# Chapter 1
# The Peripheral Nervous System: Anatomy and Function

> Restatement of the facts appears to be warranted by the misconceptions shown by many post graduate students [21].

The nervous system is the mechanism through which the organism is kept in touch with its internal structures and external environments and reacts to changes in them. *The central nervous system* – the brain and its caudal prolongation the spinal cord – is connected to the periphery by the *peripheral nervous system*. The latter includes the cranial nerves, the spinal nerves with their roots and rami, the peripheral nerves and the peripheral components of the autonomic nervous system, the sympathetic, parasympathetic and enteric divisions [16]. The peripheral nerves contain motor fibres (to end plates in skeletal muscle), sensory fibres (from organs and endings in skin, muscle, tendon, periosteum, and bone and joint), efferent autonomic fibres (to blood vessels, sweat glands and arrectores pilarum muscle), and visceral afferent fibres. In no other system is so much functional and relay capacity concentrated in so small a volume of tissue. The cervical spinal cord, with a width of about 2 cm and a depth of about 1.5 cm, contains all the apparatus transmitting control of somatic function from the neck down, together with that of control of much visceral function. Because of their greater content of connective tissue, the peripheral nerves have proportionately a lesser functional content, yet severance in an adult's arm of the median nerve of 5 mm diameter effectively ruins the function of the hand and forearm.

Twelve pairs of cranial nerves arise from the brain and brain stem. The second of these, the optic nerves, are in fact prolongations of the central nervous system. Thirty one pairs of spinal nerves – eight cervical, twelve thoracic, five lumbar, five sacral and one coccygeal – arise from the spinal cord. Each spinal nerve leaves or enters the cord by ventral, largely motor, root, and a dorsal sensory root (Figs. 1.1 and 1.2). Each sensory root splits into several rootlets as it approaches the spinal cord; these enter the cord along the line of the posterolateral sulcus. The division of the anterior roots into rootlets is less obvious and takes place nearer the cord. Because in the adult the spinal cord extends caudally only so far as the first lumbar

R. Birch, *Peripheral Nerve Injuries: A Clinical Guide*,
DOI 10.1007/978-1-4471-4613-1_1, © Springer-Verlag London 2013

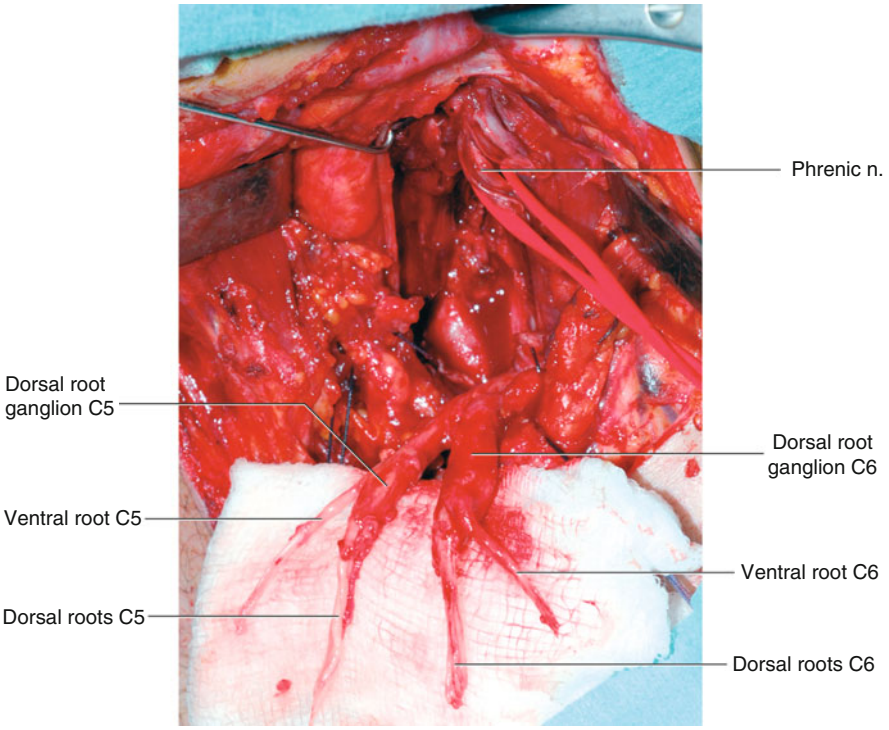


**Fig. 1.1** The fifth, sixth cervical nerves avulsed from the spinal cord. The ventral root is easily distinguishable from the dorsal rootlets. Note the dorsal root ganglion, the dural sleeve merging into the epineurium and the spinal nerve itself. The small pieces of tissue on the proximal ends of the dorsal rootlets (*below*) are probably portions of the spinal cord

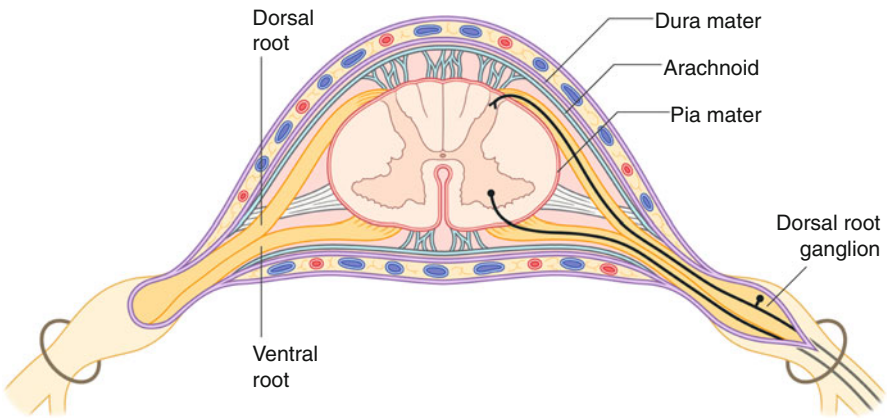


**Fig. 1.2** The origin of the roots from the cord, their junction just distal to the dorsal root ganglion, and the emergence of the nerve from the spinal cord

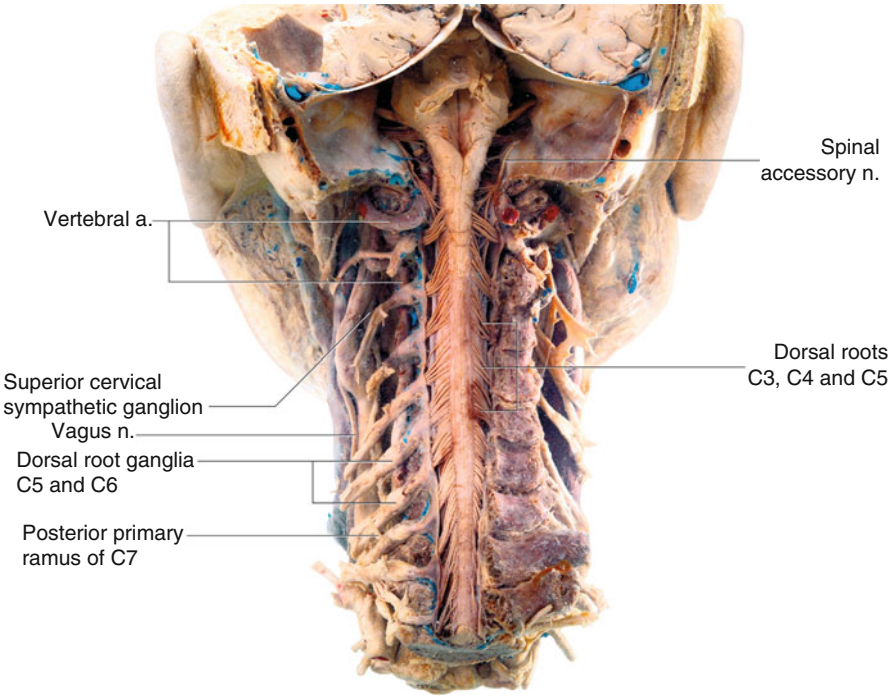


**Fig. 1.3** The brainstem and cervical cord exposed by laminectomy. The spinal accessory nerve passes anterior to the dorsal roots, and emerges through the jugular foramen accompanied by the vagus and glosso-pharyngeal nerves. The vertebral artery courses anteriorly to the spinal nerves

vertebral level, the obliquity of the emerging and entering roots in the theca increases from above downwards. The theca below the first lumbar level is occupied by the lumbar, sacral and coccygeal roots forming a leash whose appearance has been likened to that of a horse's tail (cauda equina).

The cell bodies of the fibres forming the anterior roots are mostly situated in the anterior horn of the grey matter of the spinal cord; those of the fibres of the dorsal root are in the dorsal root ganglion, situated in or near the intervertebral foramen. As they approach the foramen, the two roots join to form the spinal nerve, which outside the foramen divides into anterior and posterior primary rami (Fig. 1.3).

Three divisions of the autonomic nervous system – the sympathetic, the parasympathetic and the enteric – are usually described [16]. In each, pre-ganglionic fibres arise from cells in the brain stem or spinal cord. These relay in ganglia to post-ganglionic fibres innervating cardiac muscle, smooth muscle and glands. Most viscera are supplied by both sympathetic and parasympathetic divisions; the cell bodies of the enteric system are confined to the wall of the bowel.

## 1.1 The Cranial Nerves

The first, olfactory, mediates the sense of smell; the second, optic, mediates that of sight. The latter nerve is a prolongation of the central nervous system. The third, fourth and sixth nerves control the muscles concerned with movement of the eye. The fifth, (trigeminal) nerve has an extensive motor and sensory function, controlling the muscles of the jaw and conveying sensation from the skin of the face and the mucosa of the mouth and nose, and probably from the superficial muscles of the face. The lingual branch which conveys sensation from the tongue and buccal mucosa is, with the inferior alveolar nerve, particularly at risk during operations upon the mouth and jaws. The seventh (facial) nerve innervates the superficial muscles of the face and neck. It is remarkable for its vulnerability to damage in each of the three parts of its course – intra-cranial, intra-osseous (in the petrous part of the temporal bone) and extra-temporal. The eighth (auditory) nerve mediates the senses of hearing and of balance. The ninth (glosso-pharyngeal) nerve conveys sensibility from the pharynx and from the back of the tongue and has a small motor function. The tenth (vagus) nerve has, as its name suggests, wide ranging branches and functions, most of the latter being parasympathetic. Motor branches innervate the muscles of the larynx, and sensory branches convey sensation from it. Its recurrent laryngeal branch is, in the ascending part of its course, in close relationship with the trachea and oesophagus and with the thyroid and parathyroid glands.

The spinal part of the eleventh (accessory) nerve arises from cells in the accessory nucleus, a column of cells extending from the second to the fifth and sixth cervical segments of the cord [5]. These cells are in the dorsolateral part of the anterior horn of the grey matter. The fibres emerge segmentally from each side of the cord, to unite to form on each side a nerve which passes rostrally, posterior to the denticulate ligament, into the cranial cavity through the foramen magnum (Fig. 1.4). In the cranial cavity the nerve unites briefly with its cranial part, derived mainly from the cells in nucleus ambiguus, before passing out of the skull with it through the jugular foramen. Outside the skull the two parts separate, the cranial portion going to join the vagus nerve and the spinal part passing obliquely down the neck to innervate the sternocleidomastoid and trapezius muscles. The spinal accessory nerve is particularly at risk to the activities of surgeons in the posterior triangle of the neck yet its course here is consistent. It emerges from beneath the sternocleidomastoid muscle at about 5 mm cephalad to the point where the greater auricular nerve begins its upward course over the anterior face of the muscle.

The twelfth (hypoglossal) nerve leaves the skull through the hypoglossal canal in the occipital bone to supply the intrinsic and all but one of the extrinsic muscles of the tongue. Although there are receptor organs in the muscles of the human tongue it is likely that most of the impulses from them travel in the lingual nerve. The sensation of taste is mediated by fibres in the facial nerve (anterior two thirds of the tongue) and by fibres in the glossopharyngeal nerve (posterior one third of the tongue). In the upper part of the neck the hypoglossal nerve is joined by fibres from the anterior rami of the uppermost two cervical nerves. These soon leave the nerve to form the ansa hypoglossi from which the infrahyoid muscles are supplied.

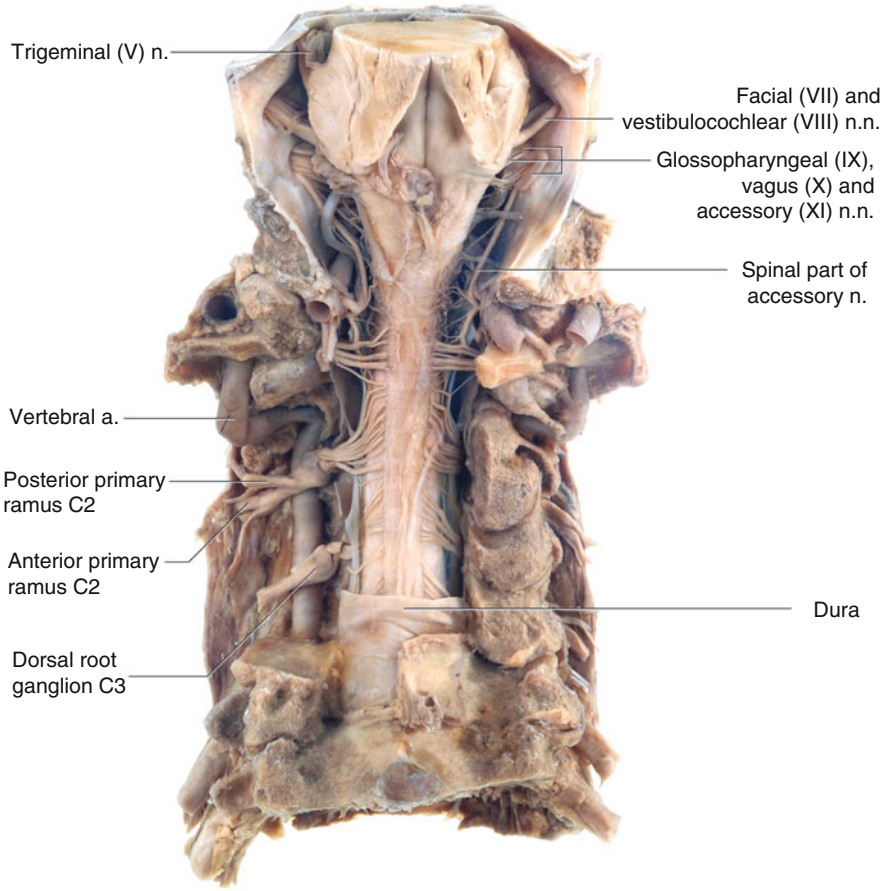


**Fig. 1.4** The junction between the spinal cord and the brain stem shown by excision of posterior bony elements. The first cervical nerve passes away from the spinal cord at almost a right angle

## 1.2 The Spinal Nerves

### *1.2.1 The Anterior Primary Rami*

The anterior primary rami of the uppermost four cervical nerves unite and branch to form the cervical plexus, through which the skin of the neck and part of the face and some of the muscles of the neck are innervated. A branch of the fourth cervical anterior ramus, with contributions from the third and fifth rami, passes caudally into the thorax as the phrenic nerve, to supply motor fibres to the diaphragm and sensory fibres to the related pleura, fibrous pericardium and peritoneum (Figs. 1.5 and 1.6).

The anterior primary rami of the lowest four cervical nerves and most of that of the first thoracic nerve unite and branch to form the brachial plexus in the lower

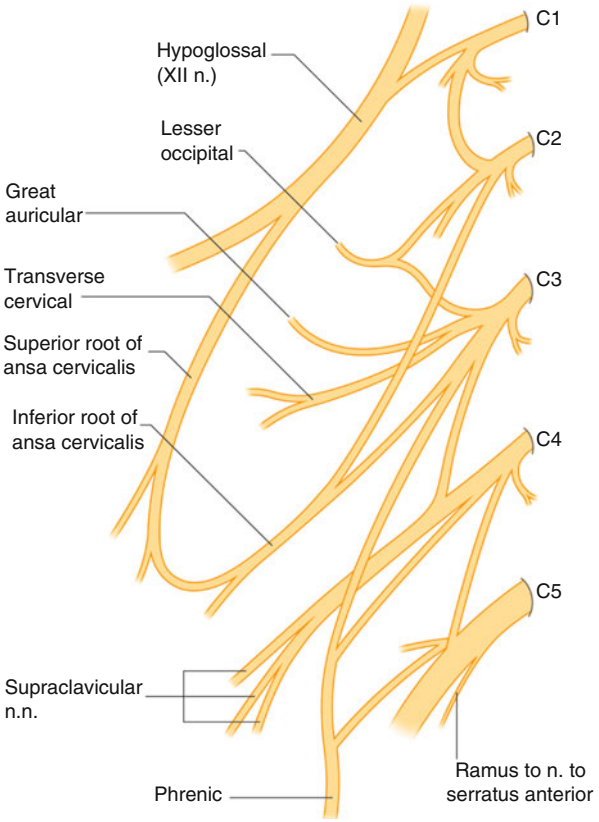


**Fig. 1.5** The right cervical plexus and its (mainly sensory) branches

part of the neck and behind the clavicle (Fig. 1.7). The upper limb receives its innervation through the branches of this important plexus. The most proximal muscles are supplied by branches from the rami; the intermediate muscles by branches from the trunks and cords; the muscles of the limb itself by branches from the main terminal nerves – the median, ulnar, musculo-cutaneous, radial and circumflex (axillary). There is a segmental pattern to this innervation: the most proximal muscles are supplied by branches of the uppermost rami; the most distal muscles are supplied by branches derived from the eighth cervical and first thoracic nerves. The segmental pattern of innervation is shown more clearly in the cutaneous supply (Figs. 1.8 and 1.9) [28]. The cervical root supply has been, as it were, extruded from the supply to the trunk. Thus, in the transition of innervation from the skin of the neck to that of the trunk there is anteriorly a change from the fourth cervical to the second thoracic segment; posteriorly. from the fifth cervical to the first thoracic segment.

An important anatomical and functional differentiation of the plexus takes place with the division of the trunks into anterior and posterior divisions. From the anterior divisions the lateral and medial cords are formed; from the posterior divisions the posterior cord is formed. The lateral and medial cords innervate pre-axial (flexor)

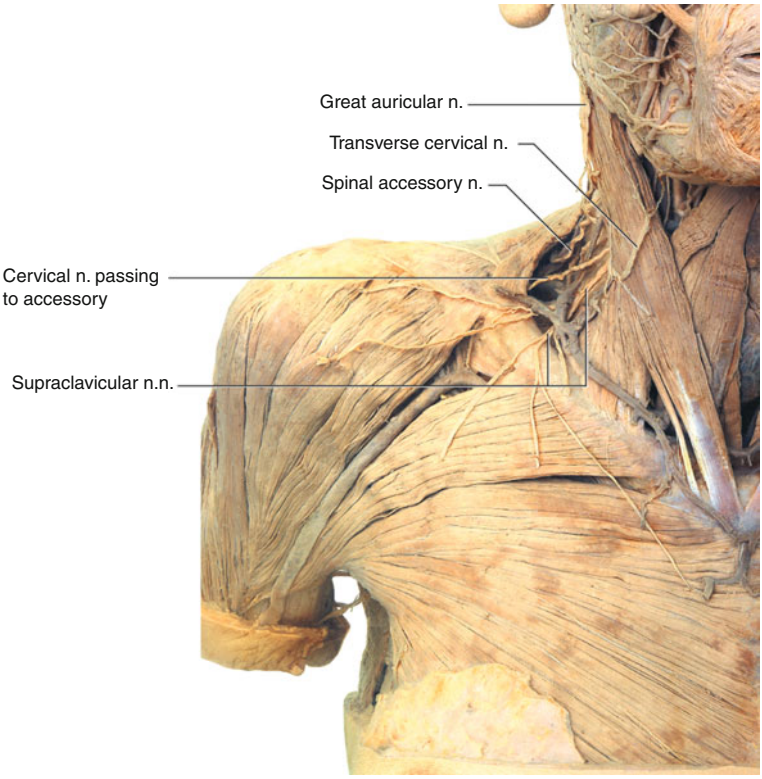


**Fig. 1.6** The relations of the right cervical plexus

musculature; the posterior cord innervates post-axial (extensor) musculature (Figs. 1.10, 1.11, 1.12, 1.13, 1.14 and 1.15).

The plexus and the distribution of its nerves vary considerably from one individual to another: the contributions made by the component nerves vary; the origin and method of formation of the main nerves vary; in some cases the contribution of the fifth nerve is large and that of the first thoracic nerve is small, while in others the reverse is the case. The truly autonomous area of cutaneous supply of each main component nerve is small and variable in extent and location. The contributions made by the fourth cervical and second thoracic nerves vary: usually their contributions are small, but occasionally the fourth cervical nerve makes an important contribution to the innervation of scapulo-humeral muscles [5].

