

Fig 5-22. The inner surface of the channel is exposed to an artificial cytoplasm; the site is dephosphorylated and channel activity ceases. Channel activity is regained when the phosphorylation enzyme system is added. (From Armstrong and Eckert, *Proc. Natl. Acad. Sci. USA* 84: 2518-2522, 1987)

and hormones acting via receptors proteins in the membrane to modulate c AMP and hence channel phosphorylation. The number of Ca channels in the heart ventricle is increased by epinephrine, the action potential is more positive and prolonged and more CaA enters the cell. Increased Ca results in a more forceful contraction. The number of systems and the subtlety of their action are expanding too rapidly to make listing them all useful.

OVERVIEW: SYNAPSES, RECEPTORS AND TRANSMITTERS

Communication between neurons is dependent on synapses. Synapses may be electrical or chemical. Electrical synapses have a cytoplasmic continuity between the pre and postsynaptic neuron. Ions flow through specialized ion channels termed gap junctions. Transmission may be bidirectional. This type of synapse may be found in glial cells.

Almost all neuronal synapses in mammals are chemical in nature. Conduction across such synapses is slower but is unidirectional. Duration is usually 15 to 20 milliseconds which is considerably longer than the axon potential (which usu-

ally has a duration of 1-2 msec). Potentials less than the threshold potential for triggering the action potential are summated at the post synaptic receptor and neuron. At a chemical synapse, pre and postsynaptic membranes are separated by a cleft composed of the extracellular space. This cleft is wider for type I synapses which are usually excitatory, utilize glutamate and involve the spiny processes on the dendrites (axodendritic). Type II synapses are usually inhibitory, utilize gamma amino butyric acid and involve the cell body (axosomatic). In general the axon terminals of the cerebral cortical pyramidal neurons are excitatory. Communication across this cleft is achieved on the release of chemical transmitters. When the action potential reaches the presynaptic terminals, calcium channels are activated and calcium ions enter the presynaptic terminal from the extracellular space. Phosphorylation of proteins (synapsin) occurs and these proteins then link the synaptic vesicles containing the transmitter to the cytoskeleton of the presynaptic terminal. The vesicles then fuse with the membrane of the terminal and in the process release their contents of transmitter. The transmitter then crosses

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the synaptic cleft and then binds to the postsynaptic receptor. This process results in a delay in transmission time of 0.5-1 millisecond.

The receptors (which have multiple subunits) gate ion channels and are of 2 types:

1. Iontropic (directly linked, fast): these receptors directly gate ion channels. They are also referred to as ligand (or transmitter) gated channels. After binding the transmitter, a conformational change occurs with opening of the ion channel. These receptors are associated with relatively fast synaptic action lasting only a few milliseconds. Examples include the glutamate (non NMDA and NMDA,) and GABA/A and the nicotinic acetylcholine receptors.

2. Metabotropic (second messenger mediated, slow): These receptors gate ion channels indirectly. Two phases occur: recognition of the transmitter and activation of the effector. In the major type of this group, the receptor molecule is coupled by a guanosine nucleotide binding protein (G- protein) to the effector molecule. Examples include norepinephrine, dopamine, serotonin, GABA/B, muscarinic acetylcholine and certain types of glutamate receptors. The receptors are large protein molecules distinct from the ion channel. **These receptors alter intracellular metabolic reactions with the production of a second messenger.** These 2nd messengers activate protein kinases-enzymes involved in the phosphorylation of substrate proteins. Much work has centered on cyclic adenosine monophosphate (cAMP). In addition to this second messenger, gaseous second messengers such as nitric oxide and carbon monoxide have been recognized. The action of these receptors is slower with onset of action taking several hundred milliseconds to seconds and with the effect on channels lasting seconds to minutes or longer. **The excitability of neurons and the strength of synaptic connections are modulated. This action is therefore sometimes referred to as modulatory.**

Overall the action of transmitters on the receptor and neuron is not all or none. The postsynaptic potentials may be summated. The specific action of a transmitter may be excitatory or inhibitory. **The specific action depends upon the receptor and not on the transmitter per se.**

The relationship of receptors and ion channels is presented in table 5-4

STRUCTURE OF THE IONOTROPIC RECEPTORS

The synaptic receptors for GABA, glycine, acetylcholine and glutamate are transmembrane proteins.

The GABA/A, glycine and nicotinic acetylcholine receptors all have a similar pentameric structure, coded by related families of genes. The 5 subunits surround a central channel pore (Fig. 5-23). For GABA/A and glycine, the channel selects for chloride anions. For nicotinic acetylcholine, the channel selects for cations such as sodium. Each subunit has four transmembrane helical domains labeled M1-M4.

In contrast, the glutamate receptors have a different proposed structure, tetramers composed of two different types of subunits. Each subunit is composed of three helical transmembrane domains and an additional helical region that dips into the membrane and lines the central pore.

The major transmitters and receptors in the central nervous system are as follows:

EXCITATORY TRANSMITTERS AND RECEPTORS:

In general, sodium channels are opened.

Glutamate: This is the major excitatory transmitter in the central nervous system. Its action is mediated by channels that conduct sodium and potassium ions.

TABLE 5-4

TYPE OF RECEPTOR	ION CHANNEL AND/OR METABOLIC EFFECT
DIRECT ION GATED	
Excitatory	Increase sodium and calcium permeability
Inhibitory	Increase chloride permeability
G-PROTEIN COUPLED	
Excitatory	Stimulate cAMP Increase intracellular calcium Decrease potassium permeability
Inhibitory	Inhibit cAMP Decrease permeability of calcium Increase potassium permeability

Increased permeability = channels open

Four receptors may be specified. Three are ionotropic, one is metabotropic.

The ionotropic receptors are named according to the specific action of synthetic agonists.

Non-NMDA receptors: these receptors gate ion channels which are permeable to both sodium and potassium but not calcium. Two types are recognized:

1. Kainate (Kainic acid) and 2.AMPA (α-amino-3-hydroxy-5methylisoxazole-4propionic acid).

As regards the kainate receptor, both kainic acid and domoic acid are agonists that are convulsant agents acting on this system. The amino acid domoic acid was implicated as a marine toxin produced by a marine organism diatom infecting mussels off the eastern coast of the Canadian Maritimes, anchovies, bivalves and crustaceans on the Pacific coast of northern California, Oregon and Washington state. This agent produces significant damage to the hippocampus resulting in seizures and disorders of recent memory (an amnesic syndrome). The anterior horn cells are also severely affected. All of these effects are considered to be due to glutamate excitotoxicity since domoic acid is 30 to 100 times more potent than glutamic acid and 3 times more potent than kainic acid.

The AMPA receptor is diffusely distributed within the central nervous system and through the opening of sodium channels produces fast excitation.

NMDA (N-methyl-D-aspartate) receptor. This receptor controls a cation channel that is permeable to calcium, sodium, and potassium ions. Opening of the channel requires extracellular glycine as a cofactor. Opening of the channel depends on membrane voltage as well as chemical transmitter. Maximum current flow occurs only after the membrane is already depolarized and glutamate is already present. Magnesium ions must also be expelled from the channel into the extracellular space for action to occur. This channel opens relatively slowly in response to glutamate as opposed to the non-NMDA receptors. However the action is still more rapid than at metabotropic receptors. Calcium ions are important in the passage of current. In contrast to the AMPA receptor, prolonged bursts of depolarization occur. At certain sites AMPA and NMDA

receptors are clustered together and interact. The following convulsant agents act at this location to enhance excitability: NMDA, quinolinic acid, low magnesium and estrogens. Progesterone metabolites may decrease action at the site. The influx of calcium has other implications. Calcium dependent enzymes and 2nd messenger protein kinase are activated with a long-standing modification in synaptic activity (long term potentiation). This has implications for both learning and more persistent seizure effects particularly as regards the hippocampus. The influx of calcium may trigger processes that contribute to apoptotic cell death (glutamate excitotoxicity).

The activation of **metabotropic glutamate receptors** also results in increased levels of intracellular calcium with the cascade actions described above.

Acetylcholine: This agent may have either excitatory or inhibitory actions depending on the receptor and site of action. **There are 2 general classes of receptors: 1. Nicotinic and 2.Muscarinic.**

Nicotinic receptors are excitatory and are found at the postsynaptic neuromuscular junction of skeletal muscle and in the peripheral autonomic ganglia and other neural crest derived tissues. The Renshaw cell of the spinal cord is activated by nicotinic collaterals of the alpha motor neuron and then feeds back to inhibit the alpha motor neuron. Nicotinic receptors are also located at presynaptic sites and when activated produce an increase in neurotransmitter release. Nicotinic receptors are ligand gated ion channels for sodium. The action is excitatory. Although nicotinic receptors are present to some degree in the brain, the major CNS receptor category for acetylcholine is muscarinic.

