# Chapter 2
# Anatomy and Physiology of Peripheral Nerves

**Hugh J. McMillan**

Neurophysiologists must demonstrate knowledge of the gross anatomy and location of peripheral nerves and muscles in order to carry out nerve conduction studies and electromyography (see Chaps. 4, 5, 6, 7, 9 and 10). However, they must also be aware of the microanatomy of nerves and as well as basic physiology in order to understand factors that can influence optimal timing of tests and/or how artifacts can influence NCS/EMG test results.

## Gross Anatomy

The peripheral nervous system includes the motor and sensory neurons, peripheral nerves, neuromuscular junctions and muscles.

Motor neurons, also known as anterior horn cells, are located in the ventral gray matter of the spinal cord. Their axonal projections or motor nerves extend from the spinal cord as ventral roots eventually innervating skeletal muscle. Each group of muscles innervated by any given level of the spinal cord is referred to as belonging to the same myotome. Sensory neurons, also known as dorsal root ganglia, lie outside of the spinal cord. Their projections extend in two directions; proximally towards the dorsal root of the spinal cord and distally towards an area of the body from which they carry sensory stimuli. The distinct region of skin innervated by each sensory level of the spinal cord is known as a dermatome. Nerve roots and their related diseases are covered in Chap. 17.

Although the most proximal segments of the motor (ventral) and sensory (dorsal) roots travel separately, the efferent motor fibers and afferent sensory fibers travel

H.J. McMillan, MD, MSc, FRCPC, FAAN
Division of Neurology, Children's Hospital of Eastern Ontario, University of Ottawa, Ottawa, ON, Canada
e-mail: hmcmillan@cheo.on.ca



H.J. McMillan, P.B. Kang (eds.), *Pediatric Electromyography*,
DOI 10.1007/978-3-319-61361-1_2

together as mixed nerves just distal to the dorsal root ganglia. There are a total of 31 spinal nerves at five different spinal levels; 8 cervical, 12 thoracic, 5 lumbar, 5 sacral and 1 coccygeal nerve roots. In addition, 10 of the 12 cranial nerves (CN III to XII) are considered part of the peripheral nervous system and will be covered in Chap. 15.

## Classification of Peripheral Nerves

Peripheral nerves are typically mixed meaning that they carry both sensory and motor fibers. However there are several examples of pure sensory nerves (e.g., lateral femoral cutaneous nerve) or pure motor nerves (e.g., posterior interosseous nerve) that branch off directly from a plexus or a larger nerve. Nerves contain various types of fibers including: (1) large myelinated, (2) small myelinated and; (3) small unmyelinated axons (Table 2.1).

Large myelinated fibers are preferentially tested by nerve conduction studies since their larger diameter (12–20 μm) axons allow these fibers to conduct the fastest of all motor fibers (70–120 m/s). Myelination of these axons further increases conduction velocity by enabling saltatory conduction which will be discussed in detail below. Myelin is produced by supportive Schwann cells that wrap or layer each axon in a fatty, protective spiral coat with numerous layers. Layering of myelin is seen quite nicely on electron microcopy (ultrastructure) of peripheral nerves (Fig. 2.1). The total thickness of myelin in a mature nerve is approximately 2/3 the diameter of the axon. Large myelinated fibers include: (1)

**Table 2.1** Peripheral nerve fiber types

| Fibre type | Diameter (μm) | Conduction Velocity (m/s) | Myelination | Function |
|---|---|---|---|---|
| *Afferent fibers* | | | | |
| IA | 12–20 | 70–120 | Large myelinated | From muscle spindles |
| IB | 12–20 | 70–120 | Large myelinated | From Golgi tendon organs |
| II | 6–12 | 30–70 | Small myelinated | From Meissner's and Pacinian corpuscles & endings in skin & connective tissue |
| III | 2–6 | 4–30 | Small myelinated | From skin; pressure afferents |
| IV | <2 | <2 | Small unmyelinated | From skin; pain (pin-prick), temperature afferents |
| *Efferent fibers* | | | | |
| Alpha | 12–20 | 70–120 | Large myelinated | To skeletal muscles |
| Gamma | 3–8 | 15–40 | Small myelinated | To intrafusal fibers of muscle spindles |
| B | 1–3 | 5–15 | Small myelinated | To pre-ganglionic autonomic efferents |
| C | <1 | <2 | Small unmyelinated | To post-ganglionic autonomic efferents |