The supply of the skin and of the hand is divided between the median, ulnar and radial nerves. The first two supply the palmar aspect; all supply the dorsal aspect. The median nerve supplies the skin of the radial side of the palm, the palmar aspects of the thumb, index and middle fingers and of the radial part of the ring finger, and the terminal parts of the dorsal aspect of these digits. The ulnar nerve supplies the

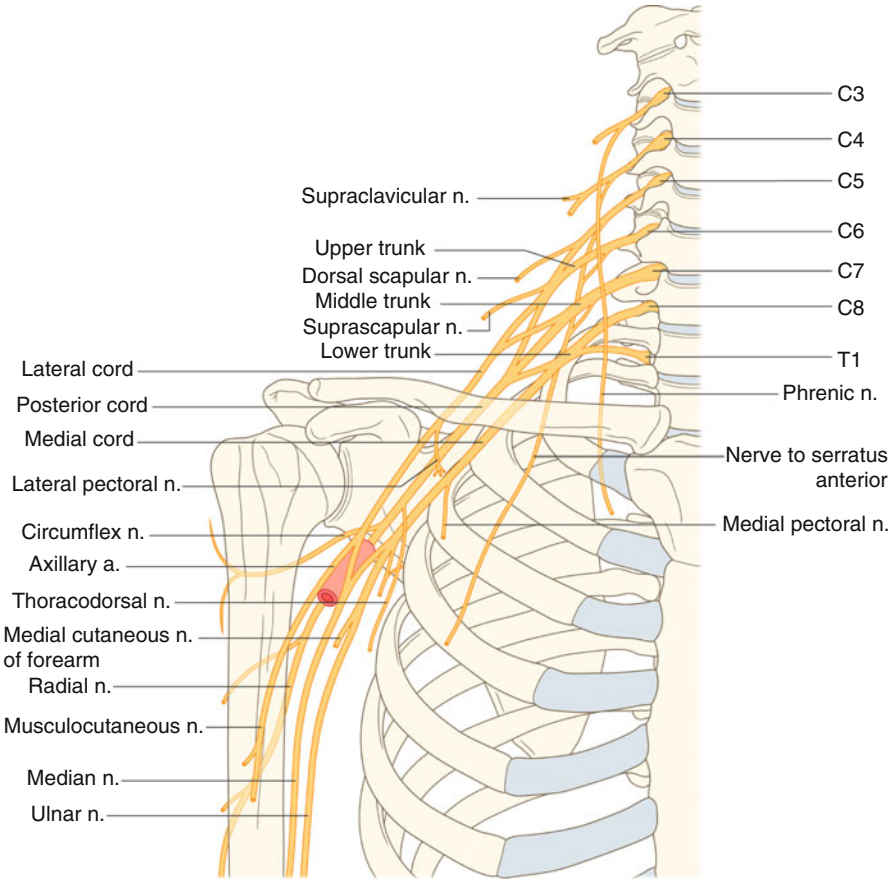


**Fig. 1.7** The right brachial plexus. Note the sequence: the anterior primary rami; trunk; divisions; cords; nerves. Note that the trunks are upper, middle and lower, and that the cords are lateral, medial and posterior from their position in relation to the axillary artery which is, in fact, variable

skin of the ulnar side of the palm, the palmar aspects of the little finger and the ulnar part of the ring finger, the dorsal aspect of the ulnar half of the hand, the little and ring fingers and the ulnar side of the proximal part of the middle finger. The radial nerve supplies the radial side of the dorsum of the hand, of the proximal parts of the thumb and index fingers and of the radial side of the middle finger. Damage to the terminal branches of these nerves of cutaneous sensation which is usually caused by a needle or scalpel often leads to pain which is quite out of proportion to the functional importance of the nerve (Figs. 1.16 and 1.17).

Whilst the variations of the distribution of the peripheral nerves are significant, the variations in the distribution of the spinal nerves forming the brachial plexus are much more important. At least one third of patients with complete lesions of C5, C6 and C7 retain powerful extension of the digits and this is seen in some patients in whom only the first thoracic nerve has survived.

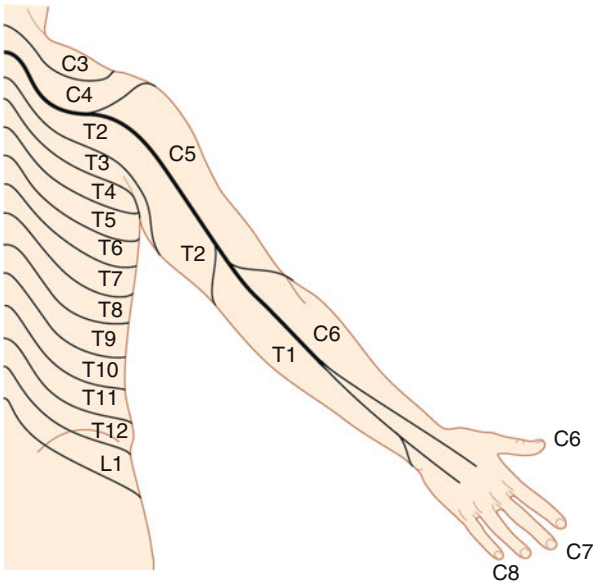


**Fig. 1.8** Approximate distribution of dermatomes on the posterior aspect of the right upper limb (From *Aids to the Examination of the Peripheral Nervous System*. 4th ed. By kind permission of Dr. Michael O'Brian and Elsevier Ltd)

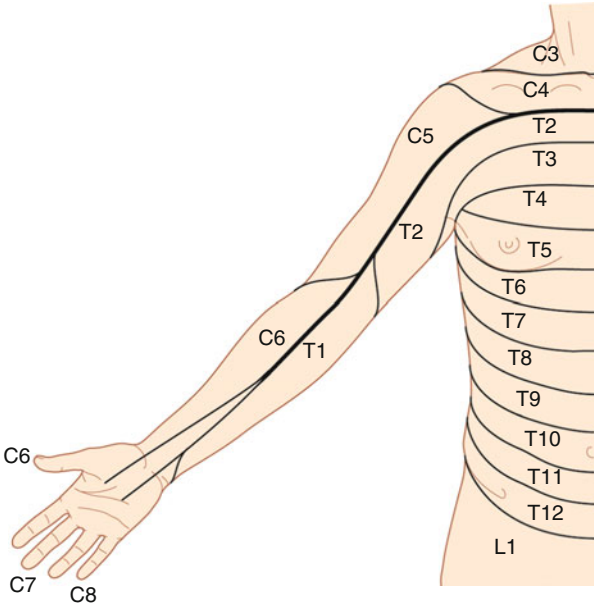


**Fig. 1.9** Approximate distribution of dermatomes on the anterior aspect of the right upper limb (From *Aids to the Examination of the Peripheral Nervous System*. 4th ed. By kind permission of Dr. Michael O'Brian and Elsevier Ltd)

### *1.2.2 Thoracic Anterior Primary Rami*

The second to the sixth thoracic anterior primary rami innervate the intercostal muscles and the skin of the anterior and lateral chest wall. Most of the first nerve goes

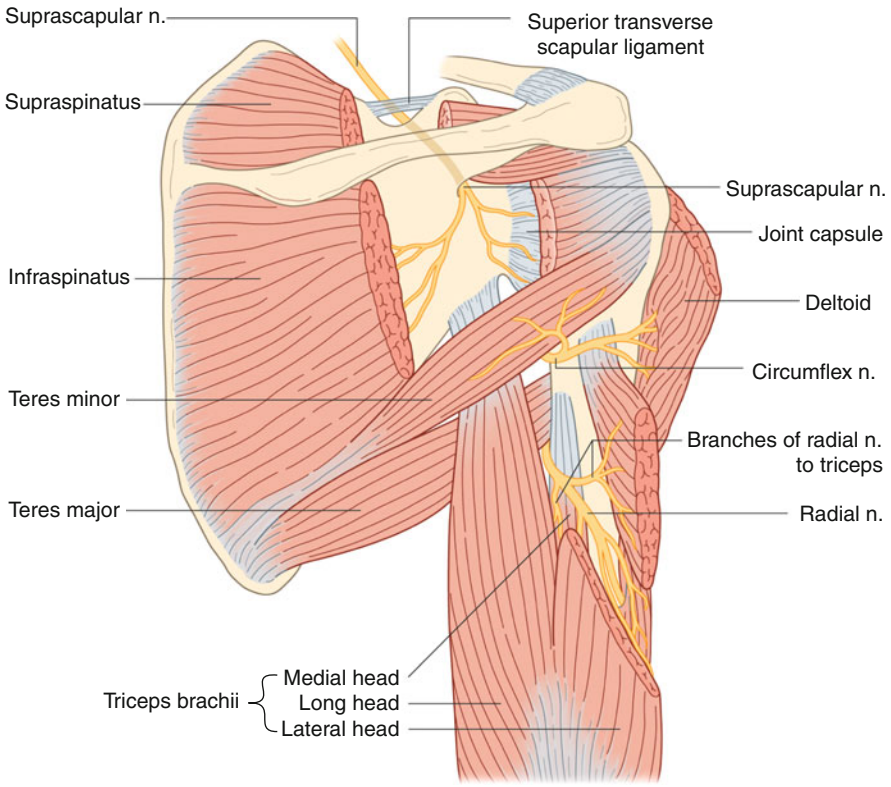


**Fig. 1.10** The right circumflex (axillary) and suprascapular nerves

to join the brachial plexus; most of the second goes as the intercosto-brachial nerve to innervate the skin of the axilla and of the medial side of the arm. The lower six thoracic anterior rami continue from the intercostal spaces to the anterior wall of the abdomen, innervating its skin and muscles. The lowest nerves supply sensory fibres to the lateral part of the diaphragm. The lowest (12th) thoracic ventral ramus, sometimes called the subcostal nerve, is larger than the others and connects with the iliohypogastric branch of the first lumbar nerve.

### *1.2.3 Lumbar and Sacral Anterior Primary Rami* (Fig. 1.18)

The first lumbar anterior primary ramus gives rise to two mainly cutaneous nerves and part of a third. The iliohypogastric, iloinguinal and genitofemoral nerves supply respectively the skin of part of the buttock, of the groin and the greater part of the external genitalia (Figs. 1.19 and 1.20). The second, third and fourth lumbar anterior rami unite and branch to form the lumbar plexus from which arise the nerves

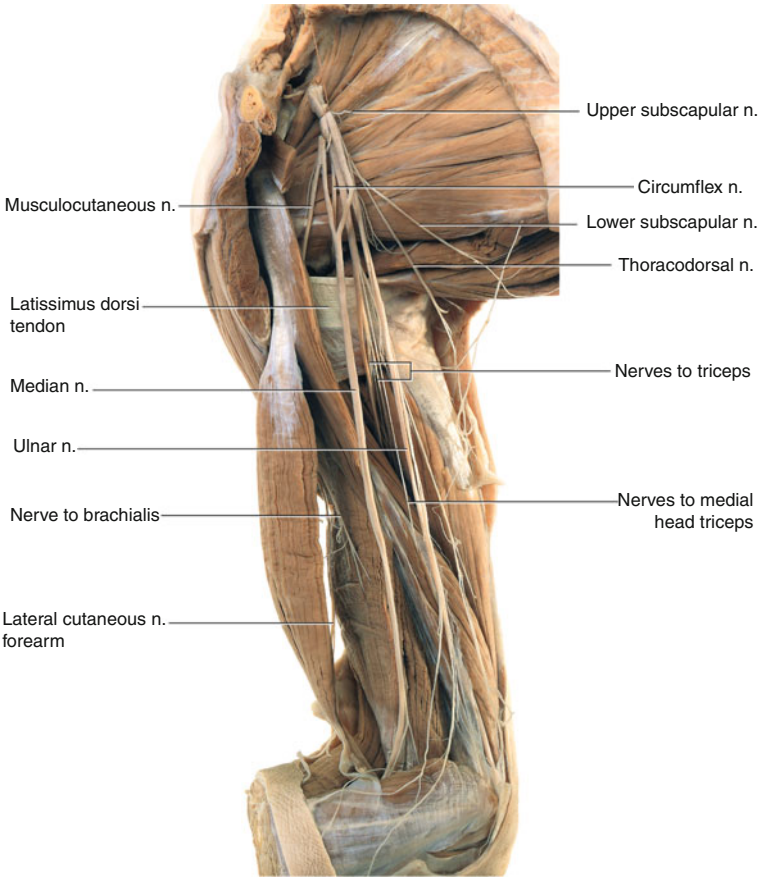


**Fig. 1.11** The main nerves in the right axilla and arm

innervating the skin of the thigh and its anterior and medial muscles. The plexus is formed in the anterior part of the psoas major muscle, in the posterior wall of the abdomen. Its terminal branches lie under the parietal peritoneum. Some of these emerge lateral and some medial to the psoas major. The most important terminal branch is the femoral nerve, which passes, lateral to the psoas major and femoral vessels, under the inguinal ligament to reach the upper part of the thigh. Through its anterior and posterior divisions it supplies the skin of the anterior surface of the thigh and the quadriceps and sartorius muscles. The saphenous branch of the posterior division descends with the femoral artery to emerge from the femoral canal above the knee and supply the skin of the medial side of the leg and foot. The obturator nerve emerges medial to the psoas major and, passing along the lateral wall of the pelvis, emerges into the thigh through the obturator foramen. Through anterior and posterior branches the adductor muscles and the skin of the medial side of the thigh are supplied.

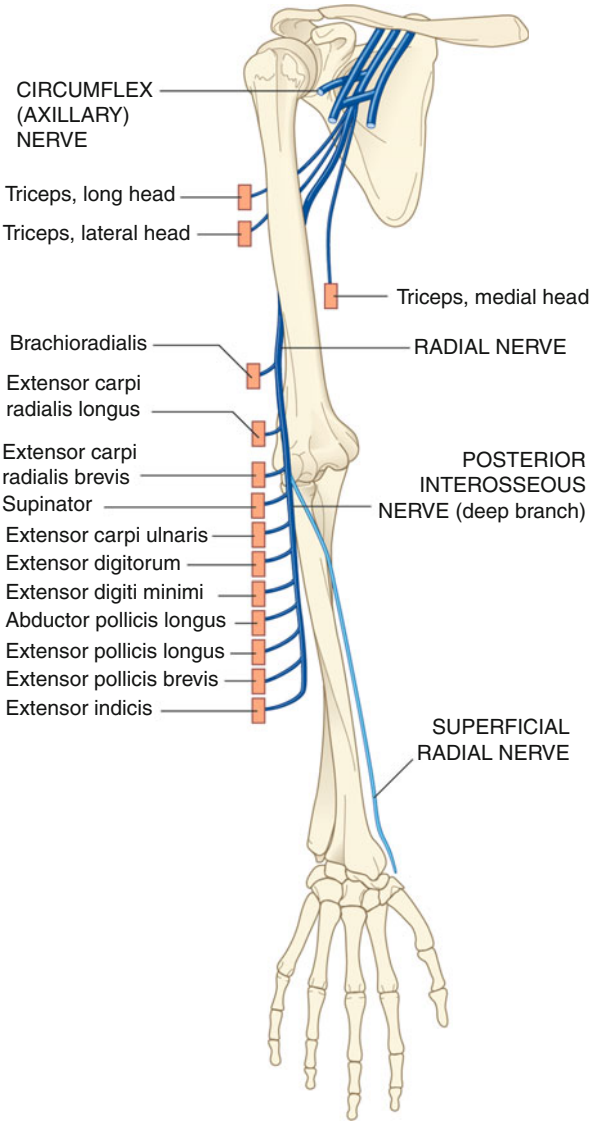


**Fig. 1.12** The right radial nerve (From *Aids to the Examination of the Peripheral Nervous System*. 4th ed. By kind permission of Dr. Michael O'Brian and Elsevier Ltd)

Part of the fourth lumbar ramus and all the fifth ventral ramus join to form the lumbo-sacral trunk, which emerges medial to the psoas major to enter the pelvis and join the first, second and third sacral nerves to form the sacral plexus on the postero-lateral wall of the pelvis (Figs. 1.21 and 1.22).

The innervation of the perineum and most of the lower limb is derived from the branches of this plexus. The sciatic nerve, the largest in the body, leaves the pelvis through the greater sciatic foramen and passes behind the hip joint into the back of

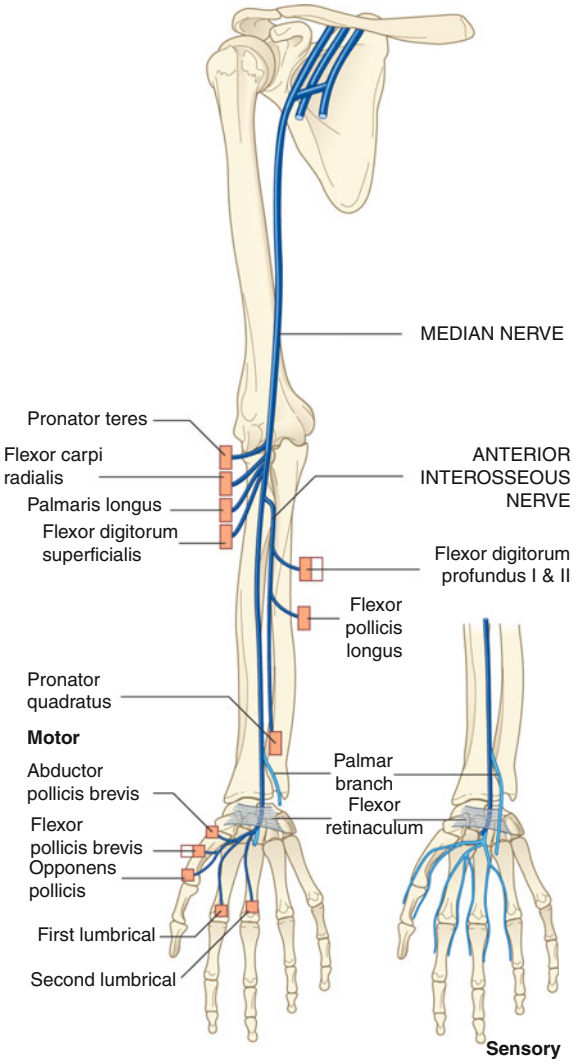


**Fig. 1.13** The right median nerve (From *Aids to the Examination of the Peripheral Nervous System*. 4th ed. By kind permission of Dr. Michael O'Brian and Elsevier Ltd)

the thigh. This great trunk has two main components, which are functionally and often anatomically quite distinct (Figs. 1.23, 1.24, 1.25, 1.26, 1.27 and 1.28). The tibial nerve innervates the medial hamstrings, it descends in the midline through the popliteal fossa into the back of the leg, to supply its superficial and deep muscles. It has an important and frequently useful branch, the sural nerve, which arises in the upper part of the popliteal fossa, descends between the two heads of gastrocnemius and pierces the deep fascia in the proximal part of the leg. Usually, a branch from the common peroneal (or fibular) nerve joins the sural nerve; at times, it is larger than the contribution from the tibial nerve. Rarely, the sural nerve arises wholly

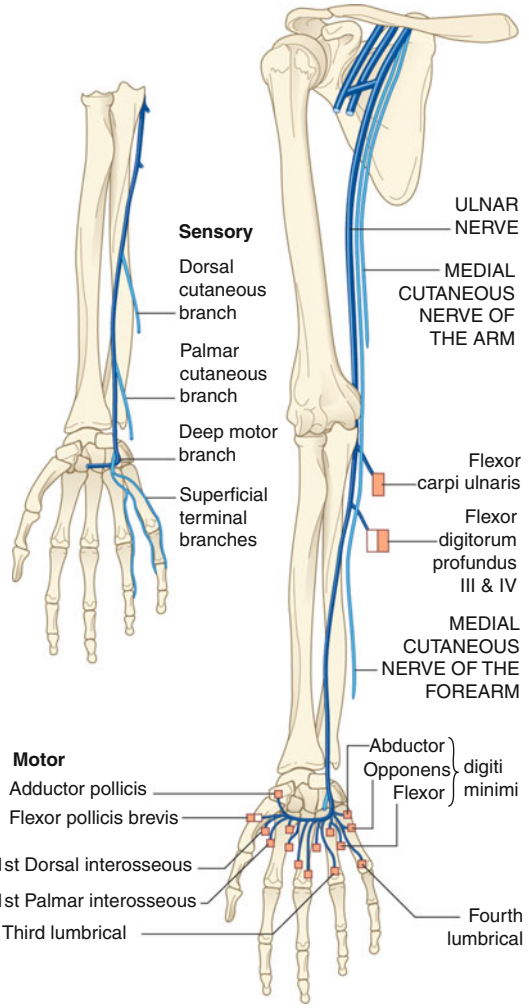


**Fig. 1.14** The right ulnar nerve (From *Aids to the Examination of the Peripheral Nervous System*. 4th ed. By kind permission of Dr. Michael O'Brian and Elsevier Ltd)

from the common peroneal division. The nerve then descends to pass lateral to the tendo Achilles to supply the skin on the lateral side of the foot. The tibial nerve continues into the foot behind the medial malleolus and through its terminal medial and lateral plantar branches supplies the intrinsic muscles of the foot and the skin of the sole. The common peroneal nerve innervates the lateral hamstring muscles in the thigh. It diverges laterally from the mid line to pass behind the head of the fibula and lateral to its neck. Here it divides into deep and superficial peroneal nerves. The former passes into the anterior compartment of the leg to innervate the anterior muscles and finally to supply the extensor digitorum brevis and the skin of the dorsum of the first inter-digital space (Figs. 1.29 and 1.30). The superficial peroneal (musculocutaneous) nerve passes deep to the upper part of the peroneus longus

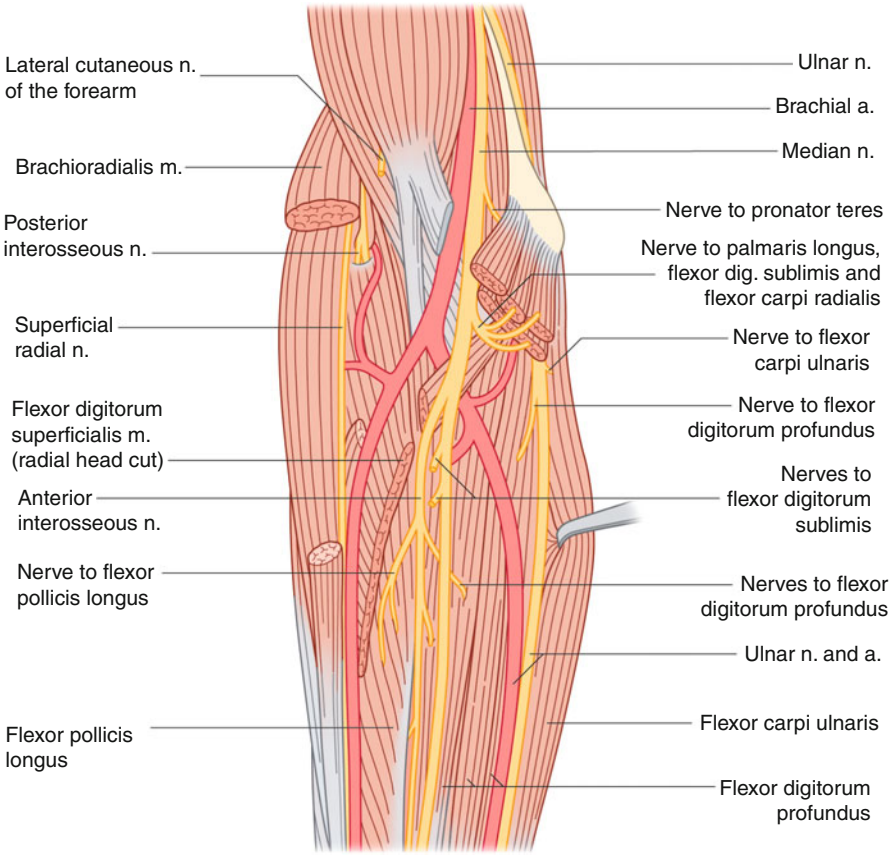


**Fig. 1.15** The anterior aspect of the right elbow

muscle to supply both peronei. Its continuation pierces the deep fascia in the distal part of the leg to supply the skin of the dorsum of the foot and anterolateral part of the ankle.