Muscarinic receptors in contrast are G-protein linked (guanosine nucleotide binding protein) and are of multiple types. M1 receptors produce a decrease in potassium conductance and have a predominantly excitatory effect. In contrast, M2 receptors increase potassium conductance and are inhibitory. When these receptors are located at presynaptic sites, the axoaxonic receptors are usually inhibitory. The postsynaptic receptor sites may be either excitatory or inhibitory. Overall most central nervous action are excitatory. These muscarinic neurons are found in the

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nucleus basalis of the basal forebrain and project to the cerebral cortex. A loss of these neurons occurs in Alzheimer's disease and contributes to memory loss (see chapter 30). Muscarinic neurons are also found in the mesopontine tegmentum, project to the thalamus and are involved in cortical activation and arousal (see chapter 29)

INHIBITORY TRANSMITTERS AND RECEPTORS:

Gamma amino butyric acid (GABA): this is the major inhibitory agent and receptor in this category. There are 2 major receptors in this category (a 3rd has recently been described).

GABA/A, an ionotropic receptor that gates a chloride (-) ion channels.

GABA/B, a metabotropic receptor that activates a 2nd messenger sequence which then activates (opens) a potassium ion channel.

Either increased intracellular chloride or decreased intracellular potassium ions would result in an increased negativity of the inside of the neuron; that is additional intracellular hyperpolarization would occur. The agent baclofen acts as an agonist at the GABA/B site.

In terms of actions of convulsant agents a number of substances are antagonist at the GABA/A receptor including bicuculline, penicillin, picrotoxin, pentylentetrazol, and estrogens. Note also that agents that inhibit GABA synthesis such as pyridoxine antagonists e.g. methoxy pyridoxine, isoniazid and l-allyl glycine may produce seizure activity particularly as regards the hippocampus. Cobalt ions may also have an acute action of this type.

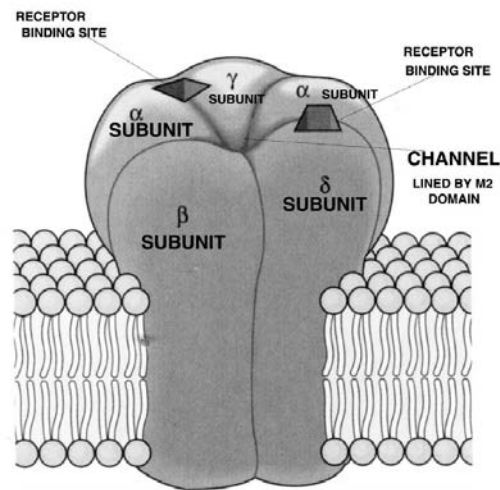
The GABA/A receptor also has subunit receptor sites for benzodiazepine, barbiturates, alcohol and steroids. Benzodiazepines potentiate the GABA induced chloride conductance by increasing the frequency of chloride channel opening. Barbiturates potentiate the duration of chloride channel opening. Estrogens decrease chloride conductance, progesterone agents potentiate chloride conductance. Note that all steroids may also have more chronic actions on the neuron that do not necessarily involve the synapse.

Glycine: The glycine receptor is similar in structure to the GABA/A and acetylcholine nicotinic receptors. Glycine activates ionotropic GABA/A receptors. Glycine receptors are primar-

ily located in the spinal cord and brain stem and to a lesser degree in other areas of the brain. At the spinal cord level, glycine is released by interneurons that inhibit antagonistic muscles (the Renshaw cell). Strychnine functions as a convulsant agent by antagonistic effects on the glycine receptor. When administered systemically this agent may produce convulsions primarily by action at the level of the spinal cord. However early studies of cortical function and connections in the 1930's and 40's employed direct application of strychnine to the pial surface of the monkey cerebral cortex to produce focal discharge (demonstrated later).

MONOAMINES:

The central monoamines include the catecholamines, serotonin and histamine. In general, these agents act at metabotropic modulatory synapses. Their action is often coupled with that of neuropeptides.



Pentameric structure of GABA Glycine, and nicotinic acetylcholine receptor channel.

Fig.5- 23 . The pentameric structure of the GABA/A, glycine and nicotinic acetylcholine receptors. Each contains a series of subunits surrounding a central pore (channel). In the case of GABA/A, and glycine the channel when open allows the passage of chloride anions producing inhibitory actions. In the case of the nicotinic acetylcholine receptor, the channel when open permits the passage of cations such as sodium producing an excitatory action. The GABA/A receptor has subunit receptor sites for benzodiazepines, barbiturates, alcohol and steroids. Modified from Kandel et al 2000.Principles of Neural Science 4th edition.New York McGraw Hill.page 200.

Catecholamines;

This group includes three biochemically related transmitters: *dopamine, norepinephrine and epinephrine*. These receptors operate through the cyclic AMP system.

Dopamine: several receptors(D1- D5) are recognized .The main receptors D1 and D2 both involve a 2nd messenger system which utilizes cyclic AMP. The action of dopamine at the D1 (and D5) receptors is to stimulate the formation of cyclic AMP; decreasing potassium conductance producing excitation. The action of dopamine at the D2 (and D3 and D4) receptors inhibits the formation of cyclic AMP. As a result potassium conductance is increased and inhibitory action results. D1 and D2 receptors are primarily located in the neostriatum and the nucleus accumbens and will be discussed in chapter 19. D3 and D4 receptors occur primarily in the limbic system. D4 receptors occur primarily in the frontal cortex. D5 receptors are found in the hypothalamus, thalamus and hippocampus.

Norepinephrine and epinephrine. In the central nervous system, neurons utilizing these transmitters are found in the locus ceruleus of the dorsal pons and the lateral tegmentum of the medulla and pons, where they have a significant role in the reticular formation and also influence areas concerned with autonomic function. Norepinephrine is also the primary neurotransmitter of the postganglionic sympathetic system. Epinephrine also functions as a circulating hormone after release from the adrenal medulla. There are a series of receptor subtypes, grouped as alpha 1, alpha 2, and beta. Alpha 1 receptors are excitatory; alpha 2 are inhibitory.

Serotonin and histamine: These transmitters will be discussed in the chapter on sleep (29).

Both have widespread effects. Both have multiple subtypes. Depending on the receptor the effect may be excitatory or inhibitory.

NEUROPEPTIDES

These agents occur in the central nervous system, endocrine and gastrointestinal system. Within the central nervous system, they are found with a high concentration in the hypothalamus, the amygdala, the autonomic nuclei, brain stem and spinal cord. In the spinal cord and brain stem, they have a role in modulation of pain. These

agents also have a significant role as modulatory associated transmitters in the basal ganglia (chapter 19).

GENETIC MUTATIONS INVOLVING CHANNELS AND RECEPTORS: Specific defects have now been identified in several varieties of presumably monogenic seizure disorders. This topic will be discussed in chapter 29.

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would appear that the continued release of acetylcholine, or possibly some other transmitter, from the nerve, is the agent responsible for this trophic influence.

Denervation Sensitivity. When the muscle is denervated, the entire surface of the muscle fiber slowly becomes sensitive to acetylcholine. After several weeks, application of ACh anywhere on the surface results in an action potential and contraction. Patients who have had a motor nerve severed show great sensitivity to injected ACh for this reason.

Reinnervation. If the cut ends of a motor nerve are rejoined, sprouts from the central end will grow down the tube left by the degenerated axon. If the distance between the cut and the muscle is short and the cut ends are well aligned, the nerve will make contact with the muscle. A new end plate will form, and muscle function will be restored. Passive exercise of the muscle during regrowth is helpful to prevent disuse atrophy and contractures.

Slow and Fast Muscles.

There are two sorts of skeletal muscle: red and white. The best known example of this difference is the white and dark meat of a chicken; the same qualitative differences appear in mammals.

Most muscles, particularly in mammals, are not pure red or white muscle but are made up of a mixture of fibers (*Fig 6-14*). The fibers in red muscles are called Type I. They are rich in mitochondria but have a relatively low myosin ATPase activity. They generate ATP from glucose as it is used. Enzymes of oxidative metabo-

lism cause the red color. Type II fibers found in white muscles have a very active myosin ATPase activity and are relatively lacking in mitochondria. Type II fibers which are responsive for quick, phasic contractions depend upon an anaerobic, glycolytic metabolism; they produce large amounts of lactic acid.

Red muscle is characterized by a long twitch time, and concomitantly a low frequency of stimulation will result in tetanus. These muscles are primarily antigravity or postural muscles; their movements are characterized by long-sustained contractions. The white muscles, on the other hand, have short twitch times and are used for quick phasic movements.

The speed of contraction is determined by the pattern of activity in the motor nerve. When nerves from fast and slow muscles are crossed, the fast muscle slows down and the slow muscle speeds up (*Fig 6-14*). When a limb is immobilized, the activity in motor nerves to a slow muscle, which is usually intense, decreases. After several weeks the speed of contraction has increased markedly. It is not clear how the pattern of activity alters the biochemical control mechanisms and the contractile properties of a muscle. Some authors suggest a second transmitter released in very small quantities from motor nerves is responsible for modulating which proteins are expressed from the muscle genome.

PART II: DISORDERS OF MUSCLE AND NEUROMUSCULAR JUNCTION

DISEASES OF MUSCLE

Most classifications divide these disorders into two groups: inherited and acquired (Morgan & Hughes 1992).

