal function of muscles is dependent on their sensory apparatus.”

Up to now, most clinical work on sensation and on recovery of sensibility after nerve injury and repair has been directed to cutaneous sensibility. Yet function such as stereognosis and proprioception must depend principally on signals from endings in muscle, tendons and ligaments. It is perhaps inadequately appreciated that there may be good recovery of sensory function of the hand with very imperfect cutaneous reinnervation, and that pain is just as likely to follow damage to a “purely motor” nerve as it is to follow damage to a “mixed” or “sensory” nerve. There is in fact no such entity as a “purely motor” nerve, except perhaps for the hypoglossal or facial. The signals from the muscles supplied by those nerves probably proceed by other cranial nerves: the lingual in the case of the hypoglossal nerve and the trigeminal and the auricular branch of the vagus in the case of the facial nerve. There are indeed a few peripheral nerves without a cutaneous sensory component: the spinal accessory; the phrenic; the anterior and posterior interosseous; the deep branch of the ulnar; the suprascapular. The content of afferent fibres in all such nerves is about 30%. Laviano (1992/93) in his thesis on “transfer of the spinal accessory nerve for the suprascapular in avulsions of the brachial plexus” shows EM photographs of portions of the suprascapular nerve taken at operation as long as 94 days after injury (Fig. 2.42). There are numerous medium-sized and small myelinated fibres in good condition: evidently, the distal processes of dorsal root ganglia. Our work along the same lines also suggests a proportion of myelinated afferent fibres for the “motor” nerve of around 30%. Laviano’s work confirms the earlier supposition (Bonney 1959) that the dorsal root ganglion cells survive for a long time the interruption of their central processes. As to the last: in a case of extensive intradural damage to the plexus we examined a specimen of suprascapular nerve taken at the time of “neurotisation” well after the period required for degeneration, and found that it contained not less than 30% of myelinated fibres. It is perhaps best to drop the terms “purely motor” and “purely sensory,” and even drop the term “mixed” applied to nerves with both motor and cutaneous sensory components. The terms





**Fig. 2.42** Intact (afferent) myelinated and unmyelinated fibres in the suprascapular nerve after avulsion lesion of the brachial plexus. Specimen taken 6 weeks after injury, when efferent fibres had degenerated, x6,600 (Electron microscopic study by Mr Stephen Gshmeissner).

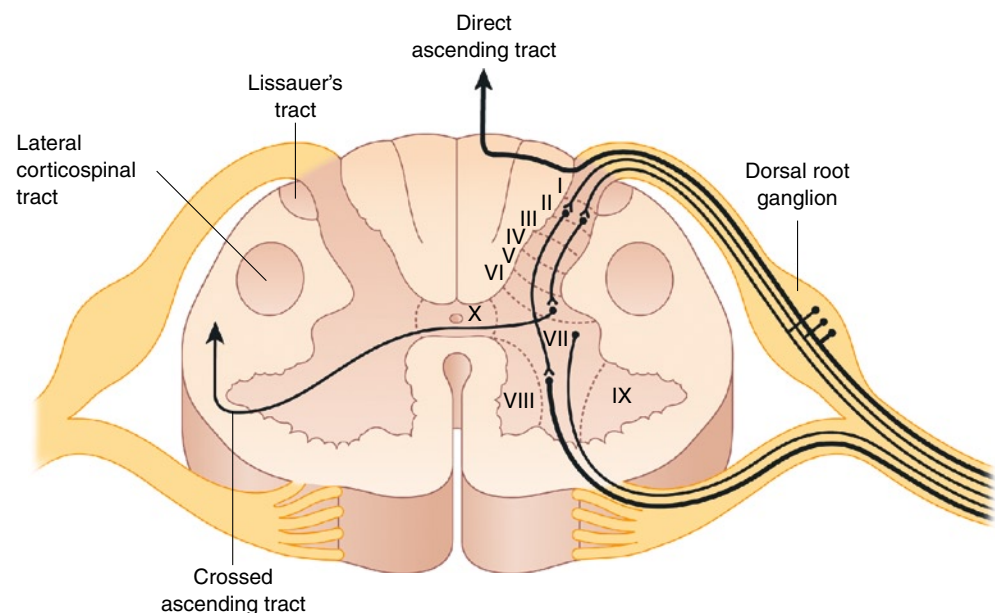
“nerves with motor and cutaneous sensory components” and “nerves without somatic motor components” are, unfortunately, cumbersome, but they do say what they mean.