The more proximal branches of the sacral plexus supply the gluteal muscles and the skin and muscles of the perineum. The superior gluteal nerve, emerging above the piriformis muscle, supplies the short gluteus medius and minimus and the tensor fasciae latae. The inferior gluteal nerve, emerging below the piriformis muscle, supplies the gluteus maximus muscle. The pudendal nerve leaves the pelvis through the greater sciatic foramen and, entering the pudendal canal through the lesser sciatic foramen, passes into the perineum to innervate its skin and muscles. As in the case of the upper limb, there is a segmental innervation of the muscles and, more easily seen, of the skin. Again, the segments innervating the limb have been extruded from the innervation of the trunk and perineum, so that in the transition from trunk to perineum there is posteriorly a segmental change

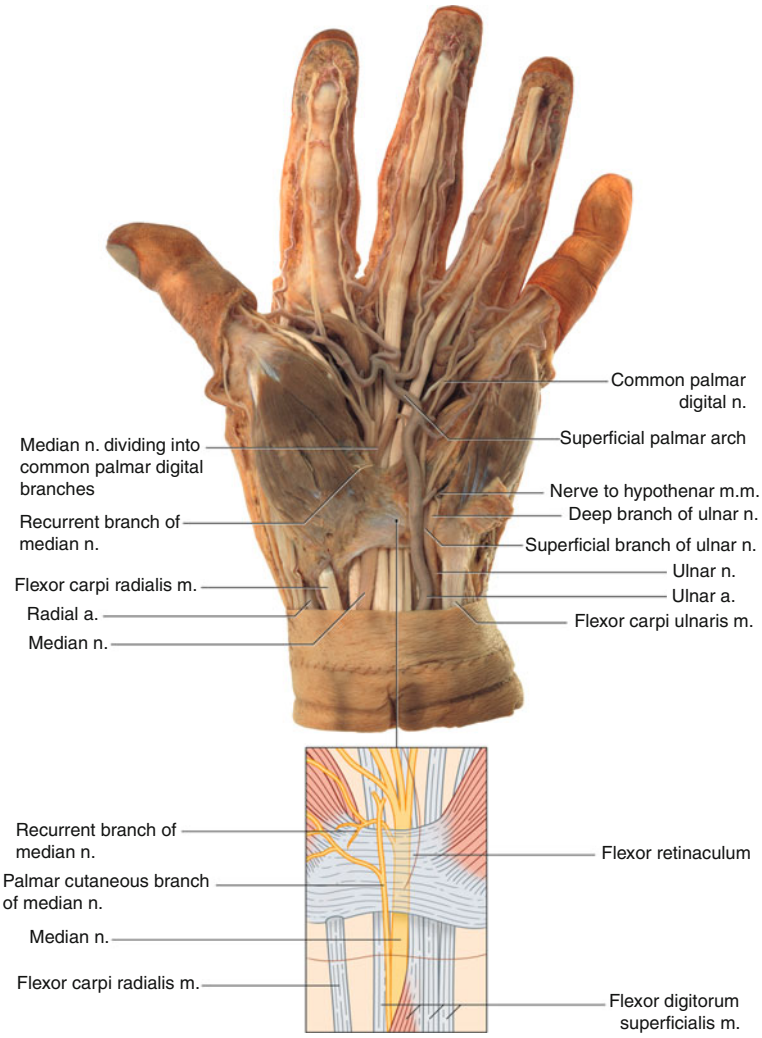


**Fig. 1.16** The median and ulnar nerves in the left hand. *Inset* shows the normal course of median nerve at the wrist and also the palmar cutaneous nerve

from the third lumbar to the third sacral dermatome. The skin of the foot is supplied by all the main nerves of the lower limb save the obturator (Figs. 1.31 and 1.32). The plantar surface is supplied by the tibial nerve through its plantar branches; the medial side by the saphenous branch of the femoral nerve; the lateral side by the sural branch of the tibial nerve, and the dorsum by the superficial and deep divisions of the common peroneal nerve. Apparently trivial injuries to the terminal branches of the nerves of cutaneous sensation sometimes cause even more trouble in the lower than in the upper limbs.

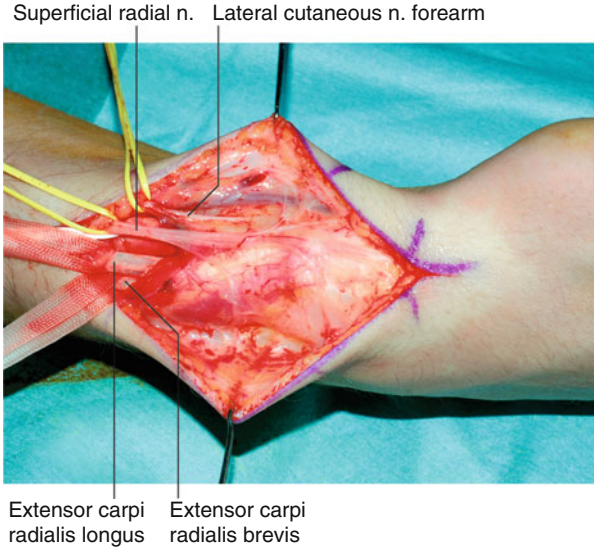


**Fig. 1.17** The terminal branches of the superficial radial and lateral cutaneous nerves of forearm seen during operation at the right wrist

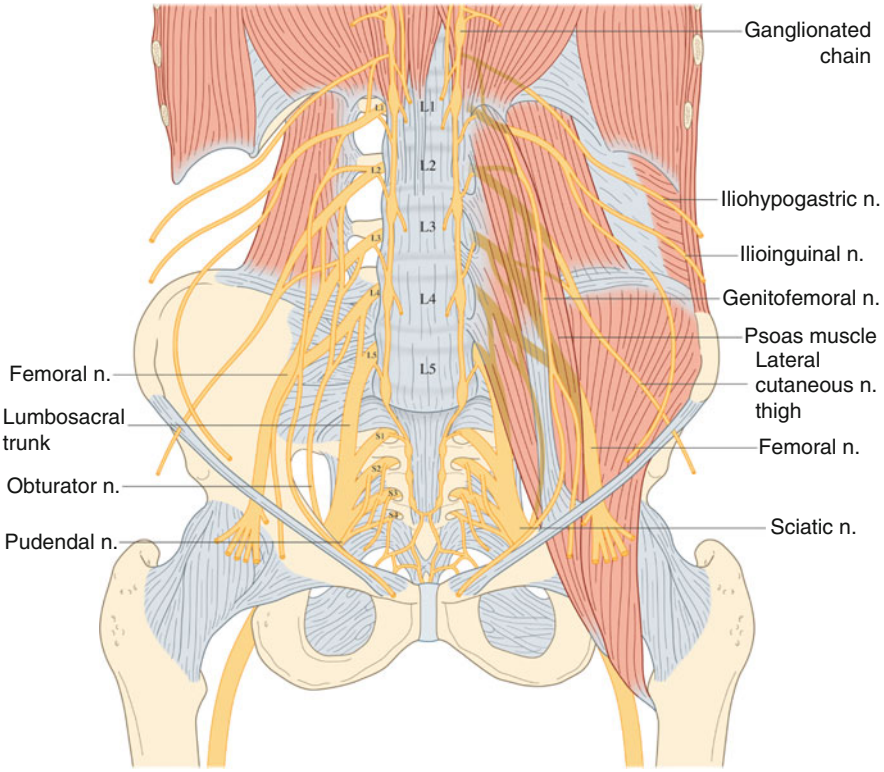


**Fig. 1.18** The femoral and sacral plexuses and the ganglionated sympathetic chain

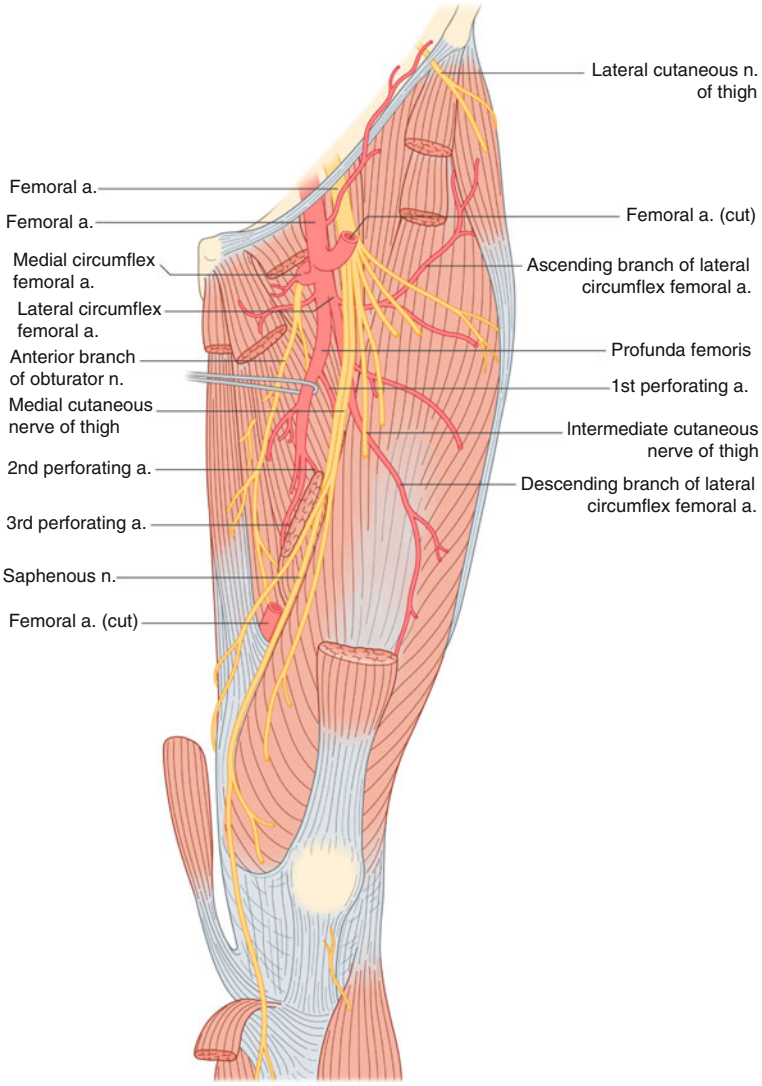


**Fig. 1.19** The left femoral nerve

### *1.2.4 The Posterior Primary Rami*

The posterior primary rami are usually smaller than the anterior. Most divide into medial and lateral branches to supply the muscles and skin of the posterior part of the neck and trunk. They do not enter the limbs.

The posterior primary rami of the uppermost three spinal nerves differ from those of the lowest five in extending their supply to the back of the head. The posterior

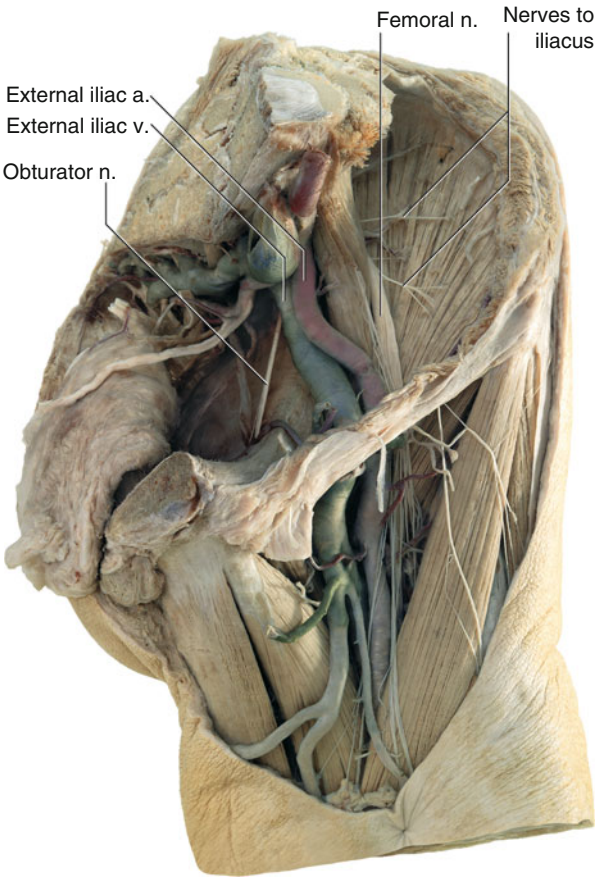


**Fig. 1.20** The left femoral nerve

ramus of the first nerve, actually larger than the anterior ramus, chiefly supplies muscles between the atlas and occiput. The posterior ramus of the second cervical nerve is the largest of the cervical posterior rami and larger than its anterior ramus. Emerging between the posterior arch of the atlas and the lamina of the axis, it divides into a large medial and a smaller lateral branch. The former goes on as the great occipital nerve to innervate the skin of the back of the scalp. At its beginning, it is in close relationship with the back of the atlanto-axial joint. The third cervical posterior ramus provides a third occipital branch. The posterior rami of the lowest five cervical nerves innervate the posterior vertebral muscles; the medial branches of the fourth and fifth rami also innervate the skin.

The thoracic posterior primary rami similarly pass posteriorly close to the posterolateral (zygapophyseal) intervertebral joints to supply posterior vertebral muscles and the skin of the back of the chest. The lumbar posterior rami are similarly disposed, but only the uppermost three reach the skin. The sacral posterior rami are small, having a small distribution to muscle and to the skin over the sacrum.

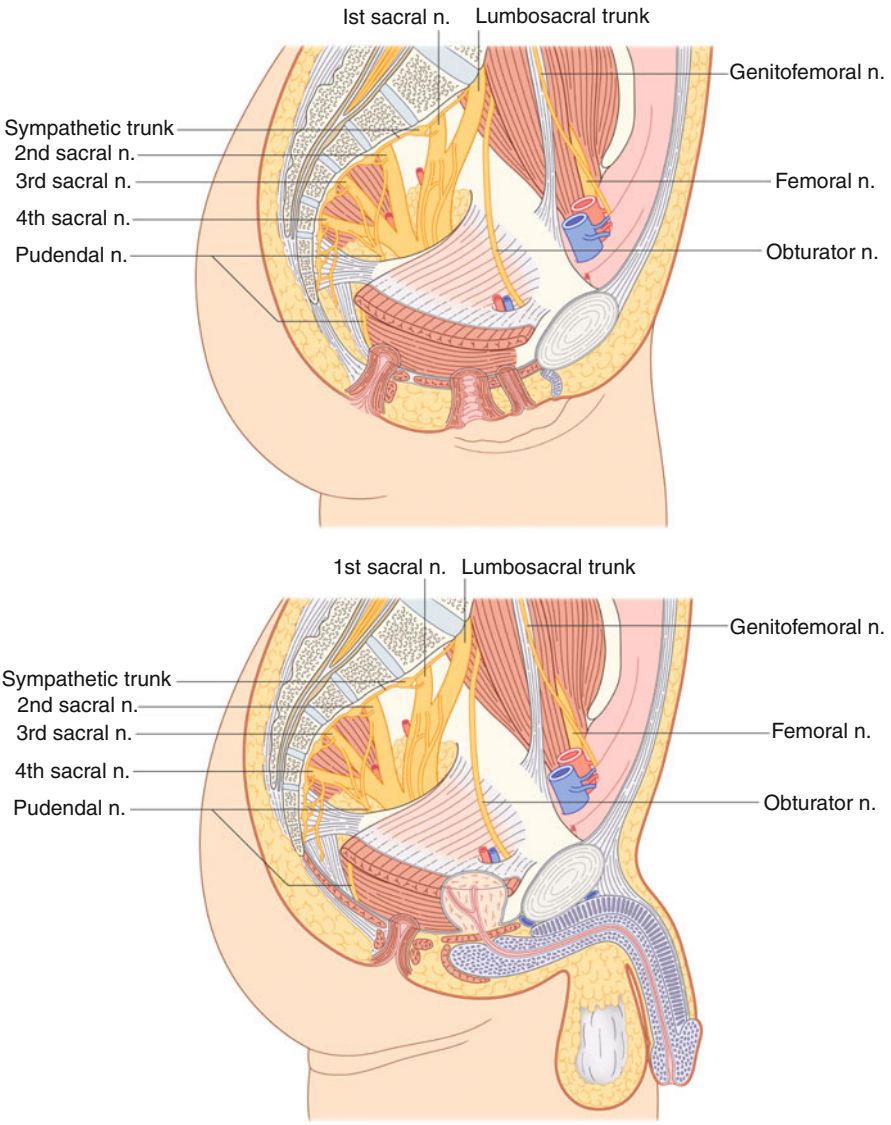


**Fig. 1.21** The relations of the left sacral plexus. (**a**) *Above*: the female pelvis. (**b**) *Below*: the male pelvis

## 1.3 The Autonomic Nervous System

The sympathetic and parasympathetic systems are characterised by having relays between their cells of origin and their terminations: in the case of the sympathetic system the relays are in paravertebral or axial ganglia; in the case of the parasympathetic system they are in or near the organs innervated (Fig. 1.33).


**Fig. 1.22** The left sacral plexus

### *1.3.1 The Sympathetic System*

The pre-ganglionic cells of the efferent fibres of the sympathetic system are in the lateral horn of the grey matter of the spinal cord from the first thoracic to the second lumbar level. Most of the ganglia are in the paravertebral sympathetic chains extending from the top to the bottom of the spinal column; others lie in autonomic plexi in the abdominal cavity. Usually there are on each side two cervical, one cervico-thoracic (stellate), eleven thoracic, four lumbar and five sacral or pelvic ganglia. Pre-ganglionic myelinated fibres enter the cervico-thoracic, thoracic and upper two lumbar ganglia in white rami from the first thoracic to the second lumbar spinal nerve. These fibres relay in the corresponding ganglia or proceed up or down the chain to relay in other ganglia of the chain or in one of the ganglia of the autonomic plexi. The distribution to the spinal nerves is by way of grey rami, which contain unmyelinated fibres, from the corresponding paravertebral ganglia. Fibres pass directly from the autonomic plexi to their destinations. Afferent fibres have their cells in the posterior root ganglia; their sites of relay are not clearly identified.

The sympathetic supply to the head and neck arises mainly from the uppermost three thoracic segments, passes cranially, and relays in the cervical ganglia to be

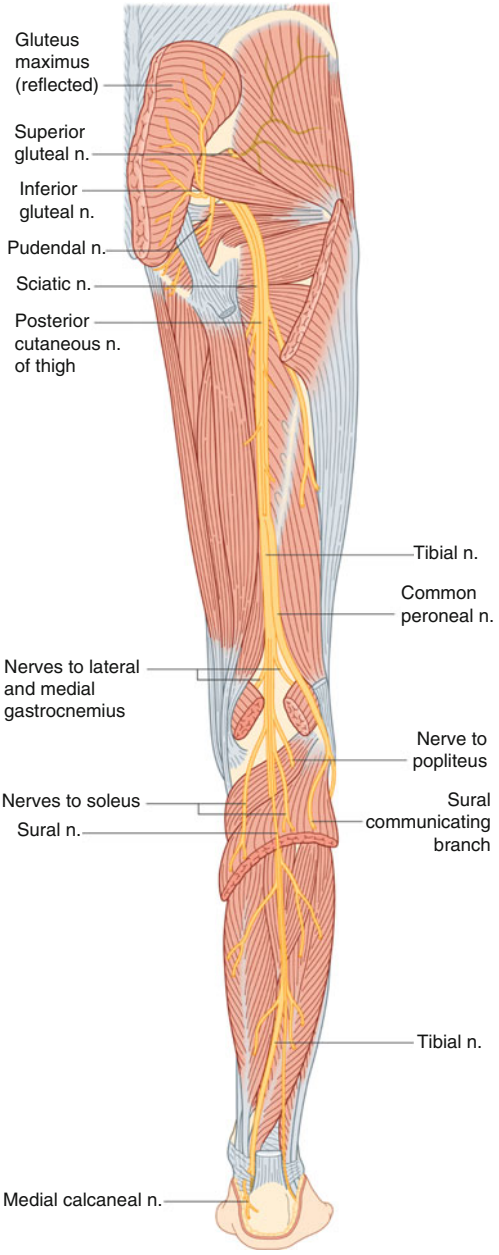


**Fig. 1.23** The right sciatic nerve and its major components in the lower limb

distributed to vessels and sweat glands and in particular to the dilator of the pupil, and the smooth muscle fibres in orbitales and levator palpbrae superioris muscles. Most of the supply to these muscles of the eye arises from the first thoracic segment (Fig. 1.34).