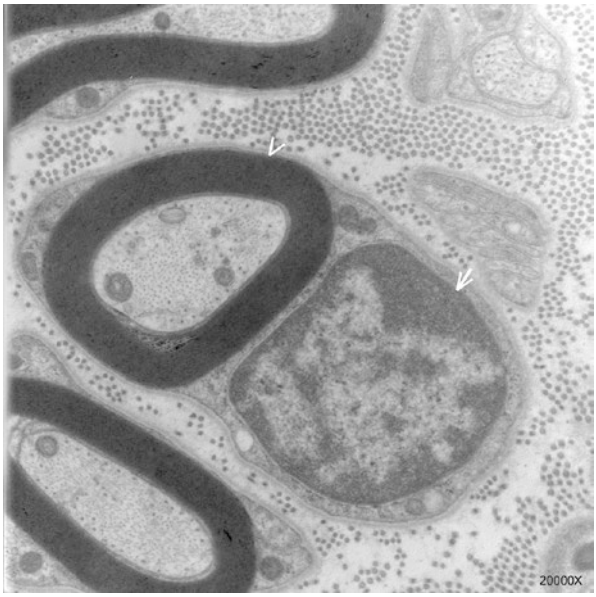


**Fig. 2.1** Ultrastructural image of a normal, large myelinated peripheral nerve (*arrow head*). The axon is seen in cross-section and has been wrapped in layers or spirals of protective myelin by the adjacent Schwann cell (*arrow*). *Photo credit: Dr. Jean Michaud, Department of Pathology, Children's Hospital of Eastern Ontario*

afferent fibers from muscle spindles and Golgi tendon organs which relay important information about joint position and stretch which is critical for our reflexes as well as; (2) motor efferent fibers travelling from the motor neurons to skeletal muscles. Peripheral nerve myelination progresses significantly during the first few years of life as is reflected in the normal neonatal ulnar nerve motor conduction velocities of 20–35 m/s which increase to adult normal values (>50 m/s) by 3–5 years of age [1].

Small myelinated fibers are approximately half the diameter of large fibers and not surprisingly conduct more slowly than their larger counterparts. Examples of small myelinated afferent fibers include axons extending from Meissner and Pacinian corpuscles. These are touch receptors located near the surface of the skin. When the corpuscle is deformed by pressure, the nerve endings are stimulated. They are well adapted to feeling rough surfaces and detecting vibration such that they respond to transient touch rather than sustained pressure. Small myelinated efferent fibers also supply the intrafusal fibers of muscle spindles as well as preganglionic autonomic efferents.

Small unmyelinated fibers are the smallest axons (<2 mm) and due to their extremely slow conduction velocity (<2 m/s) cannot be tested by conventional nerve conduction studies. Neurophysiologists must be aware of the limitations of testing such that when a small fiber neuropathy is suspected on clinical grounds, ancillary testing is considered as appropriate (see Chap. 19). Examples of small unmyelinated afferent fibers include sensory fibers carrying information regarding pain (pin-prick) and temperature sense. Small unmyelinated efferent fibers innervate post-ganglionic autonomic organs.