MUSCULAR DYSTROPHIES

The major inherited diseases are the muscular dystrophies characterized by a primary degeneration of skeletal muscle. The slow but progressive destruction of muscle results in a progressive weakness initially affecting the proximal muscles.

Duchenne's Muscular Dystrophy. The most common varieties of muscular dystrophy are X linked, almost all cases occur in males (rarely females with Turner's syndrome or X-chromosome translocation may be affected).

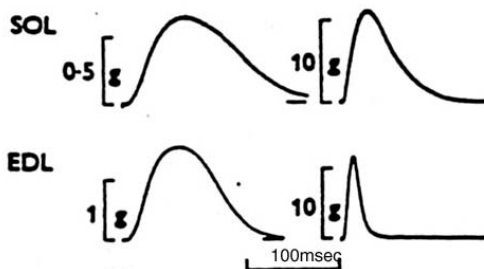


Figure 6-14. Twitch time in a fast, extensor digitorum longus (EDL) and a slow, soleus (SOL) muscle. At birth (left) the difference in twitch time is not striking, yet 5 weeks later (right) the difference is very pronounced. (From Close, R.: J. Physiol., 180:542, 1965.)

Duchenne originally described the most common type within this group in 1868. The typical patient with Duchenne's muscular dystrophy (DMD) is a boy who has delayed walking. At some point between the ages of 2 and 5 years, the patient is noted to be clumsy and slow in exercises and games. It is soon evident that proximal pelvic girdle lower extremity weakness is present. In rising from the floor the patient uses his upper extremities and hands placed on the thighs to force the body in to an erect position (*Gower's sign*), thus counteracting the weakness at hips and pelvis. At this point, marked enlargement of the calf muscles is present (pseudo hypertrophy). With progression of the disease, increasing atrophy of muscle and increasing weakness occurs. By age 12, the patient is confined to a wheel chair. Death occurs late in the teens or early twenties from respiratory complications and/or cardiac failure (heart muscle is involved). The blood creatine kinase level while the patient is still ambulatory is at least 40 times the upper limit of normal. Levels may be 300-400 times normal. The electromyogram (EMG) demonstrates myopathic features. The muscle biopsy taken early in the course of the disease before severe atrophy is present demonstrates characteristic myopathic features including: 1) wide spread necrosis and phagocytosis of muscle fibers 2) regeneration of muscle fibers, 3) marked variation in fiber size and 4) large rounded "hypercontracted hyalinized" fibers. (*Fig. 6-15*). In late stages replacement of muscle by proliferation of endomysial connective tissue and fat

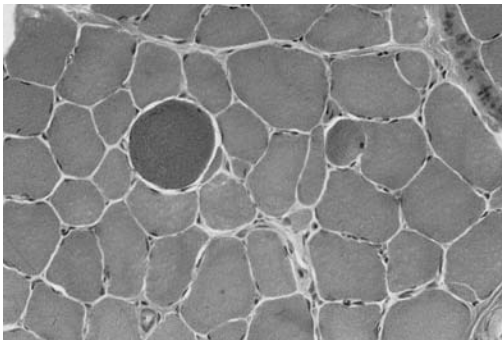


Figure 6-15. Muscle histopathology I: Duchenne's Muscular dystrophy Marked variation in fiber size is present with a large dense hypercontracted hyalinized fiber (Compare to 6-21 and 8-21). H&E x 63- Courtesy of Dr. Tom Smith, U.Mass Medical Center.

occurs.

DMD is the most common lethal, X linked disease with an estimated incidence of 1 in 4000 live male births (see Moser 1984). The maternal carrier can be identified based on family history and an elevated creatine kinase level in the carrier. A small % of carriers also have mild weakness or EMG or muscle biopsy changes. There is however a high frequency of isolated cases, 30-50% suggesting a high incidence of new mutants or mutant maternal carriers. In families at risk, prenatal diagnosis is possible (Darras et al. 1987, and see below).

Becker's muscular dystrophy. Becker's muscular dystrophy described in 1955 is a less common (1 in 20,000 male births) and less severe form of x-linked disorder. Age of onset is later; and the rate of progression is slower. The patient is still ambulatory at age 15. Life expectancy is only slightly reduced. Creatine Kinase levels are markedly increased. The EMG demonstrates myopathic features. The muscle biopsy indicates features that are similar but less marked than those noted above.

Recent major advances have been made in our understanding of the genetics and molecular biology of these disorders (Arahata et al, 1989, Hoffman et al. 1988, see also review of Rowland 1988). The precise locus has been identified: the short arm of the X chromosome at the region designated as Xp 21. The specific affected gene has been isolated and characterized. DNA analysis has shown that both DMD and BMD affect the same gene (allelic). Portions of the coding sequence of the gene have been used to produce polyclonal antisera directed against the normal muscle protein product of the normal gene. The specific protein, dystrophin, is a normal component of the plasma membrane, transverse tubule system of the normal muscle fiber. In patients with Duchenne's muscular dystrophy, the muscle contains less than <3% of the amounts of this protein found in control patients. In patients with Becker's muscular dystrophy, the dystrophin is normal but the size of the protein (molecular weight) is abnormal. Patients with an intermediate clinical course have results bridging these two disorders. Patients with other types of neuromuscular disorders have normal dystrophin.

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Thus a defective gene at this specific site may result in a total defect in a failure to produce this muscle protein (DMD) or the production of a muscle protein of abnormal size (BMD) or in various combinations of these deficits. Specific therapy has not yet been achieved. Corticosteroids may produce minor improvement (Brown 1989).

The non X-linked muscular dystrophies are less common.

Facioscapulohumeral (FSH) dystrophy:

These cases occur on an autosomal dominant basis with the gene linked to chromosome 40. The incidence is 1-2/100,000 persons. A small deletion occurs at the end of the long arm of chromosome 4q.35. The phenotypic expression is variable. Some cases begin in childhood, and have a poor prognosis. Most begin in the late teens, or early twenties with a slow rate of progression. Often the specific age of onset is difficult to identify. The name of the disease reflects the prominent early features of bilateral facial weakness and proximal upper extremity involvement with weakness of shoulder abduction and winging of the scapula. Subsequently, lower extremities are involved. In most cases little disability of significant degree occurs before the thirties or forties. Life span is relatively well preserved. Serum creatine kinase is borderline or only mildly elevated reflecting the slow rate of muscle breakdown. The EMG and muscle biopsy reflects the myopathic features.

Limb girdle dystrophies. The limb girdle dystrophies are a heterogeneous group of autosomal recessive disorders, occurring with a frequency of 1/100,000. Rarely some families follow an autosomal dominant pattern. Approximately 10% of these patients have mutations in the gene coding for sacroglycan (Duggan et al, 1997). Other mutations are also described (Dubowitz, 1997). Some begin in the upper extremities at shoulder and scapula, some in the lower extremes at pelvic girdle and knees. A few mimic Duchenne's muscular dystrophy. Progression is slow and severe disability usually not present until the thirties or even the fifties. Serum creatine kinase is moderately elevated. EMG demonstrates myopathic features; muscle biopsy demonstrates dystrophic features. From a clinical standpoint, there is considerable overlap

with cases of indolent polymyositis, motor neuron disease (spinal muscular atrophy), endocrine myopathies, and carriers of the DMD gene with minor clinical manifestations.

The following case 6-1 presented in detail on the CD ROM illustrates this disorder.

Case 6-1: This 21 year old white male college student was delayed in walking until age 2. During grammar school, he was the slowest runner in the class and could not keep up with his peers. In high school he first noted minor weakness in climbing stairs. By college he had trouble in climbing one flight. By his senior year, he had difficulty descending stairs.

Neurological Examination: *Mental status:* Intact. *Cranial Nerves:* Intact. *Motor system:* There was proximal weakness at hips (3/5) and shoulders (4/5)¹ with intact distal strength and normal muscle bulk. Gower's sign was present in attempting to stand from a recumbent position. Gait was waddling - consistent with proximal weakness at hips.

Reflexes: Deep tendon stretch reflexes² were absent at triceps and radial periosteal and trace at biceps. Patellar and Achilles reflexes were normal. Plantar responses were flexor. *Sensory system:* Intact.

Clinical diagnosis: Limb girdle muscular dystrophy or a variant of motor neuron disease (chapter 9).

¹The primary grading system for strength is that suggested by the Medical Research Council (MRC) during World War II: 0=no contractions; 1=flicker or trace of contraction; 2=active movement with gravity eliminated; 3=active movement against gravity; 4=active movement against gravity and resistance; 5=normal power. The scale is not a linear function- and because of the wide range included in grades 4 and 5 many examiners will grade 4(-), 4, 4(+) and 5(-).

²Deep tendon reflexes are graded as follows: 0=absent; trace=minimally present; 1=hyperactive; 2=normal; 3=hyperactive-brisk; 4=hyperactive-unsustained clonus; 4+ sustained clonus. As above minor gradations may be superimposed such as 2+, or 3+.

Laboratory data: *Muscle enzymes:* all were mildly elevated. *Motor and sensory nerve conduction velocities:* all were normal. *EMG:* demonstrated myopathic features with decreased amplitude and duration of motor units with a full interference pattern on volitional effort.

