

# PATHOPHYSIOLOGY OF SKELETAL MUSCLE

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*These lecture notes accompany my lectures on pathophysiology in the study module "Musculoskeletal System" at Innsbruck Medical University. The English version serves two purposes: as a learning aid for international students and to encourage German-speaking students to familiarize themselves with medical English; the lectures are delivered in German. The translation from the original [German version](#) is my own; I am afraid it will occasionally sound appalling to native English speakers, but it should at least be intelligible.*

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## 1. HOW OUR MUSCLES WORK

The functional unit of a skeletal muscle is a motor unit, which is composed of a motor neuron and a group of muscle fibers or myocytes. The axon of the motor neuron progressively bifurcates and contacts each muscle fiber in a single spot, the neuromuscular junction or motor end plate. Presynaptic boutons release acetylcholine (ACh), which activates nicotinic ACh receptors present at high density on the postsynaptic junctional folds of the muscle fiber. The activity of released ACh is terminated by acetylcholine esterase. The nicotinic ACh receptor acts as an ACh-gated nonselective cation channel, raising membrane potential to a level required to fire an action potential.

**Myasthenia gravis.** Myasthenia gravis is an acquired autoimmune disorder. Autoantibodies bind to the ACh receptor, causing internalization and degradation of the receptors. The patients develop marked muscle weakness, especially in the evening and on exercise repeats, as in climbing stairs. Antibody levels may be reined in by administration of glucocorticoids or plasmapheresis, or by surgical removal of the thymus which in many patients contains thymomas. In case antibody production cannot be thwarted, symptoms may be alleviated by cautiously antagonizing acetylcholine esterase, e. g. by pyridostigmine.

The action potential started at the motor end plate spreads along the plasma membrane of the muscle cell (sarcolemma) and propagates down transverse tubules, invaginations of the plasma membrane. Membrane depolarization activates voltage-gated L-type  $\text{Ca}^{2+}$  channels, allowing extracellular  $\text{Ca}^{2+}$  to reach the cytosol. At the same time, mechanical coupling between L-type  $\text{Ca}^{2+}$  channels and adjacent  $\text{Ca}^{2+}$  release channels (synonym: ryanodine receptors) in the membrane of the sarcoplasmic reticulum releases large amounts of calcium from the reticulum to the cytosol.

By interaction with troponin C,  $\text{Ca}^{2+}$  shifts tropomyosin from the myosin binding sites on actin, allowing myosin-actin cross-bridge cycling for as long as  $\text{Ca}^{2+}$  remains present: the fiber contracts. To terminate contraction,  $\text{Ca}^{2+}$  must be removed from the cytoplasm. Most of

the  $\text{Ca}^{2+}$  is pumped back into the sarcoplasmic reticulum by the SERCA-type  $\text{Ca}^{2+}$  pump. In contrast to active contraction, lengthening of a muscle is a passive process, accomplished by contraction of an opposing muscle group.

**Cross-bridge cycling** burns ATP. Binding of a fresh unit of ATP is required to remove the myosin heads from the actin filament. ATP is then hydrolyzed by the myosin head, leading to conformational change in which myosin "throws back its head", allowing reattachment of the head to an actin unit two positions further up the chain. While the new cross bridge is formed, both ADP and inorganic phosphate remain attached to the myosin head. Release of the phosphate then leads to the power stroke where myosin bends its head, shifting the relative positions of actin and myosin to result in contraction. The cycle ends with the subsequent release of ADP.

**Sources of energy.** As long as  $\text{Ca}^{2+}$  is present, this process would go on until ATP is depleted. And even in normal muscle activity, ATP depletes pretty fast: within a few seconds, necessitating several lines of energy backup:

1. The first backup pool is phosphocreatine. Its high-energy phosphate is transferred to ADP. This allows replenishing the ATP pool several times over, but that still covers only about 10 seconds.
2. The next store of energy within the muscle cell is glycogen. Total glycogen stored in skeletal muscle is about four times the storage capacity of the liver, at about 400g dry weight. Remember that 1g of glycogen binds 2.7 g water, so about 1.5 kg of total body weight depends on muscle glycogen storage level. Metabolizing glycogen's glucose units generates energy at several levels. Breakdown to pyruvate and further to lactate generates ATP without the need for oxygen. As long as glycogen is present, this anaerobic metabolism would allow replenishment of ATP for almost a minute even in the absence of oxygen, but would soon be limited by acidification and accumulation of lactate. In normal circumstances, oxygen is available even during intense efforts, allowing the muscle to run on a mix of anaerobic and aerobic metabolism.
3. With the help of oxygen, acetyl-CoA generated by breakdown of pyruvate and fatty acids may be burned via citric acid cycle and mitochondrial respiratory chain to yield lots of ATP, but the rate of oxidative metabolism is limited by the rate of oxygen delivery to the muscle. Lipid energy stores are inexhaustible, enabling muscular activity for many hours on end at the reduced rate limited by oxidative ATP generation capacity.