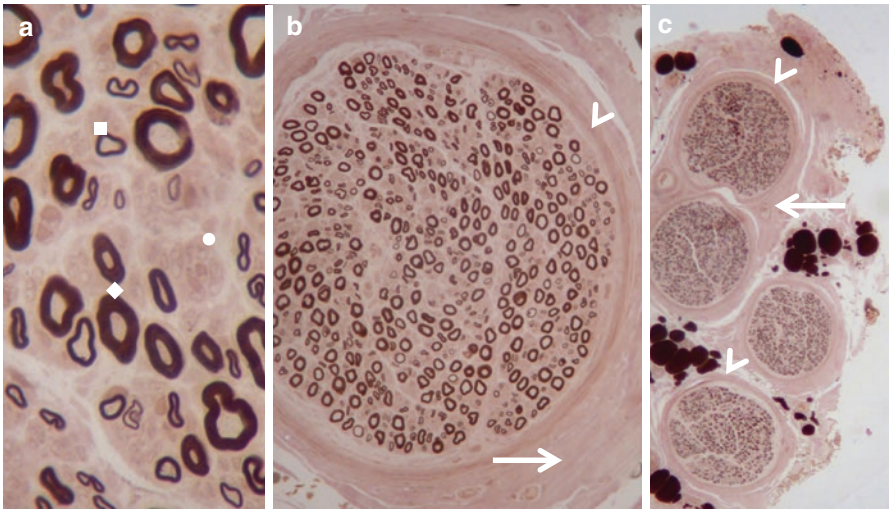


**Fig. 2.2** Normal peripheral nerve sections stained with p-phenylenediamine at (**a**) high power shows large myelinated axons (*diamond*), small myelinated axons (*square*) and unmyelinated axons (*circle*) all surrounded by endoneurium; (**b**) medium power shows a fascicle containing many axons surrounded by perineurium (*arrow head*) which in turn is surrounded by epineurium (*arrow*); (**c**) low power demonstrates how the epineurium (*arrow*) binds together multiple fascicles and also contains arterioles. *Photo credit: Dr. Gerard Jansen, Department of Pathology, The Ottawa Hospital Civic Campus*

## Nerve Microanatomy

Each peripheral nerve fiber or axon is surrounded by multiple levels of connective tissue. Endoneurium surrounds individual axons. Individual axons are clustered into fascicles that are surrounded by a layer of connective tissue called perineurium. This in turn is surrounded by a thicker layer of epineurium that binds together multiple perineurial-bound fascicles as well as arterioles (Fig. 2.2).

## Physiology

Signal transmission along peripheral nerves is based upon the presence of a stable electrochemical charge across the cell membrane of an axon, with a mechanism for rapid and reversible changes of that charge in response to stimuli.

The difference in electrochemical charge at baseline is referred to as a resting membrane potential. Ion pumps, typically requiring energy provided by adenosine triphosphate (ATP), are responsible for transporting ions such as $Na^+$, $K^+$, $Cl^-$ and $Ca^{2+}$ into or out of the cell to establish electrical and chemical concentration gradients. Typically, resting membrane potentials of most glial cells is approximately −75 mV (i.e., the cytoplasm is negative compared to the extracellular matrix). Phospholipid bilayers are hydrophobic, thereby preventing charged particles from easily moving through membranes. Despite this, functional ion pumps are required to prevent ions

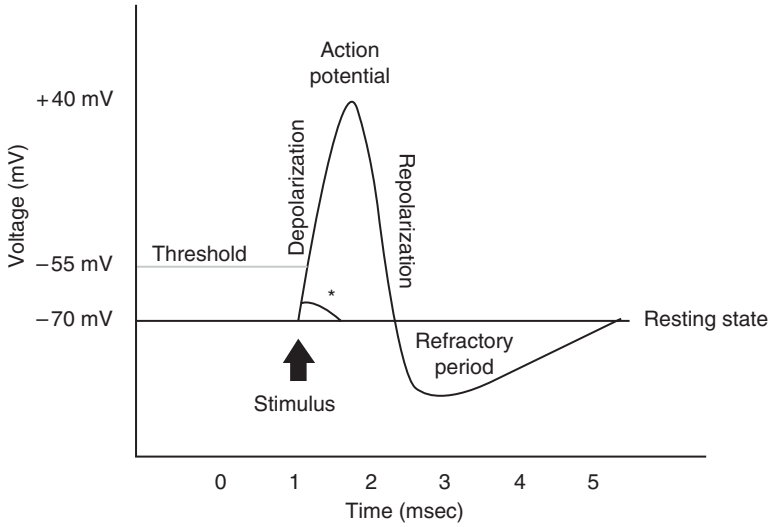


**Fig. 2.3** Action potential and the associated changes in membrane voltage. The initial horizontal line represents the resting membrane potential (−70 mV). A stimulus (*arrow*) triggers local sodium channels to open which increase the membrane potential. If insufficient sodium ($Na^+$) channels open the membrane potential does not exceed threshold and a failed potential ensues (*asterix*) where the resting membrane potential is re-established If sufficient $Na^+$ channels open and the threshold is surpassed, an all-or-none action potential is generated. The depolarization phase is characterized by $Na^+$ channels opening and the influx of $Na^+$ ions increasing the membrane potential from −70 mV to +40 mV. This change triggers $Na^+$ channels to close and $K^+$ channels to open. The repolarization phase is characterized by an efflux of $K^+$ and a return of the membrane potential to −90 mV. Since this surpasses the resting potential this is known as the refractory period. The $Na^+K^+$-ATPase pump re-establishes the concentration of ions and the resting membrane potential

from eventually diffusing across their electrochemical concentration gradients which would result in the loss of the resting membrane potential.