Muscle biopsy (left deltoid): reported significant dystrophic features: marked variation in muscle fiber size in a random distribution, central position of subsarcolemmal nuclei and a significant increase in endomysial connective tissue.

Subsequent course: The patient reported at age 38 (17 years after his initial evaluation) slow progression: he was still able to walk without assistance. Climbing stairs was a problem. Face and hands were not involved.

Muscular dystrophies with predominant involvement of cranial nerves: Cranial nerves may be affected during the course of the more common muscular dystrophies. There have however been several families described with adult onset with diseases beginning with predominant and relative selective involvement of cranial nerves. There is usually an autosomal dominant pattern of inheritance with a chronic progressive ophthalmoplegia or an oculopharyngeal dystrophy. Oculopharyngeal dystrophy begins in the 30s–40s. There are geographic familial clusters: French Canadian families in Quebec and New England, and Spanish American families in the southwestern United States. A mutated gene has been located on chromosome 14q11.2-13.

Myotonic Dystrophy: This is the most common inherited form of muscular dystrophy affecting adults. It is an autosomal dominant disorder with an estimated incidence of 1/8000 in which cranial nerve and distal limb involvement are prominent. Multiple organ systems are involved with variable expression including cataracts, baldness, mental subnormality, gonadal atrophy, other endocrine disturbances, low plasma IgG, glucose intolerance, smooth muscle autonomic involvement and cardiac conduction defects. The latter may lead to syncope and sudden death. Although cases can present in the neonatal period, the most common ages of onset are late adolescence or early adult life.

The early symptoms relate to complaints of

gait difficulty and clumsiness. At this point, the more specific diagnosis may not be apparent to the non-neurological observer. (The author once saw 6 patients in an 8-month period at an Army basic training base with this diagnosis, referred with the more general complaints). Examination however will demonstrate a distal limb weakness. Percussion of the thenar hand muscles or of the tongue will often demonstrate a myotonic reaction (prolonged contraction with delayed relaxation). Myotonia can also be demonstrated by asking the patient to squeeze the examiner fingers and to then rapidly open the hands. Myotonia of the eyelids may be noted in the continued retraction of eyelids and a lid lag after prolonged upgaze. With progression of the disease, a significant weakness and atrophy of muscles innervated by the facial, mandibular supplied muscles, and the accessory nerve to the sternocleidomastoid muscles occurs with the development of characteristic “myopathic facies.” Most patients are disabled and unable to walk by the thirties or forties. Life expectancy is reduced because of cardiac and pulmonary complications.

The creatine kinase level is usually normal. The EMG demonstrates myopathic features plus the prolonged myotonic discharges. When audio amplified, the EMG myotonic discharge sounds like a “dive bomber”. The muscle biopsy shows characteristic features of chains of central nuclei, ringed fibers and selective atrophy of type I fibers. The underlying molecular basis of myotonic dystrophy has recently been discovered. An unstable DNA fragment occurs on chromosome 19q 13 related to an expanded cytosine thymidine guanine (CTG) trinucleotide repeat at the end of a region encoding a protein kinase. Normally 5-30 repeats are present at this location. In myotonic dystrophy the number of repeats at this location is markedly increased by >10 fold. The greater the number of repeats, the more severe the disease (Wang et al, 1994). This protein kinase does have an effect on skeletal muscle voltage gated sodium channels reducing the peak sodium current. A DNA probe is available to detect the disease.

Channelopathies affecting skeletal muscle: In these disorders, mutations occur in the voltage gated channels. Table 6-1 outlines these dis-

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orders. (Modified from Cannon, S.C.1998. Ion channel defects in the hereditary myotonias and periodic paralyses. *Molecular Neurology*. Ed. Martin, JB. New York. Scientific American. pp257-277.)

TABLE 6-1 CHANNELOPATHIES AFFECTING SKELETAL MUSCLE

Disorder (Eponym) Inheritance*	Myotonia	Periodic Weakness	Locus	Channel
Myotonia congenita (Thomsen's) AD, (Becker's)-AR	Constant	None-mild	7q35	Cl-
Potassium aggravated myotonia AD	Variable	None	17q23-25	Na+ (alpha)
Paramyotonia congenita-(Eulenberg's),AD	Cold aggravated	Moderate-cold aggravated	17q23-25	Na+ (alpha)
Hyperkalemic periodic paralysis-(Gamstrop's), AD	Variable, K+ aggravated	Moderate-severe, K+ aggravated	17q23-25	Na+(alpha)
Hypokalemic periodic paralysis – None -AD	None	Severe, decreased K+ aggravates	1q21-31	Ca++(alpha)

*AD=autosomal dominant, AR=autosomal recessive

More recent studies summarized by Cannon³, have identified mutations in the potassium channels in periodic paralysis as well as those previously described in the sodium and calcium channels.

Myotonic congenita: In these disorders the myotonia occurs in relative isolation. An autosomal dominant form (Thomsen's disease and an autosomal recessive form (Becker) occur. The myotonic syndromes are characterized by an abnormal increase in membrane excitability with persistent runs of action potential in the surface membrane. Abnormal low chloride conductance has been implicated in myotonia congenita in humans, congenital myotonia of the goat and myotonia following ingestion of aromatic carboxylic acids.

Subsequent K⁺ accumulation in the transverse tubular lumen leads to excessive depolarization and the persistent firing of action potentials. Similar results occur when normal muscle fibers are placed in a chloride free solution.

Periodic paralysis (Familial Periodic Paralysis): These are relatively rare inherited

(autosomal dominant) disorder of muscle that may produce acute transient weakness. These are characterized by an episodic failure of muscle membrane excitability. The attacks are often associated with marked alterations of serum

potassium. There are hypokalemic and hyperkalemia forms. The hypokalemic form is the most common, occurring with a frequency of 1:100,000. As indicated in table 6-1 some forms may be associated with myotonia. In the hyperkalemic form the basic mutation occurs in the alpha subunit of the sodium channel. This results in a disruption of fast inactivation. A minor defect in these inactivating channels (0.8-2%) can produce myotonic runs of discharge. When $\geq 3\%$ of inactivating channels are defective, a stabilized depolarized action potential occurs. In the hyperkalemic form attacks may be precipitated by fasting, cold, stress or by rest after exercise. In the hypokalemic form, at the onset of the attack a significant movement of potassium and sodium ions into skeletal muscle occurs with a decrease in serum potassium. Microelectrode studies of muscle fibers from patients with this disorder indicate that reducing the K ion concentration in the bath solution caused the affected fibers to depolarize and become inexcitable. Normal fibers hyperpolarize under these conditions. From a molecular standpoint the missense mutation is in L-type calcium channel (alpha 1s subunit). Refer to studies of Ptacek and associates 1994. How this channel defect relates to the microelectrode studies is unclear (refer to

³ Cannon, Sc. 2002. *An expanding view for the molecular basis of familial periodic paralysis. Neuromuscul Disord.* 12:533-543.

Cannon). Attacks may be induced by the administration of insulin and glucose or of sodium chloride, by alcohol, stress, cold exposure, or by rest after exercise. In all types, mild persistent proximal weakness may develop later in the disease course. Muscle biopsy may demonstrate vascular changes and tubular aggregates.

In both forms the changes in serum levels of potassium are of such magnitude as to produce EKG changes. In the hypokalemic form, serum K may be depressed to 2-3 mEq/Liter. In the hyperkalemic form the level may be as high as 7-8 mEq/Liter. (Normal K concentration is 3.9-5.0 mEq/liter).

The following case 6-2 presented in detail on CD ROM illustrates many of the features of hypokalemic periodic paralysis.

Case 6-2: (Patient of Dr. Thomas Twitchell) This 30-yr. old white housewife had experienced episodes of night time paralysis beginning at age 9 years. These occurred several times per month but with the administration of potassium supplementation, attacks decreased to 1-2 times per year. At age 9 years she had noted a mild persistent weakness in both proximal lower extremities which was non-progressive but did result in difficulty in climbing steps. At age 30 years, episodes again became frequent related to high carbohydrate intake, cold water exposure or stress. Family history and a general physical examination were normal.

Neurological examination demonstrated only moderate weakness at hip flexors.

Neurologic diagnosis: Periodic paralysis and minor myopathic process.

Laboratory data: Erythrocyte sedimentation rate, thyroid functions, serum potassium, creatine phosphokinase, EMG and nerve conduction studies were all normal.

Diagnostic studies: Within 15 minutes of administration of glucose and insulin the patient had increased weakness in all four extremities. By 30 minutes, the potassium level had fallen from 4.7 to 2.1 mEq/liter with the associated EKG features (flat T waves). At 60 minutes, the patient had total paralysis of all four limbs (quadriplegia) and no deep tendon reflexes could be obtained. She was flaccid and unable to lift her head from the bed. However, she was conscious, she could speak, and breath and all cranial nerves

were intact She was given oral potassium and within 2 hours had returned to her baseline state. She was subsequently treated with potassium supplements plus acetazolamide, a drug which affects sodium potassium transport.