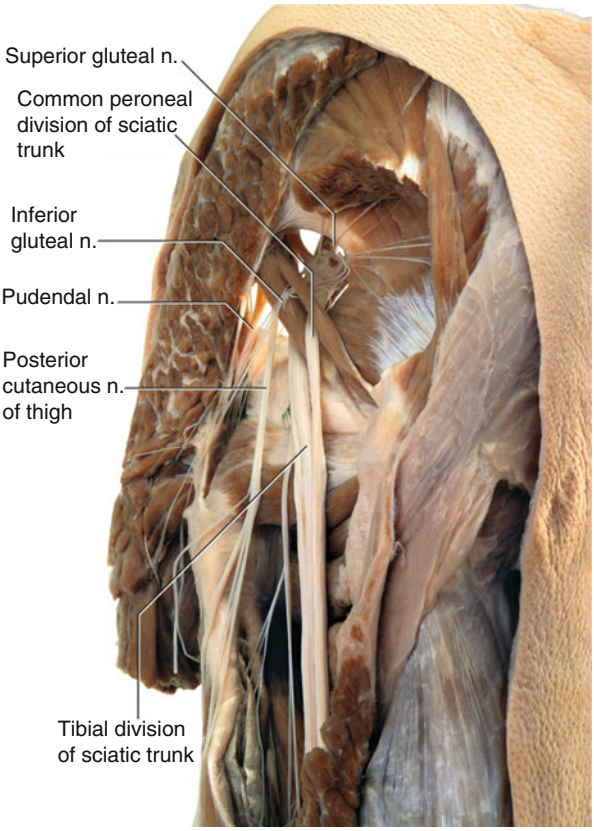


**Fig. 1.24** The right sciatic nerve and its two main components, the common peroneal and tibial nerves. The CPN is quite distinct and in this specimen it passes from the tibial nerve and passes separately through piriformis muscle, a not uncommon variation

The sympathetic supply to the upper limb arises principally from the second to the sixth thoracic segments. Fibres pass up the chain to the middle cervical and cervicothoracic stellate ganglia, where they relay to be distributed by grey rami to the nerves of origin of the brachial plexus.

The sympathetic supply to the lower limbs arises from the lowest three thoracic and uppermost two lumbar segments, fibres enter the first and second lumbar ganglia by white rami, descend in the chain, relay in the lumbar and sacral ganglia and are distributed by grey rami to the lumbar and sacral nerves (Fig. 1.35).

### *1.3.2 The Parasympathetic Nervous System*

The efferent outflow of the parasympathetic nervous system arises from nuclei in the mid-brain and part of the hind brain and the sacral part of the spinal cord. The pre-ganglionic fibres are distributed by the third, seventh, ninth and tenth cranial nerves and by the second to the fourth sacral spinal nerves. From the last arise the pelvic splanchnic nerves (nervi evigentes) which supply the ganglia in which the

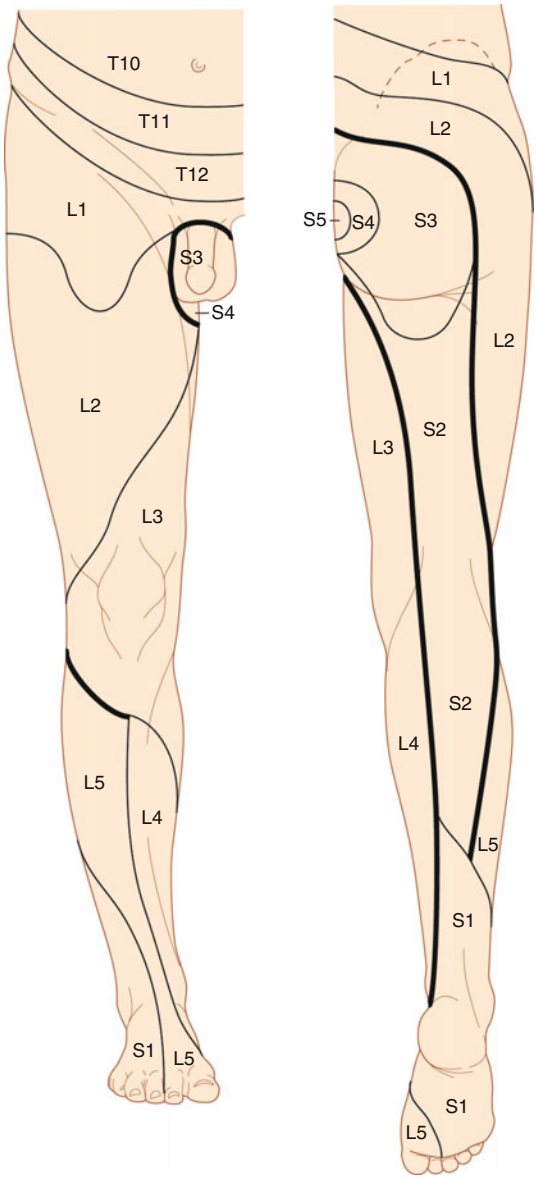


**Fig. 1.25** Approximate distribution of dermatomes on the right lower limb (From *Aids to the Examination of the Peripheral Nervous System*. 4th ed. By kind permission of Dr. Michael O'Brian and Elsevier Ltd)

pre-ganglionic fibres relay are in or near the organs supplied. The effect of parasympathetic activity is inhibitory in the heart, motor to the muscle of the bladder and bowel and dilator in small vessels. The central control of both sympathetic and parasympathetic function is exercised from nuclei in the hypothalamus which themselves receive input from higher centres. The fibres from the hypothalamus almost certainly descend in a column in the lateral part of the white matter of the spinal

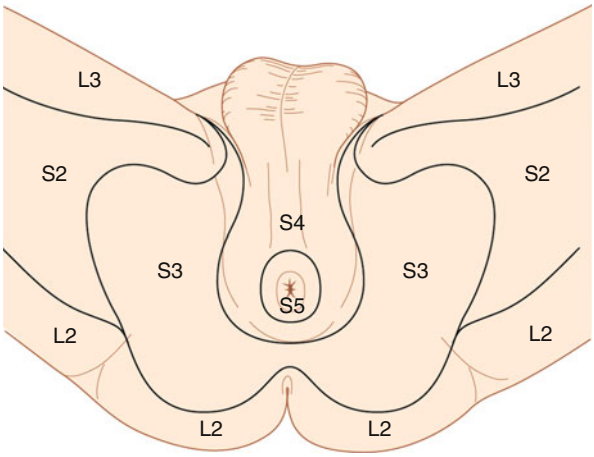


**Fig. 1.26** Approximate distribution of dermatomes on the perineum (From *Aids to the Examination of the Peripheral Nervous System*. 4th ed. By kind permission of Dr. Michael O'Brian and Elsevier Ltd)

cord [27]. Parasympathetic fibres to the papillary and ciliary muscles pass with the oculomotor (III) cranial nerve via the ciliary ganglion, those to the lacrimal, submandibular and sublingual salivary glands travel with the facial (VII) cranial nerve via the submandibular ganglion. Those to the parotid gland are conveyed by the glossopharyngeal (IX) cranial nerve.

The main visceral plexi are the cardiac, pulmonary oesophageal, coeliac, mesenteric and hypogastric. They are fed from the cervical and cervico-thoracic ganglia, from the middle and lower thoracic ganglia (the thoracic splanchnic nerves), from the lumbar ganglia (the lumbar splanchnic nerves) and from the sacral ganglia. Both sympathetic and parasympathetic systems contribute to these plexi, the vagus (tenth cranial) nerve being the principal source of parasympathetic fibres to the chest and abdomen, and the second, third and fourth sacral nerves to the pelvis. The effect of efferent sympathetic activity is to cause sweating, to constrict small vessels and to cause contraction of the arrectores pilarum muscle. The visceral actions are to stimulate the action of the heart and to cause sphincteric contraction (see Sect. 1.10.6).

## 1.4 Nerves at Risk from Musculo Skeletal Injury

The anatomical arrangements of some of the peripheral nerves make them particularly vulnerable to damage from skeletal injury. The sacral nerves are particularly at risk in fractures involving the sacral foraminae. The proximity to bone of the main nerves at the elbow render all three vulnerable to skeletal injury. The sciatic trunk is damaged by the posterior displaced head of the femur.

The circumflex nerve runs in loose fatty tissue in the axilla, but then is captured, with the posterior circumflex vessels, in a tunnel formed by the fascia of the subscapularis muscle cranially, the teres major muscle caudally and the coraco-brachialis muscle laterally, at the entrance to the quadrilateral tunnel. The neurovascular

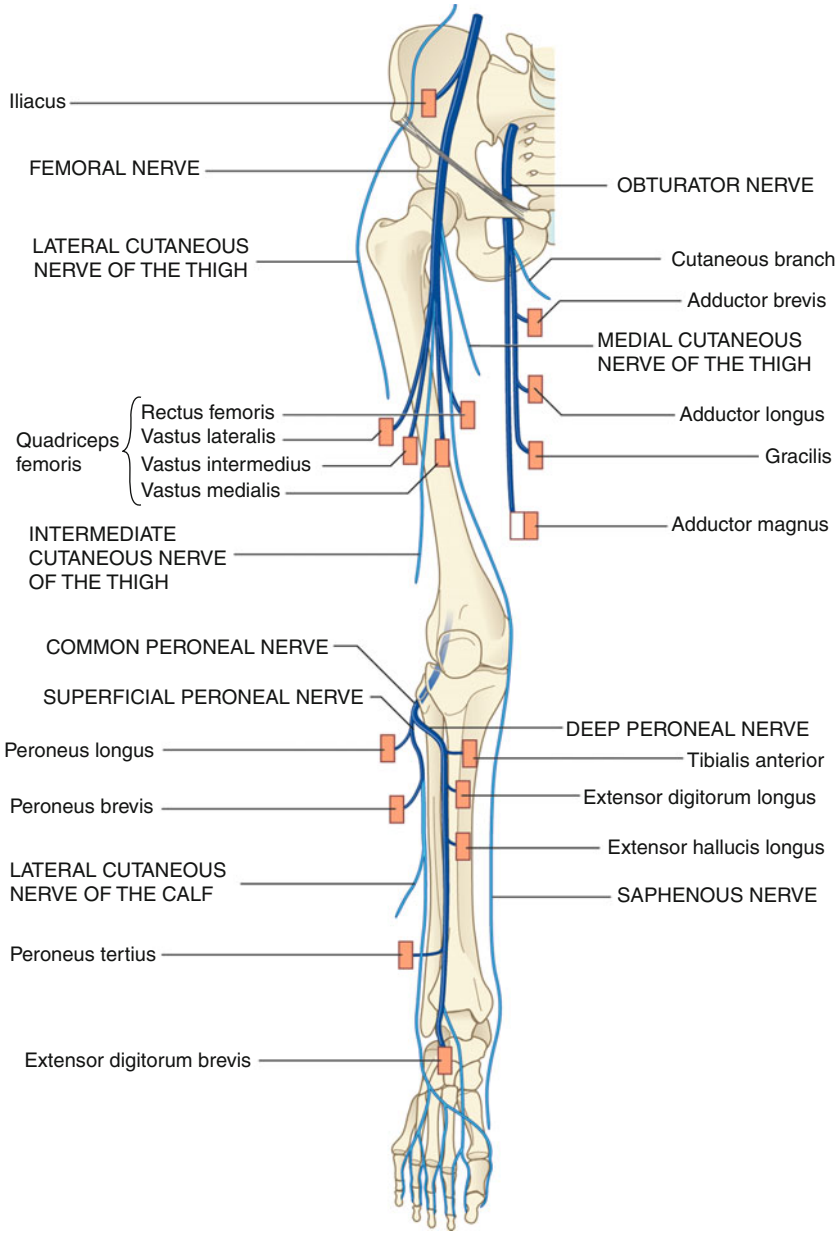


**Fig. 1.27** The nerves on the anterior aspect of the right lower limb (From *Aids to the Examination of the Peripheral Nervous System*. 4th ed. By kind permission of Dr. Michael O'Brian and Elsevier Ltd)

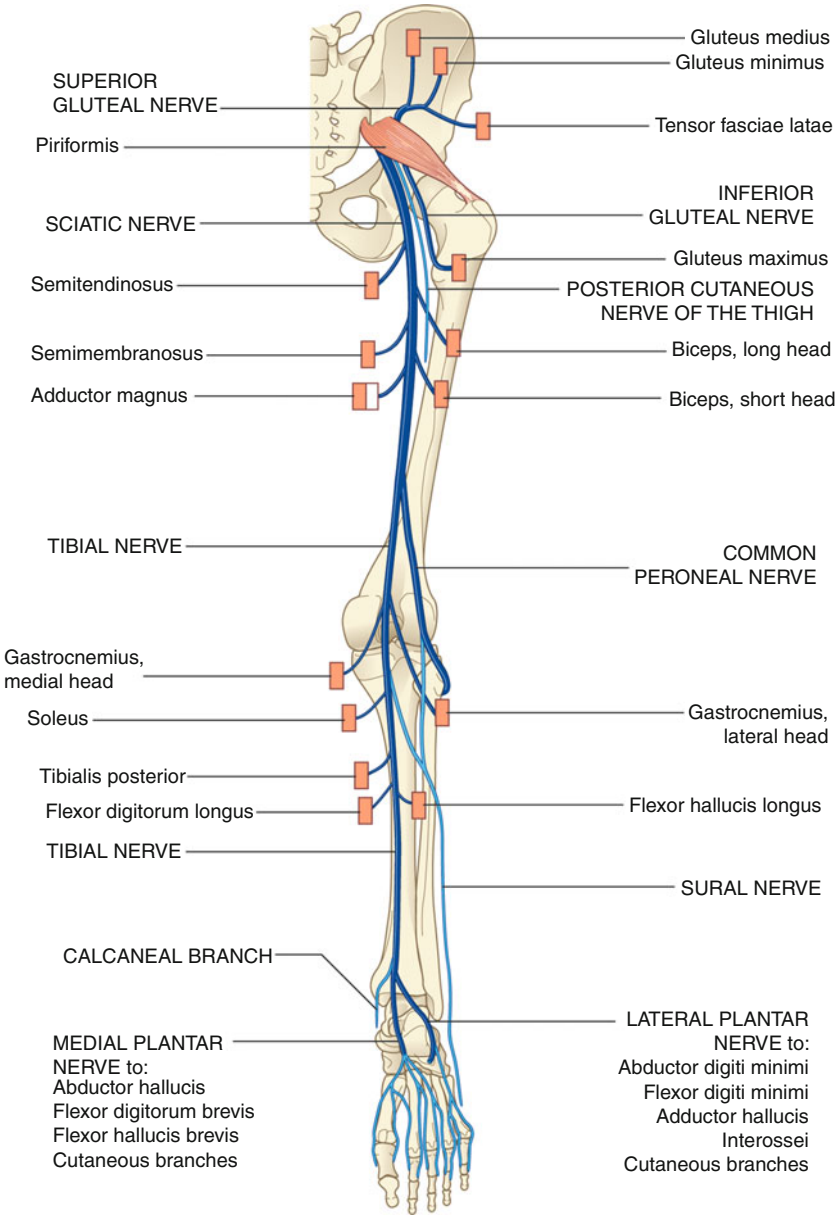


**Fig. 1.28** The nerves on the posterior aspect of the right limb (From *Aids to the Examination of the Peripheral Nervous System*. 4th ed. By kind permission of Dr. Michael O'Brian and Elsevier Ltd)

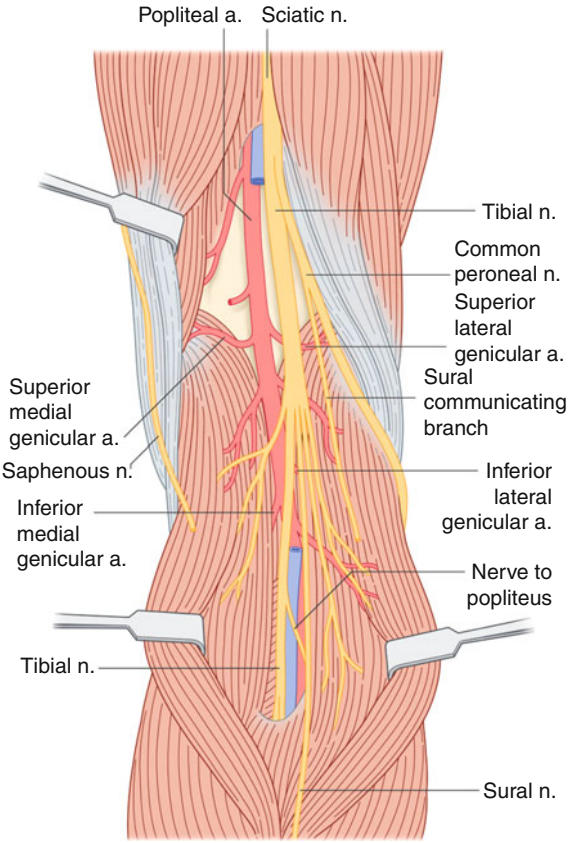


**Fig. 1.29** The right popliteal fossa

bundle is relatively fixed here and is at risk by forward displacement of the head of humerus and bleeding from the posterior circumflex vessels strangles the nerve. The radial nerve is at risk from fractures of the shaft of the humerus between the two relatively fixed points of the nerves to the lateral head of triceps and the tunnel through the inter muscular septum. The common peroneal nerve, which passes above or through the piriformis in as many as 30 % of cases, is tethered above in relationship to the piriformis and below at the neck of the fibula. The fascia surrounding the biceps femoris muscle and tendon sweeps around to embrace the nerve. The deep peroneal nerve passes rather acutely forward to enter the anterior compartment of the leg.

Sleeves of fascia surround main nerves and main vessels in some regions, an arrangement which predisposes the nerve to injury from ischaemia or compression or both, from bleeding. The anterior primary rami of C7, C8 and T1 are enclosed in quite a rigid space after they enter the posterior triangle of the neck. This is bounded, posteriorly, by the dorsal part of the first rib, the transverse processes of the cervical vertebrae and by the fascia of the levator scapulae muscle. The nerves are embraced by the scalenus anterior and scalenus medius muscles, both of which are invested in

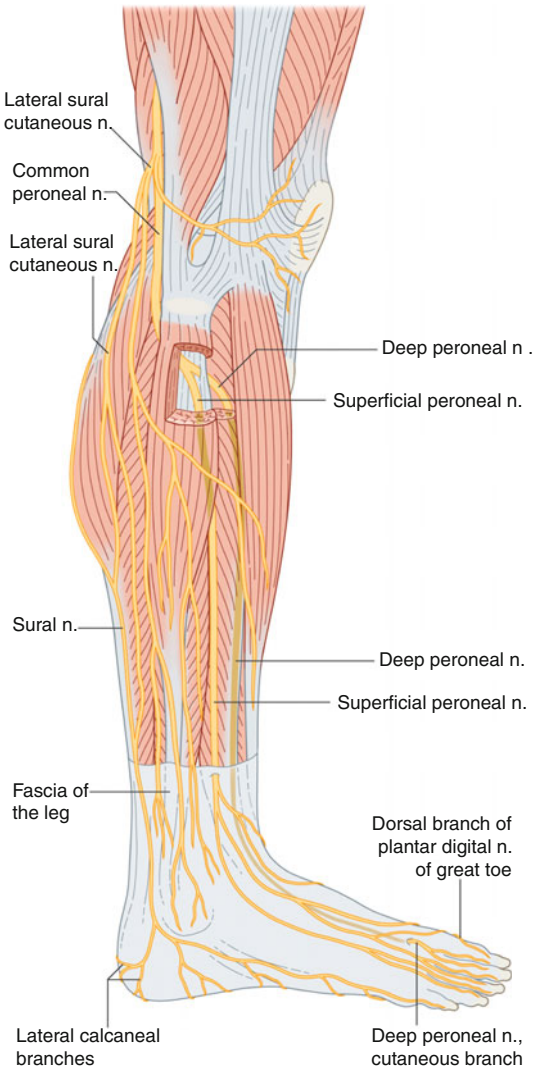


**Fig. 1.30** The course relations and branches of the right common peroneal nerve

an unyielding fascia. This is one envelope of the prevertebral fascia which also serves to bind the phrenic nerve down to the anterior face of scalenus anterior. The pre vertebral fascia is particularly well developed in front of the vertebral column and also at the base of the posterior triangle where it envelops C7, C8 and T1, the phrenic nerve, the cervical sympathetic chain, and the subclavian and vertebral arteries. Infusion of relatively large volumes of fluid, from 10 to 20 mL, deep to the prevertebral fascia for the purpose of inducing regional block may cause tamponade of the radicular vessels which enter the spinal canal and contribute to the anterior spinal artery.