Ion channels are proteins that span cell membranes and can allow the passage of specific ions through an otherwise impermeable lipid bilayer. Specific factors can trigger a conformational change in ion channel proteins, causing them to open and permit the rapid influx or efflux of ions. Ion channels can be stimulated to open by; (1) binding with a ligand (i.e., a neurotransmitter); (2) local changes in voltage (i.e., propagation of an action potential); (3) local stress or pressure (i.e., common trigger for sensory mechanoreceptors) as well as; (4) phosphorylation which more typically results in prolonged configuration changes that can modulate the resting membrane potential.

Nerve-to-nerve and nerve-to-muscle signal transmission occurs via an action potential where adjacent voltage-gated ion channels open in a stepwise manner. Action potentials have several key characteristics. First there is a threshold for the initiation of an action potential. In the case of mechanoreceptors in the skin, small amounts of pressure will cause some sodium channels to open, thereby raising the membrane potential. If the potential is raised beyond a threshold value then adjacent voltage-gated sodium channels will open, triggering an influx of sodium ions that represents the initiation of an action potential (Fig. 2.3). This action potential is

self-propagating, spreading along the length of the axon as voltage gated channels open in succession much as dominos fall in a line. If the threshold is not reached then the ion pumps will work to reestablish the resting membrane potential, and an action potential is not generated. The influx of sodium channels reverses the membrane potential from about −70 mV to +40 mV. At this point the sodium channels close and the potassium channels open. The efflux of potassium lowers the membrane potential to approximately −90 mV which repolarizes the membrane. At this time the potassium channels close. The $Na^+K^+$-ATPase pump will work to reestablish the resting membrane potential, but the brief period of time that the membrane potential remains below −70 mV is known as the absolute and relative refractory periods, namely the time where it is impossible and then more difficult for a second action potential to be generated.

## Saltatory Conduction

Schwann cells perform a similar function for peripheral nerves as that of oligodendrocytes within the central nervous system. Schwann cells provide an insulating coat of myelin to a single axonal segment of a peripheral nerve. Peripheral nerve myelin shows differences from its central counterpart, namely a greater proportion of myelin basic protein (MBP) as well as the presence of peripheral myelin protein 22 (PMP22) and myelin protein zero (MPZ or $P_0$) [2]. Overall, myelin functions to insulate the axon and increase the electrical resistance across the cell membrane. Each segment of myelin is interrupted by short, unmyelinated gaps known as the nodes of Ranvier. The high resistance along the myelinated segments prevents the electrical current from leaving the axon, allowing action potentials to 'jump' from one node of Ranvier to the next, thereby enabling the axon to to propagate action potentials at much higher conduction velocities (70–120 m/s) which are characteristic of large myelinated nerves. The jumping of conduction is referred to as saltatory conduction.

## Effects of Demyelination

Segmental demyelination due to either local nerve compression or inflammation can disrupt specific segments of myelin along a peripheral nerve axon, while other segments will remain intact. Even though the axon itself retains its structural integrity, an action potential cannot propagate normally along a myelinated nerve if a segment of that nerve is demyelinated. The explanation for this is that the voltage gated ion channels are normally located only at each node of Ranvier, thus a demyelinated stretch of an axon has very different electrophysiologic properties than a naturally unmyelinated axon. The end result is typically failure of conduction along that stretch of the axon, giving rise to the phenomenon of conduction block.

Peripheral neuropathies will be covered in Chap. 18. Once the offending agent has been removed, peripheral nerve remyelination will occur. However the remyelinated segments are typically shorter, with a corresponding increase in the number of nodes of Ranvier along the remyelinated portion of the axon, which can give rise to permanent alterations in the axon's electrophysiology properties [3, 4].

