Perspective

Structure and Biomechanics of Peripheral Nerves: Nerve Responses to Physical Stresses and Implications for Physical Therapist Practice

The structural organization of peripheral nerves enables them to function while tolerating and adapting to stresses placed upon them by postures and movements of the trunk, head, and limbs. They are exposed to combinations of tensile, shear, and compressive stresses that result in nerve excursion, strain, and transverse contraction. The purpose of this appraisal is to review the structural and biomechanical modifications seen in peripheral nerves exposed to various levels of physical stress. We have followed the primary tenet of the Physical Stress Theory presented by Mueller and Maluf (2002), specifically, that the level of physical stress placed upon biological tissue determines the adaptive response of the tissue. A thorough understanding of the biomechanical properties of normal and injured nerves and the stresses placed upon them in daily activities will help guide physical therapists in making diagnoses and decisions regarding interventions. [Topp KS, Boyd BS. Structure and biomechanics of peripheral nerves: nerve responses to physical stresses and implications for physical therapist practice. *Phys Ther.* 2006;86:92–109.]

Key Words: *Adaptation, Compression, Excursion, Force, Inflammation, Neurodynamics, Physiology, Plasticity, Sprains and strains, Stress.*

Kimberly S Topp, Benjamin S Boyd

There has been an emergence in physical therapy of evaluation and intervention based on neurodynamics, the relationship between nerve physiology and nerve mechanics.[1] To advance the clinical care of people with nerve injuries, it is essential to understand peripheral nerve structure and plasticity. The purpose of this appraisal is to review the structural and biomechanical properties of peripheral nerves and then to discuss how nerves respond to physical stresses. We will expand on the Physical Stress Theory presented by Mueller and Maluf[2] and discuss the structural and biomechanical modifications seen in nerves exposed to various levels of physical stress. We hold the premise that physical therapists who understand the adaptive responses of nerves to specific physical stresses will be better prepared to provide reasoned interventions to modify specific aspects of the stresses. These knowledgeable therapists also may educate patients in injury prevention and self-care and thus significantly improve function and quality of life.

Physical therapists with an understanding of the adaptive responses of nerves to specific physical stresses will be better prepared to provide reasoned interventions to modify specific aspects of the stresses.

Nerve Structure

The structural organization of peripheral nerves allows axons to conduct impulses that facilitate an individual's interactions with the world while directing and tolerating the myriad postures of the trunk, head, and limbs. Axons within a peripheral nerve are the lengthy extensions of cell bodies located in the dorsal root ganglia (sensory neurons), autonomic ganglia (autonomic neurons), or the ventral horn of the spinal cord or brain stem (motoneurons). Because their terminals are quite distant from the cell bodies, axons are insulated from each other, bundled together, and protected by 3 connective tissue layers—the endoneurium, the perineurium, and the epineurium (Fig. 1). Axons, Schwann cells, and endoneurial components are bundled by a sheath of perineurium to form a nerve fascicle. Several fascicles are held together by epineurial tissue to form a nerve.

Within the endoneurium, all axons are intimately associated with Schwann cells. As shown in Figure 1, the myelin of each myelinated axon is formed from the plasma membrane of a Schwann cell wrapped tightly multiple times around the axon. Thus, a single Schwann cell envelops a single myelinated axon, forming an internode. Along a myelinated axon, the points of separation between myelinating Schwann cells in series are called *nodes of Ranvier*. Unmyelinated axons are enveloped by Schwann cell cytoplasm and plasma membrane but do not have multiple wrappings of Schwann cell plasma membrane. A single Schwann cell may envelop several unmyelinated axons. The Schwann cell of each myelinated axon or group of unmyelinated axons is surrounded by a basal lamina of type IV collagen, fibronectin, laminin, and heparan sulfate proteoglycan.[3] Between the axons is a loose connective tissue of type I and type II collagen fibrils in longitudinal orientation, fibroblasts, a few mast cells and macrophages, and endoneurial fluid (Fig. 2).

Bundles of axons are grouped into fascicles by a dense connective tissue called *perineurium* (Fig. 1). The perineurium is formed by up to 15 layers of flat perineurial cells interspersed with layers of type I and type II collagen fibrils and elastic fibers in circumferential, oblique, and longitudinal orientations (Figs. 1 and 2).[4] Each layer of perineurial cells has a nearly complete basal lamina,[3] and the very organized basal lamina of the innermost layer contains laminin, as well as heparan sulfate proteoglycan and fibronectin.[5] Adjacent perineurial cells are linked by tight junctions, and the most internal perineurial cells form a perineurial diffusion barrier that functions with the blood-nerve barrier in controlling the endoneurial environment.[6,7] These layers of collagen and perineurial cells provide mechanical strength, making the perineurium the primary load-bearing portion of the nerve.[8–10]

Nerve fascicles are held together and surrounded by a connective tissue layer, termed the *epineurium* (Fig. 1). If the nerve contains more than one fascicle, the epineurium may be divided into epifascicular epineurium surrounding

KS Topp, PT, PhD, is Associate Professor, Department of Physical Therapy and Rehabilitation Science and Department of Anatomy, University of California, San Francisco, 1318 7th Ave, Box 0736, San Francisco, CA 94143-0736 (USA) (toppk@ptrehab.ucsf.edu). Address all correspondence to Dr Topp.

BS Boyd, PT, MSPT, is Staff Physical Therapist, Department of Physical Therapy and Rehabilitation Science, University of California, San Francisco.

Dr Topp and Mr Boyd coauthored this article and contributed equally in inception, development, and presentation of the novel concepts and artwork. The authors acknowledge the assistance of Christian Puttlitz, PhD, and Jerylin Gan.

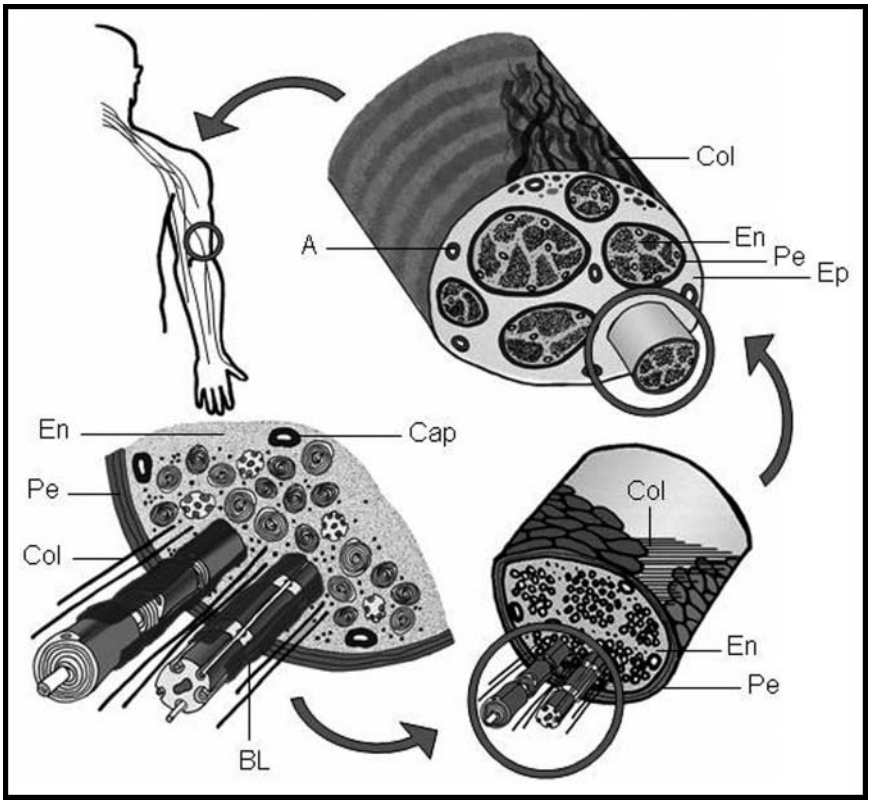


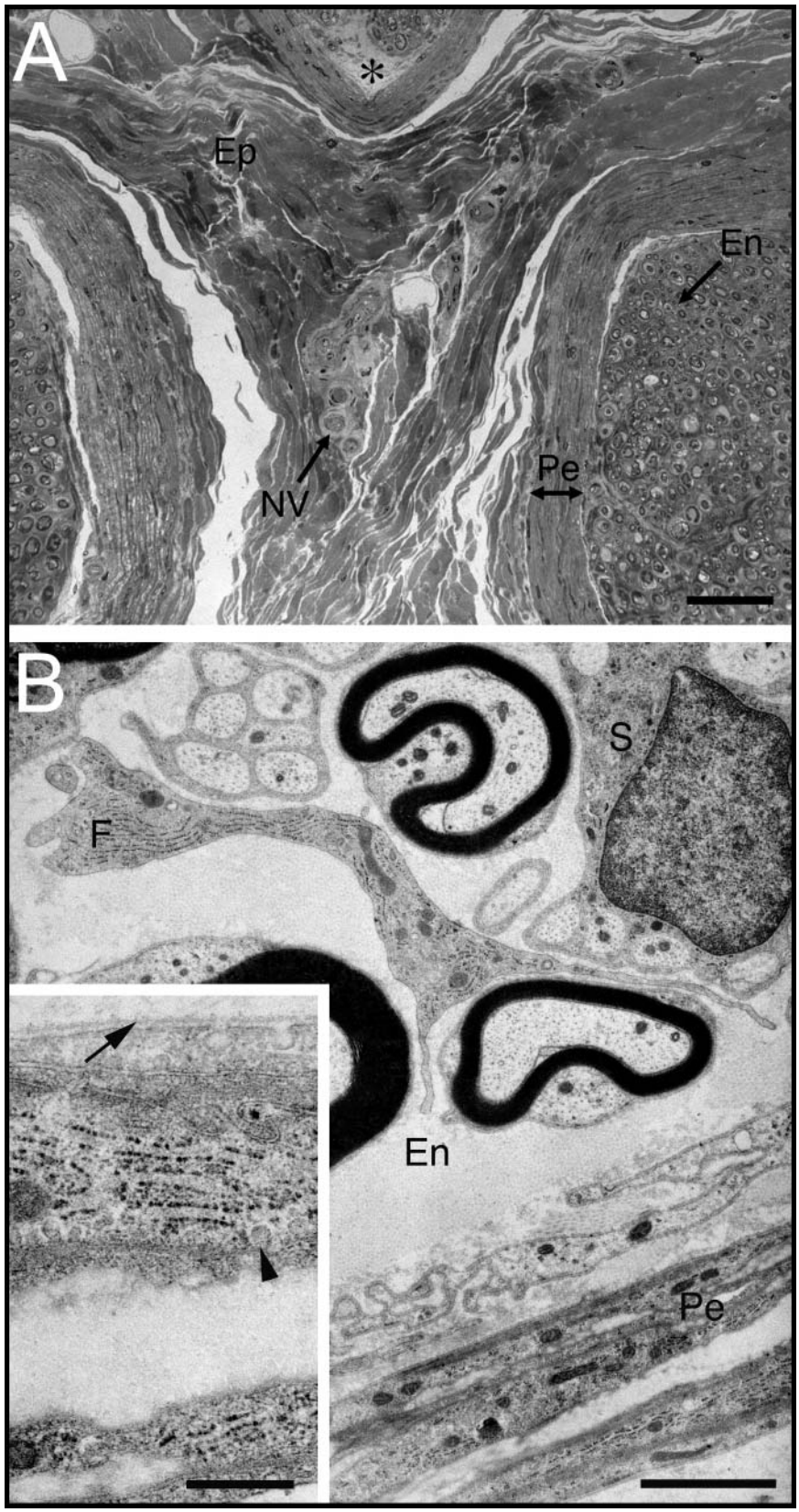
Figure 1.
Structural components of peripheral nerves. In the endoneurial compartment (En), a single Schwann cell envelops several unmyelinated axons, and another Schwann cell provides multiple wrappings of plasma membrane forming the myelin sheath of a myelinated axon. The portion of a myelinated axon myelinated by a single Schwann cell is called the internode, and internodes are separated by nodes of Ranvier. Schwann cells associated with both unmyelinated and myelinated axons are covered with a continuous basal lamina (BL). Capillaries (Cap) are present within the endoneurial compartment, and collagen fibers (Col) run primarily longitudinally between the axons. The axons, Schwann cells, collagen, and endoneurial fluid are bundled into a fascicle by the perineurium (Pe). The perineurium consists of several layers of flattened perineurial cells connected by tight junctions and covered internally and externally by a basal lamina. The layers of perineurial cells are separated by collagen fibers (Col) oriented obliquely. Several fascicles are bundled together by the epineurium (Ep) to form a nerve. The epineurium consists primarily of fibroblasts, collagen fibers (Col), and elastic fibers. The epineurium between fascicles is termed the *interfascicular epineurium*, and that encompassing all of the fascicles is termed the *epifascicular epineurium*. Arterioles (A) and veins are oriented primarily longitudinally within the epineurium.

