MAJOR REVIEW

Extraocular Muscles: Basic and Clinical Aspects of Structure and Function

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Abstract. Although extraocular muscle is perhaps the least understood component of the oculomotor system, these muscles represent the most common site of surgical intervention in the treatment of strabismus and other ocular motility disorders. This review synthesizes information derived from both basic and clinical studies in order to develop a better understanding of how these muscles may respond to surgical or pharmacological interventions and in disease states. In addition, a detailed knowledge of the structural and functional properties of extraocular muscle, that would allow some degree of prediction of the adaptive responses of these muscles, is vital as a basis to guide the development of new treatments for eye movement disorders. **(Surv Ophthalmol 39:**451–484, 1995)

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The strabismus specialist's ability to describe and diagnose eye movement abnormalities has been vastly improved by developments in electro-oculography, brainstem physiology, and central oculomotor control system modeling. Our understanding of the final common effector of eye movements, and the origin of virtually all surgical intervention in strabismus, stands in the shadow of these advances. Extraocular muscle has unique properties of structure and function[214,277] whose intricacies mirror the speed and precision of eye movements. However, we have just begun to appreciate the therapeutic potential of a detailed study of the muscles that are observed and altered every day. The successful use of botulinum toxin in strabismic disorders, and the discovery that the toxin exerts its long-term effects through one particular extraocular muscle fiber type,[274] highlights the potential for advances based upon an understanding of muscle properties. Additional pharmacologic interventions (e.g., calcium channel blockers, cellular transport toxins, growth factors) may be explored with the idea of targeting specific structural and functional properties of the extraocular muscles. Such advances are possible only within the framework of knowledge of the structural and functional properties of this unique muscle group.

New developments in pharmacology do not represent the only application of an improved understanding of extraocular muscle. Surgical manipulation has been applied to extraocular muscle for over 150 years without a clear appreciation for the structural impact of this intervention. Strabismus surgery induces a change in both load and length/tension properties, and the muscles respond with compensatory changes in

sarcomere length and/or number, fiber diameter, and fiber type percentages.[61] While these changes may neither undermine nor augment the desired result of surgery, an understanding of muscle adaptation (possibly allowing manipulation of adaptive processes) might be used to improve the efficacy of surgery. The discovery of unique sensory nerve terminals in extraocular muscle,[230,240] and the speculation that their proprioceptive function is important in both visual processing and oculomotor control, has stimulated research on patients who have had muscle resection as a part of their strabismus surgery.[30,282,283] Since marginal myotomy would remove the majority of sensory nerve endings, the normal function and consequences of the elimination of proprioceptive feedback represent vital issues.

Experimental work in muscle prosthesis, appliances, and muscle transplantation and graft growth offers the potential for augmenting the existing strabismus surgery armamentarium. Preliminary studies indicate that prosthetic materials or muscle graft/myoblast transfer procedures might be useful in replacement of dysfunctional muscle (e.g., in paralytic strabismus and extraocular muscle myopathies).[14,15,19,57,58,62] The pursuit of these studies requires an understanding of the cellular and molecular mechanisms that are involved in regulation of muscle differentiation, growth, and fiber type expression. Furthermore, extraocular muscle may exhibit a postnatal critical period not unlike that seen in the visual sensory system.[220] Mechanical or pharmacologic manipulations of extraocular muscle may likely have different consequences in children than in adults. In addition, developmental studies should allow a more thorough understanding of motility defects resulting from congenital malformations, such as Duane or Brown syndrome.

This review updates and extends the coverage of the earlier reviews by Chiarandini and Davidowitz,[54] Eggers,[84] Spencer and Porter,[277] and Spencer and McNeer.[275] We consider the unique properties of the muscles that move the eyes and relate these to the responses of extraocular muscle to naturally occurring disorders, experimental manipulations, and clinical interventions.

I. Oculomotor Physiology

Four subject areas that have direct relevance to extraocular muscle are dealt with in this section. First, the fundamental differences between motor unit properties in limb and extraocular muscle are identified. The oculomotor motoneuron has unique discharge characteristics that may have consequences for muscle structure and function. Next, the diverse eye movement systems and some features of the neural control mechanisms are briefly reviewed. To understand the diversity of extraocular muscle, the reader should appreciate the extreme demands placed upon the muscles by the wide dynamic range of the oculomotor systems. Finally, since feedback control mechanisms are used to adaptively adjust motoneuron output, possibly altering eye muscle characteristics in the process, a brief review of this literature also is indicated. Feedback mechanisms also may be of particular importance to an understanding of extraocular muscle function, since the major proprioceptive receptors may be (unintentionally or intentionally) compromised in surgical resection procedures. Together, the diversity and unique properties of the extraocular muscles are best appreciated when placed in the context of what are fundamentally unique oculomotor control systems.

A. BASIC CONCEPTS OF THE MOTOR UNIT

The motor unit, a motoneuron plus the muscle fibers that it innervates, is the basic functional unit of skeletomotor systems. Motor unit size (number of muscle fibers/motoneuron) determines the fineness with which muscle force can be increased or decreased. Small motor units allow gradual incrementation of force and usually are associated with fine control; likewise, large motor units can alter force only in large increments and usually are associated with postural or weight-bearing musculature. Spinal motoneurons exhibit a variety of discharge patterns, but rarely exceed sustained and high frequency burst discharge rates of greater than 50 spikes/second and 125 spikes/second, respectively.[44] All muscle fibers of a given motor unit are of the same type. Disorders or experimental manipulations that compromise motoneurons or neuromuscular transmission lead to atrophy and degeneration of muscle fibers. Similarly, alterations of neuronal discharge rates, via implanted stimulators or by cross-innervation with an inappropriate nerve, may change muscle fiber type composition.[145]

The localization and properties of oculomotor motoneurons have been reviewed by Evinger[86] and will be considered only briefly here. The oculomotor motoneuron (used herein generically to indicate motoneurons in oculomotor, trochlear, and abducens nuclei) represents the final

common pathway for the multiple eye movement control systems. Oculomotor motoneurons have been studied using the alert monkey model.[99,234,237,248] Passive elastic and viscous forces act to maintain a fixed eye position. The elastic forces that oppose changes in eye position are offset by the sustained, tonic discharge of oculomotor motoneurons. Motoneuron tonic discharge rates are linearly correlated with eye position and average 100 spikes/second at primary position.[237] Individual motoneurons do differ in the eye position at which they are recruited into tonic activity, their on-position. However, at least 70% of motoneurons are at threshold at primary position.[234] In contrast to the activity patterns seen for spinal motoneurons, eye muscle motor units exhibit extraordinarily high sustained discharge rates. Bi-directional modulation of the tonic discharge rate is the means of executing all smooth eye movements (vision stabilizing reflexes, pursuit, and vergence movements). Motoneurons exhibit a high frequency burst of activity (up to 600 spikes/second) to offset the viscous forces resisting ballistic-type movements (saccades and rapid phases of nystagmus), and then level off at a higher tonic discharge rate that specifies the new eye position. The motoneurons innervating the antagonist muscle pause for saccades, then level off at a lower tonic discharge rate. Physiological studies have treated oculomotor motoneurons as a relatively homogenous population, differing principally in terms of their on-position and discharge rate versus eye position characteristics. This characterization of the oculomotor motoneuron must be reconciled with the obvious diversity of extraocular muscle fiber types.

The small motor unit size seen in extraocular muscle (approximately 10 muscle fibers/motoneuron) is consistent with the precise incrementation of force that is required in fixation and eye movements. The globe represents a fixed and typically unchanging load for the extraocular muscles, although resistance to applied force can be altered by disease, trauma, or surgical intervention. Load-compensating stretch reflexes then are not necessary, and have been found to be absent from oculomotor motoneurons.[144] Moreover, the fact that extraocular muscle motoneurons exhibit discharge rates that are an order of magnitude higher than most spinal motoneurons places extreme demands upon this muscle group. Together, these two factors most likely influence the speed of contraction and fatigue resistance of extraocular muscle fiber types. The concept that structure follows function may perhaps be best demonstrated by observations that the levator palpebrae superioris and the accessory extraocular muscles (retractor bulbi, accessory lateral rectus) that are present in some species play functionally distinctive roles and exhibit significant fiber type differences from the oculorotatory muscles,[214,216,276,277] despite the fact that all derive from the same embryonic primordia.

In the past, electromyography (EMG) has been used extensively to study extraocular muscle function. EMG data first convincingly showed that Duane's retraction syndrome was an innervational abnormality, characterized by rectus muscle cocontraction. However, EMG data must be interpreted carefully and misunderstandings have resulted from the use of quantitative EMG in motor unit studies and diagnostic procedures. For example, the up- and down-shoots associated with Duanes' retraction syndrome are accompanied by EMG activity in the superior and inferior rectus muscles. This was first thought to prove a vertical innervational abnormality, but an alternative analysis suggests that elevated EMG is seen in all rectus muscles in globe retraction and may be a consequence, rather than a cause, of up-shoots and down-shoots. Similarly, evaluations made on the basis of recordings with botulinum EMG needle electrodes may require confirmation by more stringent EMG techniques. Thus, one must have an understanding of the limitations of EMG in order to critically evaluate early concepts of extraocular muscle function and dysfunction that are based upon quantitative EMG alone.

B. FUNCTIONAL TYPES OF EYE MOVEMENT

The functional demands placed upon the extraocular muscles are extraordinary. Five distinct eye movement systems (vestibulo-ocular, optokinetic, pursuit, saccadic, and vergence), collectively with a wide dynamic operative range, converge at or above the level of the oculomotor motoneuron and exert their diverse roles through the extraocular muscles (for review, see Robinson[237] or Leigh and Zee[158]). Binocular vision and high visual acuity have evolved to require very fine oculomotor control. Fixation of the visual axes must be binocularly controlled, with little margin for error, or diplopia ensues. The eye movement reflexes, vestibulo-ocular and optokinetic, represent phylogenetically old systems that provide a baseline ocular stability that is vital for clear vision and thereby provide a

platform from which to execute voluntary movements. The vestibulo-ocular reflex utilizes signals arising from head accelerations to produce eye position changes that compensate for head/body movements and prevent blur. Vestibulo-ocular reflexes are so basic to oculomotor function that comparative morphologic studies show that orientation of the semicircular canals in a position that is orthogonal to the lines of force of the eye muscles is a phylogenetically conserved feature of eye movement systems.[87] Optokinetic movements use visual cues to the same purpose and counterbalance the poor response properties of the vestibulo-ocular reflex at low frequencies of head acceleration or during constant velocity rotations. The evolution of control systems to mediate the tracking of visual targets in three dimensions correlates with the development of binocularity and high visual acuity and places the highest level of demands upon the final common pathway for eye movement control. Eye muscles can execute pursuit and vergence eye movements to maintain fixation upon smoothly moving targets at velocities at which motion is barely perceptible, yet also are capable of saccadic peak velocities of as high as 600°/second. While pursuit and vergence movements track slowing moving visual targets, saccades rapidly reorient vision to new visual, auditory, or somatosensory targets. Although skeletomotor systems may exhibit a division of labor between muscles that are postural in nature and muscles designed for rapid, voluntary movements (e.g., soleus versus gastrocnemius), eye movement systems combine an even wider range of functions into the individual oculorotatory muscles.