**Hitting the wall when running a marathon.** Marathoners run on a mix of aerobic and anaerobic ATP generation. They maximize their muscle stores of glycogen by "carbohydrate loading" in the days before the event, but even so, glycogen stores of amateur runners are depleted somewhere between km 30 and 35 (miles 19-22). At this point, the rate of energy generation comes down to that of pure oxidative fatty acid metabolism. Runners, unable to keep up the previous pace, experience this as "hitting the wall".

**Insulin sensitivity.** Muscle is the largest glycogen storage organ, with about the fourfold capacity of the liver. Under insulin stimulation, muscle is the predominant site of glucose

disposal. A single bout of exercise improves whole-body insulin sensitivity for up to 48 hours. Therefore, exercise is one of the most effective ways to prevent metabolic syndrome and type II diabetes mellitus.

**Malignant hyperthermia.** In genetically predisposed individuals carrying, e. g., allelic variants of  $\text{Ca}^{2+}$  release channel, volatile anesthetic agents and succinylcholine may cause cytoplasmic  $\text{Ca}^{2+}$  levels to remain elevated during general anesthesia. As we saw before, in the presence of cytoplasmic  $\text{Ca}^{2+}$ , cross bridge-cycling will go on indefinitely, burning massive amounts of ATP and generating massive amounts of heat in the process. This results in muscle rigidity, acidosis and very high body temperatures. Heart and breathing rates are increased yet nonetheless unable to compensate for increased  $\text{CO}_2$  production and  $\text{O}_2$  consumption. The only treatment of this life-threatening condition is dantrolene, a muscle relaxant that prevents the release of calcium by the overexcitable  $\text{Ca}^{2+}$  release channel.

**Control of power.** A single action potential in a motor unit produces only a barely perceptible twitch. A lot more is required for movements, yet most of our movements require only a fraction of the force the respective muscles would be able to generate. How do we produce increments of force? We do this by two mechanisms:

- by repeating action potentials in the same motor units (frequency summation)
- by recruiting ever larger numbers of motor units (multiple fiber summation)

However, it is important to realize that not all motor units are created equal.

**Motor unit types.** Individual motor units are homogeneous in fiber type composition. Human skeletal muscles contain several fiber types expressing different isoforms of myosin heavy chain and having distinct contractile and metabolic properties:

- Type I fibers are characterized by myosin heavy chain-1, slow-twitch contraction, a red hue due to high myoglobin concentration, high mitochondrial content, relatively low myosin ATPase activity yet high resistance to fatigue. They represent a little more than half of all fibers, generate ATP mainly by  $\beta$ -oxidation of fatty acids and are used at all exercise intensities.
- About 30-35% are Type IIa fibers, which predominantly express myosin heavy chain-2A, have intermediate characteristics, and are recruited at higher intensities.
- The remaining 10-20% are Type IIx fibers, which express mainly myosin heavy chain-2X and are characterized by fast-twitch contraction. With their high ATPase activity, they are able to generate strong force and are only recruited at high intensities like  $>75\% \text{VO}_2\text{max}$  (maximal oxygen uptake). They generate ATP mainly via glycolysis, have low mitochondrial density and are pale due to low myoglobin content, resulting in low endurance. (Rodents have an even faster type of fibers, IIb.)

Smaller motor units tend to be directed by motor neurons with smaller cell bodies. CNS stimuli of limited intensity only succeed in depolarizing the smaller motor neurons, allowing finely controlled, low-power movements by motor units composed of type I fibers. Stronger stimuli recruit incrementally larger motor neurons, resulting in activation of large type II motor units and allowing contractions of great force. Fiber type distribution is genetically

determined and varies between individuals; nevertheless, muscle plasticity allows extensive functional adaptation in response to exercise.