the entire nerve and interfascicular epineurium separating nerve fascicles (Fig. 2). The epineurial layer includes bundles of type I and type III collagen fibrils and elastic fibers, as well as fibroblasts, mast cells, and fat cells. In a slackened position in situ, the epineurial collagen fibrils have an undulated orientation that is visible as periodic light-reflecting bands.[11] The number of fascicles and the proportion of epineurial connective tissue are variable between nerves and along the length of a single nerve.[12] Axons do not remain in the same fascicle throughout their length.[13,14] The interchange of axons between fascicles may help to minimize functional deficits following partial injury to the nerve,[12] but also may result in a wide distribution of macrophages cleaning up the debris from axons undergoing Wallerian degeneration after injury. Interfascicular epineurium is loosely attached to the perineurium, allowing for sliding of one fascicle independently of an adjacent fascicle (Fig. 2).[15] There is abundant epineurial connective tissue in nerves that contain many fascicles, and the connective tissue facilitates the dispersion of compressive forces.[16]

The outermost tissue of the epineurium is attached to paraneural fascial components of the connective tissue surrounding the epineurium,[15] and the density and strength of the attachments differ along the length of a nerve. The paraneural loose connective tissue may contain a significant amount of adipose tissue, which serves to protect the nerve at sites of recurrent compression and facilitates transverse and longitudinal gliding of the nerve within the nerve bed. The epineurium is more tightly adherent to the surrounding connective tissues where vessels enter or exit the nerve and where the nerve branches.[15] Additionally, there are points at which a nerve may be firmly attached to an anatomical landmark, such as the attachment of the common peroneal nerve near the neck of the fibula.

The blood supply to nerves is provided by coiled segmental arteries that enter the epineurium periodically along the length of the nerve and form the vasa nervorum. Arteries divide into epineurial arterioles that form an anastomotic network running primarily longitudinally within the epifascicular epineurium and the interfascicular epineurium (Fig. 3). Epineurial arterioles are supplied with a perivascular plexus of serotoninergic, adrenergic, and peptidergic nerves.[17,18] Perforating arterioles cross the perineurium at oblique angles and carry a short sleeve of perineurial cells into the fascicle.[3,19] Perineurial arterioles have poorly developed smooth muscle and thus have limited ability to regulate intrafascicular blood flow.[20] Within the endoneurium, arterioles immediately turn into large-diameter, longitudinally oriented capillaries that allow blood flow in either direction (Fig. 3).[21] The endothelial cells of endoneurial capillaries are connected by tight junctions, thus forming the tight blood-nerve barrier.[7] Venules return blood to the venous system. Of note, lymphatic capillaries are present only

Figure 2.
Light and electron microscopic images of cross sections of peripheral nerve. (A) Light micrograph of a 1-μm-thick plastic section of cadaveric, human ulnar nerve taken from 3 cm proximal to the cubital tunnel and stained with toluidine blue. A neurovascular bundle (NV) is seen within the interfascicular epineurium (Ep) that separates 3 nerve fascicles. A sheath of perineurium (Pe) defines each fascicle. The endoneurium (En) is internal to the perineurial sheath. Axons are located within the endoneurial compartment. A large deposition of endoneurial collagen (asterisk) is seen in the fascicle at the top of the figure. The loose connections between the outer layer of the perineurial sheaths and the interfascicular epineurium allow for independent sliding of fascicles within the nerve. Bar=100 μm. (B) Electron micrograph of 80-nm ultrathin plastic section of rat saphenous nerve stained with uranyl acetate and lead citrate. Large myelinated and small unmyelinated axons are seen within the fascicle bounded by perineurial cells (Pe). Within the endoneurial compartment (En), Schwann cells (S), fibroblasts (F), and longitudinally oriented collagen fibers are seen. Bar=5 μm. (Inset) Perineurial cell layers have basement membranes (arrow) on their inner and outer surfaces. Many pinocytotic vesicles (arrowhead) are seen associated with perineurial cell membranes. Inset bar=500 nm.



within the epineurium; there is no lymphatic drainage from the intrafascicular or endoneurial space.[22]

Biomechanical Properties of Nerves

Under normal physiological conditions imposed by posture and movement, nerves are exposed to various mechanical stresses. *Stress* is defined as force divided by the area over which it acts[9,23–25] and can be applied to a nerve as tensile, compressive, or shear stress or as a combination of stresses (Fig. 4). Tensile stress may be applied to tissues either parallel or perpendicular to the length of the nerve, causing respective longitudinal or transverse stress in the nerve. When joint motion causes elongation of the nerve bed, the nerve is inherently placed under tensile stress and accommodates the stress by both elongating and gliding.[15] The deformation or change in nerve length induced by longitudinal tensile stress is called *strain* and is expressed typically as percent elongation.[23,26–28] Displacement or gliding of a nerve relative to the surrounding nerve bed is called *excursion*.[29–31] The direction of excursion

may be longitudinal or transverse, or both, relative to the nerve tract[31,32] and is measured in millimeters.

The direction and magnitude of nerve excursion are dependent upon the anatomical relationship between the nerve and the axis of rotation in the moving joint.[29,33] When the nerve bed is elongated, the nerve is placed under increased tensile stress. With the elongation of the nerve bed, the nerve glides toward the moving joint,[1,33,34] a movement termed *convergence*.[1] Conversely, if the nerve bed tension is relieved during joint motion, the nerve will realign along the shortened nerve bed by gliding away from the moving joint, a movement termed *divergence*.[33] Convergence in the median nerve may be demonstrated during elbow extension (Fig. 5). The motion elongates the bed of the median nerve, causing the nerve segment in the arm to glide distally toward the elbow and the nerve segment in the forearm to glide proxi mally toward the elbow. In contrast, elbow extension relieves the tensile stresses in the ulnar nerve bed, causing the ulnar nerve to diverge away from the elbow (Fig. 5). With limb movement, nerve excursion occurs first in the nerve segment immediately adjacent to the moving joint. As limb movement continues, excursion occurs at nerve segments that are progressively more distant from the moving joint.[29,33] Similarly, the magnitude of excursion is greatest in the nerve segments adjacent to the moving joint and is least in the nerve segments distant from the joint (Fig. 5).[29,33,34] The magnitude and direction of median and ulnar nerve excursion for motions of the joints of the upper limb commonly used in clinical assessment are shown in Table 1.

As tensile stresses cause measurable nerve excursion, they simultaneously produce changes in strain within the nerve. Elongation of a nerve bed during joint movement will cause an increase in nerve strain (Fig. 6). The magnitude of increased strain with limb movement is greatest in the nerve segment closest to the moving joint (Fig. 6).[33–35] The mechanical behavior of a nerve segment under longitudinal tensile force may be described by a load-elongation curve,[36] or by a stress-strain curve if the force is divided by the cross-sectional area of the nerve, and elongation is expressed as a percentage of the starting length (Fig. 7). When a load is first applied to a resting nerve, the nerve lengthens markedly relative to the applied load, as shown in the "toe region" of the curve. Structurally, the minimal longitudinal tensile load results in straightening of the wavy connective tissue and axons in the endoneurial compartment and in the disappearance of the periodic light-reflecting bands in the epineurium.[12,37,38] As the tensile load is increased, the nerve elongates at a steady rate, as demonstrated by the linear region of the load-elongation curve (Fig. 7). The slope of this portion of the curve is a measure of the resistance of the nerve to deformation and is termed *stiffness* in the load-elongation curve or *modulus of elasticity* in the stress-strain curve. A steep slope indicates that the nerve has more stiffness, has less elasticity, and is less compliant than a nerve with a shallower slope. At a certain point, the amount of applied load starts to permanently deform particular elements of the nerve. This ultimate stress or ultimate strain represents the transition between the recoverable (elastic) strain and plastic (permanent) deformation areas of the load-elongation curve. Finally, in the plastic region of the curve, the nerve reaches its ultimate elongation and undergoes mechanical failure. Minor increases in tensile load create significant elongation of the nerve because of the failure of the infrastructure of the nerve, including perineurial components. There are fewer intact structural elements to provide resistance, and at this point, the nerve behaves like a viscous material.[36]

A nerve in situ is under some tensile load, as evidenced by the fact that a nerve in situ retracts when severed. The percent change in length is termed the *in situ strain*,[37] which corresponds approximately to the transition between the toe region and the linear region of the stress-strain curve. The magnitude of the in situ strain is dependent upon the configuration of the nerve bed. In a slackened position, such as in the rabbit tibial nerve when the knee and ankle are each maintained at 90 degrees of flexion, the in situ strain is 11%.[37] Extension of the knee or dorsiflexion of the ankle places greater tensile force on the nerve in the elongated nerve bed, and the in situ strain increases from the original 11%. Interestingly, it has been suggested that the toe region of the stress-strain curve may be a property of excised nerves, as in situ nerves immediately enter the linear portion of the stress-strain curve when placed under increasing tensile stress from a "rest" position.[39] Because the in situ strain is a direct reflection of cumulative nerve positioning across multiple joints, one must consider the effect of trunk, neck, and limb positioning during clinical assessment and intervention to minimize physical stress on an injured nerve.

To elongate a nerve, thus increasing its strain, the tensile strength inherent in the nerve from elastic and connective tissues must be overcome. Elongation of a nerve is known to cause a reduction in the cross-sectional area, a property called *transverse contraction*[15] (Fig. 4). This property results in increased pressure in the endoneurial compartment. A recently proposed theoretical model suggested that the outer connective tissue tube or sheath constraining the inner pressurized neural core contributes significantly to the biomechanical properties of a nerve placed under tensile strain.[15,39] Upon elongation of a nerve, the increased pressure produced in the neural core will resist the transverse contraction and will