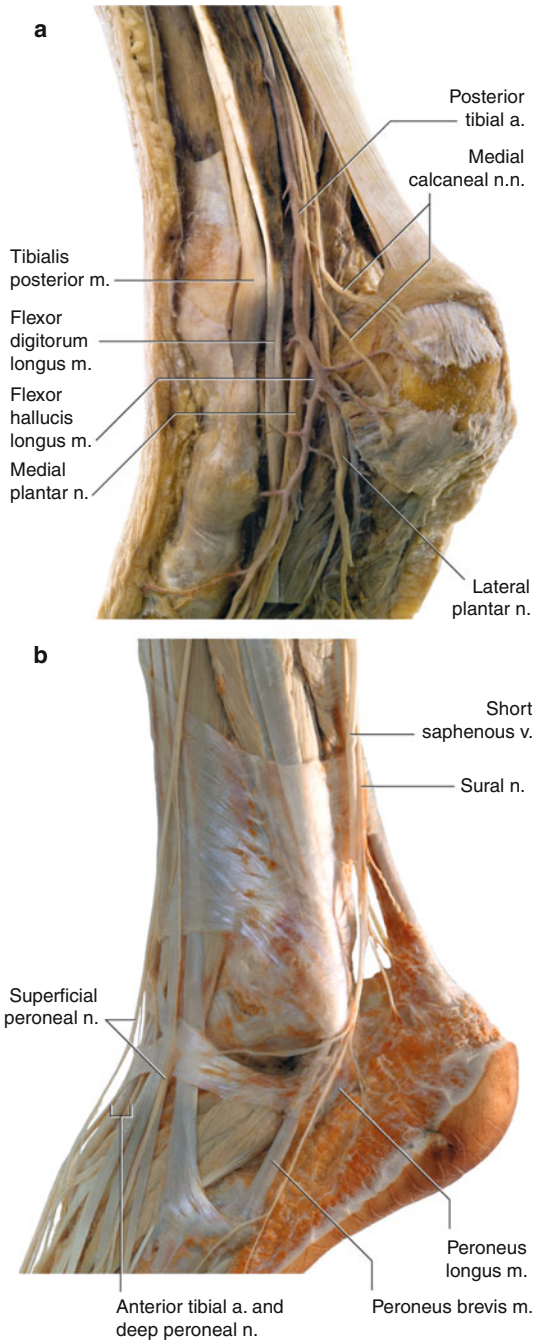


**Fig. 1.31** (**a**) *Above*: the medial aspect of the right ankle. (**b**) *Below*: the lateral aspect of the left ankle and heel

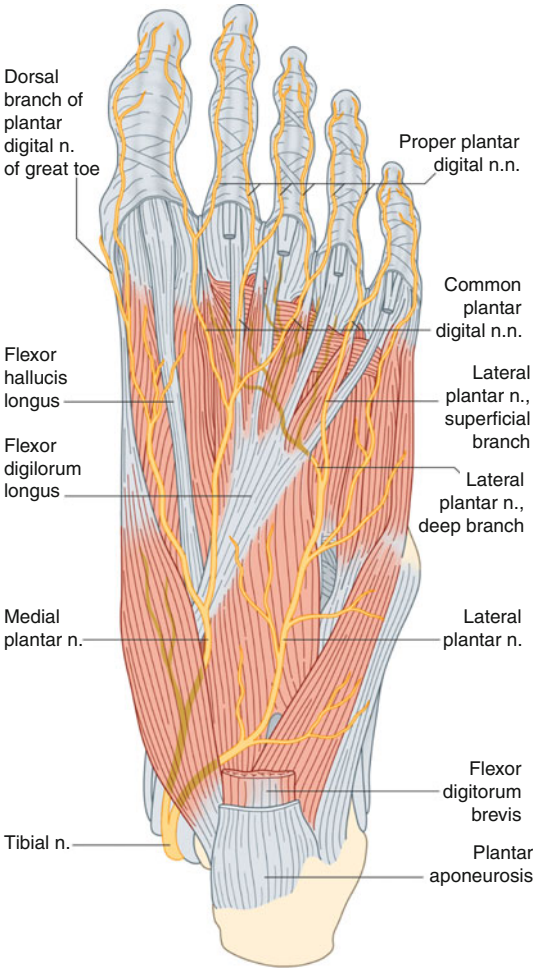


**Fig. 1.32** The sole of the left foot

The medial brachial fascial compartment extends from the axilla to the elbow, and is bounded by the tough medial intramuscular septum and the axillary sheath. Bleeding into this compartment is responsible for the majority of infraclavicular plexopathies following regional block and possibly for many of the neurovascular injuries which result from closed or penetrating missile injuries into this region. The anterior interosseous nerve and its accompanying artery may be damaged by compression because of swelling in the deepest part of the flexor compartment of the forearm (Fig. 1.36). The ulnar nerve is accompanied by the ulnar artery, in a discrete fascial compartment in the distal two thirds of the forearm. The deep peroneal nerve is accompanied by the anterior tibial artery, an end artery, throughout most of

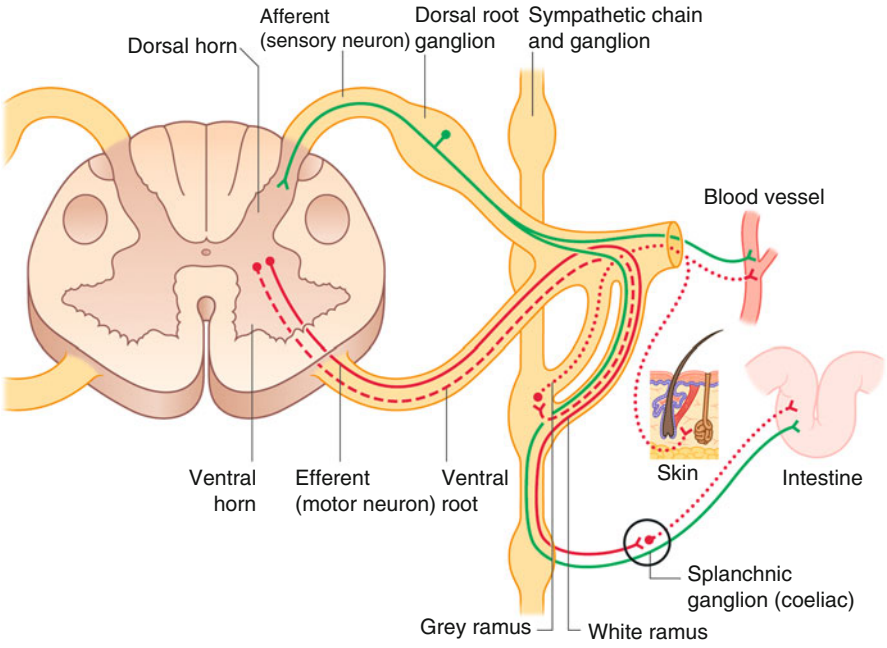


**Fig. 1.33** Efferent (*red*) and afferent (*green*) autonomic paths in the spinal cord and ganglionic chain

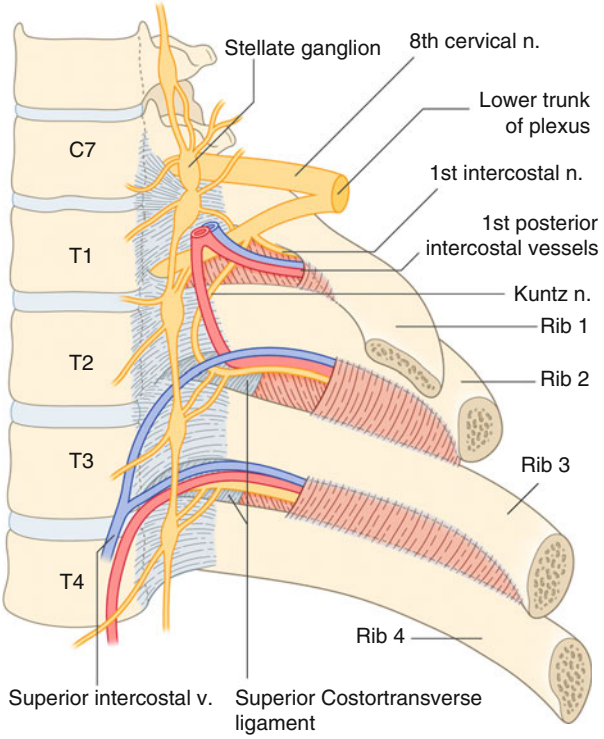


**Fig. 1.34** The relations of the cervico thoracic (stellate) ganglion

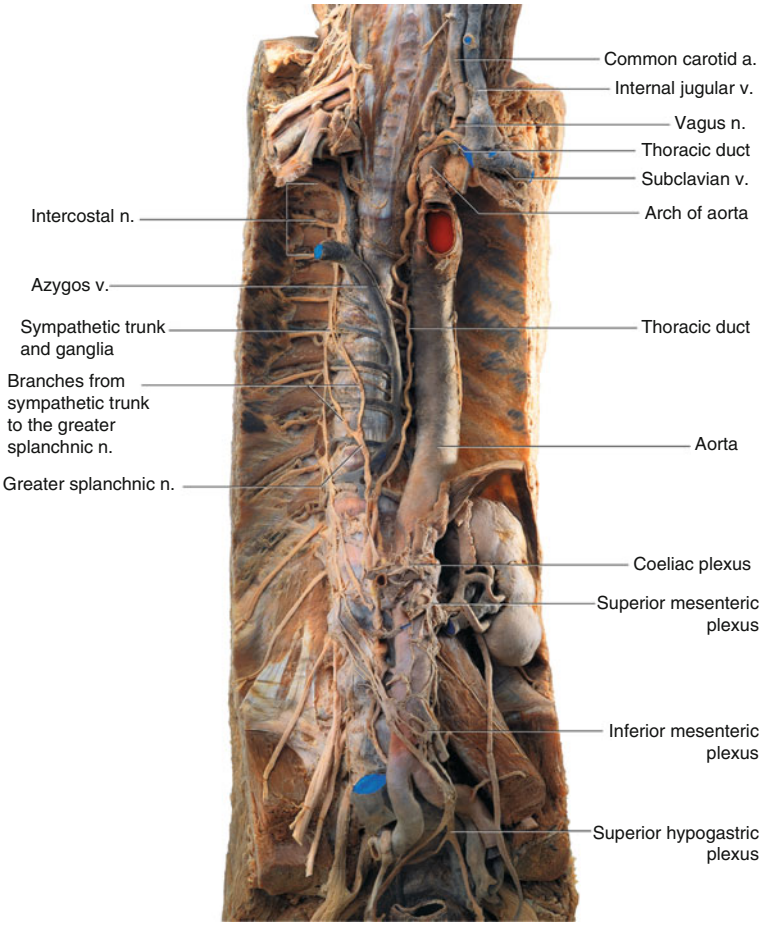


**Fig. 1.35** The autonomic nerves in the chest and abdomen

the anterior compartment of the leg (Fig. 1.37). The tibial nerve is accompanied by the posterior tibial artery in the distal one half of the leg in a sheath of fascia similar to the arrangements for the ulnar vessels and nerve. The femoral nerve is damaged by haematoma where it passes deep to the thick fascia over the iliacus muscle. The nerve is especially at risk from bleeding into the femoral triangle (Fig. 1.38).

## 1.5 The Neurone

The essential component of the system is the neurone, the nerve cell body with its dendrites and its prolongation, the axon. The neurones are the only elements in the nervous system which conduct nervous impulses. There is no continuity between

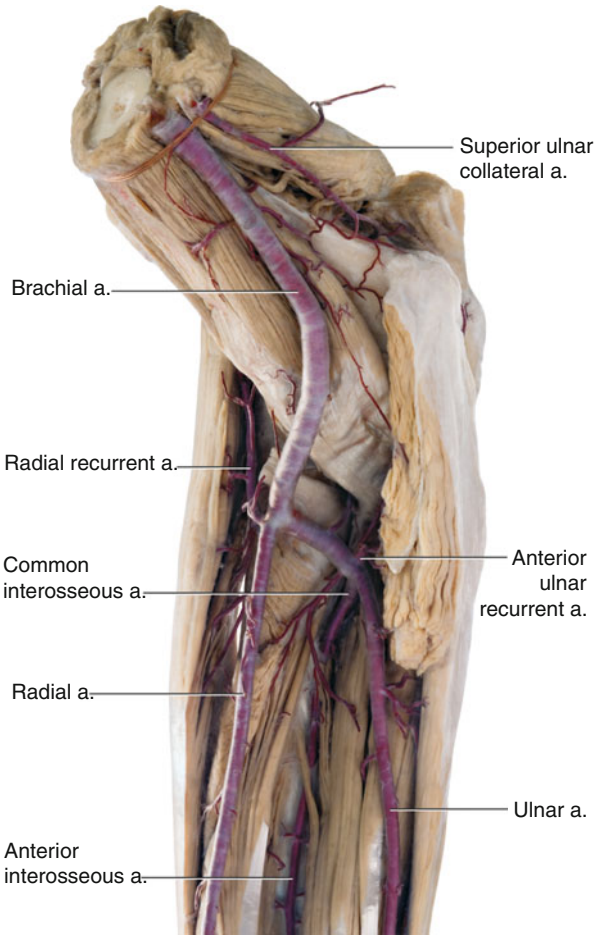


**Fig. 1.36** The collateral vessels at the elbow accompany the nerves. The specimen is the left elbow

nerve cells: the termination of the axon on a cell is no more than a contact, the synapse (Fig. 1.39). The neurone is a structural unit; it also behaves as a trophic unit; and it is dependant upon trophic support during maturation and after injury to the nerve. This support is provided by the neurotrophins.

### *1.5.1 The Neurotrophins*

Windebank and MacDonald [45] 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. Interruption of this system by division of the nerve contributes to cell

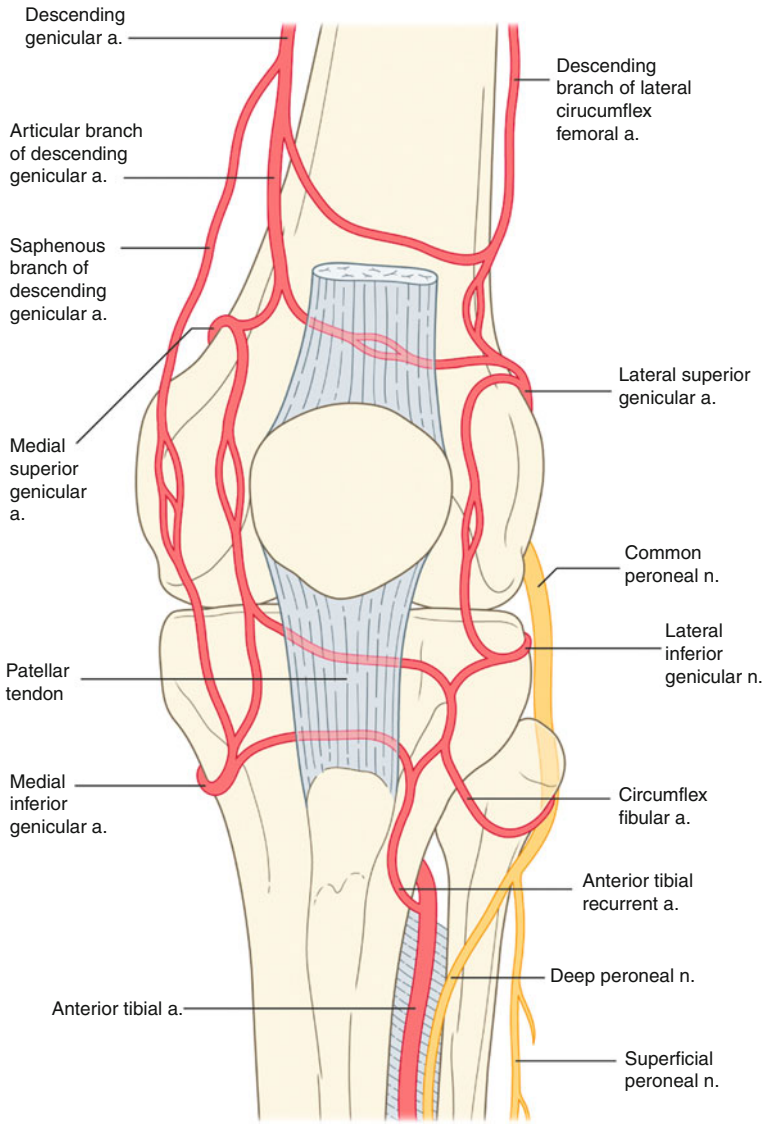


**Fig. 1.37** The collateral circulation about the knee is poor. The drawing shows the left knee

death amongst central neurones, an effect which is more severe in the immature nervous system and after axonotomy close to the neuronal cell bodies. Three major families of growth factors are recognised [6, 45].

1. The classic neurotrophins include nerve growth factor (NGF), brain derived nerve factor (BDNF) and the neurotrophins 3–7 (NT3, 4, 5, 6, 7) (Fig. 1.40). NGF is produced by cells including keratinocytes, melanocytes, vascular and smooth muscle cells, testis and ovarian cells, and endocrine and exocrine tissue.

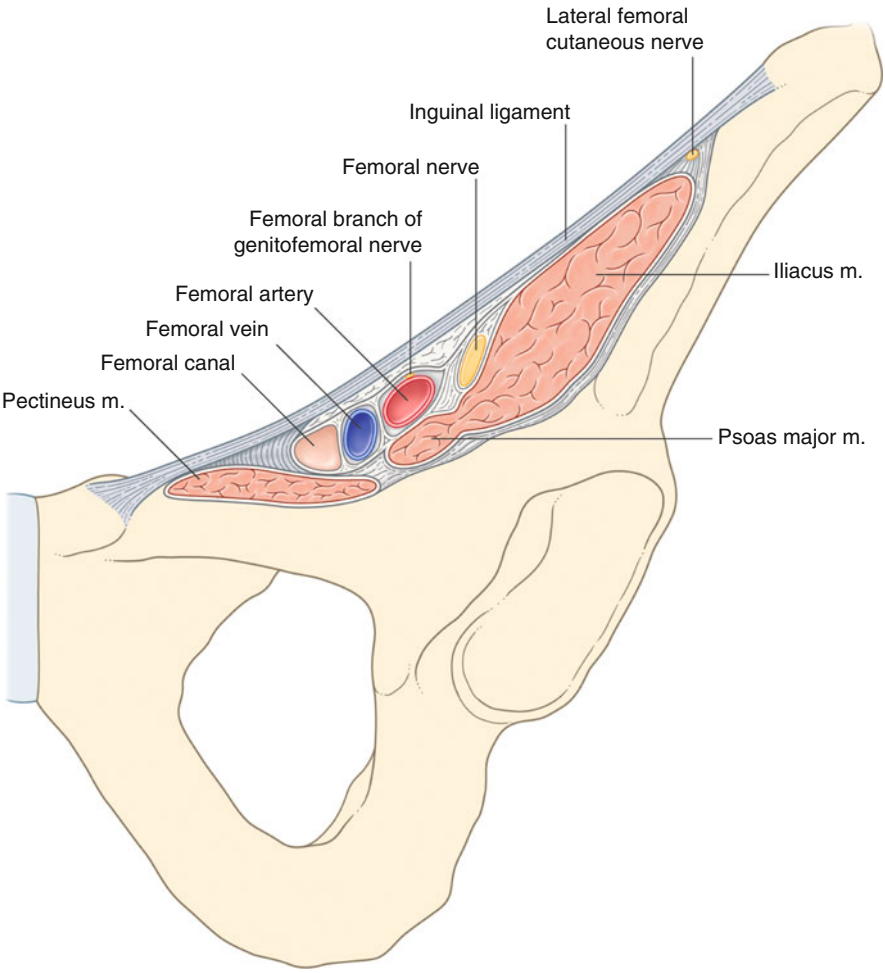


**Fig. 1.38** The femoral nerve and vessels deep to the inguinal ligament. The drawing shows the left inguinal region

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, synthesise and release NGF. Mice experimentally engineered to be deficient in TrkA do not develop thermoceptive or nociceptive neurones. Administration of NGF induces thermal and mechanical hyperalgesia, it is upregulated by inflammation and plays a key role in the pathophysiology of nociception [2]. BDNF apparently supports the development of motor neurones and their survival after axonotomy. Neurotrophin 3(NT3) is mainly expressed in muscle spindles, Merkel cells and the Golgi tendon organs.

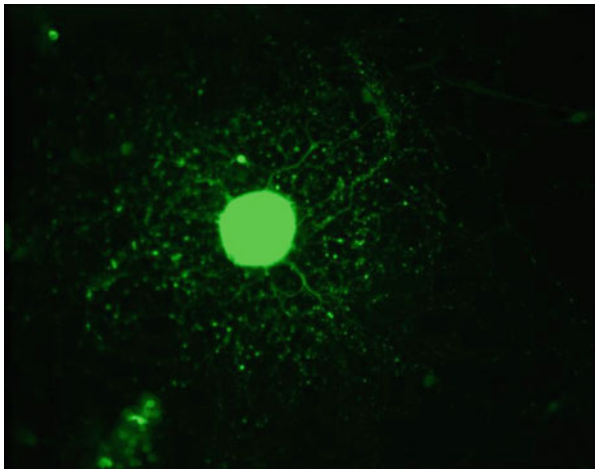

**Fig. 1.39** Cultured human dorsal root ganglion neurone immunostained for Gap 43 (growth associated protein) showing the cell body and neurites arising from the cell body ×40

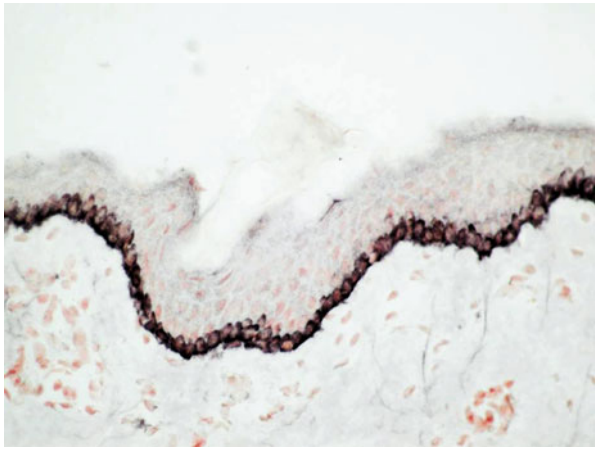

**Fig. 1.40** Nerve growth factor (NGF) immunostaining of basal epithelial cells in human glabrous arm skin ×40

This neurotrophin specifically binds to tyrosine receptor kinase C (TrkC). Mice genetically engineered to lose this receptor lack proprioceptive organs.

2. Other neurotrophins are synthesised 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 and also the tyrosine kinase receptor c-Ret (Fig. 1.41). The ciliary neurotrophic factor (CNTF) binds to its receptor and also the leukaemia inhibitory factor receptor beta (LIFR β). 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.

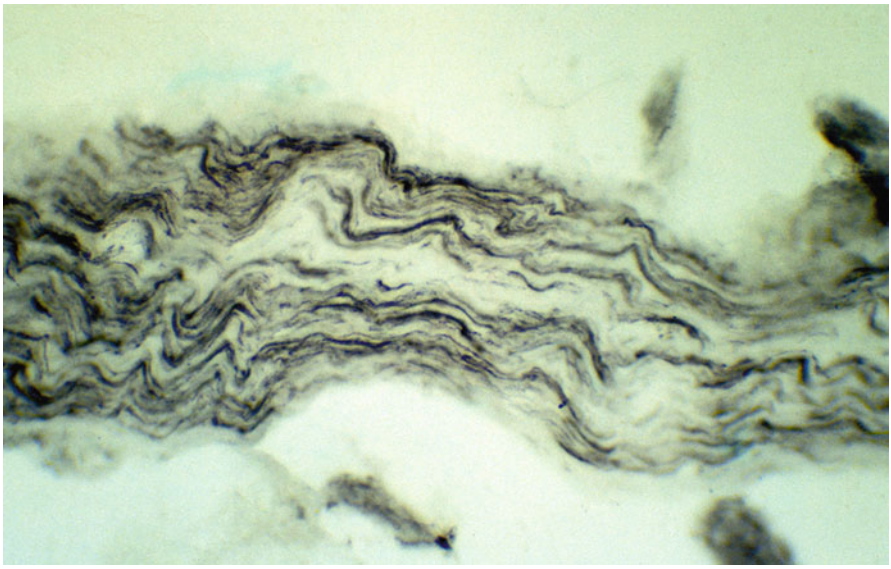

**Fig. 1.41** GDNF immunostaining in Schwann cells of healthy human sural nerve ×150

## 1.6 The Nerve Fibre

In the central nervous system the neurons 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. 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 extension of CNS structure into the base of the rootlet is cone-shaped [14] (Fig. 1.42). The axolemma and the basal lamina surrounding the Schwann cell – axon unit extends into the spinal cord and remains continuous through the TZ. In preganglionic injuries of the brachial plexus the spinal nerves are usually torn at the level of the roots or rootlets [32].