Congenital myopathies. (Refer to Fardeau, 1982). These are relatively rare disorders of muscle which primarily presents with hypotonic weakness in childhood: "the floppy infant" and delay in motor developmental milestones. The specific name assigned to each of these syndromes is based on the unique features on muscle biopsy and the special histochemical stains. The first type described by Shy and Magee in 1956 is so named because type I fibers lack mitochondria in the *central core* which instead contains disorganized tightly packed myofilaments. In *nemaline myopathy* there are peripheral collections of rod shaped bodies - possibly derived from the Z bands. In *centronuclear myopathy*, there are chains of central muscles - surrounded by a zone devoid of myofibrillar - ATPase activity.

Metabolic Myopathies: (Refer to Rowland et al 1986, DiMauro 1985, Pourmand, 2000). The metabolic myopathies are relatively rare inborn errors of metabolism. There are four major subcategories considered under the overall diagnosis of metabolic myopathy (1) defects in enzymes involved in the metabolism of glucose and glycogen with the specific defect involving the lysosomal and cytosolic enzymes: *the glycogen storage diseases*, (2) abnormalities in the metabolism of lipids, (3) abnormalities of the enzymes related to the mitochondrial respiratory chain for aerobic energy production: *the mitochondrial myopathies*, (4) abnormalities in the metabolism of adenine nucleotides. Muscle contraction utilizes ATP (adenosine triphosphate), which is converted from ADP (Adenosine diphosphate) by the action of CK (Creatine kinase).

Moderate exercise is fueled by aerobic conditions with glycogen as the main fuel source. After 5-10 minutes blood glucose is utilized. Subsequently fatty acids are utilized. After 4 hours of exercise lipids and amino acids are utilized.

In high intensity exercise anaerobic glycogen breakdown and glycolysis generate additional fuel. At rest, lipids are the predominant energy

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source.

The student is already aware that multiple enzymes are involved in the events of aerobic and anaerobic carbohydrate metabolism and in lipid fatty acid metabolism, which involve these enzymes. Depending on the specific deficit - a) there may be multiple system involvement with persistent weakness, b) selective muscle involvement with persistent weakness or c) exercise intolerance with easy fatigue and muscle cramps but with little persistent weakness. Note however that most patients with cramps or fatigue on exercise do not have a significant underlying metabolic myopathy.

The first hereditary myopathy in which a specific enzyme defects was identified McArdle's Disease falls into the last category c). The enzyme muscle phosphorylase (myophosphorylase) is absent as demonstrated on special stains for this enzyme applied to the muscle biopsy. When the patient exercises, glycogen can not be broken down to pyruvate and lactic acid and the expected rise in blood lactic acid in ischemic limb exercise fails to occur. As exercise continues, fatigue and painful cramps occur. If the patient persists, muscle breakdown will occur with a significant rise in blood and urine levels of myoglobin. Significant acute renal tubular impairment is a complication of any acute condition in which rapid breakdown of muscle occurs producing myoglobinuria. Exertional rhabdomyolysis may also occur in predisposed individuals (Greenberg&Ameson, 1966). The recent monograph edited by Pourmand (2000), provides a detailed consideration of the many other rare disorders included in this category.

In addition to the primary metabolic myopathies discussed above, secondary metabolic myopathies occur, for example endocrine myopathies, thyrotoxic periodic paralysis, drug induced myopathies and in congestive heart failure and chronic obstructive pulmonary disease.

ACQUIRED DISORDERS OF MUSCLE:

The major categories are as follows:

(1) Toxic related to alcohol and drugs such as colchicine used in the treatment of gout or the agents employed in the treatment of elevated cholesterol levels (the statins).

(2) Endocrine: Hyperthyroid (thyrotoxic

myopathy), hypothyroid (myxedema myopathy) and corticosteroid myopathy. The corticosteroid myopathy occurs not only in patients with Cushing's disease but also in many patients receiving long term corticosteroid therapy. Typically the weakness begins in the pelvic girdle and proximal muscles of the lower extremities.

(3) Trauma: Closed muscle compartment compression due to trauma or a deep unconscious state produced by drugs or, alcohol etc., may produce considerable rhabdomyolysis of an acute nature (see Owen et al 1979). Prolonged seizures or prolonged positional compression on a hard surface after a stroke may also produce this condition.

(4) Inflammatory: Inflammation of muscle may occur in a) viral disease such as influenza or Coxsackie, b) bacterial infections by staphylococcus aureus or c) in parasitic infections that are of major importance in some areas of the world, such as toxoplasmosis, cysticercosis, and trichinosis. A myopathy may also occur in HIV infection. The major considerations in this section are those cases where the polymyositis occurs on autoimmune bases.

In some cases, (idiopathic polymyositis and dermatomyositis) the autoimmune disease is restricted to muscle (plus skin in dermatomyositis). The cases cover a wide age range. The onset and source may be acute, subacute or chronic. The chronic gradually progressive pattern is the most common. Cranial nerves are usually not involved although difficulty in swallowing may be present due to posterior pharyngeal striated muscle involvement. Proximal muscles are involved predominantly in dermatomyositis. There is more diffuse involvement in polymyositis but with a proximal predominance (limb girdle and neck flexors). In dermatomyositis there is edema and bluish (heliotrope) discoloration of the eyelids, with a scaly red rash on the face (in a butterfly pattern), shoulders, upper chest, back and extensor surfaces of the limbs, Sedimentation rate and muscle enzymes are significantly increased. Muscle biopsy indicates segmental muscle necrosis, regeneration and inflammatory infiltrates, (*Fig. 6-16*). EMG indicates not only myopathic features but also the presence of fibrillations.

There is an increased incidence of underlying

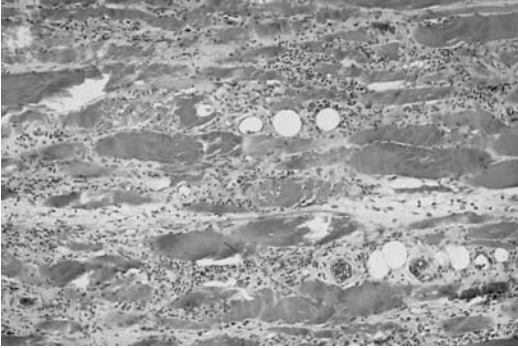


Figure 6-16. Muscle histopathology II: Polymyositis wide spread necrosis of muscle fibers is present with extensive infiltration by mononuclear inflammatory cells H&E x25. (Compare to 6-15). Courtesy of Dr. Tom Smith, Neuropathology, U. Mass. Medical Center.

neoplasm in adults with dermatomyositis and polymyositis (particularly in older adults). Common sites are lung and ovary. Overall incidence in all cases of dermatomyositis and polymyositis is 9% (Sigurgeirsson et al 1992).

The term overlap polymyositis refers to patients who develop polymyositis within the context of already existing autoimmune connective tissue diseases: systemic lupus erythematosus (SLE), rheumatoid arthritis, periarteritis nodosa, systemic sclerosis and Sjögren's syndrome. It has been estimated that 5-15% of all patients with these diseases will manifest polymyositis (Isenberg, 1984).

Most patients (60-70%) with polymyositis and dermatomyositis have a significant response to corticosteroid therapy. Non responders may require more definitive immunosuppressive therapy. Approximately one third of non-responders have another variety of myositis: *inclusion body myositis*. Such cases have a male predominance, relatively normal CPK and greater distal involvement (see discussion Dalakas 1991).

The following case 6-3 presented in detail on the CD ROM demonstrates dermatomyositis complicating ovarian malignancy.

Case 6-3: This 69-yr. old white female two weeks prior to admission developed difficulty swallowing and progressive weakness of all four extremities with proximal more than distal involvement. Three months prior to admission, she had partial resection of ovarian carcinoma, followed by radiotherapy and chemotherapy.

General physical examination: there was superficial redness and swelling involving the skin of both upper extremities. Liver was enlarged.

Neurologic examination: *Mental status:* Intact. *Cranial nerves:* The gag reflex was absent and she had difficulty handling secretions. *Motor system:* Weakness was present in all four extremities proximal greater than distal. *Reflexes:* Deep tendon reflexes were depressed in the upper extremities and absent in the lower extremities. Plantar responses were flexor. *Sensory system* was intact.

Clinical diagnosis: Dermatomyositis as a remote effect of ovarian carcinoma.

Laboratory data: *Erythrocyte sedimentation rate and muscle enzymes* were all significantly increased. *EMG* was consistent with polymyositis.

Subsequent course: Despite the administration of high dosage corticosteroids (prednisone), the patient had increasing weakness. Aspiration and increasing respiratory symptoms occurred. The patient expired 7 weeks after onset of symptoms.