### 2.4.7 Central Connections

The great array of sensory receptors in the skin and deep tissues sends back to the centre the signals of the stimuli received. Most afferent fibres, with their cell bodies in the dorsal root ganglia, enter the cord by the dorsal roots. Others, with cell bodies in the dorsal root ganglia or actually in the ventral roots, enter the cord by the latter (Fig. 2.43).

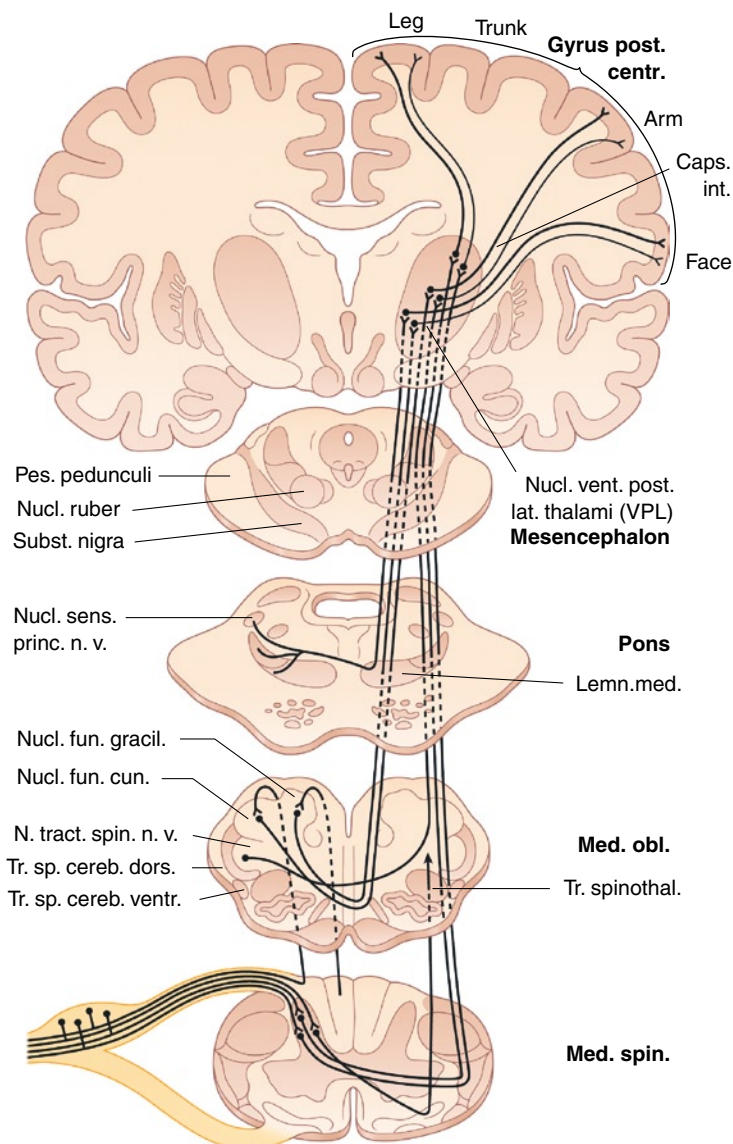
The first analysis of incoming signals takes place in the spinal cord and medulla where all fibres terminate. Most of the large myelinated fibres ascending in the dorsal columns terminate in the gracile and cuneate nuclei in the medulla. Some smaller fibres of the dorsal columns terminate and relay in the cord: these are the *propriospinal* fibres. Although the classical view of the function of the dorsal column has been challenged (Wall 1970) it is broadly true that, as Brodal (1981d) states, they “mediate sensory signals necessary for rather complex discrimination tasks” (Nathan et al. 1986).

Other afferent fibres terminate and relay in the grey matter of the dorsal horn. Each lamina (Rexed 1952, 1954; Price and Meyer 1974) of the grey matter receives afferents of specific functional modalities; each has a particular neuronal structure. Small myelinated nociceptor and thermoreceptor fibres terminate in lamina I; C fibres, nocithermo- and mechano-sensors, in lamina II (substantia gelatinosa). Larger mechano-sensor fibres terminate in laminae III and IV. These relay to cells whose axons either ascend in the dorsal columns or reach the dorsal column nuclei by the dorsolateral fasciculus. Some fibres pass through the dorsal horn to relay with the large cells in the motor apparatus in lamina IX. Some unmyelinated and small myelinated fibres enter the dorsolateral fasciculus (Lissauer’s tract) just lateral to the tip of the dorsal horn to join fibres from cells in the substantia gelatinosa.