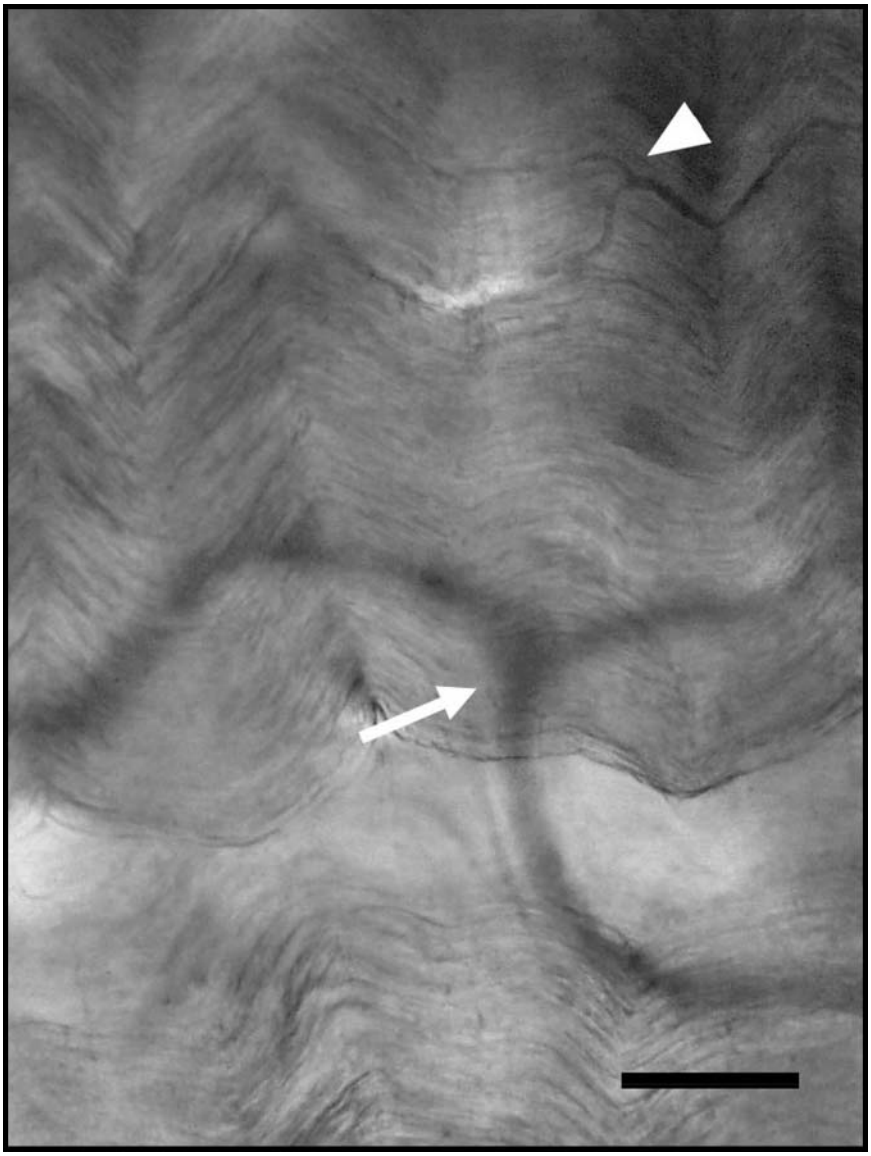


Figure 3.
Full-thickness longitudinal segment of rat sciatic nerve stained with toluidine blue for contrast. Large blood vessels are seen running primarily longitudinally in the epineurial tissue (arrow), and branches of wide capillaries are present within the endoneurial compartment (arrowhead). The undulations of axons and endoneurial capillaries present in this nerve segment are known to disappear when the nerve is placed under longitudinal tensile stress. Bar=50 μm.

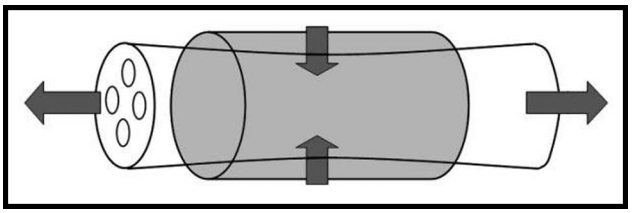


Figure 4.
Physical stresses placed on peripheral nerve. Tensile stress applied longitudinally to peripheral nerve creates an elongation of the nerve (an increase in strain). The transverse contraction that occurs during this elongation is greatest at the middle of the section undergoing tensile stress.

contribute to the stiffness of the nerve when stretched.[15] When the tensile stress is removed, it is likely that a combination of elasticity of the connective tissues and pressure within the neural core will allow recoiling of the nerve to nearly the original cross-sectional area and length. Recent studies[40,41] defined the core-sheath interface as the innermost cell layer of the perineurium and suggested that the interface provides some minimal resistance to elongation. With increasing tensile load, structural separation occurs first in the core-sheath interface, then in the axons and connective tissues in the endoneurial core, and finally in the cells and connective tissues of the perineurial and epineurial sheath. It is important to understand that diffuse damage to axons in the endoneurial core may occur long before visible damage to the epineurium.

There are a number of factors that affect nerve compliance and thus dictate the level of strain, excursion, and transverse contraction in the nerve during limb movement.[12,24,42] First, a recent study[43] measured greater nerve compliance in nerve segments that cross joints than in segments that do not cross joints. The median and sciatic nerves exhibit more strain in situ and less stiffness ex vivo in the segments that cross the elbow and hip than in distal segments that do not cross the respective joint. Although the biomechanical findings correlated with fascicle number and cross-sectional area of extrafascicular connective tissues in the sciatic nerve, there was no such correlation in the median nerve. It was initially thought that there are more fascicles and connective tissues where nerves cross joints[12] and greater stiffness in nerve segments with multiple fascicles.[9,12] However, these notions do not seem to hold true for all nerves at all joints.[43] Thus, internal neural structure is but one factor affecting nerve compliance.

Second, nerve stiffness is greater in long nerve sections and in nerve sections with numerous branches.[15] Severing nerve branches or vessels but leaving the nerve in situ results in increased compliance and decreased stiffness.[15] Excising the same nerve completely from its

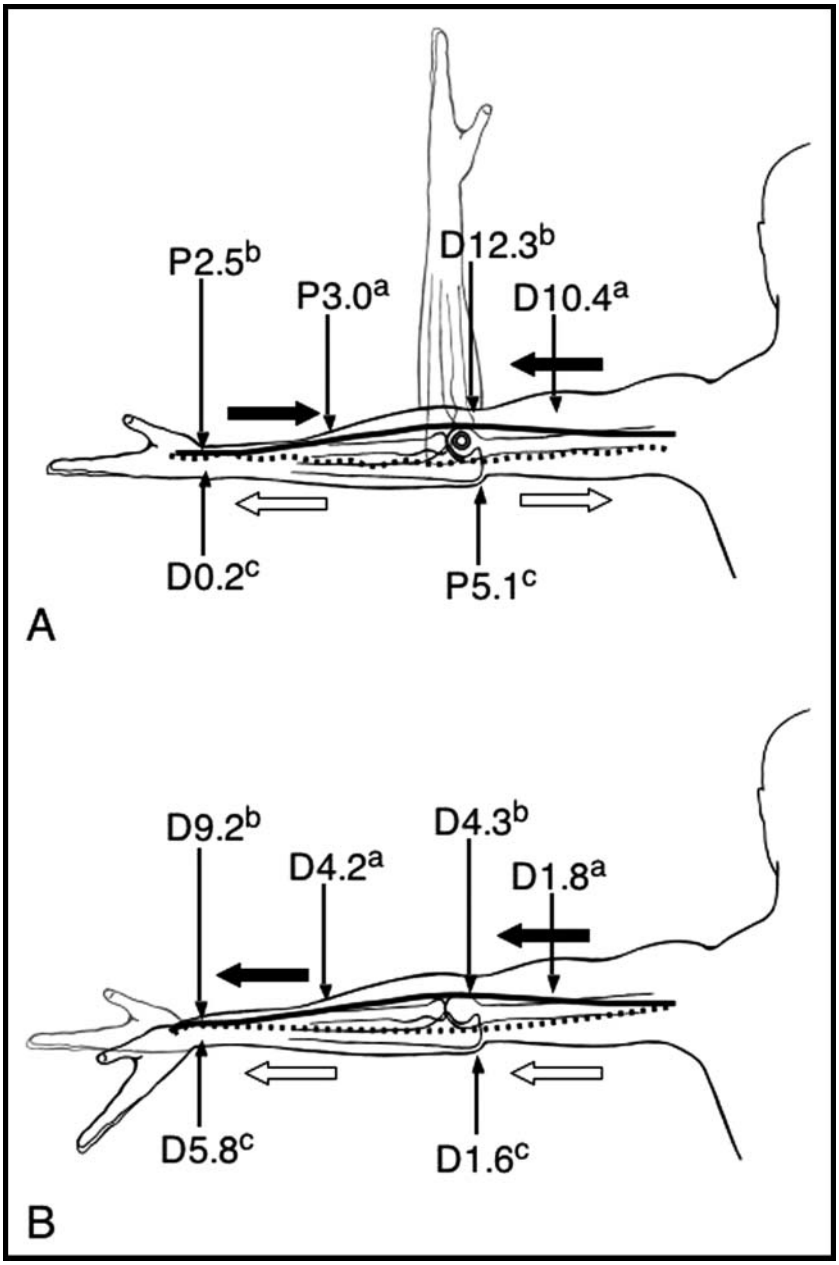


Figure 5.
Excursion of the median nerve (solid line) and the ulnar nerve (dotted line) during elbow extension followed by wrist extension. The concepts of nerve convergence toward and divergence away from a moving joint are illustrated in measurements of excursion taken at each site indicated. All measurements are reported in millimeters of proximal (P) or distal (D) excursion. The direction of excursion is also represented by solid arrows for median nerve excursion and open arrows for ulnar nerve excursion. (A) With elbow extension from 90° of flexion to 0° of flexion, the median nerve bed lengthens and the median nerve glides toward the elbow (converges). With the same joint motion, the ulnar nerve bed shortens and the ulnar nerve glides away from the elbow (diverges). (B) With wrist extension from 0° of extension to 60° of extension, both nerve beds lengthen; thus, both nerves converge toward the wrist. The magnitude of excursion is greatest closest to the moving joint. Data were obtained from: [a]Dilley et al,[29] [b]Wright et al,[27] and [c]Wright et al.[33] Measurements of nerve excursion at the wrist and elbow in panel A were extrapolated from studies of nerve excursion during elbow flexion from 0° to 90°.[27]

nerve bed results in further increases in compliance, likely because of reduced friction between the nerve and paraneural tissues[15] and possibly because of a loss of internal pressure.[39]

Third, nerve stiffness is greater when a nerve is elongated rapidly rather than slowly. In addition, the ultimate strain at the point of failure appears to be dependent on the rate of elongation. Haftek[36] measured compliance in excised rabbit tibial nerves elongated at 0.5 mm per minute to the point of failure. At this point, the nerves had a mean ultimate elongation, or strain, of 55.7%. Rydevick et al[10] elongated excised rabbit tibial nerves at 1.0 cm per minute, or 20 times faster, and found a mean ultimate strain of 38.5%. The reduction in the ultimate strain suggests that nerves elongated at a greater rate exhibit a reduction in their ability to tolerate elongation. These rate-dependent effects are characteristic of tissues that exhibit viscoelastic behavior.

When a nerve is placed under tension and maintained at that new fixed length over time, there is a reduction in the tension in the nerve or the force required to maintain the fixed length. The observed reduction in tension may be plotted in a stress-relaxation curve (Fig. 8).[25,44] The majority of relaxation occurs in the first 20 minutes of fixed elongation.[25,44] Stress relaxation in nerves that are stretched slowly is greater than in nerves that are stretched rapidly.[25,37,44–46] This phenomenon was observed when comparisons were made for rabbit tibial nerves stretched at different rates to lengths 6% longer than their resting lengths. Over the 60-minute relaxation time, there was a 57% reduction in stress in nerves elongated at 0.08% per second,[45] but only a 34% reduction in stress in nerves elongated at 3.0% per second.[44] The same effect was noted for nerves that were subjected to 12% strain.[44,45] A phenomenon analogous to stress-relaxation behavior, commonly referred to as "creep," is seen when a nerve is maintained under a fixed tensile load. Nerve tissue elongates grad-

Table 1.
Excursion in Median and Ulnar Nerves During Selected Limb Movements[a]

Nerve	Joint Movement	Site of Measurement: Mid-Arm	Elbow	Mid-Forearm	Wrist	Limb Position
Median	Metacarpophalangeal extension, digits 2–5 (90°–0°)			Dist 2.62		Unspecified shoulder and elbow; wrist neutral[b]
	Wrist extension (0°–full/60°)	Dist 1.8		Dist 4.2		90° shoulder abduction; 0° elbow flexion[c]
		Dist 2.4		Dist 4.7		45° shoulder abduction; 0° elbow flexion[c]
			Dist 4.3		Dist 9.2	90° shoulder abduction; 10° elbow flexion[d]
	Elbow extension (90°–0°)	Dist 10.4		Prox 3.0		90° shoulder abduction; wrist neutral[c]
				Prox 4.2		90° shoulder abduction; 45° wrist extension[c]
	Elbow flexion (0°–90°)		Prox 12.3		Dist 2.5	90° shoulder abduction; wrist neutral[d]
	Shoulder abduction (10°–90°)	Prox 3.4		Prox 5.2		0° elbow flexion; wrist neutral[c]
	Shoulder abduction (90°–110°)		Prox 4.4		Prox 1.4	10° elbow flexion; wrist neutral[d]
	Shoulder adduction (90°–30°)		Dist 4.7		Dist 1.5	10° elbow flexion; wrist neutral[d]
Ulnar	Wrist extension (0°–full/60°)		Dist 1.6		Dist 5.8	90° shoulder abduction; 10° elbow flexion[e]
	Wrist flexion (0°–65°)		Prox 0.1		Prox 7.8	90° shoulder abduction; 10° elbow flexion[e]
	Elbow flexion (0°–90°)		Dist 5.1		Prox 0.2	90° shoulder abduction; wrist neutral[e]
	Elbow flexion (0°–140°)		Dist 14.0			0° shoulder abduction; wrist neutral[f]
	Shoulder abduction (90°–110°)		Prox 3.3		Prox 0.4	10° elbow flexion; wrist neutral[e]
	Shoulder adduction (90°–30°)		Prox 1.7		Prox 0.2	10° elbow flexion; wrist neutral[e]

[a] All measurements are reported in millimeters of excursion in the proximal (Prox) or distal (Dist) direction. Sources are listed by authors, materials or subjects, and measurement tool.
[b] From Erel et al, live subjects, ultrasound.[31]
[c] From Dilley et al, live subjects, ultrasound.[29]
[d] From Wright et al, fresh cadaver transthoracic region, microsuture marker.[27]
[e] From Wright et al, fresh cadaver transthoracic region, microsuture marker.[33]
[f] From Grewal R, Varitimidis S, Vardakas D, et al. Ulnar nerve elongation and excursion in the cubital tunnel after decompression and anterior transposition. *J Hand Surg Br.* 2000;25:457–460, fresh cadaver disarticulated arm, steel wire marker.

ually under these loading conditions. Both stress relaxation and creep are used to quantitatively describe the viscoelastic behavior of a material[46] and may provide some protection for nerves during postures in which nerves are under prolonged lengthening and tensile loads.