C. BRAINSTEM PHYSIOLOGIC CORRELATES OF EYE MOVEMENTS

Several excellent reviews consider the central eye movement control systems.[50,97,158,237,271] This section provides a brief synopsis to allow an understanding of extraocular muscle structure and function in the context of features of the central control systems. Motoneurons innervating agonist and antagonist muscles act in a push-pull fashion, with corresponding increases and decreases in discharge rates, respectively. Normally, extraocular muscles never become slack; as agonists, their tension is dominated by their contractile force, and as antagonists, by their elastic force. The baseline neuronal discharge rate that is seen in oculomotor motoneurons is established by the vision stabilizing reflex systems. Neurons receiving primary vestibular signals synapse upon and are responsible for the tonic discharge rate in the oculomotor motoneuron. Voluntary eye movement systems operate through well-established pathways to augment or decrement this baseline rate in order to execute changes in eye position. Cortical pursuit control mechanisms match eye velocity to target velocity while tracking smoothly moving targets with the goal of minimizing retinal slip (blur). Similarly, although knowledge of the neural pathways is incomplete, cortical neurons discharging proportional to visual disparity[210a] presumably mediate disjunctive eye movements. A cluster of presumptive premotor neurons, discharging in relationship to the angle between the eyes, overlies the oculomotor nucleus and may be responsible for the activity in medial rectus motoneurons during vergence eye movements.[173,174] Reflexive and voluntary saccades are used to scan the environment and acquire targets presented by several types of stimuli; these are generated at the level of the superior colliculus or frontal/parietal cortex, respectively.[271] For saccade generation, a population of neurons with high frequency burst activity (medium lead burst neurons) directly contact the appropriate motoneuron pools and provide the presaccadic burst or pause in the motoneuron. Integration of the burst, by circuits involving the prepositus hypoglossi nucleus, results in increased/decreased activity in the tonic neuron signal, which is then fed to the motoneuron as well. Finally, the distinct eye movement systems do not operate in isolation; rather, when considering the consequences for the extraocular muscles, it must be remembered that simultaneous interaction of more than one of the control systems is the rule.

D. FEEDBACK CONTROL OF EYE MOVEMENT

All motor control systems require feedback that signals the outcome of position change commands for shortterm accuracy adjustments and as a longterm calibrator of motoneuron output. Eye movement systems have a well-established capacity to use feedback control in the adaptive regulation of motor output, thereby preventing diplopia. There are three potential sources of information available to the brain about which way the eyes are pointing: vision, corollary discharge (efference copy), and muscle proprioception. There is substantial evidence that all three of these informational sources contribute to human oculomotor control, although they may contribute differently to shortterm eye position signals or longer term recalibration mechanisms.

Vision provides accurate, albeit long latency, on-line feedback as to the outcome of eye movement commands. For example, a) pursuit movement velocity is adjusted to match target velocity, b) inaccurate targeting of saccades results in corrective saccades at short latency, and c) the use of magnifying spectacles results in rather rapid recalibration of the vestibulo-ocular reflex. In addition, a copy of the motor command signal (efference copy, corollary discharge) may be used to provide higher neural centers with short latency information as to the *intended* eye movement. The copy of the motor command most likely arises from the movement generating network proper, specifically the nucleus prepositus hypoglossi, and then is distributed to control centers as an update of the change in eye position.[110,120,279] The everyday corrections that are based upon closed-loop eye position feedback are constant but typically shortterm events and likely have no longterm consequences for eye muscle status. However, the longterm adjustments required to prevent diplopia resulting from events such as oculomotor neuropathies, myopathies, or mechanical restrictions in movement of the globe (e.g., scarring, Graves' disease) often do require lasting motoneuron gain changes (i.e., altered neuron discharge rate/eye position properties) that potentially lead to muscle hypertrophy, fiber type conversions, etc. Thus, to appreciate the diversity of the structural and functional characteristics of the extraocular muscles, the significant adaptive capacity of eye movement control systems must be understood.

Information regarding eye position change also may arise from sensory feedback from muscle receptors. Eye muscle proprioception is of considerable importance to the strabismologist since muscle resection may alter or eliminate these signals. To say that extraocular muscle proprioception is a controversial issue is putting it mildly, but in the past several years the significance of muscle feedback has become clearer.

Unlike typical skeletal muscle, the neuromuscular spindle is not the principal sensory receptor in extraocular muscle, nor is there monosynaptic feedback of muscle afference to oculomotor motoneurons.[144] Although a small number of spindles and Golgi-type tendon organs are present in primate eye muscles,[241,242] the palisade terminal (myotendinous cylinder) appears to be the primary sensory receptor.[230,240] Palisade endings are associated with the distal myotendinous junction of extrafusal fibers, specifically with the global multiply innervated muscle fiber type (described in Section II.B.3 below). The motor innervation of this particular fiber type then may act in a manner similar to gamma motoneurons in traditional neuromuscular spindles in modulating the sensitivity of the afferent nerve terminals. Both multiply innervated fibers and palisade endings are absent from the levator palpebrae superioris and retractor bulbi muscles, suggesting that these elements play a unique role in rotary eye movements. Speculation as to the signal that arises from this receptor type is not intuitive, since the global multiply innervated fiber is non-twitch and its slow contractions would not be closely time-locked to the twitch contractions of other muscle fiber types (see Section II.B.3). The primary afferent neurons providing sensory innervation of mammalian extraocular muscles are located in the trigeminal ganglion.[211,222] Beyond the immediate central projections of primary afferent neurons,[211,218] extraocular muscle afferent signals are distributed broadly within the central nervous system[2,8,42,78,80,143,147,154,155] and thus may be involved with visual and oculomotor processing at a number of levels.

Functionally, signals arising from receptors in the eye muscles have been implicated in a variety of roles (see Steinbach[281] for review). While a thorough discussion of the potential functional roles of muscle afference is beyond the scope of this review, there are areas of clinical importance that deserve mention. In particular, proprioception may specify visual direction,[39,47,100,101,229,239,265,283] modulate visual processing,[145,155] and participate in binocular functions,[162a] particularly during the critical period of development of the visual sensory system.[43,71,106,198,285,286] Moreover, abnormalities in eye muscle proprioception may contribute to fixation instabilities in congenital nystagmus[201] and to strabismus.[69] Steinbach and colleagues[282,283] have shown that proprioception contributes to spatial localization and that alterations in localization can be attributed to surgical procedures that comprise the sensory receptors (i.e., marginal myotomy). One group has argued that strabismus may be a result of an "imbalance" of proprioceptive signals.[186] Better understanding of the notion that proprioception may contribute to the development of visual and visuomotor function is of particular importance to the outcome of strabismus procedures. Given currently available data, a parsimonious hypothesis is that, in the adult, proprioception may serve as a longterm recalibration signal.

In summary, the eye movement control systems have unique and diverse properties. To ful-

ly understand the properties of extraocular muscle, the operational characteristics of oculomotor systems must always be kept in mind.

II. Extraocular Muscle Anatomy

A. GROSS ANATOMY

The extraocular muscles exert their individual actions on the globe according to the point of rotation of the globe, the bony anatomy of the orbit, and the origin and insertion of each individual muscle. Connective tissue sheaths couple the extraocular muscles to the globe and orbit[75,151] and thereby help determine muscle lines of force in all gaze positions. Restrictions imposed by orbital connective tissue planes and muscle sheaths must be considered in eye movement models and in applied aspects of strabismus surgery.[182,183,184]

For the purposes of clinical understanding, the eye may be considered to rotate about a central point. The muscles, therefore, produce movement about three axes, x, y, and z. Individual muscle fractional force vectors along each of the three axes have been calculated by Miller and colleagues.[183,184] The eye sits within the bony orbit surrounded by the extraocular muscles, connective tissue, and orbital fat. Although the reference visual axes in the human are parallel and straight ahead, the bony orbits point outward at approximately 23°. This is important to our understanding of the actions of the extraocular muscles because the origin of the rectus muscles is at the orbital apex and they insert in a spiral around the ocular limbus in such a fashion that the superior and inferior recti form an angle of 23° with the anterior-posterior visual axis in the straight ahead position. The four rectus muscles arise from a tendinous ring (the annulus of Zinn) which surrounds the optic foramen and a portion of the superior orbital fissure, surrounding the optic nerve. The medial and lateral rectus muscles lie on the medial and lateral sides of the globe respectively at approximately the horizontal meridian of the globe. The medial rectus inserts approximately 5½ millimeters from the corneoscleral limbus, the lateral rectus muscle approximately 7 millimeters. The innervation of the medial rectus muscle is via the inferior division of the oculomotor nerve while the abducens nerve innervates the lateral rectus muscle. Since the origins and insertions of these muscles are symmetric and they lie in the horizontal meridian on opposite sides of the globe, their functions are relatively simple and are antagonistic.

The superior and inferior rectus muscles also originate from the annulus of Zinn. They insert onto the sclera of the globe, at an angle of 23° with the straight ahead visual axis, and their insertions straddle the superior and inferior aspects of the vertical meridian of the globe. The inferior rectus inserts 6½ millimeters from the limbus, the superior rectus 7¾ millimeters. Thus, in addition to their primary actions of elevation for the superior rectus and depression for the inferior rectus, the vertical rectus muscles have relatively prominent secondary roles of adduction for both muscles and intorsion for the superior rectus and extortion for the inferior rectus. The relative importance of the primary and secondary actions depends on the direction of the visual axis. In lateral gaze these muscles become relatively more important in elevation and depression and relatively less important as adductors and torsions, whereas, in the adducted position, the torsional aspects become relatively more important. It should be noted, however, that in humans the principal action of these muscles is always elevation and depression with the adduction and torsional aspects remaining supplementary to the action of the obliques. The superior and inferior rectus muscles are innervated by the superior and inferior branch of the third nerve, respectively.

The superior oblique muscle, like the four recti, arises from the annulus of Zinn at the apex of the orbit; however, its functional origin is the trochlea in the superomedial orbit. In the human, this muscle is tendinous after it passes through the fibrocartilaginous ring. This tendon, after passing through the ring, is directed in a posterolateral direction inserting in the superior-posterior-temporal quadrant of the globe behind the point of rotation of the eye. The angle this vector plane makes with the straight ahead visual axis is approximately 54°. Thus, the action of this muscle changes somewhat depending upon the direction of the visual axis, with greater incycloduction in abduction and more depression when the eye is adducted. However, as noted above in the discussion of the vertical recti, the oblique muscles are not the main depressors or elevators of the eye in any position. Indeed, even with the oblique muscles completely removed from their insertions, the eye will still elevate and depress in adduction. The nerve supply to the superior oblique comes from the trochlear nerve. The interior oblique muscle arises from the medial orbital wall and inserts on the inferior-posterior-temporal quadrant of the globe behind the point of rotation of the eye. This muscle

is primarily responsible for excycloduction, abduction, and contributes to elevation when the eye is adducted. The nerve supply to the inferior oblique is from the inferior division of the oculomotor nerve.