DISORDERS OF THE NEUROMUSCULAR JUNCTION

Diseases affecting the neuromuscular junction may be classified as to location: postsynaptic or presynaptic (see Drachman 1986, 1994, Engel, 1984, Newsome-Davis 1992, Richman, 1998)

POSTSYNAPTIC DISORDERS:

Myasthenia Gravis

The major primary disease due to neuromuscular junction pathology in this country and western Europe is myasthenia gravis. The prevalence is 5-7.5 per 100,000. This is a disease characterized by fluctuating weakness of voluntary muscle worse on exercise, improved by rest and by administration of anticholinesterase drugs. This is primarily a disease of adults with onset between ages 10 and 70. However neonatal and congenital cases are recognized. The peak age of onset is between ages 20 and 30. Under age 40, females are affected more often than men in a ratio of 70:30. After age 50, there is a male predominance of 60:40. Ten % of patients have an associated tumor of the thymus gland (thymoma). These patients tend to be older with a male

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predominance.

The symptoms usually first appear in the muscles supplied by the cranial nerves. The extraocular muscles for control of eye and eyelid movement are first affected in 60% of cases and are affected at some stage in 90% of patients. In 15-20% of cases with a relatively benign course, the symptoms may remain confined to the eye muscles. These cases are termed *ocular myasthenia*. In the extensive series of Grob et al with 1487 patients followed 1940-1985) 14% of patients continued to have localized ocular myasthenia. The patient has a ptosis (closure or droop) of one or both eye lids, often most apparent on sustained upward gaze. Double vision (diplopia) results from a weakness of one or more extraocular muscles. The early occurrence of diplopia may be a reflection of the precise synchronization required between the two eyes in movement under normal conditions. A minimal weakness of one medial or lateral rectus muscle would disrupt such a precise synchronization.

Generalized myasthenia refers to progression to involve other cranial nerves and the extremity and trunk muscles. Such generalization after an ocular onset generally occurs within the first two years following onset. The patient will have difficulty swallowing (dysphagia), speaking (dysarthrias) and chewing (mandibular nerve supplied muscles). In addition a bilateral weakness of facial muscles may provide a suggestive myasthenic faces. The patient may support head or jaw with the hand to compensate for weakness. As the disease progresses, more generalized involvement of proximal limb muscles develops. In some patients there is significant involvement of the muscles of respiration. In the series of Grob et al maximum level of weakness was reached during first year in 55%, first 3 years in 70% and first 5 years in 85%. After 3-5 years, the disease stabilizes.

The prognosis depends on the age of the patient, the duration of the localized form of the disease and on the associated diseases: (thymoma, thyroid disorders other autoimmune disorders).

Myasthenia was once associated with a significant mortality due to respiratory insufficiency and infection but this mortality rate has now been markedly reduced. In the series of Gob, et

al. for patients with maximum weakness in the 1940-1957 era, mortality rate was 31% and the rate of spontaneous remission was 10%. In the 1958-1966 era, the mortality rate was 15% and rate of remission was 10%. In the 1966-1985 era, mortality rate was 7% and the remission rate was 11%.

The diagnosis is readily apparent from a clinical standpoint: Fluctuating weakness with no sensory findings ; intact reflexes and no long tract findings. However there are several confirmatory diagnostic tests. Jolly in 1895 first described the electrical test that carries his name. Repetitive stimulation of a motor nerve results in a rapid decrease in the amplitude of muscle contraction "decremental response". Jolly demonstrated that the apparently fatigued muscle would still respond to direct galvanic stimulation.

In modern clinical neurophysiology the motor nerve is stimulated at a rate of 3-5 per second and the reduction in amplitude of the muscle action potential is measured. (Abnormal is greater than 10% reduction). An agent (edrophonium or neostigmine) which blocks acetylcholine esterase, is then administered. This increases the duration of available acetylcholine at the neuromuscular junction and the decremental response is reversed.

The edrophonium (Tensilon) test can be carried out in the outpatient office. This agent when administered intravenously will often transiently reverse or reduce the signs of weakness. Clinical effect occurs in 30-60 seconds and lasts 4-5 min. Since related cholinergic agents (anticholinesterases) play a major role in therapy the test can also be performed to determine whether the patient is receiving too little or too much of the therapeutic agent.

A very specific test is the measurement of the blood level of the acetylcholine receptor antibody positive in 85-90% (see below).

Recently major advances have been made in our understanding of the underlying pathogenesis and pathophysiology of this disorder. This constitutes a major accomplishment for neurobiology that has been translated into improved results as regards therapy of the disease.

Adams and Victor (1989) have summarized the major historical landmarks in the study of myasthenia. Welch in 1877 and Erb in 1875 rec-

ognized the lack of any pathology in brain stem to explain the cranial nerve motor findings. The electrical studies of Jolly in 1895 suggested what has come to be recognized subsequently as the location of pathology: the neuromuscular junction. The term pseudoparalysis as well as myasthenia gravis was originated by Jolly since no pathology was present at autopsy. He also recommended the use of an anticholinesterase physostigmine. Walker in 1934 noted the similarity of some of the signs to those produced by the poison curare and began the use of physostigmine. Buzzard in 1905 in a detailed clinical pathological analysis of 5 cases described the lesions in thymus: thymic hyperplasia which now has been noted in over 80% of patients and the minor lymphocytic collections in muscle. Buzzard proposed that an autotoxic agent could produce all of these findings. He also noted the association of the disease with thyrotoxic cases. Simpson in 1960 proposed an autoimmune basis for the disease because of the increased incidence of other putative autoimmune disease: thyroiditis, lupus erythematosus and rheumatoid arthritis.

Electron microscopic studies by Zack et al. 1962, Engel and Sarta 1971, Engel et al 1976 had demonstrated significant changes in the postsynaptic region with shallow postsynaptic folds, a widened synaptic cleft. In contrast the presynaptic area was normal as regards the number and size of presynaptic vesicles. Fambrough, Drachman and Satyamuri, (1973) then demonstrated a marked (3 fold) reduction in acetylcholine receptors per neuromuscular junction in motor point nerve biopsies of myasthenic patients. Compared to control subjects, there were a decreased number of binding sites for a radioactive labeled snake poison, alpha bungarotoxin which can be purified from the venom of the cobra and krait. This toxin binds in an irreversible manner to the acetylcholine receptor. In 1973, Patrick and Lindstrom demonstrated that repeated immunization of rabbits with acetylcholine receptor protein derived from the electric organs of eels reproduced the disease. These animals develop all of the clinical and electrical features of myasthenia gravis. Antibodies to the ACH receptor protein could be identified attached to the ACH receptor. Moreover, nor-

mal animals receiving these antibodies also developed myasthenia.

Subsequently Lindstrom et al (1976) and several other groups reported a radioimmunoassay for acetylcholine receptor antibody. This is now a standard laboratory test for myasthenia gravis with a 90% detection rate in the serum of myasthenic patients. (The serum level does not correspond to the severity of the disease). Engel et al (1984) were able to demonstrate immune complexes at the postsynaptic junction in biopsies from myasthenic patients. When the immunoglobulin derived from the serum of myasthenic patients is administered to mice, the characteristic myasthenic syndrome develops in the recipient animal (Toyka, et al. 1974). The syndrome of neonatal myasthenia also suggests a serum or plasma transmissible factor. Fifteen% of children born to myasthenic mothers will manifest clinical signs of weakness lasting several weeks due to passive transfer of anti ACH receptor antibodies across the placenta. Circulating ACH receptor antibodies and electrophysiological findings can be demonstrated in these infants and even in additional neonates of myasthenic mothers who do not manifest clinical weakness.

Subsequent studies reviewed by Drachman (1986) suggest several mechanisms for antibody action: 1) there is a significant increase in the rate of degradation of ACh receptors, 2) the antibody actually blocks the binding sites of the acetylcholine receptor and, 3) there is a complement mediated damage to and subsequent change in the geometry of the junction with a reduction in efficiency of transmission.

Cells cultured from patients with myasthenia gravis but not from control subjects can synthesize acetylcholine receptor antibody *in vitro*. The highest levels of production are obtained from thymic cells of patients with medullary thymic hyperplasia. Peripheral blood lymphocyte lymph nodes and bone marrow also produce the ACH receptor antibody.

The role of the thymus appears critical from several standpoints. 1) The thymus has a central role in immunology. 2) The thymic hyperplasia involves the presence in the medulla of many germinal centers and surrounding T cell areas. Such germinal centers are rare in non-myasthenic thy-

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mus. 3) The thymus contains muscle like cells, and ACH receptors can be demonstrated when these cells are placed in tissue culture. Drachman (1978) has suggested that these receptor bearing muscle cells may be particularly vulnerable to immune attack. Some alteration of these cells by lymphocytes (perhaps triggered by viral infection of thymus etc.) could initiate any acute immune response directed against ACH receptors.

The essentials of therapy in myasthenia gravis follow from the neurobiology of the disease.

1) Initial therapy consists of anticholinesterase drugs. The main drug used is pyridostigmine (Mestinon) which has a somewhat longer duration of action than neostigmine. For some patients this will suffice particularly if only local ocular myasthenia is present and if this responds well.