## Injury and Regrowth (Sequence of Events Post-injury)

Axonal injury is another important consideration for the neurophysiologist. When an axon is severed it is no longer possible for an action potential to be transmitted. The proximal segment, which remains in continuity with the anterior horn cell or dorsal root ganglia, will receive nourishment from the cell body and thus remain intact. However, the portion of the axon distal to the site of injury will undergo Wallerian degeneration whereby it degenerates in an anterograde manner. Abnormalities will become apparent on nerve conduction studies 3–10 days post-injury [5, 6].

Peripheral nerve injury has been classified by Seddon into three categories. Neuropraxia is the mildest and is associated with a focal demyelination without associated axonal loss. Full recovery typically occurs over days to weeks as the Schwann cells remyelinate the affected segments. Patients suffering from neuropraxia may suffer from weakness and/or paresthesia as well as pain at the site of injury. Nerve conduction studies are preserved except perhaps at stimulation sites that are proximal to the demyelinated segment(s), as the action potentials cross the site of injury. Nerves affected by neuropraxia may demonstrate conduction block (i.e., decreased compound motor action potential (CMAP) amplitudes across the site of injury) and/or focal slowing of conduction velocity across the affected area. Needle EMG may demonstrate decreased recruitment but no active denervation (i.e., positive sharp waves or fibrillation potentials) is seen since axonal continuity persists. Axontmesis is moderate in severity, and describes the partial or complete loss of axonal continuity; however, some surrounding perineurium and/or epineurium remains intact. This is important for potential recovery as sprouting will appear from the proximal axon tips within a week of the injury and slowly grow by about 1 mm per day (1 inch per month). If there is some continuity of neural elements and/or connective tissue, then the potential for reinnervation is greater. Neurotmesis is the most severe classification of nerve injury, where there is no continuity of neural or connective tissue. As such the potential for recovery is more guarded without an anatomical pathway for reinnervation to occur. Nerve transfers and/or grafting may be considered in such cases given the uncertain potential for spontaneous recovery. Aberrant or erroneous reinnervation can occur particularly following neurotmesis. Perhaps the most familiar example is a facial synkinesis that can occur after Bell palsy. This can be manifested as involuntarily contraction of the orbicularis oris (blinking) with contraction of other ipsilateral facial muscles [7].

## Neuromuscular Transmission

The neuromuscular junction (NMJ) is the connection between a motor nerve and the muscle fiber that it innervates. It is not a physical connection but is represented by the apposition of the terminal bouton and the motor endplate on the muscle fiber. Signaling via neurotransmitters across this gap enables nerve action potentials to be translated into physical muscle contractions.

As the action potential reaches the end of the motor axon, the change in resting potential triggers the opening of voltage gated calcium channels. Calcium binds to synaptotagmin which triggers the release of packets or vesicles of acetylcholine from the terminal. Acetylcholine is released into the synaptic cleft, traveling from the terminal bouton to the motor endplate where it binds to nicotinic acetylcholine receptors (AChRs). AChRs are examples of ligand-gated ion channels. The binding of acetylcholine results in local depolarization and generation of an excitatory post-synaptic potential (EPSP). Unlike the action potential which is self-propagating, the EPSP demonstrates a decrement in both time (as the ion pumps work to restore the resting potential) and space (as the change in membrane potential becomes less as it travels farther from its site of initiation). Adjacent EPSPs are summative and if sufficient ligand-gated ion channels are stimulated the resulting EPSP will surpass the threshold, triggering a muscle action potential that ultimately leads to a physically palpable muscle contraction. Disorders of neuromuscular transmission will be discussed in Chap. 21.

## Muscle Contraction

Muscle fibers generate contractile force that is initiated by motor nerves. The term motor unit is applied to a single motor neuron and all the muscle fibers that it innervates. Most muscles contain several hundred motor units.

Muscle contraction is initiated when a sufficient number of acetylcholine molecules bind to the acetylcholine receptors (i.e., ligand-gated channels) of a motor endplate, triggering a local depolarization of the muscle membrane. Muscle fibers have similar electrical properties to those of large unmyelinated axons. After the ligand-gated channels trigger the initial depolarization, a muscle action potential then propagates along the muscle membrane (also known as the sarcolemma) via voltage gated sodium channels. The action potential also triggers voltage gated calcium channels to open at terminal tubules (t-tubules) throughout the sarcolemma. Calcium is stored in the t-tubules, which are invaginations or intracellular extensions of the sarcolemma. The opening of calcium channels leads to an influx of calcium ions into the cytoplasm, activating the contraction of proteins within the sarcomere that generates the actual mechanical force of muscle contraction.