**Substrate metabolism depending on exercise intensity and duration.** Substrate utilization depends on exercise intensity, which is best measured as percentage of maximal oxygen uptake (%  $\text{VO}_2\text{max}$ ). At low intensities, most of the required energy is provided by lipid oxidation, mostly from plasma free fatty acids. Increases in intensity are predominantly fuelled from carbohydrates, first by oxidation, but with further increases, by ever larger contributions from anaerobic glycolysis. To a large extent, this is the result of fiber recruitment. At low intensities up to 50% of  $\text{VO}_2\text{max}$ , only slow-twitch type I fibers with their high oxidative capacity for lipids are used. At increased intensities, motor units of IIa and IIx fibers are added, with increased rates of ATP production but lower oxygen consumption due to higher contributions of glycogenolysis and glycolysis.

Exercise at a moderate fixed intensity for longer durations causes a shift in substrate contribution. During the first half hour, about two-thirds of the energy comes from carbohydrate oxidation, but that percentage gradually comes down with increased duration. Once glycogen stores are depleted after about three hours, the muscle runs predominantly on lipid oxidation.

After cessation of exercise, our body's metabolic rate falls slowly back to normal, yet remains slightly elevated for up to 24 hours. In fact, exercise allows us to burn more calories while we sleep!

**Concentric and eccentric exercise.** Depending on the muscle's change in length during activity, there are three types of exercise:

- concentric exercise: the trivial case where muscle shortens while contracting.
- isometric exercise: the muscle contracts against physical resistance of equal force, causing muscle length to remain unchanged (example: biceps of a waitress carrying beer mugs at the Munich Oktoberfest). Resistance exercise at or near isometric contraction is the most efficient way to induce muscle hypertrophy.
- eccentric exercise: the muscle attempts to contract while simultaneously being passively stretched. This is used to control or cushion a movement, as with the quadriceps in stepping down stairs. This is only possible if some fibers contract and others relax at the same time, causing large differential forces that may result in structural disruption.

Delayed onset muscle soreness and muscular injury usually result from extensive eccentric exercise.

## 2. MUSCULAR FATIGUE AND PAIN

With prolonged exertion, the muscle acidifies, accumulating protons, lactate and extracellular ATP. All of these may be quantified by sensors acting as receptors of afferent neurons. Proton concentration is sensed by ASIC (acid sensing ion current) receptors, lactate via TRPV1 (transient receptor potential cation channel V1) receptors and ATP via P2X (purinergic) receptors. These metabolite receptors are localized densely on afferent neurons near blood vessels below the muscle fascia, which convey these measured values in the form of frequencies of action potentials to the brain. Increased concentrations of these metabolites evoke sensations of fatigue (e.g., pH 7.3 + 400 nM ATP + 1 mM lactate), higher concentrations additional sensations of pain (e.g., pH 7.2 + 500 nM ATP + 10 mM lactate). Only the combination of metabolites results in sensation, experimental administration of single metabolites does not cause any sensation. In effect, "muscle" fatigue is actually a function of the brain. Blocking afferent signals would allow the muscle to go on, a process likely ending in serious damage.

## 3. DELAYED ONSET MUSCLE SORENESS

While immediate muscle pain during exercise is due to metabolite accumulation, muscle soreness the next day is not. Although actual data on delayed onset muscle soreness (DOMS) are sparse, it is thought to be due to microtrauma of the muscle, which is especially likely to be caused by eccentric exercise. In part of the fibers, disruption of normal myofilament structures is observed, especially broadening, smearing or even total disruption of z-lines. In addition, intracellular proteins such as creatine kinase or myoglobin leak into the plasma, indicating damage to the cell membrane. Disrupted membranes also result in increased cytoplasmic calcium levels, which may activate calcium-dependent proteolytic enzymes and interfere with normal mitochondrial ATP production. In a second phase, macrophages and neutrophils enter to remove damaged structures, a process associated with slight inflammation and edema. Soreness is thought to result from the combined action of inflammatory bradykinin, elevated extracellular potassium, macrophage-produced prostaglandin E2 and edematous pressure. Soreness may increase with movement as mechanical pressure additionally stimulates already sensitized type III and type IV (Erlanger/Gasser nomenclature: A $\delta$  and C) nerve endings, especially at the musculotendinous junction. Attempts to treat DOMS have shown little benefit; renewed exercise seems to relieve pain most efficiently, yet this effect is temporary and soreness resumes immediately upon cessation of activity. With or without treatment, DOMS disappears after a few days.