2) Generalized myasthenia will almost always require more definitive therapy directed at the immune systems.

a) The most definitive procedure is total thymectomy. As discussed by Rowland, (1987) there is now a consensus that all adults with generalized myasthenia should have this procedure relatively early in the course of the disease. In the "maximum thymectomy" series of 72 non-thymoma patients previously with moderate to severe generalized myasthenia reported by Younger et al. (1987), 46% of patients were in complete remission (on no medication). 33% were asymptomatic on 60-240 mg of pyridostigmine daily and 10% were asymptomatic on steroids. Approximately 90% then were in complete remission or asymptomatic. An additional 6% were improved. At least 1-4 years were required to see the maximum response to therapy. There was in significant decline in the titre of acetylcholine receptor antibody. Although this was not a matched control series, the results are in striking contrast to the contemporary results of non surgical treatment of moderate to severe generalized myasthenia (see Grob. 1987). Other major centers have confirmed these results. Schumm et al. (1985) has also recommended the procedure in patients with pure ocular myasthenia, if no spontaneous remission and no satisfactory response to cholinesterase inhibitors occurs in a 6-month period. In their

series, thymectomy prevented the subsequent development of generalized myasthenia; none of 18 patients progressed over two years from ocular to generalized myasthenia.

Thymectomy was originally performed primarily to remove thymomas in patients who coincidentally also had myasthenia gravis; some improvement in the myasthenia also occurred (Blalock et al. 1939). Considerable experience in subsequent years has demonstrated a poorer response of the myasthenia in such cases of thymoma to thymectomy.

b) Other types of immunosuppression may also be employed in the pre- or postoperative period or in those patients unable to tolerate thymectomy. These include corticosteroids, plasmapheresis (plasma exchange) and cytotoxic drugs (azathioprine).

The following case 6-4 presented in detail on the CD ROM provides an example of severe generalized myasthenia gravis.

Case 6-4: This 44-year-old, obese (>300 lb.), white, married, machine operator had noted for several years, fatigue in his arms and legs at the end of a day. Approximately 6 to 7 weeks prior to admission, he began to have a marked intermittent weakness of the arms and legs. At the same time, he experienced significant slurring of words, difficulty in swallowing, fatigue of jaw muscles and drooping of the lids. All of these symptoms were transient; they were not present in the morning; they were clearly precipitated by exercise. The degree of ptosis was sufficient to result in difficulty in driving.

Neurological examination: *Mental Status:* intact. *Cranial Nerves:* there was significant bilateral ptosis of the eyelids, bilateral facial jaw and tongue weakness, all markedly increased by exercise. On repetitive upward gaze, a bilateral weakness of superior rectus developed. *Motor System:* there was a significant weakness in shoulder abductors, elbows flexor and extensors, and handgrip which was markedly increased by repetitive exercise. *Reflexes:* deep tendon reflexes, and plantar responses were all normal. *Sensory system:* intact.

Clinical diagnosis: Myasthenia gravis

Diagnostic Studies: An edrophonium (Tensilon) test demonstrated an almost immedi-

ate eye-opening effect with the disappearance of the bilateral ptosis. The ptosis, however, had reappeared 3 to 4 minutes after injection of 10 mg of the agent.

Subsequent Course: On treatment with pyridostigmine at a dosage of 90 mg 5 times per day (approximately every four hours) his ocular, bulbar and generalized weakness stabilized for three years. He then had additional exacerbations in part related to cholinergic crisis and in part related to progression of disease. The latter episodes responded to radiation of the thymus and subsequently prednisone therapy.

Other postsynaptic disorders.

These are primarily toxic disorders related to acetylcholine esterase inhibitors employed such as pesticides (eg organophosphates) or as neurotoxins in warfare or to bites from venomous snakes etc. In certain parts of the world (Sri Lanka) pesticide ingestion is a major problem.

1) *Acetylcholinesterase inhibitors:* The usual action of acetylcholine esterase at the neuromuscular junction is to rapidly terminate the action of ACH. This allows high rates of transmission across the synapse. If acetylcholine esterase is inhibited, acetylcholine remains on the receptor and in the synaptic space.

There are two classes of acetylcholine esterase inhibitors:

- a) reversible: (carbamates), and
- b) relatively "irreversible" (organophosphates)
 - a) The reversible agents include those anti ACH esterase drugs used in the treatment of myasthenia gravis. An increased availability of acetylcholine is of value in counteracting the weakness due to decreased numbers of receptors in this syndrome. Excess amounts of such drugs produce excessive amounts of acetylcholine at the receptors as noted in the above case history resulting in increased weakness referred to as "cholinergic crisis". The dose of the drug must be reduced. In the management of such patients the edrophonium ("Tensilon") test is of value.
 - b) The relatively irreversible agents (organophosphates) constitute a much more serious problem - not only does a significant acute cholinergic effect occur but there is damage to the postsynaptic membrane and delayed effects on peripheral nerve. Senanagake and

Karolliedde 1987 distinguished three syndromes. 1) The acute cholinergic syndrome is accompanied by autonomic effects, fasciculations, and at times central effects (coma) 2) The intermediate syndrome occurring in 10% of patients after recovery from the acute syndrome 24-96 hours after the poisoning is identical to an acute myasthenic syndrome with respiratory, cranial nerve and proximal limb muscle involvement. If the patient survives the respiratory problems, recovery may occur in 5-18 days. 3) A delayed distal motor neuropathy occurs in some patients at 2-5 weeks after exposure.

The organophosphates are the neurotoxic agents of chemical warfare. They are also extensively employed as pesticides. As discussed by Davis (1987) this is a major problem in the developing countries where the sale of such chemicals is often unregulated, and the chemicals are often repackaged in unlabeled containers. The original containers are often reused. The storage and use are often unsupervised and the population is often unable to read any warning label.

The magnitude of the problem is staggering. In Sri Lanka alone between 1978 and 1980, there were 80,000 patients admitted with pesticide poisoning and 6083 of these patients died. Seventy five % of all cases were due to organophosphorous. In Sri Lanka, the majority of complex cases were the result of ingestion with suicidal intent.

2) *Agents that bind to the acetylcholine receptor* and thus block access of acetylcholine to the receptor.

a) d-tubocurarine - competes for the receptor in a reversible manner. Initially a South American Indian arrow poison, this agent is now used in anesthesia.

b) Repolarizing agents: bi-quaternary ammonium salts. These resemble acetylcholine. They are agonists that initially produce depolarization and then block the site. They are utilized to produce muscle relaxation during general anesthesia and during mechanical respiration.

c) Snake toxins: derived from the venom of the cobra and krait. These snakes are common in India, Sri Lanka, Southeast Asia and Taiwan. The neurotoxic effect produced is often an acute myasthenic syndrome with respiratory paralysis.

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As discussed by Watt et al. (1986) and by Drachman (1986) for some of the toxins, - alpha cobra toxin, the binding is reversible and can be treated with anticholinesterase. For other toxins in the group, alpha bungarotoxin from the Taiwan Krait, the binding is less reversible and the effects of anticholinesterase less consistent. Some snake venoms also contain toxic agents that act at the presynaptic region (B. bungarotoxin of the krait).

PRESYNAPTIC DISORDERS:

1) Eaton-Lambert (or Lambert-Eaton) Syndrome: The patient is usually an adult who has a predominantly progressive but fluctuating proximal limb weakness. In contrast to myasthenia, there are major differences: a) Bulbar ocular and respiratory muscle involvement is not common. b) Exercise improves the weakness. c) Repetitive stimulation of the motor nerve produces an incremental response in the muscle action potential, as opposed to the decremental response of myasthenia gravis.

Most patients with this disorder have an underlying malignancy, most often a small cell carcinoma of the lung. The neuromuscular syndrome however may precede the appearance of the tumor by months or years. In some patients (1/3) a malignancy may not be identified, but there may be other evidence of autoimmune disease.

The underlying pathophysiology relates to a decrease in the release of acetylcholine quanta from the nerve terminal (not only at the neuromuscular junction but also at cholinergic nerve endings in the autonomic nervous system). As discussed by Newsom-Davis (1992), this defect in release relates to immunoglobulin G antibody that binds to presynaptic Ca channels and prevents their voltage gated opening. As the action potential enters the presynaptic region, fewer Ca channels open, less Ca⁺⁺ enters to catalyze the binding of vesicles to the surface membrane. Hence less ACH is released. The disorder may be transferred passively (via plasma from patients) to mice. The patients are improved by plasma exchange or by drugs that increase acetylcholine release. Treatment of the underlying malignancy may produce some improvement. For additional

discussion refer to Lang et al, (1998) and Sher et al, (1998).

2) Botulism: The toxin of the bacteria *Clostridium Botulinum* produces an acute syndrome of paralysis involving extraocular muscles, cranial nerves muscles of respiration and then progressively descending to involve limbs. Cholinergic autonomic junctions are also involved. Thus the pupil which is spared in myasthenia often is involved (dilated). Anaerobic bacteria that may contaminate improperly canned food or preserved meat produce the neurotoxin. Clusters of cases bring this problem to alteration the attention of public health officials. Many cases are fatal. In infants and some adults, the bacteria itself may be present in the gastrointestinal tract or in a wound producing the toxin. (See Bartlett 1986). The toxin binds rapidly to cholinergic nerve endings and blocks the quantal release of acetylcholine. Once the toxin enters the nerve ending, the available therapeutic antitoxin if administered has little action. The flaccid paralysis then is often long lasting (see Chia et al. 1986).