Although most of the fibres of the ventral roots have their cells in the ventral horn of the grey matter there are also myelinated afferent fibres which have cell bodies in the dorsal root ganglion (DRG) [31] (Fig. 1.43). The fibres of the dorsal roots have their cell bodies in the dorsal root ganglion and are unipolar in form with a single axon and no true dendrites. Each axon bifurcates into peripherally and centrally directed axons after leaving the cell body. The centrally directed branches are of smaller calibre than the peripheral ones and enter the spinal cord along the posterolateral sulcus. In the cord the fibres bifurcate into ascending and descending branches. Both branches of the smaller fibres in the lateral part of the root reach the dorsal horn of the grey matter, where they terminate having traversed between three and five segments. The branches of the larger fibres in the medial part of the root, 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

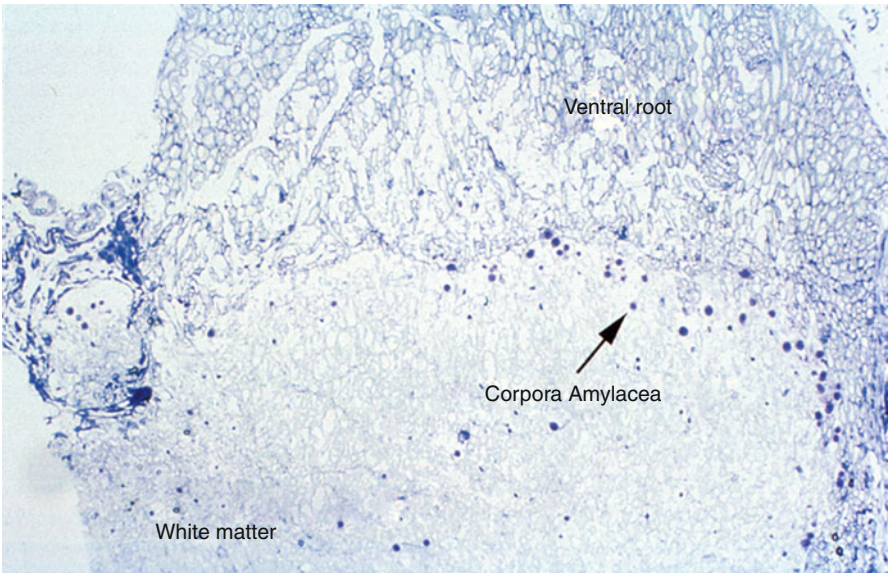


**Fig. 1.42** Morphology of the normal human spinal cord. A transverse light microscopic section at C7 showing a ventral root. A single large root in transition is demonstrated with central islands of autolysed glia. Numerous corpora amylacia are seen on the central side of the transitional zone. *Toluidine blue* ×100 (Courtesy of Editor *Journal of Bone and Joint Surgery* (British))

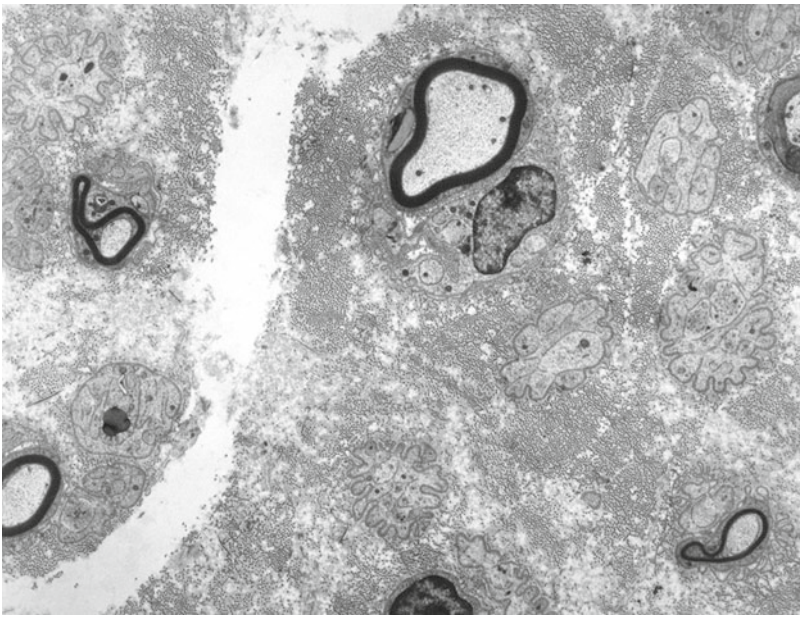

**Fig. 1.43** Afferent and efferent fibres in the ventral root. Large healthy myelinated and unmyelinated fibres in the ventral root of the eighth cervical nerve avulsed from the spinal cord 6 weeks previously. The myelinated efferent fibres have undergone Wallerian degeneration and there is much collagenisation ×5,000 (Electronmicroscopic study EM)

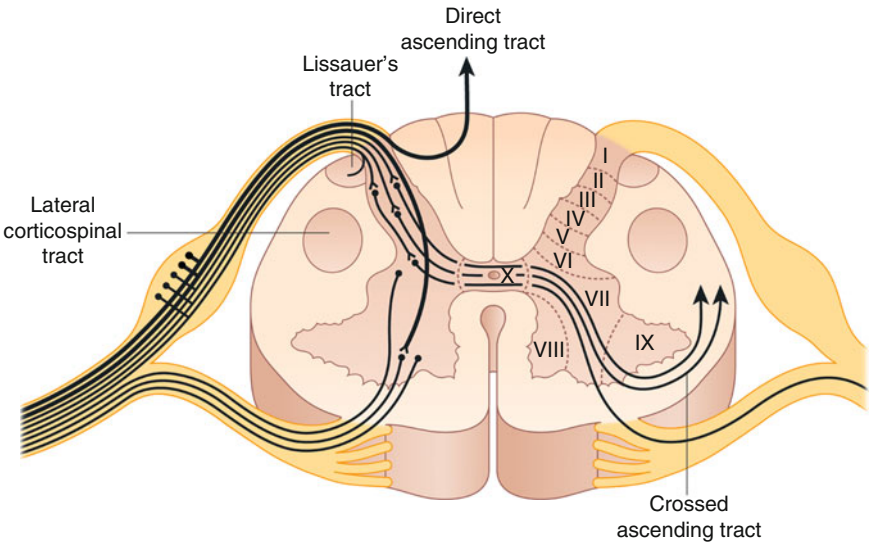


**Fig. 1.44** The paths of the afferent fibres entering and efferent fibres leaving the spinal cord. Note (*right*) the laminae of the grey matter

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. 1.44).

### *1.6.1 The Axon*

The axon is a column of neuronal cytoplasm, the axoplasm enclosed by a cell membrane, the axolemma. The axoplasm is a fluid cytosol containing formed elements, notably the cytoskeleton consisting of neurotubules, neurofilaments and matrix. In addition, there are mitochondria, axoplasmic reticulum, lamellar and multivesicular bodies, and membranous cisterns, tubes and vesicles. The cytoskeleton provides the apparatus for axoplasmic transport. The axolemma is a three-layered unit membrane about 8 nm thick. It conveys signals between the neurone and its Schwann cells which control their proliferative and myelin producing functions [4] (Fig. 1.45).

### *1.6.2 Axonal Transport*

Axonal transport is a system of intra cellular motility which enables nerve cells to deliver proteins membrane components and neurotransmitters, to the periphery,

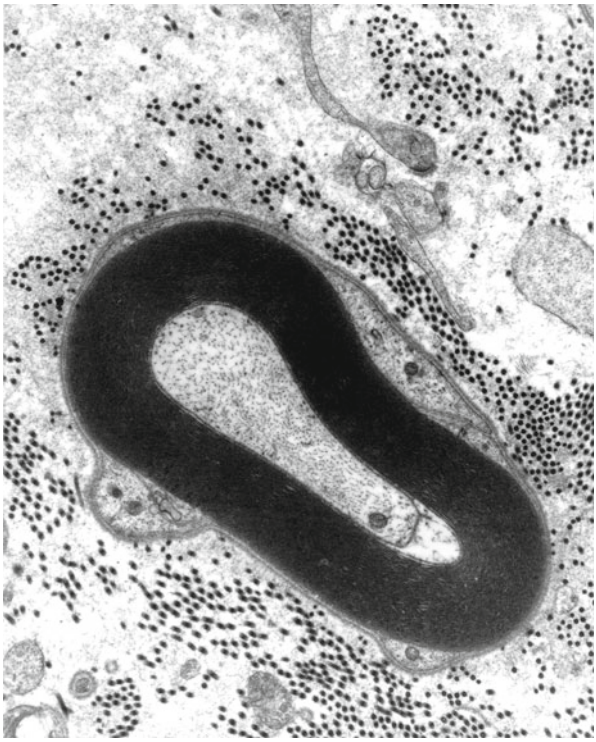

**Fig. 1.45** A large myelinated nerve fibre. It lies within the posterior root of the seventh cervical nerve which had been avulsed from the spinal cord 6 weeks previously. The axoplasm contains neurofilaments and a few neurotubules. The Schwann cell cytoplasm it is enveloped by a well defined basal lamina. There are processes from fibroblasts from within the endoneurium ×16,200 (EM)

and to return chemical signals, materials for recycling and some neurotrophins to the cell body. Two forms of transport, fast and slow, are recognised [7]. All systems are ATP dependant, and the microtubules are critical for fast axonal transport. The process is sensitive to temperature; it is sensitive to deprivation of oxygen.

The fast retrograde (centripetal) component conveys material to the cell body in microvesicles at the rate of 150–300 mm a day. The fast orthograde (centrifugal) component transports materials from the cell body at a rate of 200–400 mm/day.

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. There are two distant components [7].

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

The rate of transport of the SCa component is about the same as the rate of peripheral regeneration after axonotomy. 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.

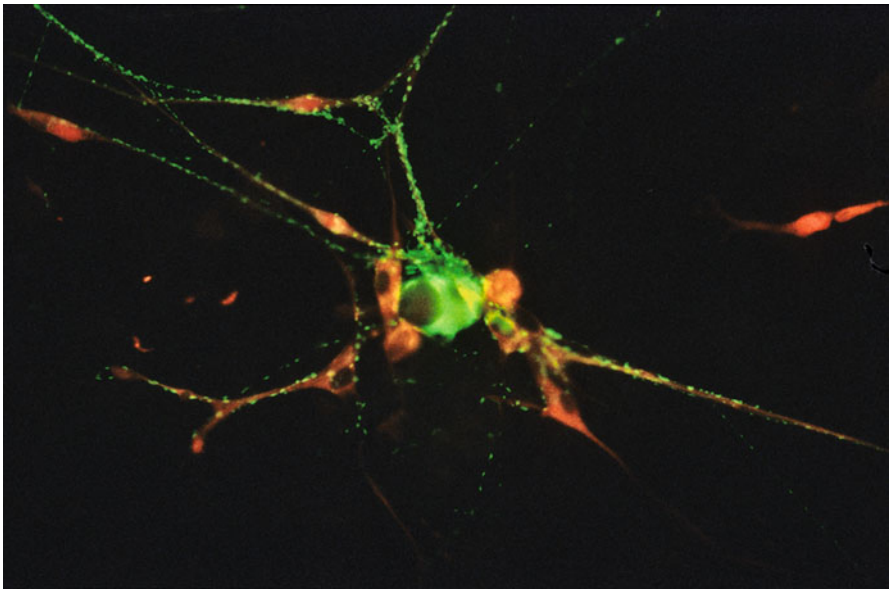

**Fig. 1.46** In vitro cultures of DRG neurones and Schwann cells. The Schwann cells are immunostained for S100 (*red*) the neurones for nerve growth factor (*green*) ×50

### *1.6.3 The Glial Cells of the Peripheral Nervous System*

The glial cells of the peripheral nervous system are essential for the development, maturation, survival and regeneration of the neurone. The myelinating and non myelinating Schwann cells are the main peripheral glial cells. Others 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. About 80 % of nuclei within the endoneurium of a normal peripheral or spinal nerve root are Schwann cells, 10 % are fibroblasts, endogenous macrophages account for between 2 and 9 %. Whilst mast cells are also seen their function is not well understood.

*The Schwann Cells* arise from the neural crest, from the same tissue that differentiates into peripheral neurones; they provide essential trophic support to the neurone during development and regeneration [18] (Fig. 1.46).

The most important component of the basal lamina is laminin which interacts with receptors including the integrins in the plasma membrane of the Schwann cell. Mice genetically engineered to produce defective laminin or a defective receptor for laminin develop profound nerve pathology and muscle dystrophy. During myelination Schwann cells radically transform their phenotype in response to signals from the larger axons.

The smaller non myelinated fibres are contained in bundles by columns of Schwann cells (Fig. 1.47).

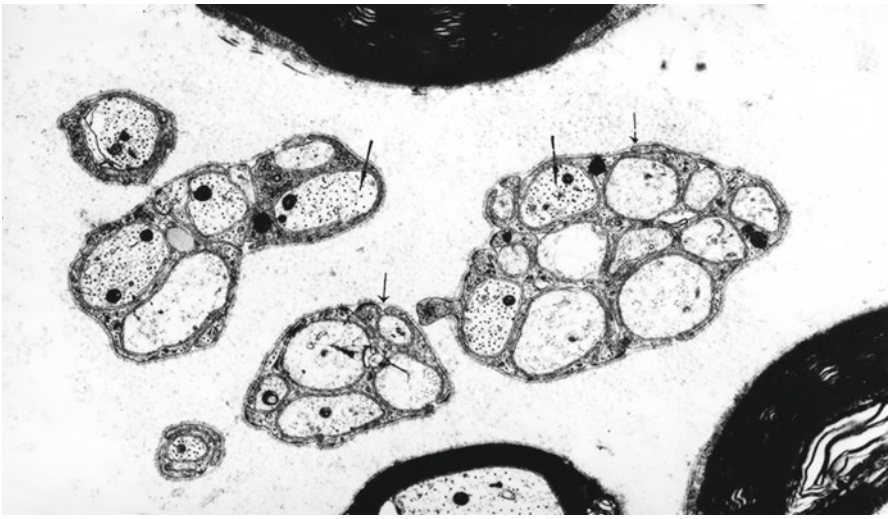

**Fig. 1.47** Clusters of unmyelinated axons (*bold arrows*), enveloped by Schwann cell cytoplasm. *Light arrows* indicate basal lamina and Schwann cells ×26,220 (EM)

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. 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. It is 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 organised 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.

### *1.6.4 The Myelin Sheath*

The diameter of the axon is one important factor which determines whether the Schwann cells will lay down a myelin sheath around it. The multilamellar sheath has a high lipid content and some protein components [40]. 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. Myelin basic protein (MBP) accounts for 5–15 % of myelinated proteins. The myelin associated glycoprotein (MAG), which forms

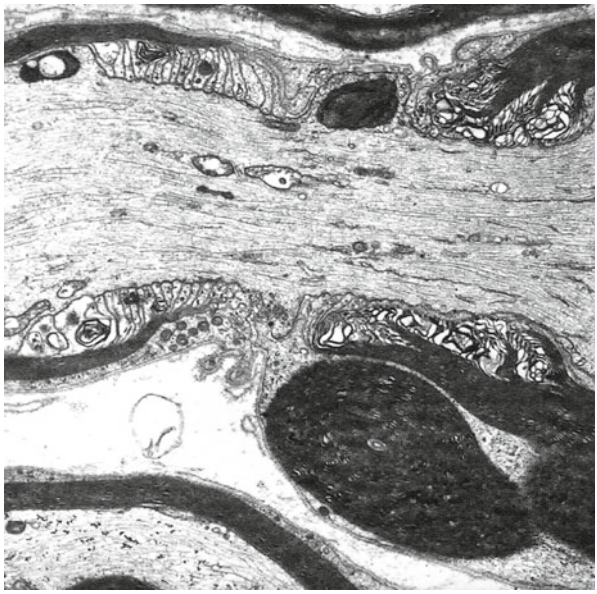

**Fig. 1.48** Longitudinal section through a node of Ranvier, showing a remyelinated heminode (*left*) adjacent to a normal heminode (*right*). Compare the complexity of the paranodal fingers of the normal myelin sheath with the simple arrangement of the paranodal loops of the thinner remyelinated sheath ×5,000 (EM)

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. The myelin sheath is traversed by cytoplasmic channels – the incisures of Schmidt-Lanterman. *The nodes of Ranvier* are short, about 1 μm in length and the axon here is constricted, 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, King and Rydmark [4] characterise the node thus: "these parts of the myelinated nerve fibres; the paranode-node-paranode (PMP) regions; constitute, structurally as well as functionally, the most spectacular parts of a myelinated nerve fibre". The PMP regions are responsible for the generating and propagation of the action potential and they are the centres for activity in the early phases of Wallerian degeneration and collateral sprouting (Figs. 1.48 and 1.49).

### *1.6.5 Conduction*

The special property of the nerve fibre is that of conducting a signal in the form of a propagated action potential This 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, −80 mV, as potassium ions flow out. The action potential is evoked by a stimulus

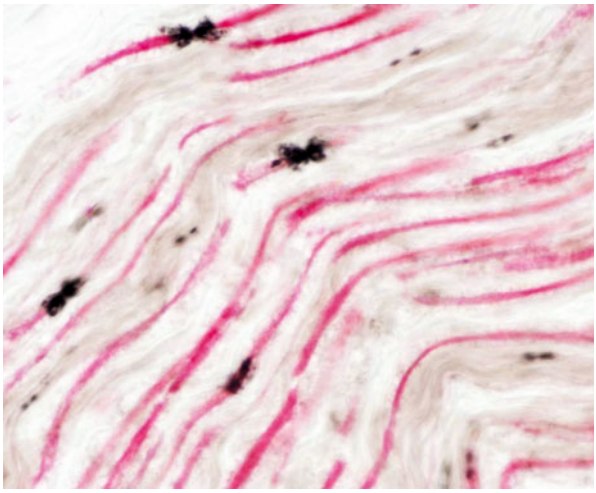

**Fig. 1.49** Double immunostaining of sural nerve showing nodes of Ranvier (*black*) stained with antibodies to junction adhesion molecule (JAM-c) and axons (*red*) stained with antibodies to neurofilaments ×40

which exceeds threshold by the all or nothing law; 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 unmyelinated fibre, a wave of depolarization 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 [37] likens this to: "a flame moving along a fuse. Just as each segment of the fuse is ignited by its upstream neighbour, each segment of axon membrane is driven to threshold by the depolarization of neighbouring 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 neighbouring, downstream, non depolarized membrane, and the cyclic propagation of the action potential is completed".

In the myelinated fibre the high resistance and lower capacitance of the myelin sheath limits depolarisation to the membrane of the axon at the node, so that current is directed towards the next node, exciting it in turn. The action potential jumps from node to node (saltatory conduction) which greatly increases the conduction velocity. The calibre of myelinated axons varies from 0.4 to 1.25 μm that of myelinated fibres from 2 to 22 μm. The largest, fastest conducting elements are the myelinated fibres of around 20 μm diameter concerned with somatic afferent and efferent activity; the smallest and slowest conducting are the fibres of around 1 μm diameter that subserve autonomic activity and delayed pain sensibility.

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

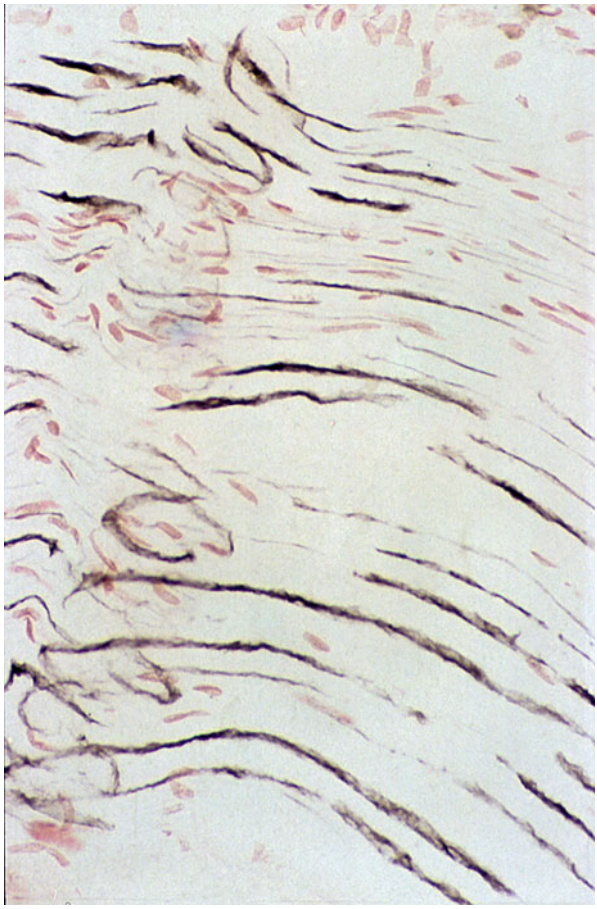

**Fig. 1.50** Sodium channel staining normal sural nerve ×40

### *1.6.6 The Basis of the Action Potential: Ion Channels*

In 1952 Hodgkin and Huxley [19] 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, now known as voltage gated ion channels. These are like membrane lodged proteins that mediate rapid ion flux ($10^6$ ions/s) across cell membranes [9]. Sodium and potassium ion channels are fairly evenly distributed along the axon membrane of nonmyelinated fibres. The sodium channels are densely concentrated at the nodes of Ranvier in the myelinated nerve fibres, whereas the potassium channels are concentrated in the axon membrane at the juxta paranode (Fig. 1.50). 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

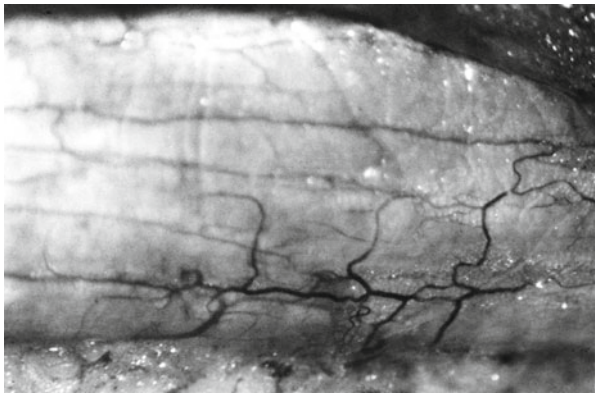

**Fig. 1.51** The extrinsic epineurial vessels of the ulnar nerve ×40

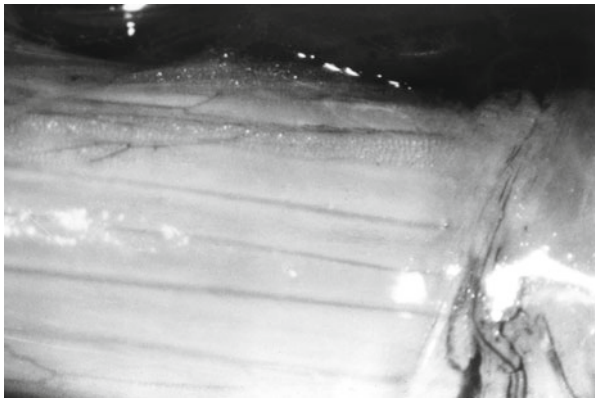

**Fig. 1.52** The bundles and epineurial vessels of the ulnar nerve after displacing the adventitia ×40

may unmask the potassium ion channels to such an extent that prolonged conduction block ensues. Demyelination is bound to lead to slowing of conduction and eventually to conduction block. Anoxia blocks conduction within 1 h.