Tensile stress applied repetitively also may alter the stress-strain curve. At strains below 8%, repetitive stretch has no effect on the stress-strain curve, as shown in a rabbit model of sciatic nerve strain in situ.[47] However, a nerve stretched repetitively to 8% or 10% strain exhibits a reduced slope of the stress-strain curve, indicating that that nerve undergoes less stress with successive elongations because of increased compliance and decreased stiffness. Note that repetitive application of a consistent tensile stress will result in a progressive increase in nerve strain. As discussed in the section on the responses of nerves to physical stress, high levels of strain will result in physiological and structural alterations in the nerve. This information provides a rationale for incorporating activity modification into patient education.

In addition to tensile stress, nerves are exposed statically and dynamically to compressive stresses. As mentioned previously, the laws of physics dictate that the cross-sectional area of a cylindrical object is reduced as the cylinder is elongated. As a nerve is elongated under tensile force, the nerve undergoes transverse contraction, which is resisted by the fluid and nerve tissue contained within the connective tissue sheath.[15,39] The magnitude of the transverse contraction stress is greatest at the center of the elongating segment[15] (Fig. 4). Nerves also may be compressed externally by approximation to adjacent tissues, such as muscle, tendon, or bone, or by pressure increases in the extraneural environment. Compression of a nerve segment causes displacement of its internal contents in transverse and longitudinal directions. As shown in rat nerve, extraneural compression causes an immediate displacement of endoneurial fluid to the edges of a compressive cuff over 5 to 10 minutes and a much slower displacement of axonal cytoplasm over the course of hours.[48] The damage to axons and myelin is greatest at the edges of the compressed zone,[48,49] where the shear forces are high-

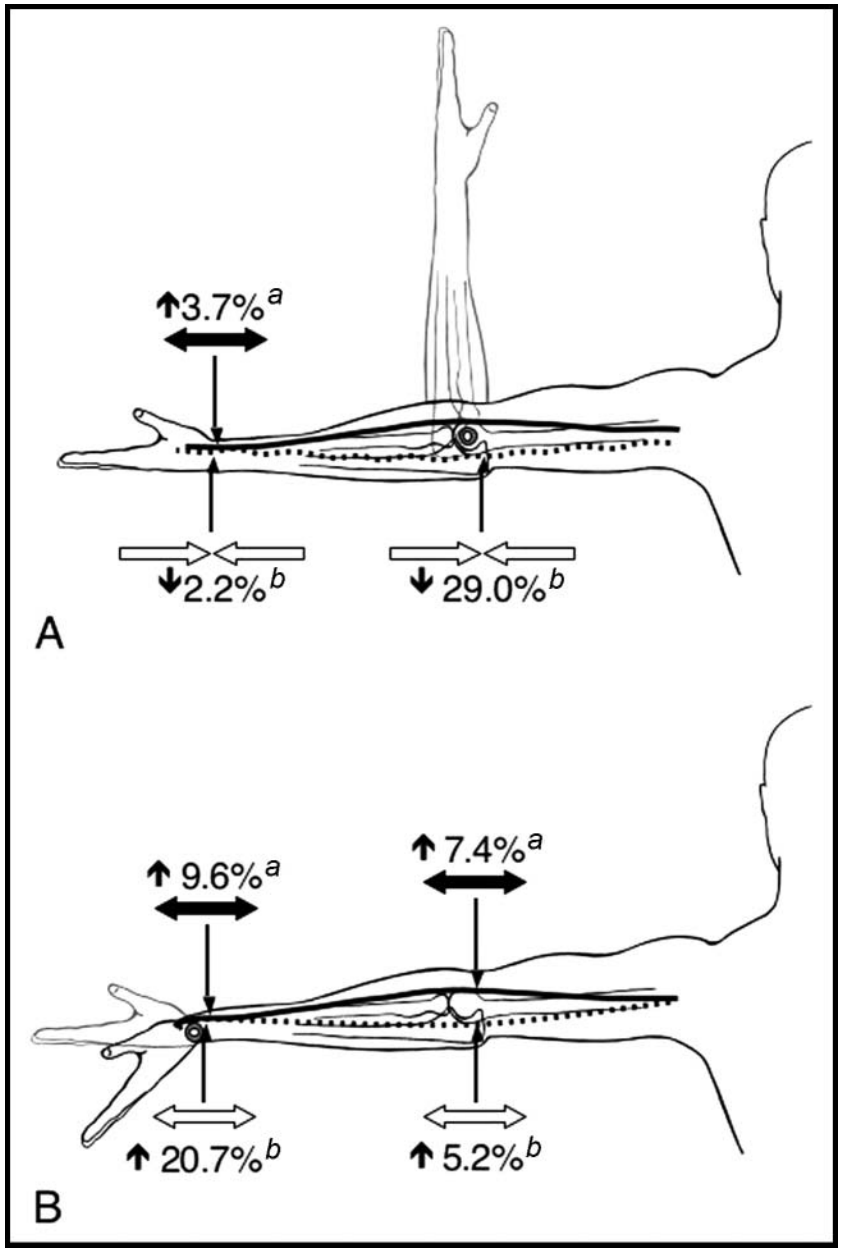


Figure 6.
Strain of the median nerve (solid line) and the ulnar nerve (dotted line) during elbow extension followed by wrist extension. Measurements at the sites indicated are reported as percent increase (↑) or percent decrease (↓) in strain. (A) With elbow extension from 90° of flexion to 0° of flexion, median nerve strain increases because of elongation of the nerve bed. Conversely, ulnar nerve strain decreases as the ulnar nerve bed shortens. (B) With wrist extension from 0° of extension to 60° of extension, the strain at the sites measured increases in both nerves as both nerve beds elongate. The magnitude of the strain is greatest closest to the moving joint. Data were obtained from: [a]Wright et al[27] and [b]Wright et al.[33] Measurements of nerve excursion at the wrist and elbow in panel A were extrapolated from studies of nerve excursion during elbow flexion from 0° to 90°.[27]

est.[50] In a carefully controlled study, Dyck and colleagues[48] demonstrated that under a compressive cuff, lengthening of internodes, cleavage of paranodal myelin, and myelin laminae overlapping nodes occurred. At the edges of the cuff, however, myelin retraction with resultant widening of nodes and paranodal demyelination occurred. These structural alterations in myelin may be expected to result minimally in impaired impulse conduction or maximally in demyelination and a conduction block.

In response to biomechanical stresses placed on a nerve as an individual assumes a posture or movement, the nerve follows the path of least resistance.[29] Combinations of tensile, shear, and compressive stresses result in combinations of nerve excursion, strain, and transverse contraction. Because the biomechanical forces on the nerve are so intricately linked, the sequencing and range of joint movement affect the magnitude and direction of excursion,[27,29] the magnitude of nerve strain,[27,29,35] and the degree of transverse contraction at different sites along the nerve.[27] An extensive review of the literature has allowed us to formulate tables of the normal ranges of excursion (Tab. 1) and strain (Tab. 2) in 2 upper-extremity nerves measured subsequent to movements of the upper extremity. It is important to note that the magnitude of strain achieved with normal range of motion approaches or exceeds the magnitude known to result in physiological changes in the nerve. In comparing data from different studies, one must make note of the test position, location of the measurement, measurement tools, and type of specimen used in each study.

Simultaneous nerve excursion, strain, and transverse contraction may be seen in the ulnar nerve as an example of responses to physical stresses imposed during movements of the upper limb. When the upper limb is maintained in a position of 90 degrees of shoulder abduction and 90 degrees of shoulder external rotation with the wrist neutral,

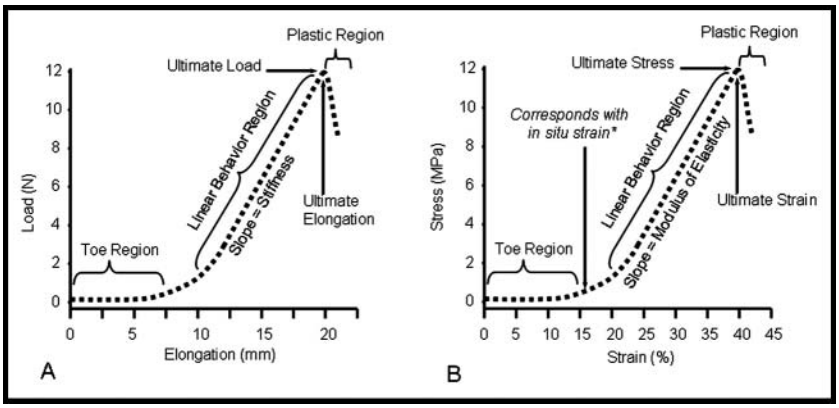


Figure 7.
Typical load-elongation and stress-strain curves for peripheral nerve. The transition between the toe region and the linear region in the stress-strain curve (asterisk) has been shown to approximately correspond with the strain in situ. The slope of the stress-strain curve is called the *modulus of elasticity* and represents the stiffness of the nerve, as seen in the load-elongation curve. If the slope is steep, then the nerve has more stiffness and is less compliant to elongation. If the slope is shallow, then the nerve has less stiffness and is more compliant to elongation. Once the nerve has reached ultimate strain, the structural integrity of the nerve is overcome and the deformation is termed "plastic" or "permanent." Modified from Kwan MK, Wall EJ, Massie J, Garfin SR. Strain, stress, and stretch of peripheral nerve: rabbit experiments in vitro and in vivo. *Acta Orthop Scand*. 1992;63:267–272, with permission of Taylor and Francis AS.