## 4. MUSCLE AND TENDON INJURY

With increasing force, larger structural damage may cause immediate injury. This affects not only the muscle fibers, but also the extracellular matrix, especially the collagen fibrils.

Collagen fibrils are found throughout the muscle around the muscle fibers, but form an ever larger percentage of the muscle's cross-sectional plane towards its origin and insertion at the bone. Disruption of this architecture also results in tearing of blood vessels with hemorrhage and immediate sudden pain. Usually caused by eccentric overload, rupture may occur within the muscle or in the tendon. Surprisingly, the healing process of muscle strains and injuries has been shown to benefit considerably from cautious application of specific lengthening (i.e., eccentric) exercises. Pulled hamstrings are typical in dancers and sports involving a lot of sprinting, like soccer. Tendons, which are hard to supply with blood due to high tissue tension, typically rupture in connection with pre-existing damage. Most frequently affected are Achilles tendon, at the knee quadriceps tendon and patellar ligament, at the elbow the proximal biceps tendon and at the shoulder the rotator cuff, especially the tendon of the supraspinatus muscle. Achilles tendon rupture typically occurs during actions involving explosive acceleration in jumping or running.

**Pharmacology cross reference:** The risk of tendon rupture is increased in patients treated with fluoroquinolone antibiotics such as Ciprofloxacin (gyrase inhibitors). Likewise, the risk is increased in patients treated with glucocorticoids, especially if these are injected directly into the tendon to treat inflammatory symptoms. Inflammatory mediators such as TNF $\alpha$  induce matrix metalloproteases, e. g., collagenase, and glucocorticoids have a suppressive effect on the transcription of the collagen type I gene. Therefore, the inflammatory process and its treatment have an additive negative effect on the tendon's tensile strength. The risk of muscle injury is increased in people taking statins.

## 5. MUSCLE CRAMPS

Muscle cramps are sudden involuntary contractions of muscle that may be excruciatingly painful. Everybody experiences a cramp now and then, but cramps may occur quite frequently in certain typical situations. A cramp may be induced easily by forcibly contracting an already shortened muscle. Some individuals are prone to nocturnal leg cramps, especially with increasing age. Cramps are common in the third trimester of pregnancy and after prolonged exercise, especially in the presence of volume and electrolyte imbalances under hot and humid conditions. Generally, circumstances causing acute reductions in extracellular volume predispose to cramps: heavy perspiration, diarrhea, vomiting, diuretic therapy or hemodialysis. In addition, cramps may be caused by neurologic disorders affecting lower motor neurons or by disorders such as liver cirrhosis or hypothyroidism.

The pathophysiology of cramps remains quite unclear. There is broad consensus that the increase in excitability is not located in the muscle cells themselves, but rather in the motor neurons, causing electromyographical discharge rates up to 150 Hz, but the consensus ends right there. The "central hypothesis" locates the trigger at the cell bodies in the ventral horn of the spinal cord, while the "peripheral hypothesis" sees the origin somewhere along the peripheral nerve, most likely near the neuromuscular junction.

What can be done against cramps? Usually, stretching the affected muscle provides immediate relief. Stretching the calf before going to bed may reduce the incidence of nocturnal leg cramps. Preventing dehydration and hyponatremia in sports is important, and magnesium substitution has been shown to have some effect in pregnancy cramps.

**Pharmacology cross reference:** Some drugs are quite effective, but carry risks of side effects which may be too onerous for a benign condition like a cramp. Quinine sulfate is the classical drug to reduce cramp incidence, but may induce problems with hearing and eyesight. Anticonvulsants reduce the excitability of motor neurons, but come with heavy side effects. In addition, creatine and the calcium channel blocker verapamil have shown some efficacy.