## 1.7 The Peripheral Nerve Trunk

A normal peripheral nerve trunk exposed at operation is enveloped in a well defined translucent envelope. This is the external epineurium (Fig. 1.51). 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. 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. 1.52). 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 vascularised 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.

### *1.7.1 The Connective Tissue Sheaths*

The axon-myelin sheath – Schwann cell complexes (nerve fibres) are arranged in bundles otherwise known as fascicles (Fig. 1.53). 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. 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. The more compact inner layer containing collagen and elastic fibres which are arranged in a wavy pattern. The perineurium, which ensheaths the bundles, is composed of flattened cell processes arranged in a wavy manner alternating with layers of collagen. It provides a barrier to diffusion. The perineurium is strong; the intrafascicular pressure can be raised to more than 300 mmHg before it ruptures The contents of the perineurium are under tension so that when it is cut they are extruded, rather like 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 themselves, there is a return to longitudinal direction of cells and fibres; there are abundant collagen fibrils. The spiral bands of Fontana represent the wavy 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.

### *1.7.2 Topographical Organisation*

Sunderland [39] mapped the arrangement of bundles along the course of nerve trunks, showing branching, fusion and changes in number. He also showed the

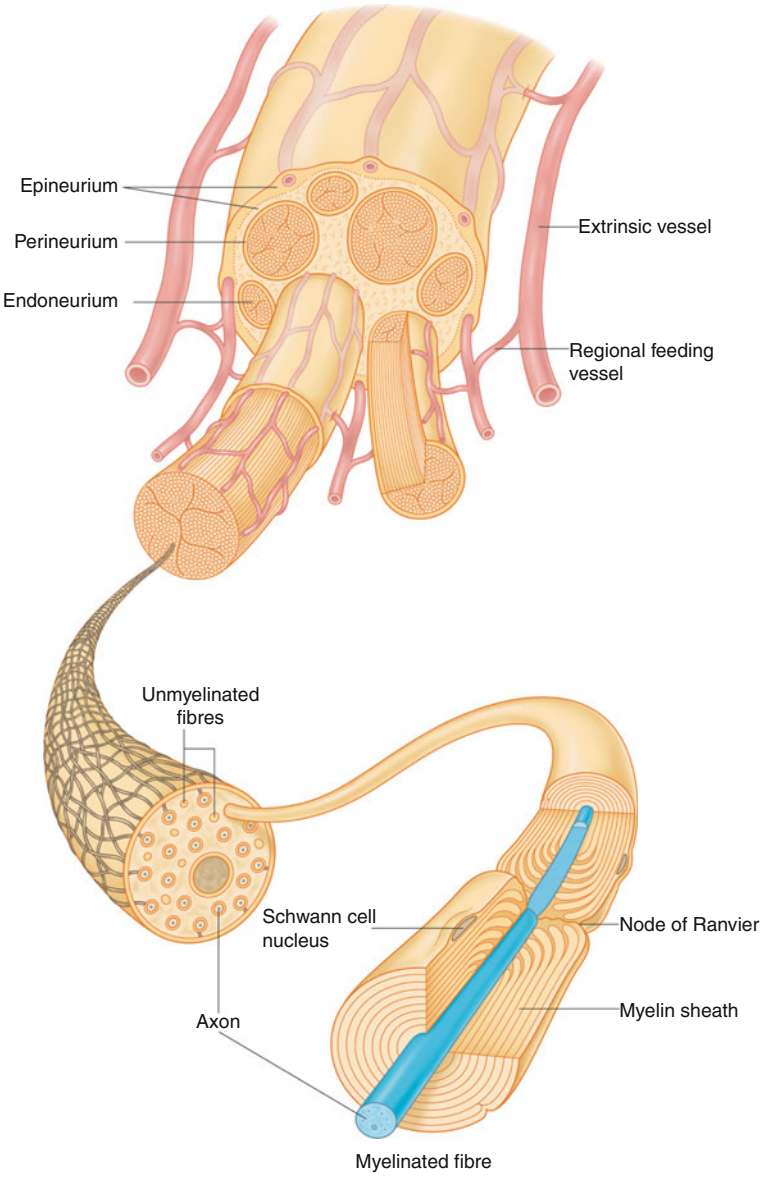


**Fig. 1.53** Fascicular arrangement of nerve fibres and their supporting structures, the vascular systems of the peripheral nerve

cross-sectional area of the nerve occupied by connective tissue was variable, ranging from 60 to 85 %. These findings have raised doubts about 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

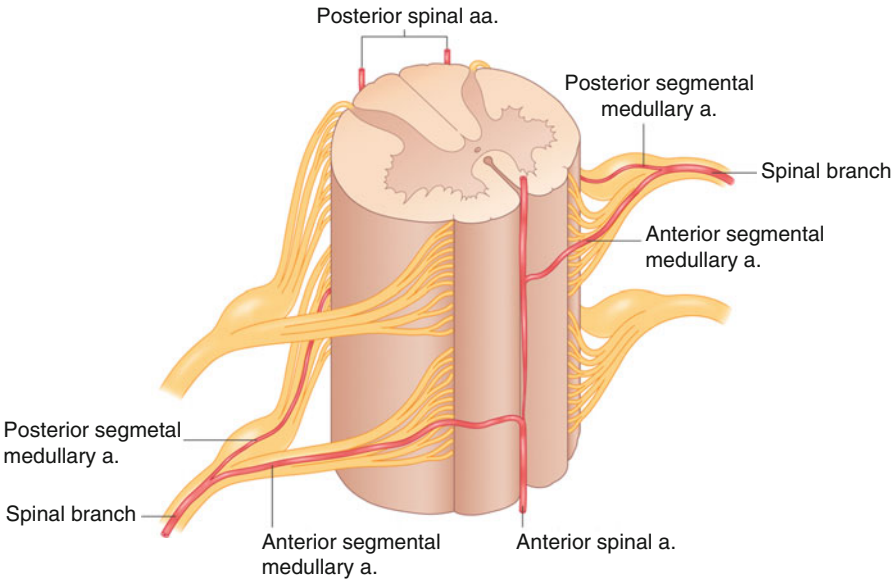


**Fig. 1.54** The segmental medullary (radicular) arteries and the anterior spinal artery in the lower cervical cord

the sensory cortex. There is extensive functional topographical segregation of fibres according to function over considerable lengths of the main trunks which permits nerve transfers. 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.

### *1.7.3 The Blood Supply of Nerves*

Nerves have a very good blood supply: they need it. There are indeed [25] intrinsic epineurial, perineurial and endoneurial plexuses, and extrinsic regional vessels in the "paraneurium". These form "separate but extensively interconnected microvascular systems" providing a wide margin of safety. The richness of the extrinsic supply varies along the course of a nerve and also between nerves [6].

The blood supply to the roots of the spinal nerves is much less robust. Woollam and Millen [46] studied the anterior spinal artery, in the foetus and in the guinea pig and rat. Relatively few radicular arteries survived into adult life. 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 Adamkievicz in the upper lumbar region (Fig. 1.54). Dommisse [13] 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". 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. Disruption, or occlusion of the radicular arteries entering the spinal canal with the spinal nerves or occlusion of the anterior spinal artery leads to the catastrophe of infarction of the anterior cord, the anterior spinal cord syndrome.

### *1.7.4 The Nervi Nervorum*

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. These are probably one factor underlying the exquisite sensitivity of nerves trapped in fibrosis.

## 1.8 Changes in Nerves with Aging

Myelination continues for the first 3 years of life and conduction velocity reaches adult levels at 5 years. In infancy there is a higher density of nerve fibres and higher blood flow to that tissue. The neurones in infancy are more vulnerable to the effects of axonotomy or avulsion. With increasing age there is increasing endoneurial collagen with demyelination and degeneration accompanied by remyelination and regeneration affecting the larger, longer MNF and larger sensory neurones. There is a slow decline in conduction velocity after the fourth decade [11]. 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.

## 1.9 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

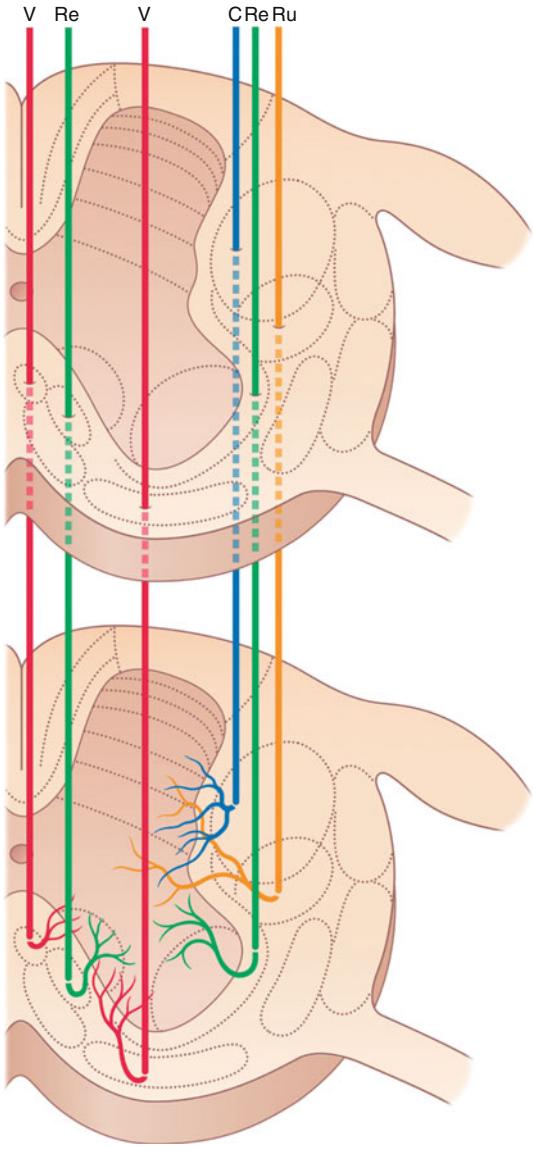


**Fig. 1.55** The major descending tracts in the spinal cord and their overlapping zones of termination in the grey matter. *C* corticospinal, *V* vestibulospinal, *Re* reticulospinal, *Ru* ruprospinal

lateral corticospinal tract. At various segmental levels impulses from this tract activate, through internuncial neurons, the motor cells in the anterior part of the grey matter (Fig. 1.55). "Extrapyramidal" tracts from the red nucleus, the vestibular nuclei and the reticular formation also influence the activity of the ventral horn neurones.

The cell bodies of the motor neurons are in Lamina IX [30] of the ventral horn of the grey matter. There are large (alpha) and small (gamma) cells. 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 [35] 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. 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.

The distribution of nerves within the muscles of the upper limb has been described by Lim and his colleagues [24]. 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. These findings support the idea of transfer of part of a muscle and they emphasise 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. 1.60) 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 fibres, 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 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.

## 1.10 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.

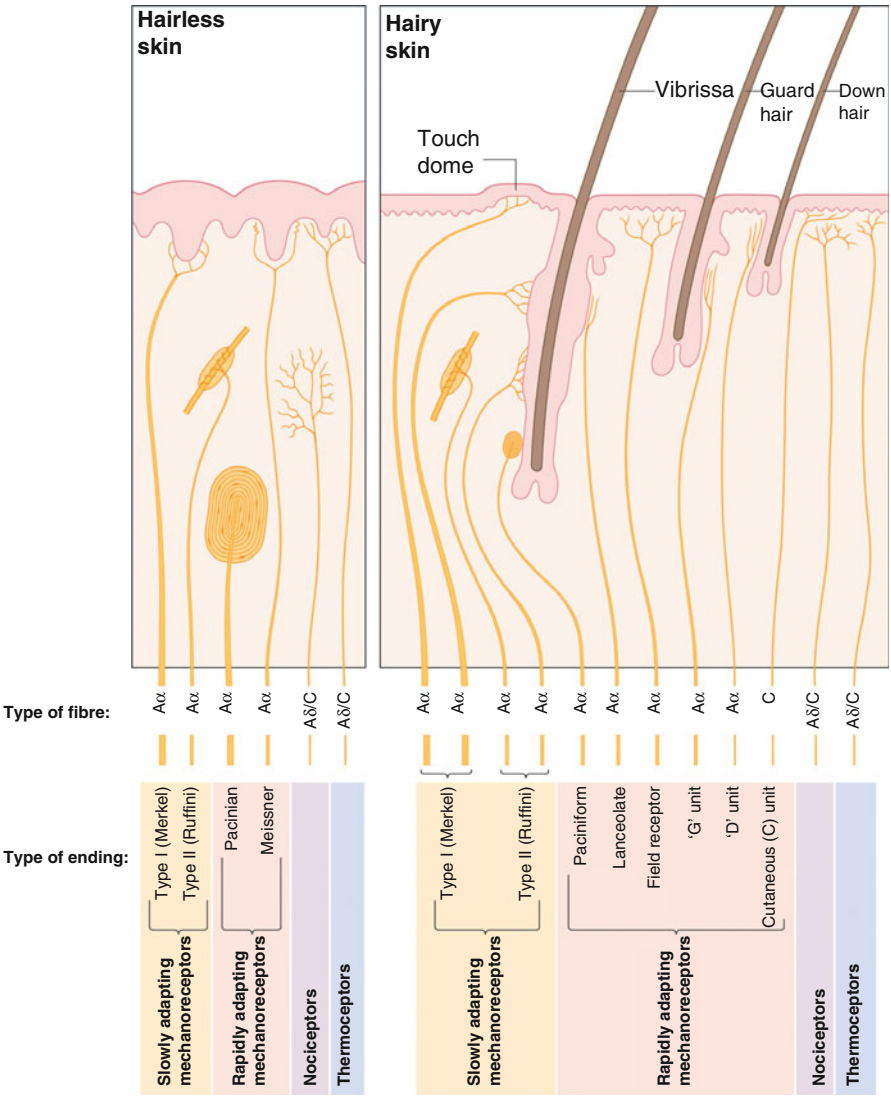


**Fig. 1.56** Cutaneous sensory receptors with nerve fibres. (*Left*) glabrous skin; (*right*) hairy skin

### *1.10.1 Cutaneous Sensibility*

There is general agreement that cutaneous receptors have a high degree of selective sensitivity rather an absolute specificity (Fig. 1.56). Adrian and Zotterman [1] pioneered methods in Cambridge in the 1920s which enabled electrophysiological studies of single afferent units. This led to extensive work with microelectrodes and with intraneural microstimulation [42]. No specialised mechanoreceptor transducers transmitting through unmyelinated fibres have been identified yet; the same is not so for nociceptors and most thermoreceptors, where the transient receptor

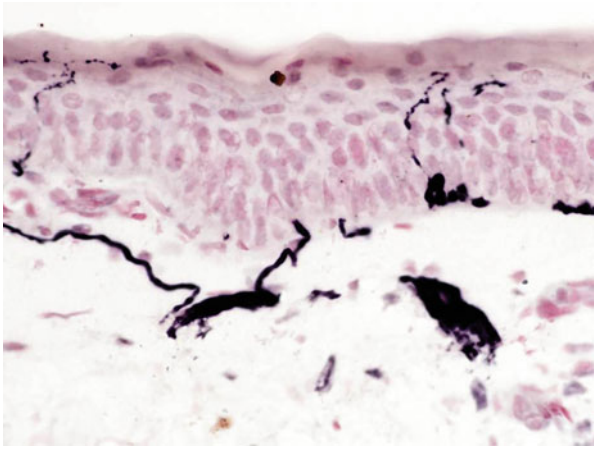

**Fig. 1.57** PGP9.5 immunoreactive nerves in skin of a patient with small fibre neuropathy Mag ×40

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. 1.57). The basis of stereognosis is a combination of stimuli from skin, tendons, muscles and joints relaying sensory information 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.

The fibres of afferent neurones are classed by their conduction velocity. Afferent fibres from the skin are divided into A-αβ, A-δ and C; muscle afferents are classed I, II, III and IV [22, 23]. 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. The neurones of C-fibres are small; those with Aδ fibres are small to medium size; those with A-αβ fibres are medium to large (Fig. 1.58).

### *1.10.2 The Skin*

The introduction of immunohistochemical staining of nerve antigens has provided new insights into innervation of the skin described by Kennedy et al. [20] “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 fibres comprise the vast majority of cutaneous innervation to the above dermal structures. The few myelinated nerve fibres terminate at hair follicles, Meissner corpuscles and Merkel complexes. The vertically orientated nerve bundles form a horizontal sub epidermal neural plexus. Epidermal nerve fibres branch from this plexus and, while penetrating the dermal-epidermal basement membrane to enter the epidermis, they

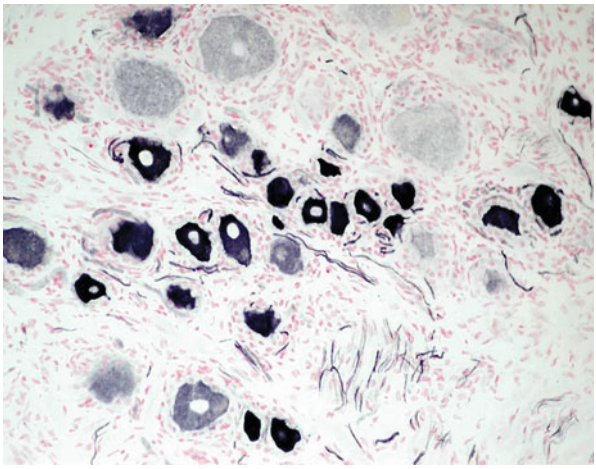

**Fig. 1.58** Small diameter nociceptor cell bodies and axons in the human dorsal root ganglion immuno reactive for the heat and capsaicin receptor TRPV1 2 weeks after avulsion injury ×20

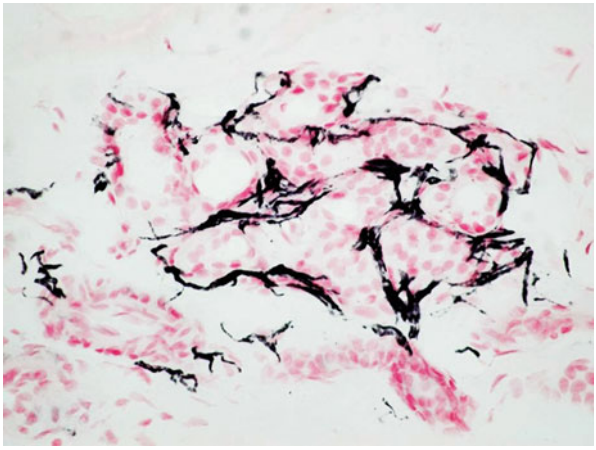

**Fig. 1.59** PGP9.5 immunoreactive autonomic nerve fibres surrounding sweat glands in the skin of a patient with small fibre neuropathy ×40

lose their Schwann cells ensheathment and collagen collar". The sweat glands are carpeted by a dense pattern of autonomic nerves (Fig. 1.59). 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.

### *1.10.3 Cutaneous Sensory Receptors*

Three types of cutaneous receptor are defined: low threshold mechanoreceptors; thermoreceptors; nociceptors.

*Low threshold mechanoreceptors*: 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. The principal mechano-receptor 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 characterised by large diffuse receptive fields. The Ruffini corpuscles provide information about finger position by responding to stretching of the skin.

*Thermoreceptors*: Cooling receptors are served by unmyelinated and fine myelinated fibres, usually serving receptor fields about 100 mm in diameter [23]. They are very sensitive to decrease in skin temperature from the normal or "neutral" level of 30–35 °C. Davis and Pope [12] 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 Temperatures above 43 °C induce firing in C-fibre polynociceptors. Temperatures above 53 °C evoked responses in fast conducting myelinated mechano-heat fibres.

*Nociceptors*: The term is applied to primary afferent units which "uniquely signal stimuli intense enough to threaten physical damage to the tissue" [23]. 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 [22]. Aδ nociceptors are high threshold mechano-receptors. Some respond to damaging heat. They conduct impulses from receptive fields of about 5 $mm^2$ 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 $mm^2$. Microneurography has clarified the physiological characteristics of the nociceptors in humans. Sharp, well localised pain follows stimulation of Aδ afferents. Stimulation of single C-afferents induces dull, burning, poor localised and delayed pain. 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 localised 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) [22].

### *1.10.4 Deep Sensibility*

Sensation is conveyed from muscles, ligaments and tendons from specialised 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. 1.60).

*Joints* are innervated by a network of rapidly conducting myelinated fibres some of which are associated with encapsulated mechanoreceptors, by high threshold, slowly conducting fibres many of which are perhaps nociceptors, and by sympathetic afferents [41].