B. CELLULAR ORGANIZATION

1. Introduction

Although extraocular muscle differs in many important respects from typical skeletal muscle, some general features are shared and a brief description of muscle is applicable. Muscle is enclosed in a collagenous connective tissue sheath, the epimysium, and merges at either end with a tendon, an aponeurosis, or the periosteum of bone. Extensions of collagen from the epimysium subdivide the muscle into individual bundles or fascicles surrounded by a well-defined collagen layer, the perimysium. The individual muscle fibers are separated from each other by a network of fine collagen fibers, the endomysium. The immediate extracellular environment, the basal lamina or extracellular matrix, interacts dynamically with the muscle fiber in a wide range of functions, including the establishment and maintenance of neuromuscular junctions.[166,245]

Individual muscle fibers are multinucleate syncytia surrounded by a cell membrane, the sarcolemma. The nuclei are elliptical in shape, exhibit a prominent nucleolus, and primarily lie just beneath the sarcolemma. Each muscle fiber is composed of myofibril units that are separated from one another by sarcoplasmic reticulum. Tubular invaginations of the sarcolemma, the t-tubule system, bring the sarcolemma into direct contact with elements of the sarcoplasmic reticulum. The myofibril is composed of a bundle of actin and myosin myofilaments regularly aligned to form repeating structures known as sarcomeres. As many as ten myosin heavy chain genes exist in mammals,[280,294] each encoding a myosin with different contractile properties. The regular alternation of actin and myosin filaments within each sarcomere gives rise to the characteristic striated pattern of skeletal muscle. Each sarcomere is composed of a dark anisotropic band (A band) flanked on either side by a light isotropic band (I band). The filaments of the I band are attached to the narrow, dense Z-line which marks the longitudinal boundary of each sarcomere. Contraction of the myofibril occurs by shortening of the sarcomere and is accomplished by the actin myofilaments sliding along the myosin filaments toward the center of the A band.

Mammalian skeletal muscles consist almost exclusively of twitch fibers that undergo an all-or-none contraction. The process of excitation-contraction coupling links neurotransmitter release by the motoneuron to a rapid muscle contraction, or twitch. Interaction of acetylcholine with muscle cell surface receptors located adjacent to the nerve terminal results in depolarization of the sarcolemma and a propagated action potential along the fiber surface and inward via the t-tubule system. T-tubule depolarization leads to the opening of sarcoplasmic reticulum calcium release channels, thereby rapidly elevating intracellular free calcium levels. Calcium, in turn, acts through a troponin-tropomyosin complex to remove barriers to the interaction of actin and myosin filaments and muscle contraction ensues. Energy requirements of the conformational change that allows actin-myosin interaction are mediated by a myofibrillar ATPase. The muscle twitch is rapidly terminated since calcium ATPase pumps in the sarcoplasmic reticulum rapidly return intracellular free calcium to resting levels. Excitation-contraction coupling has high energy requirements that are met by anaerobic (glycolytic) or aerobic (mitochondrial oxidative) mechanisms. In contrast to this scheme for twitch fibers, some adult vertebrate skeletal muscle fiber types are multiply innervated (i.e., multiple nerve contacts along their length) and may not propagate action potentials. Instead, these fibers undergo slow, graded contractions at each synaptic site instead of twitches. Such non-twitch fibers are extremely rare in mammalian skeletal muscle.

2. Traditional Muscle Fiber Type Classification

The key functional characteristics of skeletal muscle, contraction speed and fatigue resistance, have correlates in muscle fiber structure. Myofiber contraction speed is determined by myosin heavy chain isoform (including the myofibrillar ATPase), sarcoplasmic reticulum calcium pump type, and the quantity of t-tubule and sarcoplasmic reticulum elements. Fatigue resistance is directly related to dependence upon either glycolytic or oxidative enzymes, mitochondrial content, and the capillary network associated with individual myofibers. These structural characteristics are not necessarily independently regulated for individual muscle fibers, but, for example, a particular muscle fiber may exhibit interrelated properties that maximize both contraction speed and fatigue resistance. Observations of the covariance of muscle structural and

functional characteristics have led to the generation of multiple skeletal muscle classification schemes.[40,44,208] The major classification schemes agree on the existence of three to four fiber types in typical skeletal muscle: a) slow twitch, fatigue-resistant (I, SO, S); b) fast twitch, fatigue resistant (IIA, FOG, FR); c) fast twitch, fatigable (IIB, FG, FF); and d) fast twitch, intermediate (IIC, F (int.)). Not every fiber in a given muscle falls cleanly into one of these categories, lending credence to the notion that the fiber types represent points in a continuum of variability. Such classification schemes, however, are useful to the extent that they allow characterization of structural/functional properties and prediction of responses to disease processes or experimental and clinical interventions in muscles comprised of particular fiber types.

3. Extraocular Muscle Fiber Types

Extraocular muscles are unique in both their cellular organization and constituent muscle fiber types. This section should make it clear to the reader that extraocular muscle fiber types do not fit the traditional classification schemes discussed above (cf., Spencer and Porter[277] and Shall and Goldberg[259]). The rectus and oblique extraocular muscles exhibit two distinct regions (Fig. 1), each with different fiber type content: a) an outer orbital layer adjacent to the periorbita and orbital bone, and b) an inner global layer adjacent to the optic nerve and eye. While the global layer extends the full muscle length, inserting via a well-defined tendon, the orbital layer ends before the muscle becomes tendinous. The levator palpebrae superioris and the accessory extraocular muscles that are seen in many subhuman species do not exhibit this layered organization.

Early studies identified two fundamental muscle fiber types in the extraocular muscles on the basis of their histological appearance.[153a] The appearance of Fibrillenstruktur fibers was similar to that described for the typical twitch fiber above. By contrast, Felderstruktur fibers were thought to be multiply innervated and exhibited the morphological and physiological properties of the multiply innervated, slow fibers that are more commonly found in skeletal muscles of amphibians and avians. There is a conspicuous absence of a true slow-twitch fiber type in most of the extraocular muscles;[64,277] the levator palpebrae superioris is the exception.[216] Thus, we must approach extraocular muscle as clearly distinct from limb muscle, but with the goal of devising an adequate system of categorizing fiber types.

Some more recent characterizations of extraocular muscle[82,231] have caused considerable confusion in that they did not distinguish between subtypes of fibers and were in error regarding fiber innervation pattern. The classification system of Durston[82] divided extraocular muscle fibers on the basis of their light microscopic appearance with trichrome stain. Staining of the intermyofibrillar material (mitochondria, sarcoplasmic reticulum) allowed resolution of three groups, termed coarse, granular, and fine. The coarse fiber type was thought to be multiply innervated (and the equivalent to the Felderstruktur fibers described above), although later histochemical and ultrastructural studies showed that only small, fine fibers exhibited this characteristic. Thus, publications prior to about 1982 that used the coarse-granular-fine system must be carefully examined for this error. Since then, thorough comparisons of the characteristics of traditional skeletal muscle fiber types with those of extraocular muscle show a lack of equivalence in fiber types.

The extraocular muscle fiber classification system in most popular usage at present is descriptive, allows comparison of data from all mammalian species, and uses the easily recognizable feature of location, "color," and innervation pattern.[204,205,277] This approach resolves six fiber types (Fig. 1). Distinctions as to location (orbital or global layer) and color (red, intermediate, or white) can be made on the basis of virtually any type of microscopic examination. Although these two characteristics together allow definitive identification of fiber type, the innervation pattern also can be assessed at light or electron microscopic levels with acetylcholinesterase staining. Spencer and Porter[277] have compared most of the earlier extraocular muscle fiber classification schemes. The reader is referred to this source for a reconciliation of many of the earlier classifications and for a more complete reference listing.

a. Orbital Singly-innervated Fiber

This is the predominant fiber type (80%) in the orbital layer of rectus and oblique muscles. Neuromuscular contacts are at a single site, but nerve terminals spiral around the fiber,[243] leading to the earlier misinterpretations of their innervation status.[82] Trichrome staining reveals a coarse appearance due to high intermyofibrillar material content. This fiber exhibits the fast type of myofibrillar ATPase and high oxidative enzyme activity, but also appears to be capable of anaerobic metabolism. The presence of small myofibrils that are well delineated by sarcoplasmic reticulum also corresponds with a fast-twitch fiber profile. In the innervation zone (midportion of fi-

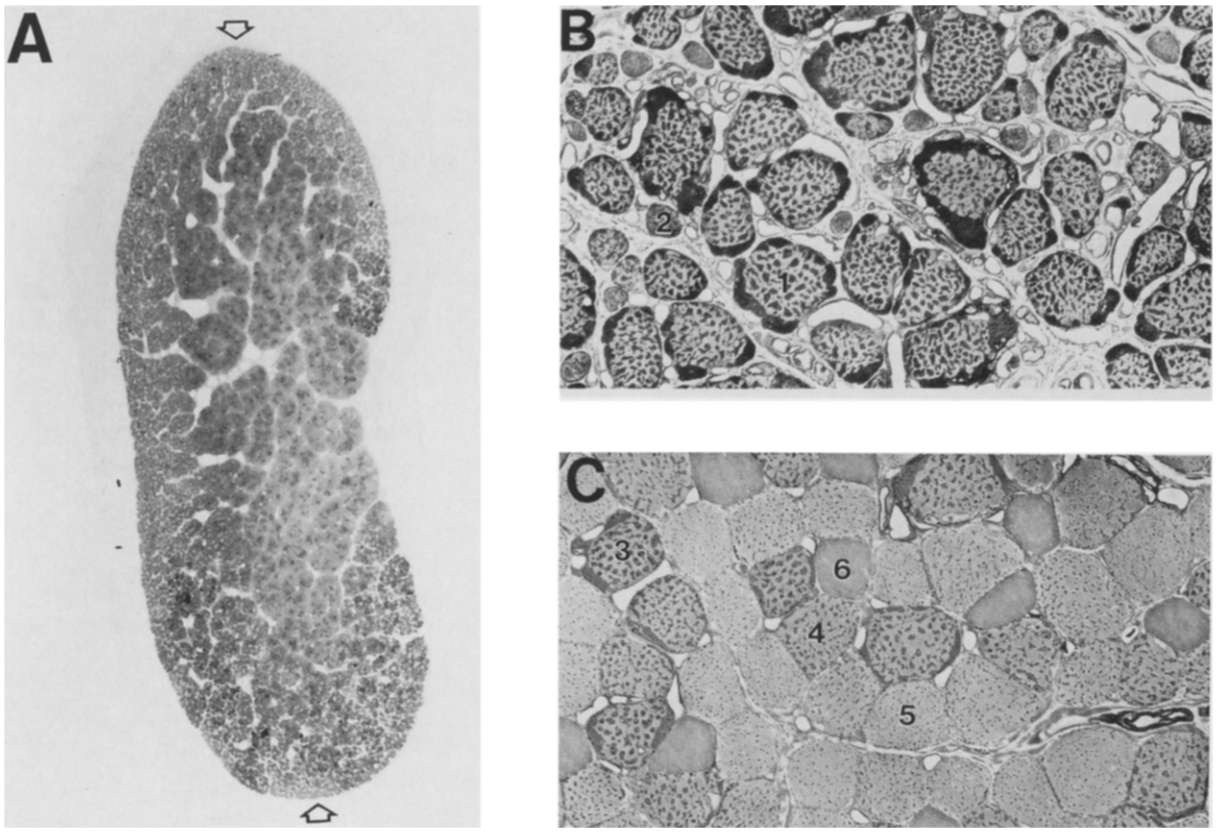

Fig. 1. Light photomicrographs of monkey medial rectus muscle. *A.* Low magnification micrograph indicating orbital (left) and global (right) muscle layers. Orbital layer extends around much of the perimeter of the muscle (limits of layer are indicated by open arrows), while global layer (larger fibers in center, filled arrow) fills the central portion of the muscle. *B.* High magnification micrograph of the orbital layer illustrating orbital singly innervated (1) and orbital multiply innervated (2) fiber types. *C.* High magnification micrograph of the global layer illustrating the three global singly innervated fiber types (3, global red; 4, global intermediate; 5, global white) and the global multiply innervated (2) fiber type. Original magnification: ×21 (A), ×410 (B,C).