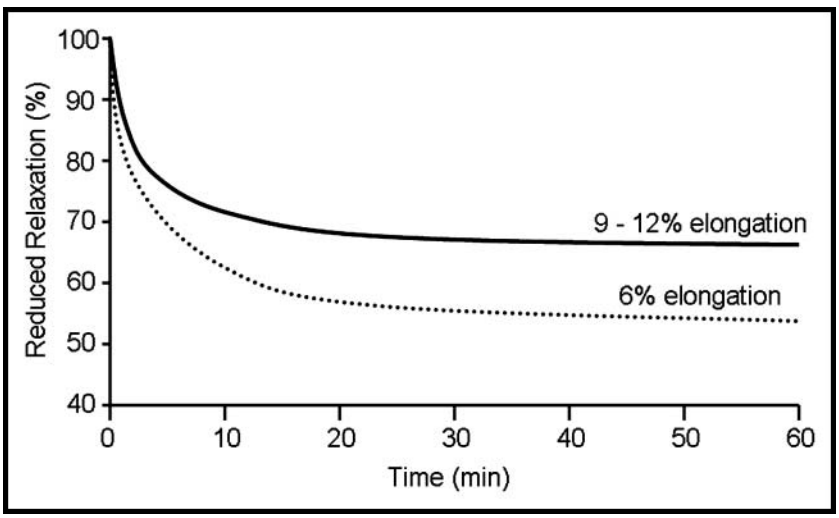


Figure 8.
Stress-relaxation curve demonstrating viscoelastic properties of peripheral nerve. When a nerve is elongated and the new length is kept constant, there is a rapid reduction in the stress within the nerve, expressed as percent reduced relaxation. Most of the relaxation occurs in the first 20 minutes. The degree of elongation affects the amount of stress relaxation that will occur. The dotted line represents a nerve that has been elongated to 6% above its resting length. The solid line represents nerves that have been elongated to 9% and 12% above their resting lengths. Greater stress relaxation was documented in nerves that underwent less elongation.[25,44] Modified from Kwan MK, Wall EJ, Massie J, Garfin SR. Strain, stress, and stretch of peripheral nerve: rabbit experiments in vitro and in vivo. *Acta Orthop Scand*. 1992;63:267–272, with permission of Taylor and Francis AS.

and when the elbow is moved from 90 degrees of flexion to full extension, the ulnar nerve bed is shortened and the tensile stress on the nerve is decreased. With this motion, there is divergence of the ulnar nerve away from the elbow (Fig. 5), decreased nerve strain, especially at the elbow (Fig. 6), and decreased compression within the cubital tunnel.[27,29,33] When the wrist then is extended from neutral to full extension, the ulnar nerve bed is lengthened, resulting in convergence of the nerve toward the wrist (Fig. 5), an increase in nerve strain (Fig. 6), and transverse contraction greatest in the nerve segment across the carpal bones and at the tunnel of Guyon.[27,29,33] The magnitude of nerve strain and excursion will be greatest near the wrist, and the fascicles will rearrange as the nerve assumes a flattened oval shape. Because the nerve does not lie directly on the rotational axis of joint motion, the fascicles farthest from the axis will undergo greater strain than those closer to the center of rotation[51] The magnitude of these biomechanical effects will depend upon the rate at which the limbs are moved, the time spent in each position, and the temporal aspects of the movement if the motion is repetitive. A thorough understanding of the anatomical and biomechanical relationships of nerves and surrounding tissues is necessary to interpret the responses of patients to postures and movements of the trunk, head, and limbs.

Responses of Nerves to Physical Stresses

The structural and biomechanical properties of a normal nerve may be modified as the nerve responds to the physical stresses placed upon it through extrinsic movements and postures. In this discussion, *physical stress* is defined as the force or load acting on a given area of tissue.[23–25] As put forth by Mueller and Maluf[2] in their Physical Stress Theory, the level of physical stress placed on a biological tissue dictates the adaptive response of the tissue. Several concepts outlined in the Physical Stress Theory expand on this tenet.

Table 2.
Percent Strain in Median and Ulnar Nerves During Selected Limb Movements[a]

Nerve	Joint Movement	Site of Measurement: Axilla	Elbow	Wrist	Limb Position
Median	Wrist extension (0°–full/60°)	3.04 ↑	3.72 ↑	8.34 ↑	Unspecified[b]
			2.0 ↑		80° shoulder abduction; 90° elbow flexion[c]
			7.4 ↑	9.6 ↑	90° shoulder abduction; 10° elbow flexion[d]
	Elbow extension (90°–0°)	8.73 ↑	8.44 ↑	4.81 ↑	Unspecified[b]
			3.6 ↑		80° shoulder abduction; 60° wrist extension[c]
				3.7 ↑	90° shoulder abduction; wrist neutral[d]
	Shoulder abduction (90°–110°)		9.1 ↑	3.7 ↑	10° elbow flexion; wrist neutral[d]
	Shoulder adduction (90°–30°)		4.2 ↓	3.8 ↓	10° elbow flexion; wrist neutral[d]
Ulnar	Wrist extension (0°–full/60°)		5.2 ↑	20.7 ↑	90° shoulder abduction; 10° elbow flexion[d]
			0.3 ↑		80° shoulder abduction; 90° elbow flexion[c]
	Elbow flexion (0°–90°)		29.0 ↑	2.2 ↑	90° shoulder abduction; wrist neutral[e]
	Elbow flexion (0°–140°)		22.0 ↑		0° shoulder abduction; wrist neutral[f]
	Elbow flexion (60°–full/140°)		5.77 ↑		90° shoulder abduction; wrist neutral[g]
			5.3 ↑		90° shoulder abduction; wrist neutral[h]
	Elbow extension (90°–0°)		2.2 ↓		80° shoulder abduction; 60° wrist extension[c]
	Shoulder abduction (90°–110°)	8.6 ↑	0.5 ↑		10° elbow flexion; wrist neutral[d]
	Shoulder adduction (90°–30°)	9.9 ↓	0.1 ↓		10° elbow flexion; wrist neutral[d]

[a] All measurements are reported as percent increase (↑) or percent decrease (↓) in strain. Sources are listed by authors, materials or subjects, and measurement tool.
[b] From Kleinrensink et al, embalmed cadavers, buckle force transducer.[35]
[c] From Byl et al, fresh cadavers, differential variable reluctance transducer.[28]
[d] From Wright et al, fresh cadaver transthoracic region, microsuture marker.[27]
[e] From Wright et al, fresh cadaver transthoracic region, microsuture marker.[33]
[f] From Grewal R, Varitimidis S, Vardakas D, et al. Ulnar nerve elongation and excursion in the cubital tunnel after decompression and anterior transposition. *J Hand Surg Br.* 2000;25:457–460, fresh cadavers, disarticulated arm, steel wire marker.
[g] From Toby and Hanesworth, fresh cadavers, microstrain gauge.[26]
[h] From Hicks D, Toby B. Ulnar nerve strains at the elbow: the effect of in situ decompression and medial epicondylectomy. *J Hand Surg Am.* 2002;27:1026–1031, fresh cadavers, microstrain gauge.

First, levels of physical stress lower than the levels required for tissue maintenance (low stress) result in a reduced ability of the tissue to tolerate subsequent stress and are consistent with tissue plasticity and response to functional demand. Second, levels of physical stress in the range required for tissue maintenance (normal stress) result in no tissue adaptations and are considered to maintain a state of equilibrium. Third, physical stress levels that exceed the range required for tissue maintenance (high stress) result in an increase in the tolerance of the tissue for stress in an effort to meet the mechanical demand. Fourth, physical stress levels that exceed the capacity of some components of the tissue (excessive stress) result in tissue injury. Fifth, levels of physical stress that are extreme (extreme stress) result in tissue death. Finally, it is important to note that the physical stress level is a composite value with variable components of magnitude, time, and direction or type of stress. We have reviewed the literature to clarify how peripheral nerves adapt to physical stresses and provide information to help guide physical therapy interventions when disuse, overuse, or injury have altered the functional zone of the nerve (Fig. 9). In the functional zone, the physical stresses on the nerve are sufficient to maintain a state of equilibrium and normal physiological function. In the dysfunctional zone, various levels of physical stress have altered the ability of the nerve to tolerate subsequent stress.

Immobilization Stresses

Under conditions of immobilization, such as casting, splinting, and bracing, peripheral nerves are exposed to levels of physical stress that are lower than those necessary to maintain the nerves in a state of equilibrium or in a functional zone (Fig. 9). According to the Physical Stress Theory, nerve will undergo predictable physiological and structural modifications proportional to the levels of reduced stress and the duration of immobilization.[2] Immobilization induces cell biological changes in axons and axon terminals[52–54] and structural changes in myelin and nerve connective tissue layers that likely alter the ability of nerves to tolerate subsequent physical stress. In experimental animal models, immobilization carried out by plaster casting of the limb or external fixation of the skeleton results in myelin degeneration and deposition of collagen in the endoneurium. Unfortunately, these studies have not included an evaluation of perineurial or epineurial tissues. Specifically, immobilization of the hind limb of rats for as little as 3 weeks produces myelin degeneration, seen as myelin debris at

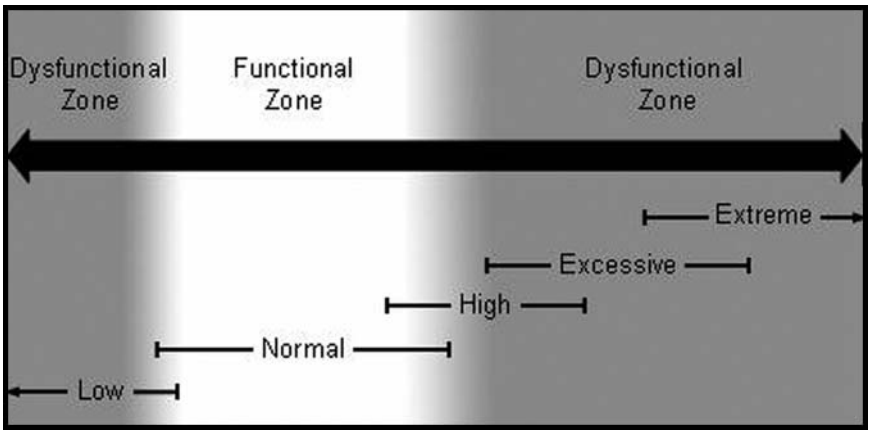


Figure 9.
Continuum of physical stress states. The white area represents the functional zone in which the physical stresses on the nerve are sufficient to maintain a state of equilibrium and normal physiological function. The shaded areas represent dysfunctional zones resulting from various levels of physical stress placed on the nerve tissue. Under conditions of prolonged low stress, the functional zone will shrink in width and shift to the left, reducing the ability of the tissue to tolerate subsequent stresses even of previously normal levels. Under conditions of high stress, the functional zone may expand and shift to the right, improving the ability of the tissue to tolerate subsequent physical stress. If the nerve is exposed to prolonged or repeated excessive stress, the functional zone will shrink in width. Although scarring of damaged tissue may enable the nerve to tolerate subsequent physical stresses, the physiological function of the nerve will be reduced. Exposure to extreme stress will result in disruption of axon continuity or neural cell death and significantly reduced physiological function.

the neuromuscular junction.[55] Immobilization for 6 weeks causes the deposition of endoneurial collagen and an alteration in large-diameter myelinated fibers.[56] There is a measurable increase in the ratio of small- to large-diameter fibers, resulting in a reduction in the mean fiber diameter.[56–58] With periods of immobilization of up to 16 weeks, the reductions in fiber diameter continue,[57,59] there is an overt loss of myelinated fibers,[57] an increase in myelin debris, and large deposits of collagen are seen in the endoneurium.[56]

No studies have measured excursion, strain, or the ability to withstand compression in nerves following periods of immobilization. Although one might hypothesize that the deposition of endoneurial collagen will make a nerve more resistant to tensile stress, the loss of myelin and axonal girth likely has the opposite effect. We hypothesize that after a period of immobilization, the width of the functional zone on the continuum of physical stress states will shrink and shift toward the left (Fig. 9). The affected tissue will have a narrower range within which it can function and will be less tolerant of high absolute stresses. When the limb is remobilized during rehabilitation, care should be taken to monitor pain, paresthesia, and protective reflexes that may signal the limit of the tolerance of the nerve to tensile stress.[60,61] Rehabilitation should include gradual increases in stress levels from low to normal to high until adaptive physiological responses restore the ability of the nerve to tolerate noninjurious stress levels.

Lengthening Stresses

Nerves are exposed to various levels of longitudinal tensile stress during limb-lengthening procedures, such as distraction osteogenesis (Ilizarov procedures), traction injuries, and stretching maneuvers. The tissue response is dependent upon the magnitude and duration of the tensile stress. The extant data indicate that lengthening of 6% to 8% for a short duration causes transient physiological changes that appear to be within the normal stress tolerance of the tissue, whereas acute strains of 11% and greater cause long-term damage and may be considered to be excessive or extreme stress states.