The sarcomere is the basic contractile unit of muscle. Several key filaments exist. Actin filaments are known as the “thin filaments”. They are anchored at the dark

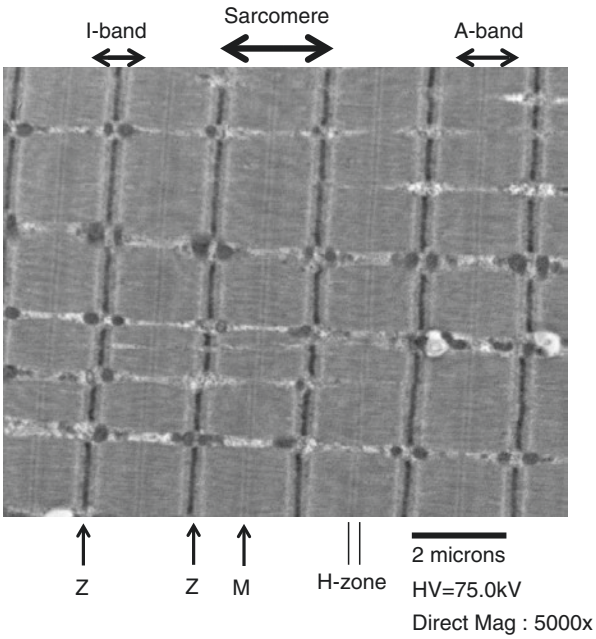


**Fig. 2.4** Ultrastructural image (electron microscopy) of a normal skeletal muscle fiber that is contracted. These myofibers are comprised of alternating dark and light bands each representing the basic contractile unit of muscle known as the sarcomere. Individual sarcomeres are bordered by the dark, vertical Z-lines which act as anchors to which actin filaments attach. The lighter I-bands represent actin without overlying myosin. The darker A-band represents actin with overlying myosin. During muscle contraction, actin filaments are pulled over myosin causing shortening of the I-band as seen in this photo. *Photo credit: Dr. Jean Michaud, Department of Pathology, Children's Hospital of Eastern Ontario*

stripes within the muscle known as the Z-line (Fig. 2.4). One sarcomere is measured as the distance between two adjacent Z-lines. The actin filaments give rise to two 'bands' that are visible by electron microscopy. The I-band is the segment of actin that does not have overlying myosin filaments; it is located immediately next to the Z-band to which it is anchored. The A-band is the segment of actin that does have overlying myosin. Myosin filaments are known as the "thick filaments". The H-zone is the area containing myosin without overlying actin filaments. The M-line is a thin line in the center of the myosin molecule that is formed by cross-connecting elements of cytoskeleton.

Calcium binds to another protein called troponin which causes tropomyosin to slide over actin and muscle contraction to occur. Energy from adenosine triphosphate (ATP) is required to release the myosin head from actin allowing the muscle to relax. It is notable that ATP expenditure is directly related to relaxation of the sarcomere rather than its contraction. This is referred to as the sliding filament theory of muscle contraction.