ber), immunoreactivity for myosin heavy chain in the rat shows the presence of a fast myosin isoform,[135] although not the expected IIA isoform.[41] Away from the innervation zone, individual fibers show longitudinal variations in ultrastructure and also stain with the generic fast myosin antibody, as well as antibodies for a IIA myosin isoform and a myosin heavy chain isoform that typically is seen only in embryonic/neonatal fibers.[41,135] In addition, a unique myosin gene is expressed only in extraocular muscle;[10,179,247,294] the fiber type specificity of this myosin isoform is unclear, but may involve this fiber type. Consistent with the oxidative enzyme pattern, mitochondria are numerous and form dense clusters. The individual muscle fibers are ringed by capillaries. On the basis of oxidative capacity, this fiber type likely is the most fatigue-resistant mammalian skeletal muscle fiber type. Most extraocular muscle types are conserved across species. The orbital singly innervated fiber type (and its counterpart, global red singly innervated type) represents an exception in that higher species, with the demands of high visual acuity and extended oculomotor range, have an increased mitochondrial content in this fiber type. Normal eye muscle tension levels never drop below 8–12 grams;[68] this fiber type most likely is a major contributor to the sustained force levels. While there are some similarities with the skeletal muscle type IIA fiber type, the high fatigue resistance and unique myosin isoform profile that are inherent in orbital singly innervated fibers preclude drawing exact parallels between these types.

b. Orbital Multiply Innervated Fiber

This fiber accounts for the remainder of fibers (20%) in the orbital layer and corresponds to a subset of the fine type of Durston.[82] This fiber type exhibits multiple nerve terminals distributed along its length. Physiological studies may be interpreted as indicating that this fiber type has twitch capability near its center and is non-twitch

proximal and distal to the end plate band.[132] Consistent with these observations, the orbital multiply innervated fiber exhibits structural variation along its length.[72a,73] In its center, on the basis of ultrastructure and myofibrillar ATPase, this type appears to be moderately fast-twitch and resembles the skeletal muscle IIC type. Oxidative metabolic capacity is less than is typical for IIC fibers. By contrast, the proximal and distal portions of this fiber type exhibit the slow myofibrillar ATPase type and the fine structural characteristics of slowly contracting fibers. Myosin heavy chain expression is consistent with this profile in that mid-fiber regions stain for a fast isoform and proximal/distal regions stain for the embryonic/neonatal only.[135] The longitudinal differences in this fiber type may reflect innervation by motoneurons with differing functional characteristics (see Jacoby et al[135]). The collective features of this fiber type are unlike any that previously has been described in skeletal muscle and it is difficult to draw conclusions regarding its function.

c. Global Red Singly Innervated Fiber

This fiber constitutes about one-third of the fibers in the global layer and would be termed coarse by previous criteria.[82] The histochemical, ultrastructural, and myosin heavy chain expression profile of this fiber type closely resembles that of the orbital singly innervated fiber. However, the global type does not exhibit the longitudinal variations in ultrastructure and does not coexpress the fast and embryonic/neonatal myosin isoforms.[41] Moreover, these fibers express the IIA myosin isoform throughout their length. Together, these observations suggest similarities with the skeletal IIA fiber type, but again the high mitochondrial content is very different from typical IIA fibers. Functionally, this profile suggests that global red singly innervated fibers are fast-twitch and highly fatigue resistant.

d. Global Intermediate Singly Innervated Fiber

This type constitutes approximately one-quarter of the fibers in the global layer. Myofibrillar ATPase and ultrastructural characteristics indicate that this is a fast-twitch fiber type, with myosin isoform immunoreactivity characteristic of type II fibers, probably type IIB.[41] The trichrome appearance is granular and moderate levels of oxidative enzymes and anaerobic enzymes are apparent. This fiber has numerous medium-sized mitochondria that are distributed singly or in small clusters. Myofibrillar size and sarcoplasmic reticulum content are intermediate between the other two types of global singly innervated fibers. Overall, this is a fast-twitch fiber with an intermediate level of fatigue resistance, probably lying between skeletal types IIA and IIB in fatigability.

e. Global Pale Singly Innervated Fiber

This fiber type comprises one-third of the global layer. The fibers are most analogous to skeletal type IIB fibers with respect to the modest levels of oxidative enzymes, high anerobic metabolic capacity, and a fast type ATPase profile. The myosin heavy chain profile is most likely of the IIB type.[41] The fiber appears granular by trichrome stain and acetylcholinesterase localization shows a single locus of large end plates. This fiber exhibits few small mitochondria that are singly arranged between myofibrils. The overall fiber profile is consistent with a fast-twitch type that is used only sporadically because of low fatigue resistance.

f. Global Multiply Innervated Fiber

This fiber constitutes the remaining 10% of the global layer. Acetylcholinesterase staining reveals numerous small superficial grape-like endings distributed along the longitudinal extent of the individual fibers, as well as staining at the myotendinous junction in association with palisade endings that are presumed to serve a sensory function. These fibers previously have been described in primates as being singly innervated;[82] but, as noted above, this was in error. This fiber type contains very few, small mitochondria that are arranged singly between the myofibrils. The myofibrils are very large and sarcoplasmic reticulum development is so poor that myofibril separation is often indistinct. The ultrastructural profile of this fiber resembles that of slow, tonic muscle fibers in amphibians. The myosin expression profile includes slow-twitch (type I), slow tonic, and, at least in rabbit, an α-cardiac myosin heavy chain isoform.[134,209,210,239a] Like amphibian muscles, the global multiply innervated fiber type exhibits a slow graded, nonpropagated response following either neural or pharmacologic activation.[31,32,56] There is no counterpart to this fiber type in any other human skeletal muscle.

4. Accessory Extraocular Muscles

Examination of the fiber type composition of the levator palpebrae superioris and accessory extraocular muscles found in other mammals is a useful exercise. Knowledge of the structural sim-

ilarities and differences between these muscles and the oculorotatory muscles may promote an understanding of how the different muscle fiber types contribute to function.

The levator palpebrae superioris muscle serves a functional role that is distinct from the other extraocular muscles. The levator acts to maintain eyelid position and terminate blinks, and has commensurate differences in its fiber type composition.[216] Briefly, this muscle lacks the distinctive layered organization, lacks the multiply innervated fiber types, but instead exhibits a fiber profile that includes the three singly innervated types seen in the global layer of rectus muscles plus a true slow-twitch fiber type not seen in other extraocular muscles. The conspicuous absence of the multiply innervated fibers from the levator may reflect a prominent role for this fiber type in finer control of fixation and smooth eye movements.

The retractor bulbi serves in the reflexive retraction of the globe into the orbit following corneal stimulation and exhibits a fiber type composition in keeping with this functional role. The retractor bulbi of the rat contains two to three fiber types,[108,206] all of which are the fast, fatigable fibers that would be expected of a muscle that is only transiently activated. The rat retractor expresses only the fast myosin heavy chain isoforms, predominantly type IIB.[41] The retractor bulbi is an excellent example of epigenetic influence over muscle fiber type composition, since it arises from the same primordia as the oculorotatory muscles but exhibits only fast-twitch, fatigable fiber types. By contrast, the accessory lateral rectus of the monkey, which appears to be a remnant of the retractor bulbi, has evolved to contain fiber types much like those found in the global layer of rectus and oblique muscles, including the global multiply innervated type.[276] Changes in the monkey accessory lateral rectus, versus the retractor, suggest that it has evolved to assume a function closer to that of the rectus muscles.

III. Embryology

A. MUSCLE ORIGINS

Two theories exist as to the early events in the ontogenesis of the extraocular muscles. One holds that the anlagen of each muscle condenses from one of three distinct precursors, separately and at distinct times.[102,103] The alternative theory[257,258] is that the extraocular muscles develop concurrently from a single mesenchymal condensation that subsequently divides into separate superior and inferior mesodermal complexes. Individual extraocular muscles may receive contributions from both mesodermal complexes (medial and lateral recti) or may arise from only one or the other complex (remainder of the oculorotatory muscles plus the levator palpebrae superioris). During organogenesis, the developing brainstem also is segmented into regions known as rhombomeres that give rise to the cranial nerves.[165] Each of the oculomotor nerves arises from particular rhombomeres, reflecting the segmental nature of the cranial nerves. A caudal to rostral internuclear gradient for the genesis of oculomotor motoneurons has been described in rats.[6,7] The majority of motoneurons in abducens, trochlear, and oculomotor nuclei are postmitotic by the time the eye muscles are forming. Recent studies suggest that aggregates of myoblasts may be contacted by oculomotor nerves *prior* to migration and carry their innervation with them into the developing orbit.[13,291] Whether innervation first occurs in the orbit or while myoblasts are still adjacent to the neural tube, the close proximity of the anlagen of the extraocular muscles may actually facilitate development of anomalous innervation of eye muscles. The classic clinical example of this relationship is Duane's retraction syndrome wherein the congenital absence of the abducens nerve results in the "inappropriate" innervation of the lateral rectus by the oculomotor nerve. A similar outcome has been seen in a transgenic mouse model in which the oculomotor and trochlear nuclei are absent and the abducens nerve may sprout to innervate incorrect muscles (J.D. Porter, R.S. Baker, and A.P. McMahon, unpublished).

At a cellular level, recent studies have established that the myoblasts that form the extraocular muscles arise from cranial mesoderm, while the orbital connective tissues have an unusual origin from neural crest.[70,192] A rostral, unpaired mesodermal condensation (the prechordal plate) and contributions from some of the seven paired condensations of paraxial mesoderm (the somitomeres; these are loosely analogous to somites) form the eye muscles. There are conflicting opinions as to whether prechordal mesoderm contributes directly to the formation of extraocular muscle,[70] or if cells originating from this site first migrate into the somitomeres, which secondarily give rise to myoblasts that populate the orbit.[290] The precursor cells migrate together in compact aggregates to form condensations around the developing eye. It is the number and fate of these orbital condensations that have led to the controversy detailed above. Once muscle

precursor cells are in the primitive orbit, the primary myotube alignment pattern apparently is specified by cell-cell interactions with the neural crest-derived connective tissue, as the proper spatial orientation is obtained even if the myoblasts are from mesoderm that was transplanted to the head from an inappropriate source.[191]

B. MYOGENESIS

After muscle precursor cells migrate into the orbit, myogenesis follows the same general stages that have been described for other skeletal muscles.[145,257] Six distinct myogenically defined cell lineages have been identified in extraocular muscle primordia,[164] and may correspond to the six adult muscle fiber types. Close similarities are found between the development of human and macaque monkey extraocular muscles; thus, we have studied subhuman primates in detail. As in other skeletal muscles, the extraocular muscles are generated from at least two waves of myogenesis that form primary and secondary generation myofibers.[212] In the monkey, myoblasts fuse to form primary myotubes prior to embryonic day 62, while secondary myotubes appear between embryonic days 62-92 (term in the monkey is about 165 days). As in other skeletal muscles, the secondary myotubes form in close association with primary myotubes. While muscle fibers still are homogeneous and relatively undifferentiated, early neuromuscular contacts are observed (by embryonic day 62[212]). By embryonic day 92, cytological differences between singly innervated and multiply innervated fiber types can be distinguished. All primary and secondary generation fibers are generated and maturing by embryonic day 121. As a general rule, the phylogenetically "old" global multiply innervated fibers are the first to form, while fibers in the orbital layer mature last.