Although there are innumerable factors that influence the concept of a threshold for strain-induced nerve injury, common positions used to assess the neurodynamics of the upper limb may result in nerve strain that approaches or exceeds the 11% strain that is known to result in long-term damage (Tab. 2). To date, there have been no studies in which strain measurements and subjective responses have been recorded simultaneously during limb positioning. Nevertheless, extrapolation of the strain data from a study of the median nerve in fresh human cadavers[28] with the responses obtained from live human subjects undergoing similar positioning[61] may provide some understanding of the linkage between nerve strain and subject tolerance. In cadavers, positioning in shoulder depression, 90 degrees of shoulder abduction, 90 degrees of shoulder external rotation, 70 degrees of forearm supination, 60 degrees of wrist extension, full finger extension, and full elbow extension resulted in 7.6%±8.2% ($\overline{X}$±SD) strain in the median nerve measured just proximal to the wrist.[28] Adults who were healthy and who were placed in this same position lacked 12±13 degrees ($\overline{X}$±SD) of elbow extension because of substantial discomfort in the limb.[61] The subjects reported pain of 5.1±1.9 ($\overline{X}$±SD) on a 10-point visual analog scale, and 36% of the subjects reported paresthesia in the upper limb. Taken together, these findings suggest that many people are unable to tolerate levels of strain below the theoretical 11% threshold. The responses likely signal physiological alterations induced by position-induced nerve strain.

The patency of perineurial arterioles and venules, and thus nerve perfusion, may be impaired during tensile loading of a nerve or in the presence of abnormally high endoneurial pressure.[62] Several investigators have studied the changes in nerve blood flow induced by progressively increasing nerve strain. Although blood flow was not significantly altered by elongation of the femur of rats, which resulted in 6% sciatic nerve strain,[63] flow was impaired with acute 8% strain.[64] Full recovery of flow occurred after relaxation of the acute 8% strain.[64] Blood flow was reduced as much as 70% when an 8.8% strain in the rabbit sciatic nerve was maintained for 1 hour and, upon release, blood returned at a hyperemic flow of 151% of the baseline value.[25] Importantly, the reperfusion of tissue may be as damaging as the initial ischemia, as a recent study[65] has demonstrated oxidative injury to endothelial cells and Schwann cell apoptosis in the reperfusion period after 4 hours of ischemia. Such reperfusion injury brought about by activated inflammatory cells occurs in many tissues, including cardiac muscle, skeletal muscle, and lung parenchyma (reviewed in Eltzschig and Collard[66]).

Studies of the rat sciatic nerve have demonstrated that blood flow is reduced by 50% with a strain of 11%[63] and by as much as 100% with a strain of 15.7%.[67] Minimal recovery of blood flow occurs after a 15% strain.[64] When maintained for 30 minutes, rat sciatic nerve strains of 16%, 24%, and 32% resulted in reductions in blood flow of 30%, 65%, and 80%, respectively.[68] Modest, but prolonged, reductions in blood flow alter nerve conduction and axonal transport. When maintained for 1 hour, a strain in the rabbit tibial nerve of only 6% was sufficient to cause a 70% reduction in the amplitude of the compound action potential,[45] a composite of all axons conducting action potentials in response to a maximal stimulus. A 12% strain maintained for 1 hour completely blocked nerve conduction, with minimal recovery by 1 hour after release.[45] In a more recent study,[68] strains of 24% and 32% resulted in a 50% reduction in somatosensory evoked potentials. As might be expected, 24% and 32% strains also induced histologic and functional changes, including epineurial and perineurial tears, disrupted axons, and significantly reduced sciatic nerve function. Axonal transport was not impaired at a strain of 6% but appeared to be reduced by more than 50% at a strain of only 11%.[63]

Prolonged lengthening, such as that which occurs with osteogenic lengthening procedures (Ilizarov procedures), will lead to a maintained state of heightened stress within a nerve. In this situation, the level of stress is dependent upon the rate of lengthening, the total increase in length, and the duration of lengthening and will determine where the nerve falls on the continuum of physical stress states. For example, a rate of lengthening of 0.5 to 1.0 mm per day, the most commonly used clinical distraction rate, is within the high-stress range and results in physiological and morphological changes without significant functional impairment. However, as discussed below, when the rate of elongation is greater than 1.0 mm per day the stress is within the ranges of excessive stress to extreme stress, and significant axonal injury and functional impairment occur.

Slow elongation of a peripheral nerve has been demonstrated to result in significant changes in the electrophysiological properties of the nerve, and elongation rates of 1.0 mm per day or less appear to be well tolerated. In a rat model, femoral lengthening at rates of 0.5, 1.0, and 1.5 mm per day reduced the compound action potentials in the sciatic nerve by 22%, 25%, and 47%, respectively.[69] Similarly, the conduction velocities were reduced by 2%, 6%, and 15%. Up to the rate of 1.5 mm per day, there were no significant changes in animal gait, as measured by the Sciatic Functional Index. In humans undergoing bilateral limb lengthening for congenital dwarfism, a tibial elongation rate of 1.0 mm per day caused reductions in the motor nerve conduction amplitudes in the deep peroneal nerve in 8 of 10 limbs and in the tibial nerve in 6 of 8 limbs.[70] There was no change in sensory conduction in the sural nerve. Despite the reductions in the motor nerve conduction amplitudes, the patients did not exhibit weakness on clinical examination. However, when the elongation rate was increased to 2.1 mm per day in a rabbit model of femoral lengthening, a complete loss of electrophysiological responses was observed.[71] Although function was not assessed in the study, the electrophysiological changes would be expected to cause profound functional impairment.

Slow elongation of nerves has been shown to cause modifications in myelin, axon degeneration and regeneration, and deposition of endoneurial collagen. The capacity for remodeling during elongation is remarkable. In a rat model of femur elongation at a rate of 1.0 mm per day, internode length was increased by 17% over 14 days[72] and by as much as 91% over 70 days.[73] With the use of biochemical markers, the elongation was seen to induce myelin production, as measured by an increased level of messenger RNA for P0, a major myelin glycoprotein, in Schwann cells.[72] Although there was evidence of local demyelination and remyelination in some axons when the limb was lengthened at 1.0 mm per day, changes in endoneurial edema, myelin debris, axon diameter, and myelin sheath thickness were not statistically significant.[72,73] In the rat model, femur elongation at rates of 0.5, 1.0, and 1.5 mm per day caused reductions in the number of axons in the sciatic nerve by 7%, 10%, and 18%, respectively.[69] Similarly, in a model of mandibular distraction at a rate of 1.0 mm per day,

the inferior alveolar nerve showed a reduced number of axons, demyelination, and proliferation of Schwann cells during elongation, followed by remyelination in the 2 to 3 weeks after elongation.[74] The deposition of endoneurial collagen has been seen with elongation at rates of 1.5 mm per day in rats,[69] and 2.1 mm per day in rabbits.[71]

Rehabilitation following lengthening stress must be based on knowledge of the magnitude and duration of the stress and the expected state of the injured nerve at the time of evaluation and intervention. For example, extreme tensile stress to the brachial plexus may induce demyelination, disruption of axons, and perineurial tears. Mobilization must be initiated cautiously and conservatively, avoiding normal to high stresses and allowing injured nerves time to heal. When the healing process is well under way, normal stresses may restore the nerves to their proper biomechanical and functional states. In another clinical example, during limb-lengthening procedures carried out at a safe rate of elongation, careful monitoring of nerve function may help to maintain the width of the functional zone at the new length of the nerve. After the procedure, the novel range of motion may be maintained by providing normal and occasionally high stresses.

Compression Stresses

Compression on a nerve may be the result of extraneural force or may occur as transverse contraction secondary to increased longitudinal strain (Fig. 4). Compression stress of a low magnitude and a short duration may result in reversible physiological and minor structural changes. Compressive stress of a high magnitude, however, may result in structural alterations in myelin sheaths and even disruption of axons. Low-magnitude compressive stress applied over a long period of time may cause significant structural changes in the nerve secondary to impairment of blood flow and sequelae of ischemia.

As with strain-induced injury, a threshold for compression-induced nerve injury is difficult to determine. Common functional positions may result in compression pressures that approach or exceed the 20 to 30 mm Hg demonstrated to impair nerve blood flow.[75] The carpal tunnel is a site well known for compressive damage to the median nerve and thus has been well studied. Carpal tunnel pressure in subjects who were healthy was measured at 3 to 5 mm Hg with the wrist in a neutral position.[76–78] Simply placing the hand on a computer mouse was shown to increase the tunnel pressure from the resting 5 mm Hg to 16 to 21 mm Hg,[79] and actively using the mouse to point and click increased the tunnel pressure to 28 to 33 mm Hg, a pressure high enough to reduce nerve blood flow. Interestingly, carpal tunnel pressure was shown to increase to 63 mm Hg with 40 degrees of wrist extension and 0 degrees of metacarpophalangeal flexion,[80] and the anatomy of adjacent structures is thought to play a large role in these positional increases in carpal tunnel pressure.

Computer modeling has shown that muscle bellies of the long finger flexors enter the proximal aspect of the tunnel during wrist extension[80]; indeed, Byl et al[28] found significant distal muscle bulk of the flexor digitorum superficialis in a study of the median nerve in fresh human cadavers. Similarly, the lumbrical muscles are known to enter the distal aspect of the tunnel during metacarpophalangeal flexion, and computer modeling suggests that when the metacarpophalangeal joints are flexed to 90 degrees, the lumbrical muscles remain in the carpal tunnel, even when the wrist is extended.[80] Note that the use of a computer keyboard with flexed digits and extended wrists compromises the carpal tunnel from both distal and proximal aspects. In subjects with carpal tunnel syndrome, pressure in the carpal tunnel was 32 mm Hg with the wrist in a neutral position and rose to a mean of 110 mm Hg with full wrist extension in subjects with carpal tunnel syndrome.[76] These tunnel pressures exceed the threshold of 20 to 30 mm Hg for vascular perfusion even at rest. Taken together, these findings suggest that even functional positions, such as the use of a computer keyboard and mouse, place the wrist in a position of increased carpal tunnel pressure, compromising nerve blood flow and placing people at risk for median nerve injury.

Direct damage to myelin and axons has been shown to occur with extraneural compression of as low as 50 mm Hg maintained for 2 minutes,[48] and the percentage of damaged fibers increases with increasing force. Ten days after the application of compressive stress at 50 mm Hg, 30% of the axons in the region under the compressive cuff showed evidence of demyelination, focal myelin thickening, remyelination, and axonal degeneration or regeneration.[48] Acute compressive stress of a sufficient magnitude to sever axons results in a well-characterized process of Wallerian degeneration and axon regeneration (reviewed in Sunderland[12]). As an example, a compressive pressure of 300 mm Hg maintained for 2 minutes causes the degeneration of 15% of distal fibers, documented 7 to 10 days after injury.[48] The changes in nerve biomechanics after an extreme crush injury have been documented in a murine model.[24] Nerve strength and stiffness are greatly reduced in the first 2 days after injury and increase significantly with tissue repair and collagen deposition, peaking at 12 days after injury. Similarly, after nerve transection and repair, the repaired segment is more stiff than the normal nerve until remodeling is sufficient and compliance returns to normal 7 weeks after repair.[81]

Intraneural blood flow and adenosine triphosphate-dependent axonal transport are important physiological parameters that are easily disrupted by compressive stress. With a rabbit model, it has been shown that acute extraneural compression of as little as 20 mm Hg reduces intraneural venular blood flow.[75] Arterial and endoneurial capillary blood flows were stopped at pressures of 50 to 70 mm Hg[67] and 80 mm Hg,[75] respectively. Interestingly, in humans, intraneural blood flow and sensory responses are blocked at extraneural tissue pressures 45 mm Hg below the mean arterial pressure.[82] A compressive stress of only 30 mm Hg, if maintained for 2 hours, results in endoneurial edema,[83] and, if maintained for 8 hours, results in endoneurial pressure high enough to subsequently impair blood flow.[84] The endoneurial edema is thought to result from ischemic damage to endoneurial capillary endothelial cells and an alteration in the blood-nerve barrier. The same compressive stress of 30 mm Hg applied for 8 hours is sufficient to impair both anterograde axonal transport and retrograde axonal transport.[85,86] Increasing pressure results in greater tissue damage, as a compressive force of 150 mm Hg maintained for 30 minutes was shown to induce a degeneration of 30% of the distal fibers,[48] and compressive forces of 200 and 400 mm Hg maintained for 2 hours were shown to block axonal transport for 1 and 3 days, respectively.[87]

The pathological consequences of prolonged compression include subperineurial edema; inflammation; deposition of fibrin; activation of endoneurial fibroblasts, mast cells, and macrophages; demyelination; axon degeneration; and fibrosis.[83] Compression of a very long duration has been modeled in animals with loose ligatures,[88] Silastic* tubes,[89,90] and pressure balloons placed within an anatomical tunnel.[91] The pathological findings are thought to result from both inflammatory and cellular phenomena and include changes in the blood-nerve barrier, thickening of the perineurium and epineurium, thinning of myelin, demyelination and degeneration of axons in the fascicle periphery, and slowed nerve conduction velocity.