**Fig. 2.43** The laminae of the grey matter with direct ascending, crossed ascending and internuncial tracts.

**Fig. 2.44** Ascending tracts in the cord, brain stem and cortex. Note the relay of the directly ascending tracts in the gracile and cuneate nuclei in the medulla (after Brodal 1981a).



Some fibres cross the midline to terminate in laminae I and V of the contralateral dorsal horn. There is a complex network of interconnecting fibres in the dorsal horn and in the substantia gelatinosa in particular. Sensory input is first analyzed and modified here. Secondary neurones in the dorsal horn give rise to fibres which ascend or descend for a few segments in the cord. They give rise principally to the fibres that, crossing the midline, ascend in the long tracts in the antero-lateral segment of the spinal cord (Fig. 2.44).

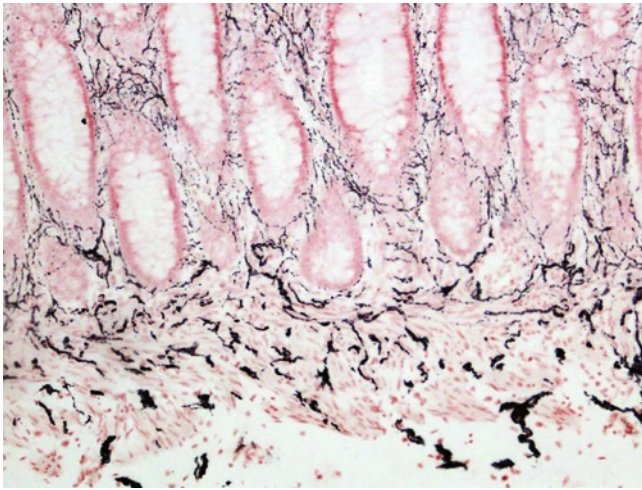
The transmission of impulses from the nuclei of the dorsal column is influenced by fibres descending from the sensory motor cortex (Gordon and Jukes 1964). This influence is predominantly inhibitory. The ascending fibres of those nuclei form the medial lemniscus of the brainstem, crossing the midline in the medulla to end in the thalamus. The final resolution of sensory impulses takes place in the somatosensory areas of the cerebral cortex (Mountcastle 1957). Not

even in this last analysis are afferent functions separated completely from motor function: stimulation of any of these areas produces motor effect (Woolsey 1964).

#### 2.4.8 Visceral Afferents

Schott's (1994) principal proposition was that "sympathetically determined" pain was so determined because the afferent pathways were in the autonomic nerves. He noted the finding by Varro and colleagues (1988) of calcitonin gene-related peptide (CGRP) in visceral afferents, admitting that selective histochemical markers for specifically pain-serving afferents were not, at that time, available. In developing his thesis Schott reverted to the conception of a system of visceral afferents which comprised not only fibres from organs





**Fig. 2.45** Afferent fibres in the enteric division of the autonomic system. Nerve fibres within the mucosa and submucous plexus of human rectum stained with antibodies to sensory sodium channel (Nav1.7), x10 (Courtesy of Professor Praveen Anand).

generally classed as “viscera” but also afferents from blood vessels (Fig. 2.45). The evidence for the presence of a system for conveying from all viscera sensations both perceived and unperceived rests largely on indirect observations: the truly autonomic functioning of viscera: the production of pain by mechanical stimulation of peripheral arteries and veins; the operation of “referred pain” mechanisms; pain after operations on the sympathetic chain; the lack of “visceral sensibility” when the function of visceral afferents is impaired by age. There is evidence from the work of Sugiura and colleagues (1989) that visceral afferents terminate in laminae IV, V and X of the dorsal horn as well as in laminae I and II. They were also traced up and down in the cord and crossing the midline. In their final “conclusion,” Sugiura and colleagues (1989) proposed that their morphological observations suggested that “the somato-visceral convergence could occur in the superficial dorsal horn of the spinal cord,” and that “the scattered and extensive distribution of the terminal fields of single visceral C-afferent fibres may be one basis for the poor localisation of visceral sensation.”