Despite the considerable prenatal development that occurs in extraocular muscle, there is significant postnatal maturation of these muscles,[116,277] even in the primate.[212] As with other skeletomotor systems, in the oculomotor system there is an overproduction of motoneurons and competition for synaptic sites, resulting in the activity-dependent adjustment of motoneuron number to target size.[266,268,269] In typical skeletal muscle, multiple axons contact a muscle fiber at a single site, but, through competitive interactions, all but one axon is eliminated. A percentage of motoneurons die during this perinatal process. Similarly, the singly innervated fibers in extraocular muscle most likely exhibit this same transient and focal multiple innervation of muscle fibers. However, the rules that govern neuromuscular junction formation and stabilization must be quite different for multiply innervated fibers. Instead of neuromuscular junction formation at one site that precludes the formation of junctions at other sites on the same fiber, multiply innervated fibers must allow synaptogenesis at sites that are distributed along their length. The mechanisms responsible for the formation of either focal or distributed neuromuscular junctions in extraocular muscle have not yet been elucidated.

By birth, the six fiber types are recognizable in monkey extraocular muscles.[212] Beyond the postnatal increase in size of all fiber types, muscle maturation ocurring after birth in the monkey largely involves increases in the mitochondrial content of the orbital singly innervated fiber type (J.D. Porter, R.S. Baker, and R.F. Spencer, unpublished). This postnatal shaping of fiber characteristics occurs in the human as well and likely is critical for appropriate function of eye movement systems. During the postnatal period the definitive muscle characteristics are established. This period roughly corresponds with the period of visual system maturation, and eye muscle characteristics are subject to aberrant development and/or developmental delays. We have proposed that there may be a critical period for eye muscle development during the first 3–6 months after birth, during which time the eye muscles acquire the structural/functional characteristics demanded by binocular vision, but are more susceptible to insult than in the adult (see also Sections V.A and VI.D).

Few studies have examined the pattern of myosin heavy chains expressed by particular extraocular muscle fiber types during development. Rodents are appropriate for thorough analysis of developmental myosin isoform expression, since: a) eye muscle fiber types are largely conserved across mammalian species; b) the relatively low cost and compressed developmental period in rodents facilitates these studies; and c) probes for myosin expression show a degree of species specificity and most probes work well in rodents. In the prenatal rat, all muscle fibers in oculorotatory and retractor bulbi muscles express the embryonic myosin isoform.[41] Just before birth, large primary myofibers stain for slow myosin and the surrounding secondary fibers stain for fast myosin. Embryonic myosin is first lost from global layer singly innervated muscle fibers during the first postnatal week. Loss of

the embryonic isoform from global multiply innervated fibers comes later. The expression of the slow-tonic and extraocular muscle-specific myosin heavy chain genes is seen in the late prenatal period and first postnatal week, respectively.[171,294] Embryonic myosin is suppressed last from the innervation zone of orbital singly and multiply innervated fiber types, but is retained in the proximal and distal regions of both types. Normally, skeletal muscle myosin expression undergoes transitions from embryonic to neonatal to adult isoforms. By contrast, embryonic myosin is not lost from the proximal and distal portions of both orbital layer fiber types, thus the developmental myosin heavy chain genes may not be completely repressed in these adult extraocular muscle fiber types. This atypical developmental regulation of myosin gene expression in extraocular muscle is unique and may be a contributing factor to their unusual capacity to adapt to changing innervation levels and/or disease states.

C. GENETIC REGULATORY FACTORS

Little is known regarding the genetic mechanisms that may be responsible for many of the unique features of the extraocular muscles. Studies of myosin-heavy chain protein and gene expression suggest that extraocular muscle has a broader developmental potential than virtually all other skeletal muscles.[10,294] It is now recognized that, when compared to other skeletal muscles, the extraocular muscles exhibit remarkable diversity among fiber types at the transcriptional, translational, ultrastructural levels. Given their origin from cephalic mesoderm, the heterogeneity of extraocular muscle may reflect the developmental potential of a unique population of muscle precursor cells. The fiber type fate of embryonic, fetal, or adult (satellite cell) myoblasts is unknown, although the early formation and maturation of multiply innervated fiber types is suggestive of a role of embryonic (or primary) myoblasts in their genesis. The disparate origins of mesenchyme that forms orbital tissues[192,193] makes study of the specificity of early cell-cell interactions difficult. An understanding of these interactions is necessary in order to address the mechanisms that may be responsible for specification of the patterned spatial distribution of fiber types into distinct layers and the unusual phenotype of individual fiber types in these muscles. Modification of extraocular muscle primordia into heat-producing cells in billfish,[29] and into electric organs in weakly electric fish,[162] represent extremes in the genetic potential of muscle precursor cells. The developmental mechanisms responsible for this unusual fate have not yet been uncovered, but the phenomenon does serve to highlight the unique character of these muscles. Natural mutants and transgenic models that involve the neural and myogenic regulatory genes may be exploited in order to analyze some of the developmental mechanisms in this novel system.

D. EPIGENETIC REGULATORY FACTORS

There is evidence that the sequential development of extraocular muscle fiber types reflects, at least in part, the functional pressures coinciding with the maturation of visual and visuomotor systems. During infancy, the postnatal maturation of extraocular muscle parallels the maturation of the retinal circuitry[3] and the establishment of interocular alignment.[38] The most significant change in the postnatal maturation of extraocular muscle, at the structural level, is the increase in mitochondrial content. Thus, there is a strong correlation between the structural basis for fatigue resistance in the eye muscles and the increasing reliance upon eye movements. Experimental monocular deprivation paradigms produce reductions in both contraction velocity and fatigue resistance of extraocular muscle, as well as corresponding alterations in muscle morphology.[160] Altered visual processing presumably would change the patterned activity of oculomotor motoneurons and thereby directly alter the biochemical and morphological properties of some or all of the extraocular muscle fiber types. These data suggest that the maximum potential for fatigue resistance in a muscle fiber may be set genetically, but whether the potential is achieved in a particular fiber type is contingent upon the level of demand placed upon the muscle. The extraocular muscles of Siamese cats, a species with abnormal development of retinogeniculate pathways, also are structurally altered.[160] The impact that monocular deprivation or strabismus would have upon many other muscle properties, such as myosin isoform expression, has not yet been addressed. While it is likely that the basic motor mechanisms for vestibulo-ocular, pursuit, and saccadic eye movements are in place at birth (albeit with properties different from the adult's), the sensory functions of spatial localization and retinal slip detection are immature.[9,90,114,189,202,260,261] The postnatal development of sensory input and feedback systems, and the corresponding changes in motor system parameters (gain, time constant, etc.), then parallels and ex-

erts influence upon the fiber type characteristics of extraocular muscle.

Recently, *in vitro* techniques have been used to examine the specificity of neural influences upon developing extraocular muscle.[221] Motoneuron-containing slices of either fetal rat spinal cord or midbrain were cocultured with neonatal rat extraocular muscle. Thigh muscle cocultured with spinal motoneurons served as a control. During the first few weeks in culture, cells originating from both types of muscle explants developed into myotubes. Myotubes became innervated and contractile and maturation rate was not affected by myotube source. During this time, muscle explant development was not dependent upon motoneuron source. However, after the third week *in vitro,* muscle survival became dependent upon the type of motoneurons with which extraocular muscle was cocultured. Eye muscle degenerated when cocultured with spinal cord motoneurons, but thrived when cocultured with midbrain motoneurons, many of which are the appropriate oculomotor motoneurons. These results provide evidence that the trophic requirements of eye muscle are different from those of other skeletal muscles, and further suggest that maldevelopment of this specific nerve/muscle interaction may play a role in congenital strabismus and amblyopia. Along these lines, Porter and Baker[213] have shown that a monkey species that is prone to development of strabismus *(Macaca nemestrinia)* exhibits developmental features in extraocular muscle that can be interpreted as the result of altered motoneuron discharge rates in this species. Thus, all members of this species may be prone to strabismus, as evidenced by the transient pathology in their extraocular muscles, but only 5% actually develop esotropia.[34,35,149,150,225]

In addition to the neural influences, skeletal muscle precursor cell proliferation, differentiation, and survival are regulated by soluble growth factors, hormones, and cell adhesion molecules.[91,138,200,267] Epigenetic factors can act as both positive and negative muscle growth regulators. Although it is likely that multiple peptide growth factors affect extraocular muscle differentiation, the role of growth factors remains largely unexplored in this system. Basic fibroblast growth factor (FGF) can be localized within chick extraocular muscle and is developmentally regulated.[138] Interestingly, another neurotrophic factor, nerve growth factor (NGF), prevents the loss of bipolar cortical neurons resulting from surgical strabismus in rats.[77] Although the direct effect of NGF is at the developing visual cortex, growth factor alterations in visual development may indirectly alter the maturation of eye movement systems and have consequences for extraocular muscle. In addition, thyroid hormones cause profound hypertrophic effects on extraocular muscles in adults (see Section VI.C). Nuclear triiodothyronine (T_3) receptors are abundant in orbital layer fibers compared to other skeletal muscle types,[250] suggesting that T_3 has a unique functional role in extraocular muscle.

The atypical pattern of myosin expression in extraocular muscle most likely has its origins in development. A key issue is why the developmental myosin heavy chain genes are not completely repressed in extraocular muscle, as they are in most other skeletal muscles. Establishment of innervation and the physical loading of muscle may be, in part, responsible for the developmental myosin heavy chain transitions.[48] Thus, extraocular muscle may continue to express embryonic and neonatal isoforms as a result of their small, unchanging load—the eye. Alternatively, when other skeletal muscles are immobilized in a stretched position they may exhibit re-expression of embryonic myosin.[175] Perhaps the retention of embryonic myosin in the orbital singly innervated fiber, but not in its close counterpart in the global layer (the global red singly innervated), is related to differing muscle force dynamics for the two layers. The maintenance of extraocular muscle force levels at a minimum of 10 g,[66] even in extreme off-direction gaze positions, is most likely due to the continuous activity of this particular fiber type. This level of sustained force may be responsible for maintenance of the expression of embryonic myosin in the adult.

Thus, although the developmentally primitive myosin-heavy chain isoforms are retained in extraocular muscle, differences between extraocular and skeletal muscles may be related more to functional than to embryological factors (see Spencer and Porter[277]). That is, factors such as the load distribution among orbital and global layers, the continuing influence of multiple innervation of some fiber types, and motoneuron discharge rates that are an order of magnitude higher than those seen for other skeletal muscles all must play important roles in shaping fiber phenotype. Indeed, the complex pattern of myosin expression suggests that development of the different extraocular muscle fiber types, particularly those of the orbital layer,[135] is not regulated solely by developmental stage-specific factors; rather, some fiber types may be particularly sus-

TABLE 1

Projected Functional Properties of Extraocular Muscle Fiber Types

	Orbital		Global			
	SIF (1)	MIF (2)	Red SIF (3)	Int SIF (4)	White SIF (5)	MIF (6)
% of layer[a]	80%	20%	33%	25%	32%	10%
Contraction mode	twitch	mixed[d]	twitch	twitch	twitch	non-twitch
speed	fast	fast/slow	fast	fast	fast	slow
Fatigue resistance[b]	high	variable[e]	high	intermediate	low	high
Recruitment order[c]	1st	3rd	2nd	5th	6th	4th

[a]Percentages from Spencer and Porter ('88).
[b]Fatigue estimates based upon fiber morphology (Spencer and Porter, '88) and motor unit data of Shall and Goldberg ('92).
[c]Based upon Robinson ('78) model.
[d]This fiber type shows longitudinal variations in properties; twitch in mid-portion, non-twitch at proximal and distal ends.
[e]Shall and Goldberg ('92) suggest that the slowest contracting twitch units exhibit a wide range of fatigability.

ceptible to extrinsic factors that modulate their expression. The plasticity that is implicit in myosin expression of extraocular muscle may be particularly important in light of the degree of adaptive regulation of motoneuron firing rates that is seen in the oculomotor control systems (see Section I.D).