Compression of a low magnitude and for a brief duration is well tolerated by nerves and constitutes normal stress. As discussed, however, if compression is maintained and ischemia ensues, then this high stress results in endoneurial edema and fibrotic changes that may alter the biomechanical responses to subsequent stress. Compression of a sufficient magnitude to sever axons will cause an immediate reduction in the mechanical strength and stiffness of a nerve. In this case, during the early postinjury period, care should be taken to protect the injured segment from normal physical stress. Two to 3 weeks after injury, however, the injured site will have greater biomechanical stiffness than the uninjured segments. For this reason, the nerve length necessary for full range of motion will come from the more compliant, uninjured segments before the more stiff, repaired segment. After several weeks, the physical stresses on the healing nerve segment may be slowly increased in an effort to achieve remodeling of the connective tissue and a return to the functional zone on the continuum of physical stress states.

In the case of chronic compression, decompression is paramount. Physical therapy intervention should focus on reduction of inflammation, improvement in blood flow, and enhancement of the capacity of the nerve for strain and excursion along its full length in an effort to reduce the physical stress on the compressed region. An example of this complex challenge may be seen in the interventions for carpal tunnel syndrome. Subjects with carpal tunnel syndrome have been shown to have higher pressures in the carpal tunnel than control subjects, and carpal tunnel pressure is altered by muscle activity and wrist posture (reviewed in Rempel and Diao[92]). Furthermore, a recent study[31] demonstrated that the median nerve in subjects with carpal tunnel syndrome had a reduced capacity for transverse excursion in the radial direction during extension of the digits at the metacarpophalangeal joints. The challenge for the physical therapist is to reduce carpal tunnel pressure, improve blood flow through the tunnel, and restore nerve excursion. Thus, treatment should include traditional modalities for which there is supportive literature and training in correct postures to reduce compressive stress on the nerve during use of the limb. Additionally, treatment should include mobilization exercise techniques based on nerve anatomy and should be directed toward the restoration of nerve strain and excursion that should occur normally during limb movement.[93–95]

Repetitive Stresses

Vibration constitutes one form of repetitive stress. We know from studies of humans who use hand-held vibrating tools that vibration stresses can cause reductions in tactile sensation, as well as other sensory disturbances[96] and reduced grip force.[97,98] Furthermore, myelin breakdown and fibrosis have been seen in the dorsal interosseous nerve at the wrist in people with vibration-induced neuropathy.[99] Long-term exposure to vibration stresses has been shown to result in the grouping of muscle fiber types in muscle biopsies, indicative of denervation and reinnervation.[98] Pathophysiology also has been seen in animal models of vibration stress. In the rat hind limb, vibration at 82 Hz and a 0.21-mm amplitude for 5 hours per day for 5 days was enough to cause endoneurial edema and morphological alterations in unmyelinated axons of the plantar nerves.[100] Similarly, vibration of the

* Dow Corning Corp, 2200 W Salzburg Rd, Midland, MI 48640-8531.

rat tail at 60 Hz and a 0.4-mm amplitude for 2 to 4 hours per day for 6 days per week resulted in reduced motor nerve conduction velocity and degeneration of paranodal myelin after 400 hours of vibration.[101] Importantly, it appears that the pathologic changes resulted from direct physical trauma, as nerves distant from the source of the vibration were spared.[100]

Repetitive movements, such as those that occur in work-related musculoskeletal disorders, were discussed in detail recently by Barr and Barbe.[102] The stresses placed upon the tissues may be variable in terms of type, magnitude, frequency, and duration, and the combination of these factors may place nerves in normal to extreme levels of physical stress. The chronic inflammation associated with repetitive movements places nerves under constantly higher hydrostatic compressive stress, which may increase further with contraction of the surrounding muscles. Chronic inflammation elicits within the nerves a remodeling response that seeks to add mechanical stability.[103] The most common outcome is the deposition of collagen in the connective tissue layers, which leads to decreased compliance of the nerves to elongation. As with chronic compression, the approach for assessment and treatment of injuries attributable to repetitive movements must address the chronic inflammatory state and connective tissue changes. Of primary importance in interventions for all stress-induced injuries are the identification and characterization of physical stresses and the modification of their components, magnitude, time, and direction, as outlined in the physical stress theory.[2]

Summary

Knowledge of the normal cellular structure and biomechanical properties of peripheral nerves and the responses of nerves to physical stresses assists physical therapists in making diagnoses and decisions regarding interventions. A thorough examination and a focused evaluation should result in an assessment indicating the level of stresses to which the nerves are or have been exposed. This assessment should guide treatment interventions to normalize the stresses on the nerves, be they rest, soft tissue or neurodynamic mobilization, stretching, modalities, exercise, or patient education. Treatment rationale should be based on an educated understanding of the biomechanical properties of normal and pathological nerves. The concept of a continuum of low-normal-high-excessive-extreme stresses may be used as a training tool for patient education, pointing out examples of daily activities that fall under the different categories. Patients should be encouraged to identify where their daily stresses fall on this continuum and, through activity modification, education, and physical therapy intervention, strive to achieve a better balance of these stress states to improve the health of the peripheral nervous system.

References

1 Shacklock M. Neurodynamics. *Physiotherapy.* 1995;81:9–16.

2 Mueller M, Maluf K. Tissue adaptation to physical stress: a proposed "physical stress theory" to guide physical therapist practice, education, and research. *Phys Ther.* 2002;82:383–403.

3 Thomas P. The connective tissue of peripheral nerve: an electron microscope study. *J Anat.* 1963;97:35–44.

4 Gamble H, Eames R. An electron microscope study of the connective tissues of human peripheral nerve. *J Anat.* 1964;98:655–663.

5 Schiff R, Rosenbluth J. Ultrastructural localization of laminin in rat sensory ganglia. *J Histochem Cytochem.* 1986;34:1691–1699.

6 Shanthaveerappa T, Bourne G. The "perineural epithelium," a metabolically active, continuous, protoplasmic cell barrier surrounding peripheral nerve fasciculi. *J Anat.* 1962;96:527–537.

7 Rechthand E, Rapoport S. Regulation of the microenvironment of peripheral nerve: role of the blood-nerve barrier. *Prog Neurobiol.* 1987;28:303–343.

8 Sunderland S, Bradley K. The cross-sectional area of peripheral nerve trunks devoted to nerve fibres. *Brain.* 1949;72:428–449.

9 Sunderland S, Bradley K. Stress-strain phenomena in denervated peripheral nerve trunks. *Brain.* 1961;84:125–127.

10 Rydevik B, Kwan M, Myers R, et al. An in vitro mechanical and histological study of acute stretching on rabbit tibial nerve. *J Orthop Res.* 1990;8:694–701.

11 Stolinski C. Structure and composition of the outer connective tissue sheaths of peripheral nerve. *J Anat.* 1995;186:123–130.

12 Sunderland S. The anatomy and physiology of nerve injury. *Muscle Nerve.* 1990;13:771–784.

13 Sunderland S. The intraneural topography of the radial, median, and ulnar nerves. *Brain.* 1945;68:243–299.

14 Sunderland S. The intraneural topography of the sciatic nerve and its popliteal divisions in man. *Brain.* 1948;71:242–273.

15 Millesi H, Zoch G, Reihsner R. Mechanical properties of peripheral nerves. *Clin Orthop Relat Res.* 1995;314:76–83.

16 Sunderland S. The connective tissues of peripheral nerves. *Brain.* 1965;88:841–854.

17 Appenzeller O, Dhital K, Cowen T, Burnstock G. The nerves to blood vessels supplying blood to nerves: the innervation of vasa nervorum. *Brain Res.* 1984;304:383–386.

18 Rechthand E, Hervonen A, Sato S, Rapoport S. Distribution of adrenergic innervation of blood vessels in peripheral nerve. *Brain Res.* 1986;374:185–189.

19 Burkel W. The histological fine structure of perineurium. *Anat Rec.* 1967;158:177–189.

20 Bell G, Weddell A. A descriptive study of the blood vessels of the sciatic nerve in the rat, man and other mammals. *Brain.* 1984;107:871–898.

21 Bell M, Weddell A. A morphometric study of intrafascicular vessels of mammalian nerve. *Muscle Nerve.* 1984;7:524–534.

22 Dyck P, Giannini C, Lais A. Pathological alterations of nerves. In: Dyck P, Thomas P, Griffin J, et al, eds. *Peripheral Neuropathy.* 3rd ed. Philadelphia, Pa: WB Saunders Co; 1993:515–595.

23 Abrams R, Butler J, Bodine-Fowler S, Botte M. Tensile properties of the neurorrhaphy site in the rat sciatic nerve. *J Hand Surg Am.* 1998;23:465–470.

24 Beel J, Groswald D, Luttges M. Alterations in the mechanical properties of peripheral nerve following crush injury. *J Biomech.* 1984;17:185–193.

25 Driscoll P, Glasby M, Lawson G. An in vivo study of peripheral nerves in continuity: biomechanical and physiological responses to elongation. *J Orthop Res.* 2002;20:370–375.

26 Toby E, Hanesworth D. Ulnar nerve strains at the elbow. *J Hand Surg Am.* 1998;23:992–997.

27 Wright T, Glowczewski FJ, Wheeler D, et al. Excursion and strain of the median nerve. *J Bone Joint Surg Am.* 1996;78:1897–1903.

28 Byl C, Puttlitz C, Byl N, et al. Strain in the median and ulnar nerves during upper-extremity positioning. *J Hand Surg Am.* 2002;27: 1032–1040.

29 Dilley A, Lynn B, Greening J, DeLeon N. Quantitative in vivo studies of median nerve sliding in response to wrist, elbow, shoulder and neck movements. *Clin Biomech.* 2003;18:899–907.

30 McLellan D, Swash M. Longitudinal sliding of the median nerve during movements of the upper limb. *J Neurol Neurosurg Psychiatry.* 1976;39:566–570.

31 Erel E, Dilley A, Greening J, et al. Longitudinal sliding of the median nerve in patients with carpal tunnel syndrome. *J Hand Surg Br.* 2003;28:439–443.

32 Smith S, Massie J, Chesnut R, Garfin S. Straight leg raise: anatomical effects on the spinal nerve root without and with fusion. *Spine.* 1993;18:992–999.

33 Wright T, Glowczewski F, Cowin D, Wheeler D. Ulnar nerve excursion and strain at the elbow and wrist associated with upper extremity motion. *J Hand Surg Am.* 2001;26:655–662.

34 Boyd BS, Puttlitz C, Gan J, Topp KS. Strain and excursion in the rat sciatic nerve during a modified straight leg raise are altered after traumatic nerve injury. *J Orthop Res.* 2005;23:764–770.

35 Kleinrensink G, Stoeckart R, Vleeming A, et al. Mechanical tension in the median nerve: the effects of joint position. *Clin Biomech.* 1995;10:240–244.

36 Haftek J. Stretch injury of peripheral nerve: acute effects of stretching on rabbit nerve. *J Bone Joint Surg Br.* 1970;52:354–365.

37 Kwan M, Wall E, Massie J, Garfin S. Strain, stress and stretch of peripheral nerve: rabbit experiments in vitro and in vivo. *Acta Orthop Scand.* 1992;63:267–272.