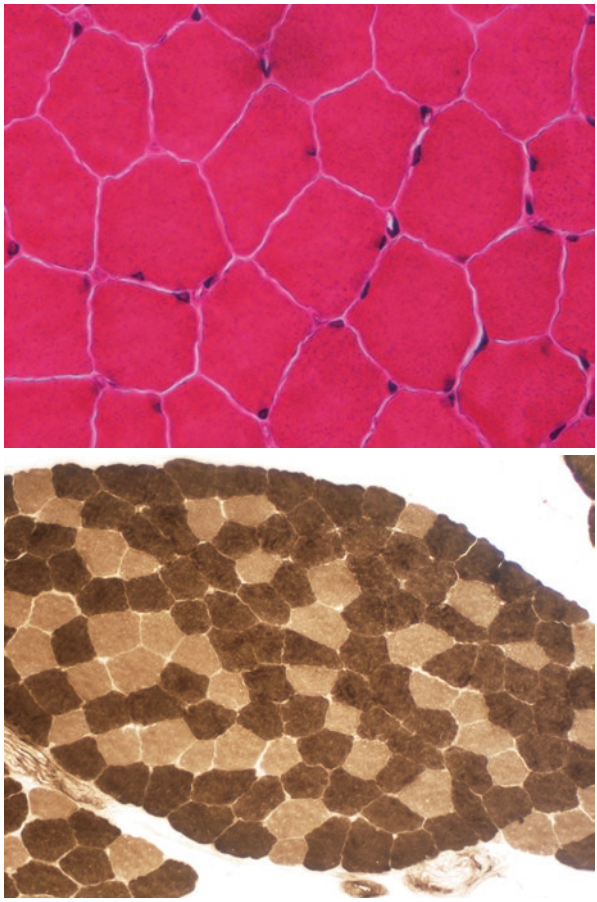

**Fig. 2.5** Microscopic view of normal skeletal muscle seen in cross section, H&E (60× magnification) and ATPase 9.4 staining (20× magnification) showing Type 1 and Type 2 muscle fibers. *Photo credit: Dr. Jean Michaud, Department of Pathology, Children's Hospital of Eastern Ontario*

Disorders of the sarcomere can give rise to a variety of muscle diseases, most notably congenital myopathies which will be discussed in Chap. 22.

## Classification of Skeletal Muscle Fibers

Skeletal muscle fiber types cannot be reliably distinguished on routine Hematoxylin and Eosin (H&E) staining, though sometimes type I fibers may appear darker due to a higher concentration of mitochondria. To distinguish among fiber types consistently, other stains are preferred.

Type 1 fibers are known as slow-twitch oxidative fibers. They demonstrate high oxidative and low glycolytic activity. These fibers are resistant to fatigue and subsequently used in longer-duration, lower-intensity exercise such as low-intensity jogging and maintenance of posture. The abundance of mitochondria in these fibers

causes them to stain darkly on preparations for oxidative enzymes such as nicotinamide adenine dinucleotide tetrazolium reductase (NADH-TR), cytochrome oxidase and succinic dehydrogenase. They also stain darkly on ATPase preparations at pH 4.6 and lightly at pH 9.4. Type 1 fibers correspondingly have low glycogen content (Fig. 2.5).

Type 2 fibers can be divided into two subtypes: Type 2B, also known as fast-twitch glycolytic fibers, demonstrate high glycolytic and low oxidative activity. They are sensitive to fatigue and are recruited for short-duration, high-intensity exercises such as sprinting. The lower abundance of mitochondria in these muscles causes them to stain lightly with preparations for oxidative enzymes thereby differentiating them from Type 1 fibers. Type 2A fibers show an intermediate pattern. Although they are fast-twitch they are more fatigue resistant than Type 2B fibers, and are thus known as fast-twitch oxidative fibers. They show a mix of oxidative and glycolytic capacity thereby showing an intermediate pattern of staining for oxidative enzymes (most noticeable on ATPase preparations at pH 4.6).

Knowledge of fiber type variability can help distinguish among forms of congenital myopathies and metabolic muscle diseases. Of note, type 1 and type 2 muscle fibers show similar electrophysiological properties on routine needle EMG studies, and such examinations cannot distinguish between them.

## References

1. Thomas JE, Lambert EH. Ulna nerve conduction velocity and H-reflex in infants and children. J Appl Physiol. 1960;15:1–9.
2. Shy ME, Garbern GY, Kamholz J. Hereditary motor and sensory neuropathies: a biological perspective. Lancet Neurol. 2002;1:110–8.
3. Smith KJ, Hall SM. Nerve conductions during peripheral demyelination and remyelination. J Neurol Sci. 1980;48:201–19.
4. Fullerton PM, Gilliatt RW, Lascelles RG, Morgan-Hughes JA. The relation between fibre diameter and internodal length in chronic neuropathy. J Physiol Lond. 1965;178:26.
5. Pilling JB. Nerve conduction during Wallerian degeneration in man. Muscle Nerve. 1978;1(1):81.
6. Chaudhry V, Cornblath DR. Wallerian degeneration in human nerves: serial electrophysiological studies. Muscle Nerve. 1992;15(6):687–93.
7. Kimura J, Rodnitzky RL, Okawara SH. Electrophysiological analysis of aberrant regeneration after facial nerve paralysis. Neurology. 1975;25:989–93.