## 6. TRAINING ADAPTATION

Acute bouts of exercise cause changes in metabolite concentrations that are registered by molecular sensors and feed back into the regulation of gene expression. Of the many sensor types recognized, let's consider three by way of example:

- Oxygen deficit sensing: acute exercise utilizes large quantities of oxygen, thereby reducing partial oxygen pressure in muscle fibers. This stabilizes HIF-1 (hypoxia-induced factor 1), a transcription factor which enhances expression of, e. g., enzymes of the glycolytic pathway. Likely, this mechanism is responsible for the beneficial effects of altitude training.
- Energy deficit sensing: exercise burns ATP; increased levels of AMP allosterically activate AMP-activated protein kinase (AMPK), which suppresses glycogen synthesis and protein synthesis but promotes glucose transport and lipid oxidation. Chronic AMPK activation induces mitochondrial biosynthesis.
- Overload sensing: high-force resistance exercise activates phospholipase D via a pathway that is not yet sufficiently clear. Phospholipase D liberates phosphatidic acid from the sarcolemma. Phosphatidic acid activates mTOR (mammalian target of rapamycin). Via several pathways, mTOR increases ribosomal capacity and translation of mRNA, resulting in increased muscle protein synthesis. In combination with adequate dietary protein intake, this mechanism induces the hypertrophy phenotype desired by devotees of six pack abs and bulging biceps.

The first two mechanisms indicate that for optimal training adaptation, we need bouts of high-intensity exercise: the lowest levels of intracellular oxygen and the highest levels of AMP are reached at the highest intensities of muscle activity. Of course, high intensities can only be maintained for short durations. If we want to maximize this effect, we can only add additional bouts of intensive exercise separated by intervals of recovery. By that, we arrive at **high-intensity interval training** (HIIT), which is a necessary component of optimal training even for endurance sports.

Thus, every workout strains the musculoskeletal system and may cause a little damage here and there, but is followed by an acute regenerative change in gene expression: mRNA levels

from many genes go up. This mRNA response is short-lived, but results in the synthesis of additional units of muscle proteins and enzymes. The proteins have a longer half-life than the mRNA and start to accumulate. In other words: in the immediate aftermath of acute exercise, the muscle's functionality is reduced, but this phase is followed by a wave of regenerative overcompensation. With proper timing of training units, levels of functionally important proteins, e. g., myosin, actin, enzymes, mitochondrial proteins, can be nursed to higher levels. Over time, this process leads to an increase in whole-muscle metabolism and exercise performance.

From this, it is clear that dosage and timing of exercise is crucial. If the bouts of exercise are too intense and/or timed too closely, there is not enough opportunity for regenerative overcompensation and the muscle is progressively weakened: we have overtraining or, rather, detraining. If exercise units are timed too infrequently, the window of regenerative overcompensation has passed and the system is back to where it had been before: we never reach higher levels. The trick is to place the next bout of exercise right on top of the overcompensation phase. We need the bouts of exercise to trigger the response, but we do actually improve during the ensuing phases of rest.

Physical training is systematic exercise in the continuum between the two extremes of aerobic (endurance) and resistance (strength). The two forms of exercise cause different adaptations:

- Resistance exercise induces muscle hypertrophy, with increased fiber size via myofibrillar protein synthesis. Affected muscles grow in volume and power. These adaptations occur most prominently in type II fibers, with concomitant increases in anaerobic capacity.
- Aerobic exercise increases endurance capacity by increases in mitochondrial protein synthesis and oxidative function, mitochondrial density, capillarization and lactate tolerance. After six weeks of aerobic training, muscle mitochondrial density increases 50-100%. Systemic effects include a marked increase in cardiac stroke volume with concomitant reduction in resting heart rate and improvements in cardiovascular risk profile.

One of the gene expression regulators most clearly associated with mitochondrial biogenesis is PGC-1 $\alpha$  (peroxisome proliferator-activated receptor gamma coactivator 1 $\alpha$ ). PGC-1 $\alpha$  is a transcriptional coactivator regulating many genes in energy metabolism. PGC-1 $\alpha$  overexpression increases mitochondrial biogenesis, respiratory capacity, ATP synthesis and improves exercise performance. In addition, PGC-1 $\alpha$  is required for exercise-induced angiogenesis.

## 7. GENETIC MODIFYERS OF MUSCLE FUNCTION

Polymorphisms in genes encoding proteins important for muscle activity affect athletic performance. Let's have a look at just one out of numerous examples: a SNP in  $\alpha$ -actinin-3, a protein helping to crosslink actin filaments in type II fibers. Two alleles are distributed over the human population with roughly comparable frequency: the R allele contains an arginine in



position 577, while the X allele contains the nonsense mutation R577X, a stop codon leading to a protein fragment that is rapidly broken down. In Europe, about 18% of the population is XX homozygous, completely lacking  $\alpha$ -actinin-3. No disease phenotype is associated with this deficiency; the very similar protein  $\alpha$ -actinin-2 works as a backup. Elite sprint and power athletes have significantly higher frequencies of the 577R allele than controls, while endurance athletes tend to have higher frequencies of the X allele. Recall that endurance exercise relies mainly on Type-I fibers, where  $\alpha$ -actinin-3 plays no role.