38 Pourmand R, Ochs S, Jersild R Jr. The relation of the beading of myelinated nerve fibers to the bands of Fontana. *Neuroscience.* 1994;61: 373–380.

39 Walbeehm E, Afoke A, de Wit T, et al. Mechanical functioning of peripheral nerves: linkage with the "mushrooming" effect. *Cell Tissue Res.* 2004;316:115–121.

40 Tillett R, Afoke A, Hall S, et al. Investigating mechanical behaviour at a core-sheath interface in peripheral nerve. *J Peripher Nerv Syst.* 2004;9:255–262.

41 Georgeu G, Walbeehm E, Tillett R, et al. Investigating the mechanical shear-plane between core and sheath elements of peripheral nerves. *Cell Tissue Res.* 2005;320:229–234.

42 Borschel G, Kia K, Kuzon W, Dennis R. Mechanical properties of acellular peripheral nerve. *J Surg Res.* 2003;114:133–139.

43 Phillips J, Smit X, De Zoysa N, et al. Peripheral nerves in the rat exhibit localized heterogeneity of tensile properties during limb movement. *J Physiol.* 2004;557:879–887.

44 Wall E, Kwan M, Rydevik B, et al. Stress relaxation of a peripheral nerve. *J Hand Surg Am.* 1991;16:859–863.

45 Wall E, Massie J, Kwan M, et al. Experimental stretch neuropathy: changes in nerve conduction under tension. *J Bone Joint Surg Br.* 1992;74:126–129.

46 Grewal R, Xu J, Sotereanos D, Woo S-Y. Biomechanical properties of peripheral nerves. *Hand Clin.* 1996;12:195–204.

47 Orf G, Wust R. Mechanical loading of peripheral nerves during remobilisation of the affected member after end-to-end anastomosis. *Acta Neurochir (Wien).* 1979;49:103–121.

48 Dyck P, Lais A, Giannini C, Engelstad J. Structural alterations of nerve during cuff compression. *Proc Natl Acad Sci U S A.* 1990;87: 9828–9832.

49 Hodgson A. Avoiding tourniquet-induced neuropathy through cuff design. *Biomed Instrum Technol.* 1993;27:401–407.

50 Lundborg G. *Nerve Injury and Repair.* New York, NY: Churchill Livingstone; 1988:64–101.

51 Millesi H. The nerve gap: theory and clinical practice. *Hand Clin.* 1986;2:651–663.

52 Suliman I, Lindgren J, Gillberg P-G, et al. Effect of immobilization on skeletal muscle nicotinic cholinergic receptors in the rat. *Neuro-Report.* 1997;8:2821–2824.

53 Marcianak M. Morphometric ultrastructural evaluation of the axonal endings in the neuromuscular junctions of pigeons after long lasting limitation of movement. *Exp Pathol.* 1983;23:27–34.

54 Baranski S, Marcianak M. Stereological ultrastructural analysis of the axonal endings in the neuromuscular junction of rats after a flight on Biosputnik 782. *Aviat Space Environ Med.* 1979;50:14–17.

55 Pachter B, Eberstein A. The effect of limb immobilization and stretch on the fine structure of the neuromuscular junction in rat muscle. *Exp Neurol.* 1986;92:13–19.

56 Malathi S, Batmanabane M. Effects of varying periods of immobilization of a limb on the morphology of a peripheral nerve. *Acta Morphol Neerl Scand.* 1983;21:185–198.

57 Malathi S, Batmanabane M. Effects of immobilization of a limb on the maturation of a peripheral nerve in kittens. *Acta Anat.* 1988;132: 191–196.

58 Eisen A, Bellavance A, Carpenter S, Karpati G. The effects of muscle hyper- and hypoactivity upon fiber diameters of intact and regenerating nerves. *J Neurol Sci.* 1973;20:457–469.

59 Appenzeller O, Ogin G, Palmer G. Fiber size spectra and cyclic AMP content of sciatic nerves: effect of muscle hypoactivity and hyperactivity. *Exp Neurol.* 1976;50:595–604.

60 Balster S, Jull G. Upper trapezius muscle activity during the brachial plexus tension test in asymptomatic subjects. *Man Ther.* 1997;2: 144–149.

61 Coppieters M, VanDeVelde M, Stappaerts K. Positioning in anesthesiology: toward a better understanding of stretch-induced perioperative neuropathies. *Anesthesiology.* 2002;97:75–81.

62 Kalichman M, Myers R. Transperineurial vessel constriction in an edematous neuropathy. *J Neuropathol Exp Neurol.* 1991;50:408–418.

63 Tanoue M, Yamaga M, Ide J, Takagi K. Acute stretching of peripheral nerves inhibits retrograde axonal transport. *J Hand Surg Br.* 1996;21:358–363.

64 Clark W, Trumble T, Swiontkowski M, Tencer A. Nerve tension and blood flow in a rat model of immediate and delayed repairs. *J Hand Surg Am.* 1992;17:677–687.

65 Iida H, Schmeichel A, Wang Y, et al. Schwann cell is a target in ischemia-reperfusion injury to peripheral nerve. *Muscle Nerve.* 2004;30: 761–766.

66 Eltzschig H, Collard C. Vascular ischaemia and reperfusion injury. *Br Med Bull.* 2004;70:71–86.

67 Ogata K, Naito M. Blood flow of peripheral nerve effects of dissection, stretching and compression. *J Hand Surg Br.* 1986;11:10–14.

68 Jou I, Lai K, Shen C, Yamano Y. Changes in conduction, blood flow, histology, and neurological status following acute nerve-stretch injury induced by femoral lengthening. *J Orthop Res.* 2000;18:149–155.

69 Skoulis T, Vekris M, Terzis J. Effect of distraction osteogenesis on the peripheral nerve: experimental study in the rat. *J Reconstr Microsurg.* 1998;14:565–574.

70 Galardi G, Comi G, Lozza L, et al. Peripheral nerve damage during limb lengthening: neurophysiology in five cases of bilateral tibial lengthening. *J Bone Joint Surg Br.* 1990;72:121–124.

71 Shibukawa M, Shirai Y. Experimental study on slow-speed elongation injury of the peripheral nerve: electrophysiological and histological changes. *Orthop Sci.* 2001;6:262–268.

72 Hara Y, Shiga T, Abe I, et al. P0 mRNA expression increases during gradual nerve elongation in adult rats. *Exp Neurol.* 2003;184:428–435.

73 Abe I, Ochiai N, Ichimura H, et al. Internodes can nearly double in length with gradual elongation of the adult rat sciatic nerve. *J Orthop Res.* 2004;22:571–577.

74 Hu J, Zou S, Tang Z, et al. Response of Schwann cells in the inferior alveolar nerve to distraction osteogenesis: an ultrastructural and immunohistochemical study. *Int J Oral Maxillofac Surg.* 2003;32:318–324.

75 Rydevik L, Lundborg G, Bagge U. Effects of graded compression on intraneural blood flow: an in vivo study on rabbit tibial nerve. *J Hand Surg Am.* 1981;6:3–12.

76 Gelberman R, Hergenroeder P, Hargens A, et al. The carpal tunnel syndrome: a study of carpal canal pressure. *J Bone Joint Surg Am.* 1981;63:380–383.

77 Szabo R, Chidgey L. Stress carpal tunnel pressures in patients with carpal tunnel syndrome and normal patients. *J Hand Surg Am.* 1989; 14:624–627.

78 Rojviroj S, Sirichativapee W, Kowsuwon W, et al. Pressure in the carpal tunnel: a comparison between patients with carpal tunnel syndrome and normal subjects. *J Bone Joint Surg Br.* 1990;72:516–518.

79 Keir P, Bach J, Rempel D. Effects of computer mouse design and task on carpal tunnel pressure. *Ergonomics.* 1999;42:1350–1360.

80 Keir P, Bach J, Rempel D. Effects of finger posture on carpal tunnel pressure during wrist motion. *J Hand Surg Am.* 1998;23:1004–1009.

81 Bora F, Richardson S, Black J. The biomechanical responses to tension in a peripheral nerve. *J Hand Surg Am.* 1980;5:21–25.

82 Szabo R, Gelbermann R, Williamson R, Hargens A. Effects of increased systemic blood pressure on the tissue fluid pressure threshold of peripheral nerve. *J Orthop Res.* 1983;1:172–178.

83 Powell H, Myers R. Pathology of experimental nerve compression. *Lab Invest.* 1986;55:91–100.

84 Lundborg G, Myers R, Powell H. Nerve compression injury and increased endoneurial fluid pressure: a "miniature compartment syndrome." *J Neurol Neurosurg Psychiatry.* 1983;46:1119–1124.

85 Dahlin L, McLean W. Effects of graded experimental compression on slow and fast axonal transport in rabbit vagus nerve. *J Neurol Sci.* 1986;72:19–30.

86 Dahlin L, Sjostrand J, McLean W. Graded inhibition of retrograde axonal transport by compression of rabbit vagus nerve. *J Neurol Sci.* 1986;76:221–230.

87 Rydevik B, McLean W, Sjostrand J, Lundborg G. Blockage of axonal transport induced by acute, graded compression of the rabbit vagus nerve. *J Neurol Neurosurg Psychiatry.* 1980;43:690–698.

88 Bennett G, Xie Y-K. A peripheral mononeuropathy in rat that produces disorders of pain sensation like those seen in man. *Pain* 1988;33:87–107.

89 Mackinnon S, Dellon A, Hudson A, Hunter D. Chronic nerve compression: an experimental model in the rat. *Ann Plast Surg.* 1984;13:112–120.

90 O'Brien J, Mackinnon S, MacLean A, et al. A model of chronic nerve compression in the rat. *Ann Plast Surg.* 1987;19:430–435.

91 Diao E, Shao F, Liebenberg E, et al. Carpal tunnel pressure alters median nerve function in a dose-dependent manner: a rabbit model for carpal tunnel syndrome. *J Orthop Res.* 2005;23:218–223.

92 Rempel D, Diao E. Entrapment neuropathies: pathophysiology and pathogenesis. *J Electromyogr Kinesiol.* 2004;14:71–75.

93 Cook A, Szabo R, Birkholz S, King E. Early mobilization following carpal tunnel release. *J Hand Surg Br.* 1995;20:228–230.

94 Tal-Akabi A, Rushton A. An investigation to compare the effectiveness of carpal bone mobilisation and neurodynamic mobilisation as methods of treatment for carpal tunnel syndrome. *Man Ther.* 2000;5: 214–222.

95 Akalin E, El O, Peker O, et al. Treatment of carpal tunnel syndrome with nerve and tendon gliding exercises. *Am J Phys Med Rehabil.* 2002;81:108–113.

96 Akesson I, Lundborg G, Horstmann V, Skerfving S. Neuropathy in female dental personnel exposed to high frequency vibrations. *Occup Environ Med.* 1995;52:116–123.

97 Necking L, Friden J, Lundborg G. Reduced muscle strength in abduction of the index finger: an important clinical sign in hand arm vibration syndrome. *Scand J Plast Reconstruct Surg Hand Surg.* 2003;37: 365–370.

98 Necking L, Lundborg G, Lundstrom R, et al. Hand muscle pathology after long-term vibration exposure. *J Hand Surg Br.* 2004;29: 431–437.

99 Stromberg T, Dahlin L, Brun A, Lundborg G. Structural nerve changes at wrist level in workers exposed to vibration. *Occup Environ Med.* 1997;54:307–311.

100 Lundborg G, Dahlin L, Hansson H, et al. Vibration exposure and peripheral nerve fiber damage. *J Hand Surg Am.* 1990;15:346–351.

101 Chang K, Ho S, Yu H. Vibration induced neurophysiological and electron microscopical changes in rat peripheral nerves. *Occup Environ Med.* 1994;51:130–135.

102 Barr A, Barbe M. Pathophysiological tissue changes associated with repetitive movement: a review of the evidence. *Phys Ther.* 2002;82: 173–187.

103 Clark B, Barr A, Safadi F, et al. Median nerve trauma in a rat model of work-related musculoskeletal disorder. *J Neurotrauma.* 2003;20: 681–695.