IV. Specificity of Function in Extraocular Muscle

The functional properties of the extraocular muscles have been studied in man and various experimental models using modern imaging techniques,[182,183,263] *in vivo* length-tension measurements,[21,24,66,68,98,184,235,238,264] and single motor unit recording techniques.[22,23,66,96,98,109,115,159,178,190,254,259] The prior, simplistic concept that eye muscle consists of a small, slow contracting fiber system for fixation and slow eye movements and a large, fast contracting fiber system for saccades and the fast phases of nystagmus is no longer tenable. This section briefly reviews current knowledge of the functional characteristics of extraocular muscle and how the different anatomical muscle fiber types might contribute to eye movements (for summary, see Table 1).

A. DIVISION OF LABOR IN EXTRAOCULAR MUSCLE MOTOR UNITS

The ultimate goal of correlative anatomical and physiological studies of extraocular muscle has been to uncover any association of specific muscle fiber types with specific eye movement functions. The segregation of function among different motor unit types has been a long-debated issue in the field of oculomotor system research. At the moment, the best resolution of this issue can be described as theoretical, with reasonable circumstantial evidence.

Jampel[136] theorized that a slow or tonic muscle system (the multiply innervated fibers) and a twitch system (the singly innervated fibers) operate as two distinct control systems. Eye muscle motor units were thought to subserve discrete functional types of eye movement, rather than collectively adding to muscle force without regard to eye movement type. This scheme required that slow and fast eye movements were mediated by separate parallel pathways, each with its own supranuclear control mechanisms, motoneuron subgroups, and muscle units. An extension of this hypothesis implies that different muscle fiber (motor unit) types may subserve vergence, saccadic, pursuit, vestibulo-ocular, and optokinetic movements.

More recent studies argue against the concept of tonic fibers being involved only with slow eye movements and twitch fibers functioning in association only with rapid eye movements. Instead, the motoneurons and muscle fibers represent a final common pathway for all oculomotor systems. Intraoperative electromyographic studies[66,254] have used electrode arrays to record simultaneous activity in multiple motor units. The activity of single motor units was tightly correlated with a given eye position, regardless of which

eye movement subsystem was used to attain that position. In addition, electromyography showed that orbital layer fibers are recruited before those near the globe, but that all fiber types participate in every type of movement.[23,66,254] Scott and Collins[254] concluded that the histologic muscle fiber types are functionally differentiated on the basis of the *amount of work performed,* rather than on the basis of the type of eye movement to which they contribute.

Single motoneuron recording studies in the chronic alert monkey lend support to the Scott and Collins[254] concept of oculomotor motor unit function. As noted above (Section I.A), the sustained discharge of oculomotor motoneurons is tightly linked to eye position for all motoneurons and individual motoneurons participate in all types of conjugate eye movements.[99,234,248] Likewise, studies of medial and lateral rectus motoneuron discharge patterns during vergence eye movements[174] show that a) individual motoneurons participate in both vergence and saccades, and b) all motoneurons that are at threshold at primary position will increment or decrement their sustained discharge rates in association with disjunctive eye movements. Therefore, there *is* a division of labor in oculomotor units, but the division is not based upon eye movement type.

The contractile and fatigability parameters of the extraocular muscles identify these muscles as among the fastest and most fatigue resistant skeletal muscles.[22,23,64,96,98,109,115,159,178,190,259] On the basis of morphologic data, there are as many as six potential motor unit types (Section II.B.3). Although extraocular muscle exhibits twitch contraction velocities that are much higher than those of the fastest limb muscles, these muscles also are characterized by low tension output, perhaps reflecting their unique myosin composition.[247] Close and Luff[64] demonstrated that isometric twitch contractions occur about twice as fast in extraocular versus limb muscle, yet the relationship between speed of sarcomere shortening and relative load is about the same for these two muscle groups. These authors conclude that the relationship between shortening speed and the duration of myofilament activity is not the same for twitch fibers in extraocular and limb muscle. Moreover, extraocular muscle blood flow, and thus potential oxidative capacity, is the highest of any skeletal muscle.[295] Collectively, these data reinforce the notion that extraocular muscle is fundamentally different from other skeletal muscle.

The diversity of extraocular muscle fiber types creates a dichotomy in light of what appear to be homogeneous oculomotor motoneuron discharge properties. If all oculomotor motoneurons exhibit a stereotyped burst-tonic discharge pattern, and motoneuron activity has an important influence upon fiber characteristics, how does the wide range of eye muscle fiber types come about? This issue can be rationalized by the recognition that oculomotor motoneurons differ in their recruitment thresholds and firing rate versus eye position characteristics to the extent that a diverse range of muscle fiber types could be supported. Robinson[236] has proposed a model illustrating the relationship that extraocular muscle fiber types might bear to motoneuron recruitment order. In saccades or quick phases of nystagmus, all motor units are recruited synchronously and burst, regardless of whether or not their positional threshold for a step (tonic) change in discharge is attained. Thus, during saccades there likely is no differential in the recruitment order of the different muscle fiber/motor unit types. However, after the rapid component of the saccade, or in slow, smooth movements, the recruitment of individual motoneurons into sustained discharge is eye position-dependent. Motor units containing orbital singly innervated fibers and global red singly innervated fibers are thought to be recruited first, well in the off-direction of muscle action. Those motor units containing the multiply innervated fiber types are recruited next, probably near primary position where their fine increments of force would be of value in fixation. The increasingly faster, but fatigable fibers are recruited last, at positions well into the on-direction of muscle action. This notion is supported by data from Scott and Collins.[254] Thus, while the global intermediate and global white singly innervated fiber types would be transiently recruited during all on-direction saccades, they would be recruited into continuous activity only in intermediate to extreme positions of gaze.

There are indications that oculomotor motoneuron size is correlated with contraction velocity and tension production, thereby suggesting that the size principal (that motoneurons are recruited sequentially according to soma diameter) may apply to oculomotor motoneurons as well.[22,190] Interestingly, the orbital layer of the monkey medial rectus is innervated by a distinct subpopulation of small diameter motoneurons,[45] that, if recruitment proceeded according to a size principal, might be recruited early. Current

knowledge of the structural and functional characteristics of the extraocular muscles then lends support to the Robinson model of recruitment in these muscles. The caveat of the model, however, is that rigid experimental tests have not yet been accomplished and indeed will be difficult to perform.

B. OPERATIONAL PROPERTIES OF EXTRAOCULAR MUSCLE

Miller and colleagues[182,183] have argued that an understanding of extraocular muscle function cannot be obtained solely from anatomical study of static, fixed specimens, but instead requires the evaluation of muscle paths at different gaze positions and innervation levels. Using high resolution CT and MRI techniques, individual muscles are observed to swing in toward the optic nerve with contraction and outward with relaxation, traversing distances between 1.5 to 3.7 mm in man. That excursions of this magnitude occur during the normal functioning of extraocular muscle is important to an understanding of the consequences of Graves' ophthalmopathy. Apart from the "bowing" in the radial direction, rectus muscle paths are surprisingly stable relative to the orbit. This was predicted by biomechanical modeling,[184,235] and confirmed using CT in humans,[263] conventional X-ray imaging in alert monkeys,[183] MRI in normal humans,[182] and MRI in humans before and after muscle transposition surgery.[182a] Studies of human orbits have made it clear that, in the vicinity of the globe equator, the rectus muscles pass through connective tissue pulleys that are elastically suspended from the orbit.[75,75a,221a] These pulleys act as mechanical origins to determine eye muscle planes, that is, directions of rectus muscle action. Biomechanical modeling predicts that transposition surgery that altered the pulleys would have different, generally larger, effects than conventional surgery.[182a]

Oculomotor motor units are sequentially recruited to produce force levels adequate to acquire and maintain the desired eye position (see Collins[66]). Extraocular muscles show a significant degree of activity even when the eye is directed well into the off-direction of muscle activity. Collins[66] argues that this sustained activity in some fibers eliminates muscle slack, thereby permitting eye movement systems to operate within a linear region of muscle length-tension curves at all times. The continued development of models of orbital mechanics requires knowledge of *in situ* extraocular muscle length-tension characteristics in normal individuals and in disease. Static length-tension data describes the range of force that is possible for extraocular muscle to achieve. However, muscle force is not only a function of length, but also of innervation level. Collins and colleagues[66,254] have defined the term "operational envelop" for eye muscle as the range of lengths and tensions that are allowed by the range of innervation actually seen *in situ*. The operational envelop represents only about 20% of values possible on the static length-tension curve. If innervation levels are such that extraocular muscle force is equal to or exceeds 10 g, the extraocular muscle length-tension curves become straight parallel lines. Since the resting tension of innervated extraocular muscle always exceeds 10 g, eye muscles operate along the linear portion of the length-tension curves. At the molecular level, muscle force generation is linear when the sarcomeric actin and myosin contractile filaments exhibit partial overlap at rest and the sarcomeres are not fully shortened in maximal contractions. Since eye muscle typically operates at less than its resting length, eye movements are normally executed by muscles with optimal sarcomere organization and, thus, linear force generation. It must be recognized that muscle resection/recession procedures will alter the operational envelop[235] (see Section VI.D) unless the muscle responds with compensatory adjustments in sarcomere length or number. The potential for adaptive changes in the cellular and molecular characteristics of extraocular muscle as a consequence of strabismus surgery represents a key issue about which there is little information (see Section VI.D). Recently, a high performance, implantable force transducer has been developed[183] that may prove to be of considerable utility in assessing orbital statics and dynamics in health and disease. Data from this device should increase the empirical content of biomechanical strabismus models,[184,184a,235] advancing quantitative diagnosis and treatment.

V. Pharmacology and Toxicology

This section is not intended to be an exhaustive review of the pharmacology and toxicology of extraocular muscle. Particular agents of direct relevance to the ophthalmologist interact with extraocular muscle in a manner that may be very different from their usual effects upon skeletal muscle. Due to the unique properties of extraocular muscle, the possibility must be considered that any pharmaceutical may exert a differential effect upon extraocular versus other skeletal

muscles. This section reviews the consequences that botulinum toxin, succinylcholine, calcium channel blockers, and local anesthetics have for extraocular muscle structure and function, including the identification of any fiber type-specific effects.

A. BOTULINUM TOXIN

Clostridium botulinum produces seven serologically distinct toxins that are powerful neuroparalytic agents.[262] Botulinum toxin acts by blocking the calcium-dependent release of acetylcholine at the neuromuscular junction.[72] Scott and colleagues[251,256] first documented the potential use of pharmacologic agents to weaken extraocular muscles, thereby suggesting an alternative to surgical manipulation in the treatment of strabismus. Botulinum toxin since has been used in oculomotor and abducens nerve palsy, to alleviate strabismus subsequent to surgery for retinal detachment, to reduce muscle contractures, and in endocrine myopathy.[181,251,252,255] The advantages of botulinum for the strabismus surgeon are that the toxin injection does not require general anesthesia and does not create scar tissue that is usually associated with surgery. The A serotype of botulinum toxin has emerged as the most clinically useful pharmacologic agent in the treatment of the ophthalmologic disorders of strabismus and blepharospasm,[83,153] and also in a variety of focal dystonias and in systemic neuromuscular diseases.