## 2.5 Cortical Maps

The fact that individual movements were controlled by specific areas of the cerebral cortex was recognized in the latter part of the nineteenth century and a “body map” of the sensory cortex was developed by Penfield and Boldrey (1937). The extensive observations made by these early workers do not support the notion of a rigid motor and sensory homunculus. Graham Brown and Sherrington (1912) and Sherrington and Leyton (1917) recognized the functional instability of

cortical motor points. A motor response might be elicited by stimulation of the post central cortex after preliminary stimulation of the precentral gyrus, a process that they termed facilitation. Repeated stimulation of the face area of the motor cortex in chimpanzees was followed by swift expansion of the region to embrace the territory originally representing the hand. Repeated stimulation sometimes induced a change from flexion to extension, a phenomena that they termed “reversal.” A third phenomenon, of “deviation of response” was recognized: “a cortical point can also influence the motor response of another whose response is neither diametrically opposed to nor identical with or very closely similar to its own” (Graham Brown and Sherrington 1912). Penfield and Boldrey (1937) mapped the areas of motor function by direct stimulation of the cerebral cortex during operations in 163 patients which were conducted under local anesthetic for the purpose of removing tumor or epileptogenic foci. Localisation was sharply defined for finger movements but very much less so for movements of the tongue and the jaws. Stimulation of the post central gyrus usually evoked a sensory response but this was by no means sharply defined. Even in the best defined map of finger sensation over one-sixth of the 158 points of stimulation actually lay in the pre central gyrus (Fig. 13 in the original paper). On 11 occasions stimulation of the cortex evoked a sensation of pain and in 13 more a sensation of cold.

Patrick Wall (Wall 1977) provided clear evidence of plasticity within the adult somatosensory system by recording from single neurones and dorsal column nuclei and finding striking changes in the size of the receptive fields soon after partial deafferentation. Wall suggested that these changes might be caused by the unmasking of synapses normally ineffective or silent. The concepts of brain plasticity are reviewed by Lundborg (2004a) in his excellent monograph. Lundborg says that:

brain plasticity implies the capacity of cortical synapses to change their function as circumstances require. In a short term perspective, they may rapidly alter their function, as a result of unmasking or potentiation of already existing synapses. In a more extended perspective, the synapses may increase or decrease in actual numbers and new dendrites may be formed.

(Lundborg 2004c). He continues: “cells that fire together, wire together i.e. neurones become involved in accomplishing the same function and learn to work together efficiently. This phenomenon is named Hebbian learning. Conversely, cells that fire apart, wire apart – i.e. neurones that are not involved in accomplishing the same function learn to ignore each other.” (Hebb 1947) We touch upon other aspects of brain “plasticity” in later chapters but should not forget the salutary observations of Ramachandran and Hirstein (1998): “it is an embarrassing fact that despite five decades of single unit physiology in animals, studied in excruciating detail, we still have no clear idea of how the brain works or why cortical maps exist.”

## 2.6 Synaptic Activity

The transmission of impulses at synapses is chemical, by the release of neurotransmitters causing a change in the permeability and hence the electrical polarisation of the post-synaptic membrane. Such changes may be excitatory or inhibitory; they are usually short-lived, because of early inactivation of the neurotransmitter. This is not of course the whole process: the effect of some neurotransmitters may be more prolonged or even permanent. In addition, some substances released at synapses may simply modify the response of the post-synaptic membrane to neurotransmitters. The general term “neuromediators” has been applied to substances released at synaptic endings; “neurotransmission” implies a direct effect on post-synaptic membrane; “neuro-modulation” implies alteration of its response to a neuromediator (Wigley et al. 2008).

The best-known mediator and the one that has longest been known, is of course acetylcholine, synthesized by motor neurones and released at the motor terminals in skeletal muscle and at the synapses in sympathetic and parasympathetic ganglia. The other well-known mediators belong to the monoamine group: they are noradrenaline, adrenaline, dopamine, serotonin and histamine. Noradrenaline is the chief transmitter at the endings of sympathetic ganglionic neurones. Adrenaline too is present in peripheral neural pathways. Nitric oxide (NO) mediates smooth muscle relaxation at autonomic synapses. The other monoamines are chiefly present in the central nervous system. Gamma amino butyric acid (GABA) is a major inhibitory transmitter which is released at the terminal of such local circuit neurone systems as the inhibitory Renshaw loop. Glycine is another example of an inhibitory transmitter which is particularly prominent in the lower brain stem and spinal cord. Glutamate and aspartate are widely distributed excitatory transmitters. The range of *neuropeptide* modulators is very wide, including those associated with the function of the hypothalamus and hypophysis, corticotrophin, beta-endorphin, the enkephalins, calcitonin-related gene peptide and nerve growth factors. In the field of peripheral nerves, the last is of great and growing importance; the beta-endorphins and enkephalins are important in the consideration of the mechanism and treatment of pain.

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