*The muscle spindles*: It is over a hundred years since Sherrington [36] demonstrated by ventral root section that "in a muscular nerve-trunk from one-third to one-half of the myelinated fibres 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. Muscle spindles signal the length of extrafusal muscle at rest, during contraction and relaxation and the speed of change. 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. Innervation by large afferent fibres is copious: the muscle spindle and the Golgi tendon organ account for nearly all group 1 afferent axons from muscles. There are three types of specialised 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 [3]. The spindles vary in length from a few millimetres to a centimetre. Each spindle receives up to 25 terminal branches of motor and sensory axons, together with autonomic innervation. The motor axons are the β and γ 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. Banks [3] 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 muscle spindles and 45 Golgi 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 [10].

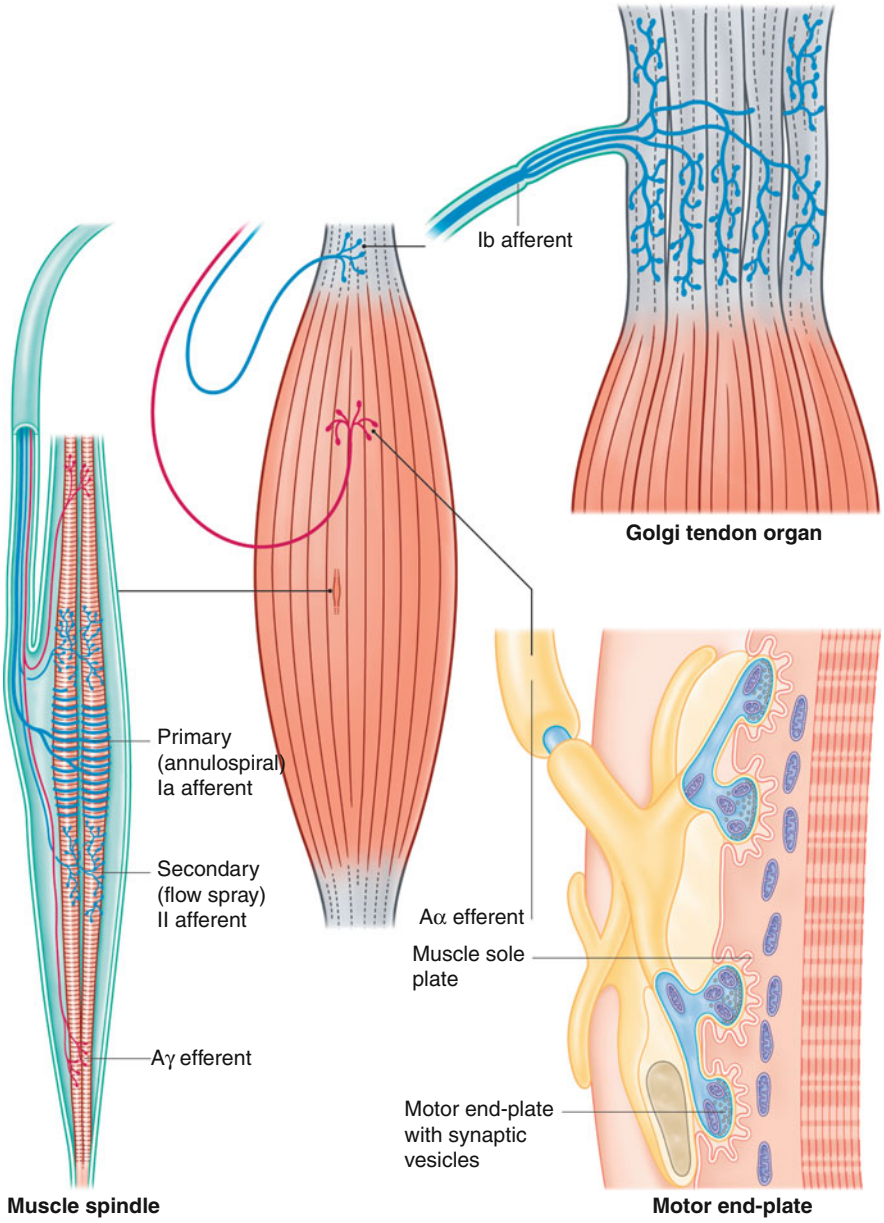


**Fig. 1.60** The afferent and efferent innervation of skeletal muscle

*The Golgi tendon organs*: Scott [34] characterises the second of the two encapsulated mechano-receptors in muscle. The Golgi organ senses maintained tension in 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 mechanoreceptors 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.

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 % [6] (Fig. 1.61). 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 "nerves with motor and cutaneous sensory components" and "nerves without somatic motor components" are, unfortunately, cumbersome, but they do say what they mean.

### *1.10.5 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 cells in the dorsal root ganglia, enter the cord by the dorsal roots. Others, with cells in the dorsal root ganglia or actually in the ventral roots, enter the cord by the latter (Fig. 1.62).

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

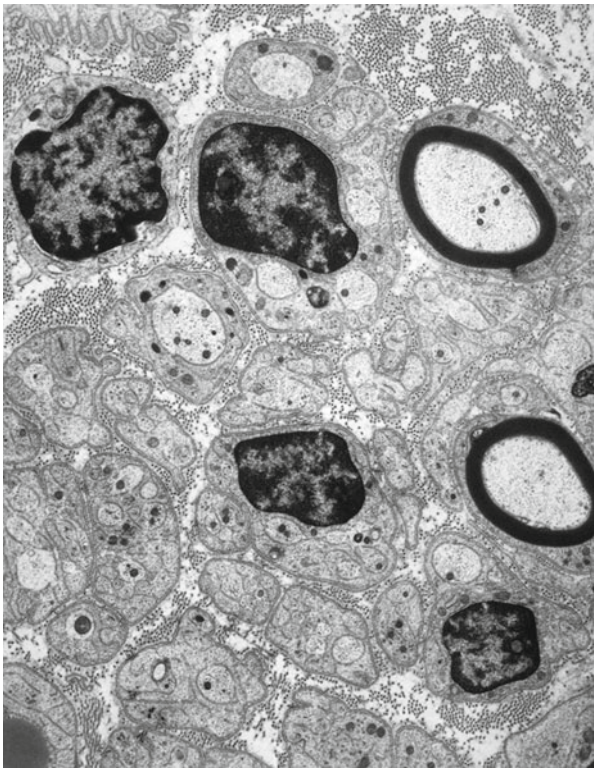

**Fig. 1.61** Intact (afferent) myelinated and unmyelinated fibres in the suprascapular nerve after avulsion lesion of the brachial plexus. Specimen taken 6 weeks after injury, when efferent fibres had degenerated ×6,600 (EM)

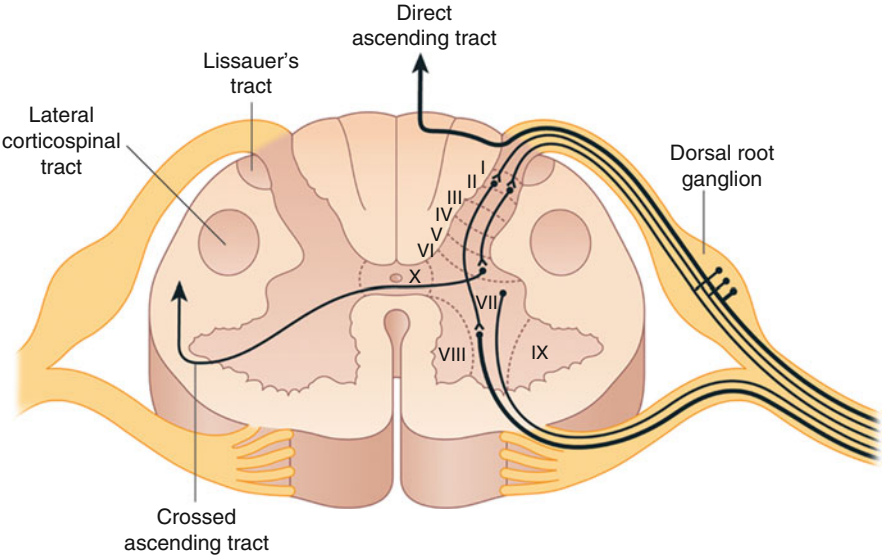


**Fig. 1.62** The laminae of the grey matter with direct ascending, crossed ascending and internuncial tracts

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 [43], it is broadly true that, as Brodal [8] states, they "mediate sensory signals necessary for rather complex discrimination tasks" [8].

Other afferent fibres terminate and relay in the grey matter of the dorsal horn. Each lamina of the grey matter receives afferents of specific functional modalities; each has a particular neuronal structure [29, 30]. Small myelinated nociceptor and thermoreceptor fibres terminate in lamina I; C fibres, nocithermo- and mechanoreceptors, in lamina II (substantia gelatinosa). Larger mechanoreceptor 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. 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 analysed and modified here. Secondary neurons 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 anterolateral segment of the spinal cord (Fig. 1.63).

The transmission of impulses from the nuclei of the dorsal column is influenced by fibres descending from the sensory motor cortex [17]. 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 [26]. Not even in this last analysis are afferent functions separated completely from motor function: stimulation of any of these areas produces motor effect.

### *1.10.6 Afferent Autonomic Pathways*

The first evidence for the presence of a system for conveying from all viscera sensations both perceived and unperceived rested 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 [33]. Autonomic afferent fibres have their cells of origin in the dorsal root ganglia and in some cranial ganglia. Their peripheral processes run with efferent fibres, terminating in receptor endings in the walls of viscera and vessels. The cell bodies of afferent fibres in the enteric division lie in the wall of the gut (Fig. 1.64). Some

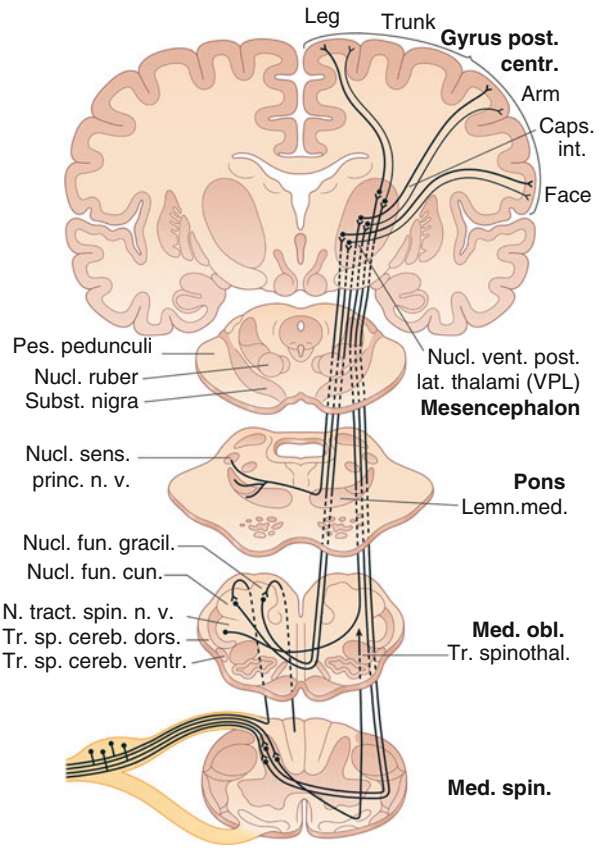


**Fig. 1.63** Ascending tracts in the cord, brain stem and cortex. Note the relay of the directly ascending tracts in the gracile and cuneate nuclei in the medulla

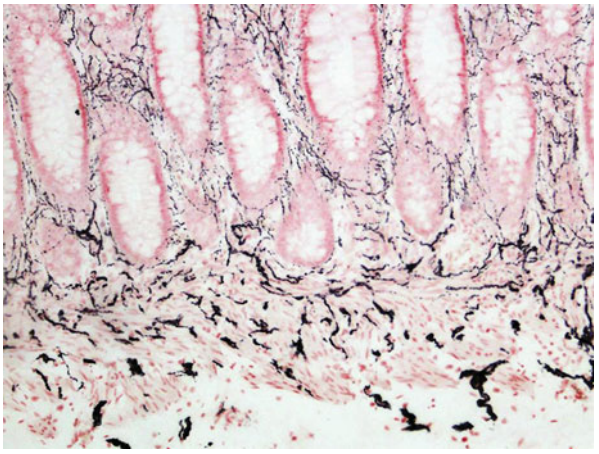

**Fig. 1.64** Afferent fibres in the enteric division of the autonomic system. Nerve fibres within the mucosa and submucous plexus of human rectum stained with antibodies to sensory sodium channel (Nav1.7) ×10

impulses from these endings mediate sensations such as hunger, distension of the bladder and perhaps pain. Most, presumably, are concerned with the initiation of visceral reflexes. The afferent component of the enteric division is described by Furness [15]. Sugiura et al. [38] found that visceral afferents terminate in laminae IV, V and X of the dorsal horn as well as in laminae I and II, and 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".

## 1.11 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; "neuromodulation" implies alteration of its response to a neuromediator [44].

The best-known mediator and the one that has longest been known, is of course acetylcholine, synthesised by motor neurons 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 neurons. 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.

## References


1. Adrian ED, Zotterman Y. The impulses produced by sensory nerve endings. Part 2. The responses of a single end organ. J Physiol. 1926;61:151–71.
2. Anand U, Otto WR, Casula MA, Day NC, Davis JB, Bountra C, Birch R, Anand P. The effect of neurotrophic factors in morphology TRPVI expression and capsaicin responses of cultured human DRG sensory neurons. Neurosci Lett. 2006;399(2006):51–6.
3. Banks RW. The muscle spindle. In: Dyck PJ, Thomas PK, editors. Peripheral neuropathy. 4th ed. Philadelphia: Elsevier Saunders; 2005. p. 131–50, Chapter 6.
4. Berthold CH, King RHM, Rydmark M. The myelinated nerve fibres. In: Dyck PJ, Thomas PK, editors. Peripheral neuropathy. 4th ed. Philadelphia: Elsevier Saunders; 2005, Chapter 3.
5. Birch R. The peripheral nervous system: gross anatomy. In: Birch R. Surgical Disorders of the Peripheral Nerves. 2nd ed. London: Springer; 2011. p. 1–42, Chapter 1.
6. Birch R. Microscopic function of the nervous system, its function. In: Birch R. Surgical Disorders of the Peripheral Nerves. 2nd ed. London: Springer; 2011. p. 43–76, Chapter 2.
7. Brimijoin S. Axonal transport: properties, mechanisms and role in nerve disease. In: Dyck PJ, Thomas PK, editors. Peripheral neuropathy. 4th ed. Philadelphia: Elsevier Saunders; 2005. p. 387–409, Chapter 18.
8. Brodal A. The fibers in the dorsal funiculi and the medial lemniscus. In: Brodal A, editor. Neurological anatomy. New York/Oxford: Oxford University Press; 1981. p. P74–84.
9. Chiu SY. Channel function in mammalian axons and support cells. In: Dyck PJ, Thomas PK, editors. Peripheral neuropathy. 4th ed. Philadelphia: Elsevier Saunders; 2005. p. 95–112, Chapter 4.
10. Cooper S, Daniel PM. Muscle spindles in man: their morphology in the lumbricals and the deep muscles of the neck. Brain. 1963;86:563–88.
11. Cowen T, Ulfhake B, King RHM. Aging in the peripheral nervous system. In: Dyck PJ, Thomas PK, editors. Peripheral neuropathy. 4th ed. Philadelphia: Elsevier-Saunders; 2005. p. 483–507, Chapter 22.
12. Davis KD, Pope GE. Noxious cold evokes multiple sensations with distinct time course. Pain. 2002;98:179–85.
13. Dommisse GF. The arteries and veins of the human spinal cord from birth. 1st ed. Churchill Livingstone: Edinburgh; 1975.
14. Fraher JP. The CNS-PNS transitional zone. In: Dyck PJ, Thomas PK, editors. Peripheral neuropathy. 4th ed. Philadelphia: Elsevier Saunders; 2005. p. 67–78, Chapter 3.
15. Furness JB. Novel gut afferents: intrinsic afferent neurons and intestinofugal neurons. Auton Neurosci. 2006;125:81–5.
16. Gardner E, Bunge RP. Gross anatomy of the peripheral nervous system. In: Dyck PJ, Thomas PK, editors. Peripheral neuropathy. 4th ed. Philadelphia: Saunders Elsevier; 2005. p. 11–34.
17. Gordon G, Jukes MGM. Descending influences on the exteroceptive organizations of the cat's gracile nucleus. J Physiol. 1964;173:291–319.
18. Hall SM. The response to injury in the peripheral nervous system. J Bone Joint Surg Br. 2005;87B:1309–19.
19. Hodgkin AL, Huxley AF. A quantitative description of membrane current and its application to conduction and excitation in nerve. J Physiol. 1952;117:500–44.
20. Kennedy WR, Wendel-Schafer-Crabb G, Polydefkis M, McArthur J. Pathology and quantitation of cutaneous innervation. In: Dyck PJ, Thomas PK, editors. Peripheral neuropathy. 4th ed. Philadelphia: Elsevier Saunders; 2005. p. 869–95, Chapter 34.
21. Last RJ. Innervation of the limbs. J Bone Joint Surg Br. 1949;31B:452–64.
22. Lawson SN. The peripheral sensory nervous system: dorsal root ganglion neurones. In: Dyck PJ, Thomas PK, editors. Peripheral neuropathy. 4th ed. Philadelphia: Elsevier Saunders; 2005. p. 163–202, Chapter 8.

23. Light AR, Perl ER. Peripheral sensory systems. In: Dyck PJ, Thomas PK, Griffin JW, Low PA, Poduslo JF, editors. Peripheral neuropathy. 3rd ed. Philadelphia: WB Saunders Company; 1993.
24. Lim AYT, Pereira BP, Kumar VP, de Coninck C, Taki C, Baudet J, Merle M. Intramuscular innervation of upper limb skeletal muscles. Muscle Nerve. 2004;29:523–30.
25. Lundborg G. Vascular systems. In: Lundborg G, Nerve injury and repair. 1st ed. Edinburgh: Churchill Livingstone; 1988. p. 32–43.
26. Lundborg G. Sensation and sensorimotor integration in hand function: brain plasticity and cortical remodelling. In: Lundborg G. Nerve injury and repair: regeneration, reconstruction and cortical remodelling. 2nd ed. Philadelphia: Elsevier/Churchill Livingstone; 2004. p. 198–223, Chapters 8 and 9.
27. Nathan PW, Smith MC. The location of descending fibres to sympathetic pre-ganglionic vasomotor and sudomotor neurons in man. J Neurol Neurosurg Psychiatry. 1987;50:1257–62.
28. Nathan PW, Smith MS, Cook AW. Sensory effects in man of lesions of the posterior columns and some other afferent pathways. Brain. 1986;109:1003–41.
29. Price DD, Meyer DJ. Physiological laminar organization of the dorsal horn of *M. mulatta*. Brain Res. 1974;79:321–5.
30. Rexed B. The cytoarchitectonic organisation of the spinal cord in the cat. J Comp Neurol. 1952;96:415–95.
31. Schenker M, Birch R. Intact myelinated fibres in biopsies of ventral spinal roots after preganglionic traction injury to the brachial plexus. A proof that Sherrington's "wrong way afferents" exist in man? J Anat. 2000;197:383–91.
32. Schenker M, Birch R. Diagnosis of level of intradural ruptures of the rootlets in traction lesions of the brachial plexus. J Bone Joint Surg Br. 2001;83B:916–20.
33. Schott GD. Visceral afferents: their contribution to "sympathetic-dependent" pain. Brain. 1994;117:397–413.
34. Scott JJA. The Golgi tendon organ. In: Dyck PJ, Thomas PK, editors. Peripheral neuropathy. 4th ed. Philadelphia: Elsevier Saunders; 2005. p. 151–61, Chapter 7.
35. Sharrard WJW. The distribution of the permanent paralysis in the lower limb in poliomyelitis. J Bone Joint Surg Br. 1955;37B:540–58.
36. Sherrington CS. On the anatomical constitution of nerves of skeletal muscles: with remarks on recurrent fibres in the ventral spinal nerve-root. J Physiol. 1894;17:211–58.
37. Standring S. Conduction of nervous impulses. In: Standring S, editor. Gray's anatomy. 40th ed. Edinburgh: Churchill Livingstone/Elsevier; 2008. p. 63–4.
38. Sugiura Y, Terui N, Hosoya Y. Difference in distribution of central terminals between visceral and somatic unmyelinated (C) primary afferent fibres. J Neurophysiol. 1989;62:834–40.
39. Sunderland S. Intraneural topography. In: Sunderland S. Nerve and nerve injuries. Edinburgh/London: E & S Livingstone; 1968. …Median nerve, p. 758–69; ulnar nerve, p. 816–25; radial nerve, p. 905–14; sciatic nerve, p. 1029–46.
40. Suter U, Martini R. Myelination. In: Dyck PJ, Thomas PK, editors. Peripheral neuropathy. 4th ed. Philadelphia: Elsevier Saunders; 2005. p. 411–31, Chapter 19.
41. Takebayashi T, Cavanagh JM, Kallukuri S, Chen C, Yamashita T. Sympathetic afferents from lumbar intervertebral discs. J Bone Joint Surg Br. 2006;88B:554–7.
42. Torebjörk E, Schmelz M. Single-unit recordings of afferent human peripheral nerves by microneurography. In: Dyck PJ, Thomas PK, editors. Peripheral neuropathy. 4th ed. London: WB Saunders Co; 2005. p. 1003–14, Chapter 38.
43. Wall PD. The sensory and motor role of impulses travelling in the dorsal columns towards the cerebral cortex. Brain. 1970;93:505–24.
44. Wigley C, Felts P, Standring S. Mechanism of synaptic activity. In: Standring S, editor. Grays anatomy. 40th ed. Edinburgh: Churchill Livingstone/Elsevier; 2008. p. 46–8.

45. Windebank AJ, McDonald ES. Neurotrophic factors in the peripheral nervous system. In: Dyck PJ, Thomas PK, editors. Peripheral neuropathy. 4th ed. Philadelphia: Elsevier Saunders; 2005. p. 377–86, Chapter 17.
46. Woollam DHM, Millen JW. Discussion on vascular disease of the spinal cord. Proc R Soc Med. 1958;51:540–3.