The typical skeletal muscle response to systemic botulism or to focal injection of botulinum toxin is denervation atrophy.[81] All muscle fiber types atrophy following onset of the toxin paralysis. Fiber size and subcellular characteristics are restored after motoneuron sprouting restablishes functional innervation.[33,81,119,127,223] The fiber type content of the orbicularis oculi muscle is similar to other skeletal muscles,[216] thus it is not surprising that limb and eyelid muscles react to botulinum in a similar manner.[119,223] This reversibility in botulinum toxin paresis[33,127,168,215,223] explains the need to repeatedly reinject orbicularis oculi muscles of blepharospasm patients. By contrast, single botulinum injections may provide permanent correction of strabismus. When injected into extraocular muscle, botulinum toxin does not produce the generalized atrophy that involves all fiber types, but instead causes specific, longterm changes in one particular muscle fiber type. Spencer and McNeer[274] have shown that the cross-sectional area and mitochondrial content of monkey orbital singly innervated fibers are permanently reduced by toxin treatment. The findings of these authors, and observations that the toxin alters passive stiffness in eye muscle,[148] argue that the fiber type-specific consequences of botulinum affect the behavior of the entire muscle. Based upon the projected function of this fiber type (see Section IV.A), reduction in the functional capacity of the orbital singly innervated fiber would produce the desired static position change to correct strabismus. The occurrence of ptosis subsequent to rectus muscle injections for strabismus has been correlated with atrophy in the levator palpebrae superioris.[278] Interestingly, the consequences of the toxin for extraocular muscle are more severe when used in infant and juvenile monkeys.[177,274,278] The fact that botulinum toxin causes more severe alterations in orbital singly innervated fibers that are still maturing (4-6 months after birth) is consistent with the notion that there is a critical period in the postnatal development of extraocular muscle (see Section III.B). The clinician must appreciate this aspect of the postnatal development of extraocular muscle since interventions during the overlapping critical periods of visual and muscular development are vital for successful treatment of strabismus and amblyopia.

B. SUCCINYLCHOLINE

Succinylcholine is a depolarizing blocker of neuromuscular transmission for typical mammalian skeletal muscle fiber types. By contrast, in extraocular muscle, succinylcholine selectively activates the multiply innervated fibers (while the global type is involved, the degree of activation of orbital multiply innervated fibers is unclear). Succinylcholine induces graded contractions that produce ocular alignment under general anesthesia that approximates that seen in the awake patient.[185] These data have been interpreted to indicate that the multiply innervated fiber types play a role in establishment of primary ocular alignment.

C. CALCIUM CHANNEL BLOCKERS

Organic calcium channel blockers, like diltiazem and verapamil, interfere with excitation-contracting coupling in cardiac and vascular smooth muscle by blocking entry of extracellular calcium. The poor development of the sarcoplasmic reticulum in extraocular muscle multiply innervated fibers suggests that the contractile process in these fibers is dependent upon extracellular calcium, rather than intracellular stores,

and thus might be antagonized by cardioactive and vasoactive calcium blockers. Jacoby and colleagues[55,133] demonstrated that reduction in extracellular calcium concentration greatly reduces the tension development in extraocular global multiply innervated fibers and tested the hypothesis that diltiazem then would alter resting eye position. Diltiazem produces a severe reduction in tension development in isolated multiply innervated fibers and causes shortterm alterations in eye position when injected into single extraocular muscles.[133] The identification of specific means to block tension development in the global multiply innervated fiber type should facilitate studies of the functional role of this fiber type in fixation and eye movements and has potential for treatment of strabismus. Thus far, data suggest that the hypothesis that multiply innervated fibers are recruited near primary position[236] is correct. However, diltiazem also may antagonize the calcium-mediated neurotransmitter release process, so a caveat must be introduced to these findings. Further exploration of calcium channel blockers in treatment of strabismus and ocular motility disorders, by specifically targeting the global multiply innervated fiber type, requires resolution of the limitations imposed by the short duration of activity of these agents. Calcium channel blockers, however, may have an ophthalmic application as an adjuvent therapy to doxorubicin in chemomyectomy of the orbicularis oculi for blepharospasm.[176]

D. LOCAL ANESTHETICS

Retrobulbar application of the aminoacyl class of local anesthetics (lidocaine, mepivacaine, bupivacaine) is widely used for peripheral nerve blocks in routine ophthalmic surgeries, including cataract procedures. Although the myotoxic effects of these agents have been known for some time,[25] it has not been generally appreciated that aminoacyl anesthetics may have consequences for extraocular muscle function. The myotoxicity of the aminoacyl anesthetics is of such significance that they have been used as a model system for studies of muscle degeneration and regeneration.[93,112,137] The undesirable effects of the local anesthetics are believed to result from sarcolemmal disruption and displacement of calcium from intracellular stores. Supraphysiologic intracellular free calcium levels trigger proteases, thereby resulting in myofilament breakdown and fiber necrosis.

That the ophthalmologic use of aminoacyl anesthetics may be accompanied by ptosis and diplopia was reinforced by studies that used direct extraocular muscle injections in an attempt to reduce the systemic toxicity of these agents in cataract surgery.[228] The subsequent development of strabismus in these patients was thought to result from a direct myotoxic action of mepivacaine and bupivacaine. Consistent with this notion, retrobulbar anesthetic injections were shown to cause significant pathology in rat extraocular muscle.[49,199] Given the skeletal muscle toxicity of these agents, it is somewhat surprising that more patients do not experience complications of ocular motility. The direct injection of single extraocular muscles may be the important factor in determining the absence or occurrence of deleterious responses. In patients suspected of having anesthetic-evoked strabismus, MRI reveals cystic enlargement, probably reflecting fibrosis caused by drug toxicity and complicated by ischemia. For some reason, the inferior rectus may be more prone to involvement, thereby resulting in a noncomitant vertical deviation that may vary depending upon the relative degree of muscle restriction versus muscle weakness. Local anesthetic toxicity as a cause of strabismus subsequent to cataract surgery is one of several mechanisms considered in a recent study.[113]

Consistent with the hypothesis that eye muscle toxicity requires direct muscle injections, retrobulbar applications of bupivacaine in a monkey model cause a severe response only in one muscle fiber type (the global pale singly innervated fiber type).[219] Since mitochondria can serve as a calcium sink, perhaps this one fiber type is involved, and all other extraocular muscle fiber types are spared, because of their mitochondrial content. Dose-related limits on this protection may explain the finding that direct injections into individiual extraocular muscle to produce more significant pathology. Muscle injections with anesthetics for diagnostic purposes[167] may not be advisable for this reason. It is clear that as yet unidentified mechanisms operate to give a significant degree of protection to primate extraocular muscles such that they do not exhibit the pathology seen in other muscles. The differential involvement of extraocular versus other skeletal muscles in local anesthetic toxicity correlates with, and may be a direct result of, the different fiber type composition of these muscle groups. Since local anesthetic toxicity invokes calcium-mediated cell damage, the relative sparing seen with these agents may be related to the response of extraocular muscle in Duchenne muscular dystrophy (Section VI.B).

VI. Response to Disease and Manipulation

This section reviews literature pertaining to alterations in extraocular muscle by specific disease entities or clinical/experimental manipulations. The focus is upon a variety of common states in which the eye muscle response is novel. Borchert[36] has reviewed the extraocular muscle consequences of rarer ocular mitochondrial cytopathies, dystrophies, and myopathies, and the reader is referred to this source for review.

A. MYASTHENIA GRAVIS

Myasthenia gravis is an autoimmune disorder that specifically targets acetylcholine receptors at the neuromuscular junction. Antibody-receptor interactions block neuromuscular transmission and subsequently destroy the receptor complex. The extraocular muscles are particularly vulnerable in myasthenia patients, with ocular symptoms that include ptosis and diplopia appearing early in onset of the disease.[65,74,140,270] It is well documented that central adaptive mechanisms operate to partially compensate for weakened muscles in myasthenics;[249] motoneuron gain increases help to offset inconsistencies in neuromuscular transmission. However, the differential involvement of extraocular muscle, or muscle fiber types, in myasthenia is controversial.

The advanced, and sometimes exclusive, involvement of the extraocular muscles in myasthenia gravis has been attributed to differences in the acetylcholine receptor types expressed in extraocular versus typical skeletal muscles.[128,195,196,203] The two identified acetylcholine receptor isoforms are developmentally regulated and are comprised of α, β, and δ subunits plus either γ or ε subunits in the stoichiometry $\alpha_2\beta\gamma\delta$ (embryonic) or $\alpha_2\beta\varepsilon\delta$ (adult). In typical skeletal muscle, the establishment of functional innervation serves to signal the replacement of the γ subunit of the embryonic isoform by an ε subunit to yield the adult isoform. By contrast, adult extraocular muscle retains expression of the embryonic acetylcholine receptor isoform, most likely at the neuromuscular junctions of the multiply innervated fiber type(s).[140,196] Since myasthenics may exhibit antibodies that preferentially bind to the neuromuscular junction of either the singly or the multiply innervated fiber type,[196] the differential involvement of extraocular muscle may relate to the specific compromise of neural transmission in the multiply innervated fiber. (It is not yet clear whether this autoantibody appears early in the course of the disease, thereby producing early onset of ocular symptoms, or if one or both of the multiply innervated fiber types are involved.) The presence of only the antibody to the embryonic acetylcholine receptor in ocular myasthenics may explain why many are seronegative on routine testing. However, there is no stereotypical pattern of extraocular muscle involvement in ocular myasthenia. A hypothesis that invokes the targeting of multiply innervated fibers in ocular myasthenia is consistent with the expected ocular motility disorders[296] and with the outcome of computer modeling of the consequences for eye movement control.[1] However, while the positional deficit causing diplopia in ocular myasthenics is consistent with the hypothesis that multiply innervated fibers are recruited near primary position and aid fixation,[236] the early detection of ptosis is problematic since the levator palpebrae superioris does not contain either of the multiply innervated fiber types (see also Section II.B.4).[216] Thus, the early or exclusive involvement of extraocular muscle in myasthenia gravis might be related as much to sensitivity resulting from their normally high activation rates as to acetylcholine receptor properties that are peculiar to this muscle group.

B. MUSCULAR DYSTROPHY

The muscular dystrophies are a group of genetically determined disorders that are characterized by progressive degeneration of muscle tissue with no associated morphological abnormalities in the peripheral or central nervous system.[79] Oculopharyngeal dystrophy specifically alters oculomotor and pharyngeal motor function, but the sequelae for the extraocular muscles are poorly understood. Duchenne muscular dystrophy is an X-linked recessive disease that results in widespread, progressive degeneration of axial and appendicular skeletal muscle, as well as smooth and cardiac muscle.[51,194,246,293] The genetic defect leads to a deficiency of a subsarcolemmal protein known as dystrophin.[126] Consequently, it is proposed that dystrophin is a link between the cytoskeleton and the basal lamina and, therefore, may play a critical role in maintaining the integrity of the sarcolemma.[46,85,130]

A characteristic feature of dystrophin deficient muscle fibers is a significant elevation in intracellular free calcium levels both at rest and following stimulation.[20,92,287,288] This elevation is noted in fibers prior to any morphological evidence of degeneration.[27] The cause for this elevation is thought to be due to either a disruption of sarcolemmal integrity, and/or to an increase in the

probability of opening of voltage-independent, calcium-specific "leak" channels that have been reported in the sarcolemma of myotubes.[76,92] Dystrophin, therefore, is thought to directly or indirectly play a role in maintaining sarcolemmal integrity and/or in regulating the calcium "leak" channels.