3) Antibiotics: The aminoglycoside antibiotics: neomycin, streptomycin, and kanamycin act to interfere with the quantal release of acetylcholine. In most patients this presents no significant clinical problem. However when blood levels are high due to high dosage or renal failure and when the patient has myasthenia or a sub-clinical myasthenia there may be the presentation of an acute paralysis. Most often there is an associated factor of anesthesia and the patient fails to regain normal ventilation after anesthesia has been discontinued. The effects may also be seen with other type of antibiotics.

4) Spider venom: Black widow. This toxin produces rapid release of quanta of acetylcholine storage vesicles. The clinical syndrome is characterized by severe muscle contraction followed by paralysis.

FOR DETAILED CASE HISTORIES, SUGGESTED READINGS and BIBLIOGRAPHY: REFER TO CD ROM

strated severe problems:

1) On attempted gaze to the left; a total paralysis of left CN VI plus a lesser paresis of conjugate lateral gaze as regards the right eye.

2) On gaze to the right a) full abduction of the right eye, b) some adduction of the left eye but this was incomplete, and c) coarse nystagmus of the abducting right eye.

3) In primary gaze, the left eye was slightly medial.

4) Convergence was intact for both eyes.

5) Up gaze was intact but minor vertical nystagmus was present.

Conclusions were:

1) Left CN VI paralysis.

2) Left lateral gaze center involved

3) Left medial longitudinal fasciculus involved.

The remainder of the neurological examination was normal.

Clinical Diagnosis: Tumor in pons at the level of the facial colliculus.

This case has been reported in detail by Jockel et al, 1986.

CASE HISTORY 11-2.

This 16-year-old, white male in November was first noted to be lethargic. Gradually from November to March there was progressively poor performance in school with apathy and somnolence. In December the patient had the onset of diplopia with difficulty in reading. In March of the next year he began to sleep throughout the day and could be awakened only with difficulty. Headaches on arising, with nausea and vomiting had been noted. In April evaluation at the Buffalo General Hospital had revealed that the pupils failed to respond to light but did respond to accommodation. Upward gaze was intermittently defective, and conjugate lateral gaze was intact. Findings improved to some degree over a 3-day period.

On the day of admission, an episode of urinary incontinence occurred.

Neurological Examination:

1. *Mental status:* All areas were relatively

intact except for a slowness of response, emotional lability, and immaturity of behavior and questions.

2. *Cranial nerves:*

a. The right eye was deviated outward; the patient was unable to converge. There was a paralysis of upward and downward gaze. Bilateral lid ptosis was present. However, spasm of the eyelids was easily stimulated. Pupils were sluggish in response to light. The right pupil was slightly larger than the left. Horizontal nystagmus was present.

b. The jaw jerk was hyperactive.

c. Guttural and lingual sounds were slurred in a pattern that was consistent with pseudobulbar palsy.

d. Hearing was decreased bilaterally.

3. *Motor system:*

a. Strength was intact.

b. Spasticity was present on passive motion in the lower extremities and possibly in the upper extremities.

c. There was slowness in alternating hand movements. A fixed facies was present.

d. A bilateral intention tremor was present on finger-to-nose testing.

e. Gait was broad-based with truncal ataxia.

4. *Reflexes:*

a. Deep tendon reflexes were hyperactive bilaterally with ankle clonus.

b. Plantar responses were extensor bilaterally (bilateral sign of Babinski).

Clinical Diagnosis: Possible pineal region tumor.

ADDENDUM:

Anatomical Basis of Decerebrate Rigidity.

(*Fig 11-12*) The studies of Sherrington demonstrated that the corticospinal tracts—that is, pyramidal tracts—were not involved in decerebrate rigidity since with hemisection of the brain stem at the intercollicular level the unilateral rigidity which occurred was ipsilateral to the hemisection. Sherrington also was able to indicate that deafferentation decreased rigidity in a limb. Decerebrate rigidity was conceived to be a release phenomenon.

The studies of Magoun and Rhines (1946)

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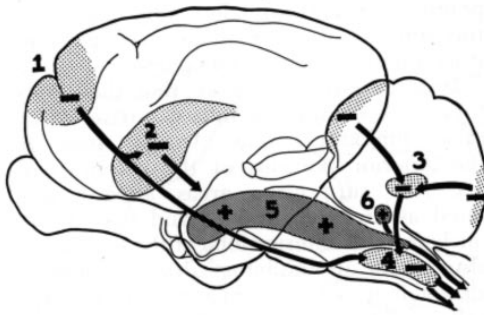


Figure 11-12 Reconstruction of the cat's brain showing the suppressor and facilitatory systems concerned in spasticity. Suppressor pathways are 1, corticobulboreticular; 2, caudatospinal; 3, cerebelloreticular; and 4, reticulospinal. Facilitatory pathways are 5, reticulospinal and 6, vestibulospinal. (From Lindsley, D. B., Schreiner, L. H., and Magoun, H. A.: J. Neurophys., 12:198, 1949.)

demonstrated that stimulation of the reticular formation in a ventromedial area of the medullary tegmentum produced a decrease in decerebrate rigidity, a decrease in the quadriceps deep tendon reflex, and a decrease in the movement which could be elicited by simultaneously stimulating the motor cortex. This area was labeled the *bulbar reticular inhibitory area*. From an anatomical standpoint the inhibitory area of the medulla corresponds to the nucleus reticularis gigantocellularis. The neurons of this nucleus give rise to the lateral reticulospinal tract which is found in the lateral column of the spinal cord.

In contrast, stimulation of a region of the reticular formation in the pons and midbrain resulted in an increase in the degree of decerebrate rigidity. In addition, the quadriceps deep tendon reflex (the knee jerk) was increased and responses to stimulation of the motor cortex were facilitated. This facilitatory area extends into the subthalamus, the adjacent hypothalamus, and the intralaminar areas of the thalamus (e.g., centrum medianum). This area in the more lateral tegmental reticular formation in the pons and midbrain may be termed a *brain stem* (or *bulbar reticular*) *facilitatory area*. From an anatomical standpoint the facilitatory area of the pons corresponds to the nucleus reticularis pontis oralis and caudalis.* The neurons of this nucleus give rise to that medial reticulospinal tract found

in the anterior column.

It is important to note that the inhibitory area of the medulla is driven from other inhibitory areas. Among these are the anterior portions of the cerebral cortex (the suppressor areas indicated as areas 4S and 8) and the caudate nucleus. The anterior lobe of the cerebellum also exerts an inhibitory driving influence although it is uncertain whether this cerebellar influence is as significant in primates and man as in the cat. It is now recognized that flexors and extensors are not equally affected by these facilitatory and inhibitory systems. Rather, it is more proper to speak of these areas as *bulbar reticular extensor inhibitory area* (since actually flexor tone is increased by stimulation of these areas) and *bulbar reticular extensor facilitatory area* (since flexor tone is decreased by stimulation of this area). In the decerebrate animal the effects of the extensor facilitatory system predominate because the extensor inhibitory system must be driven from higher centers. These higher centers, of course, are disconnected from the inhibitory area in the brain stem by the section through the brain stem. On the other hand, the facilitatory center is driven by afferent inputs from below, that is, the collaterals of ascending sensory fibers derived from the spinothalamic tracts and the trigeminal system.

These brain stem reticular areas give rise to reticulospinal pathways which descend to the spinal cord level to influence stretch reflexes. In addition, vestibular centers give rise to facilitatory vestibulospinal pathways which may also influence to some degree stretch reflexes.

As regards the effects of these brain stem reticular centers on stretch reflexes, one may postulate two possible mechanisms of action. There might well be a facilitation or inhibition of large alpha motor neurons. On the other hand, these centers might exert their effects through a facilitation or inhibition of the small gamma neurons. This latter situation would alter tension on the spindle and change the rate of discharge of the muscle spindle.

Granit and Kaada have demonstrated that stimulation of the facilitatory area did augment the spindle discharge. Stimulation of the inhibitory area reduced the spindle discharge. Both effects, then, were exerted via the gamma

system. Classic decerebrate rigidity may be considered essentially "*gamma rigidity*."

Alpha rigidity is less common and results when the cerebellum, particularly the anterior cerebellum, is destroyed in the decerebrate preparation (anemic decerebrate preparation) produced by vascular occlusion. The facilitatory effect may be exerted on the alpha motor neuron by the vestibulospinal tract. There is some evidence that although alpha rigidity may occur in the cat, this is probably not a significant form of rigidity in the primate.

*As discussed previously the nucleus gigantocellularis and the nucleus reticularis pontis oralis and caudalis may be considered as a relatively continuous cell column within the reticular formation, with a major role in reticulospinal motor activities. The other major cell groupings are the paramedian cell groups (paramedian reticular nuclei and reticulotegmental nucleus) concerned with cerebellar relationships and the lateral reticular nucleus. This lateral area of reticular formation is the major relay area for afferent collateral input to the reticular formation.