In sports today, talent scouting means phenotype screening to identify kids with favorable combinations of "athletic" alleles. Genetic testing is expected to complement this process in the near future. Athletic top results are only achieved if optimal training regimes coincide with the most favorable genetic backgrounds.

## 8. GENETIC DISEASES

Many genetic diseases affect the function of skeletal muscle. Examples are:

**Muscular dystrophies** are characterized by creeping death of muscle cells due to deficiencies of one out of many different proteins, leading to progressive weakening of the muscles. One of these proteins is dystrophin, affected in Duchenne and Becker types of muscular dystrophy. Dystrophin is a component of a large cross-membrane protein complex tethering intracellular myofilaments to extracellular matrix fibers. Dystrophin acts like a shock-absorbing spring. In its absence, the force of contraction leads to repeated injuries of the cell membrane, causing eventual death of the cell and replacement by adipose cells. The dystrophin gene is our largest gene, representing 0.08% of the human genome, located on the X chromosome. It takes 16 hours to produce the huge primary transcript and splice it into the mRNA consisting of 79 exons. Sporadic mutations occur frequently, accounting for a third of disease cases. X-linked inheritance means the disease primarily affects boys. Depending on the individual mutation, the amount of remaining dystrophin determines the severity of the disease. In Becker muscular dystrophy, a truncated dystrophin remains partially functional, allowing survival into old age.

**Glycogen storage diseases:** in light of the importance of glycogen to cover energy requirements of muscle, defects in glycogen synthesis or metabolism are bound to negatively impact muscle function.

**Mitochondrial diseases:** for mitochondria, the most efficient generator of ATP, the same argument is valid. The subclass of mitochondrial diseases affecting neuromuscular functioning is termed mitochondrial myopathies. The defects may reside in mitochondrial DNA or in nuclear genes encoding macromolecules imported into mitochondria.

## 9. TOXINS

**Botulinum toxin** is a protein-neurotoxin produced by *Clostridium botulinum*. The heat-labile toxin has occasionally caused food poisoning when spores of the anaerobically growing bacterium contaminated canned food. It is one of the most potent toxins known, with a lethal dose (LD50) of 1-2ng/kg when injected or ten times that when inhaled. The toxin is taken up into axon terminals and proteolytically degrades one of three proteins termed SNAP-25, VAMP/Synaptobrevin or syntaxin, all of which are required for vesicle fusion with the presynaptic membrane of the motor end plate. Release of acetylcholine is decreased, causing flaccid paralysis. Death may result from respiratory failure.

Pharmacology cross reference: diluted botulinum toxin has been used to treat strabismus, with injection into selected extraocular muscles every six months. In addition, it is used for several conditions in which a relaxation of specific muscles is desired, as in various forms of dystonia. Cosmetically, it is being used to prevent or lessen wrinkles by paralyzing facial muscles, with the inevitable side effect of reducing facial expression.

**Tetanus toxin** is another protein-neurotoxin produced by *Clostridium tetani*. The anaerobically growing bacterium is feared in wound infections. As with botulinum toxin, tetanus toxin is taken up into axon terminals, but in this case, predominantly inhibitory interneurons releasing glycine or  $\gamma$ -aminobutyric acid (GABA) in the spinal cord are affected. Breakdown of VAMP/Synaptobrevin in these Renshaw cells, which have a relaxing effect in the fine-tuned closed loop system regulating muscle tonus, causes a long-lasting spasm at the slightest stimulus to the motor neuron. Clinical tetanus starts at the shortest nerves, leading to the characteristic symptoms of *risus sardonicus* and lockjaw. Death may result from breathing problems due to the spastic paralysis. As in botulism, binding of the toxin is irreversible, necessitating intensive care for weeks or months until new axon endings have grown. Tetanus is easily prevented by vaccination with an inactivated form of the toxin, tetanus toxoid, which induces neutralizing antibodies.

**Curare** is a common name for plant extract poisons used by indigenous South American people for arrows or blowgun darts. The alkaloids competitively and reversibly inhibit the nicotinic ACh receptor, causing flaccid paralysis.