Despite the progressive degeneration of muscle tissue that occurs throughout the body in this disease, the rotatory extraocular muscles appear to be spared. Clinical eye examinations on late stage Duchenne patients have revealed the absence of both nystagmus and significant eye movement deficits.[139] The presence of normal saccade metrics in these patients suggests that, unlike all other skeletal muscles, the extraocular muscles may not exhibit the pathology that characterizes this disease. Hence, although dystrophin is absent in the extraocular muscles, morphological studies in animal models of Duchenne's have reported the absence of the focal areas of degeneration and regeneration that are seen in other muscles.[141,224] Our detailed analyses of the mdx mouse, the accepted model of Duchenne's, have revealed that features of the six fiber types are indistinguishable from controls.[226] Evidence of frank degeneration, followed by replacement with regenerated fibers, is not seen in the extraocular muscles. However, the retractor bulbi muscles, which also lack dystrophin, do undergo a degenerative/regenerative cycle which continues until approximately one-half of the fibers have centrally located nuclei by postnatal day 120.[141] Consequently, in extraocular muscle, adaptive compensatory mechanisms capable of dampening the effects of the degenerative processes may have developed and, therefore, total disruption of cellular integrity is circumvented. One potential mechanism for protection might be the higher capacity of extraocular muscle to scavenge free radicals. The results of preliminary studies have suggested that superoxide dismutase activity may be considerably higher than in other skeletal muscles.[227] This finding therefore suggests that extraocular muscle may be more efficient in removing the free radical superoxide anion.

C. THYROID DISORDERS

Graves' disease is an autoimmune disorder generally characterized by hyperthyroidism. Autoantibodies act on the thyroid follicular cell thyrotropin (TSH) receptor, stimulating iodination of thyroglobulin and synthesis of thyroid hormone by activating the adenyl cyclase-cAMP second messenger system. Consequently, circulating thyroid hormone levels are elevated, whereas TSH levels are reduced by means of a negative feedback system involving the hypothalamic-pituitary axis.[152] It is not known if this thyroid-related pathology is responsible for the ophthalmopathy frequently associated with Graves' hyperthyroidism. There is much speculation, however, about the existence of an autoantigen coexpressed in the thyroid gland and the orbit. The recognition of such a molecule by circulating lymphocytes would result in the propagation of the immune response, providing the link between Graves' hyperthyroidism and ophthalmopathy. Two likely candidates for the hypothetical antigen include the thyrotropin receptor and a 64 kDa protein coexpressed in thyroid and eye muscle.[89a,244]

Most of the signs and symptoms of Graves' ophthalmopathy can be explained by the mechanical effects of increased tissue volume within the orbit. Fells and colleagues[89b] have recently reviewed the pattern of histopathological changes that occur in extraocular muscle in association with Graves' hyperthyroidism. This condition primarily results from the enlargement of the extraocular muscles due to an abnormal accumulation of glycosaminoglycans in the connective tissue of the endomysium and orbital fat. Reports that the sarcomeric organization of the muscle fibers remains intact suggest that the primary pathogenesis of Graves' ophthalmopathy does not specifically target extraocular muscle fibers.[129,284] Alterations in these muscles may be secondary to elevated intraorbital pressure, compounded by the absence of any orbital lymphatic drainage. In this scheme, injury is provoked instead by an immune response mediated by activated fibroblasts. By contrast, other reports suggest that extraocular muscle fibers proper may be targeted by cell-mediated cytotoxicity in Graves' ophthalmopathy.[28,292] Finally, the high levels of triiodothyronine (T_3) receptor in some eye muscle fiber types[250] may be responsible for the demonstrated effects of hyperthyroidism upon these muscles.[289]

The pathogenic mechanism underlying Graves' ophthalmopathy most likely involves circulating T cells directed against an antigen on thyroid follicular cells recognize this same antigen on orbital fibroblasts. After orbital infiltration by T cells, these activated CD4 cells secrete various cytokines into the surrounding tissue.[11,12] Heufelder, Bahn, and colleagues have provided important mechanistic evidence regarding the

role of cytokines and orbital fibroblasts in the pathogenesis of Graves' disease,[121-125] although their in vitro studies do not provide conclusive information for disease in man. These studies have shown that interferon gamma, interleukin 1 alpha, and tumor necrosis factor are present in the orbital connective tissue of patients with ophthalmopathy and act preferentially on orbital fibroblasts to stimulate their proliferation as well as glycosaminoglycan production.[121,122,123,180] These effects ultimately lead to the accumulation of glycosaminoglycans, an elevated connective tissue volume, and fibrotic restriction of extraocular muscle movement. Cytokines also stimulate certain immunomodulatory proteins in the orbit responsible for perpetuation of the immune response. Human leukocyte antigen (HLA-DR) is crucial to antigen recognition by T cells. Recent evidence suggests that HLA-DR is expressed in orbital fibroblasts from patients with Graves' ophthalmopathy, but not in normal subjects.[122,123] Furthermore, orbital fibroblasts are more sensitive to the induction of HLA-DR after treatment with interferon gamma than abdominal fibroblasts.[124] Intercellular adhesion molecule 1 (ICAM 1) is also expressed in orbital fibroblasts and its expression can be induced in vitro by the cytokines listed above.[122] ICAM 1 expression in orbital fibroblasts can also be stimulated by administration of serum immunoglobulins from patients with severe ophthalmopathy.[121] Another immunomodulatory protein possibly involved in the pathogenesis of Graves' disease is a 72 kDa heat shock protein which has been detected on the cell surface of cultured orbital fibroblasts.[125] Heat shock proteins act to stimulate cell proliferation and cell protection against stressful stimuli in addition to their role in antigen presentation in association with HLA-DR. Interactions between these immunomodulatory proteins and the regulation of their expression may control the orbital infiltration and targeting by T cells.

D. CHANGES AS A CONSEQUENCE OF STRABISMUS, MUSCLE DENERVATION, AND STRABISMUS SURGERY

Disruption of the length-tension relationships in the extraocular muscles is an inevitable consequence of both strabismus and the surgical correction of strabismus. Clearly, static muscle length changes require the operation of adaptive mechanisms that reestablish optimal sarcomere length. The division of labor among multiple motor unit types would lead one to the expectation that pathology or adaptive changes might involve particular muscle fiber types. Yet, with some exceptions, it is difficult to decipher a clear pattern in the literature regarding the pathologic or adaptive changes that occur in these muscles.[26,161,169,170,272,273] The development of muscle structure-function models of strabismus has been hindered as many prior morphopathological studies changes have not been specific as to particular fiber type involvement. In addition, it is not clear as to whether the alterations in muscle structure are a primary cause or a secondary consequence of strabismus.

Paralytic strabismus has the potential to produce both denervation atrophy in one muscle and adaptation to decreased muscle length in the antagonist. Botulinum toxin, as discussed above (Section V.A), causes a transient denervation of extraocular muscle, but induces permanent fine structural reorganization in a one-muscle fiber type. Changes in the mitochondrial content and cross-sectional area of this fiber type have been interpreted to reflect the important role of the orbital singly innervated fiber type in maintenance of eye position (see Section V.A).[274] Similarly, the denervation and subsequent reinnervation of extraocular muscles via nerve transection a) produces less atrophy than would be expected in a skeletal muscle, b) exhibits a reduction of mitrochondria from the orbital singly innervated fiber type not unlike that seen with botulinum, and c) does not show the postparetic fiber type grouping that typifies reinnervated skeletal muscle.[17,59,217] Fortuitously, the botulinum-induced reduction in the contractile force and fatigue resistance of the orbital singly innervated fiber type is precisely the manipulation that the strabismologist would need to effect a static eye positional change. Along these same lines, the finding of developmental aberrations in the orbital singly innervated fibers of a monkey strain that is prone to strabismus[213] further supports the notion of involvement of this fiber type in strabismus.

Alterations in the shortened antagonistic muscle in strabismus are perhaps best documented by observations of resected muscles in overacting inferior oblique.[272] These authors have shown specific changes in the global intermediate singly innervated fiber type, including central aggregation of mitochondria. While alterations were confined to one particular fiber type, their interpretation is difficult as this pathology is seen in a variety of ocular motility disorders. Perhaps the most significant difficulty that blocks a thorough understanding of muscle pathology in strabis-

mus is the absence of the orbital muscle layer from the distal segment of the muscle. Since the orbital layer is constantly active in maintenance of eye position, and thus likely involved in strabismus, the inability to sample it in typical resections from positional disorder cases leaves a significant gap in the literature.

Finally, there is limited information regarding the consequences that resection and recession of extraocular muscles may have for myofiber contractile efficiency. Following adductor muscle weakening, lateral rectus muscles undergo a transient reduction in twitch tension, with restoration to control values by six weeks after surgery.[63] These data are consistent with the operation of adaptive processes at the myofiber level. Recently, Guyton and Weingarten[111] suggested that sarcomeric adaptation may play an important role in longterm ocular realignment and maintenance of orthophoria. Hypothetically, changes in muscle length at rest require corresponding changes in the number of sarcomeres in muscle fibers or else the sarcomeric overlap of actin and myosin filaments would not be optimal and muscle length-tension curves likely would be nonlinear. While there is evidence for adjustment of sarcomere length/number in other motor systems, there has been only limited exploration of this issue in the oculomotor system.[60,253]

E. MUSCLE REPLACEMENT AND AUGMENTATION

The introduction of completely new motor units is a potential means of restoring contractility in the vector plane of a paretic muscle. Procedures for the restoration of function in dystrophic or weakened skeletal muscle take two forms: a) grafting of an entire muscle or muscle segment, and b) transfer of muscle precursor cells. Both techniques have been used to improve function in limb muscles and in the muscles of facial expression (using grafts[117,118,197] or myoblast transfer[187,188,207]). Although these techniques have considerable potential for the treatment of ocular myopathies, their applicability for paralytic strabismus and ptosis has received only limited attention. In some cases, the insertion of noncontractile material as a muscle replacement or to lengthen existing muscle has potential. This section explores a variety of means for augmenting or replacing extraocular muscle.

1. Muscle Grafts

Several investigators[88,104,105,131,146] have reported successful regeneration of nerve guided by the basal lamina of skeletal muscle. New muscle fibers also may grow in freeze-killed muscle grafts.[188] Muscle regeneration is at least partially dependent upon an intact basal lamina serving as a scaffolding.[5] Thus, extraocular muscle might regenerate within freeze-killed or fresh matrices derived from extraocular or other skeletal muscle. We currently are investigating the ability of such grafts to support new extraocular muscle growth.[15,18,19,57,58,62] Axon-depleted nerve sheaths provide an excellent matrix for extraocular muscle growth, allowing the growth of muscle fibers up to 2 cm in length within 12 weeks.[16,18] The ability to grow muscle prior to transplantation could give greater flexibility to the site of tendon attachment in transposition procedures and allow the lengthening of muscle with contractile material or permit the growth of extraocular muscle grafts for transplantation to the vector plane of paretic muscles. Work is underway in our laboratory to find a suitable biodegradable polymer to use as a support matrix for growing extraocular muscle fibers in vitro.

2. Myoblast Transfer

Skeletal muscle retains a regenerative potential in the adult by sequestering a stem cell population, satellite cells, within the basel lamina of intact muscle fibers in order to cope with injury and/or normal degenerative processes.[5,163,172] Once activated, satellite cells proliferate and fuse to generate myotubes that will form adult fiber types. Myoblast transfer therapy attempts to exploit the regenerative capacity of satellite cells. The utilization of myogenic cells in therapeutic procedures is an extension of the idea of tissue grafting in the treatment of disease.

The development of in vitro systems to selectively culture satellite cells has made it possible to grow large numbers of muscle precursor cells that are suitable for transfer to myopathic muscle tissue. Myoblast transfer therapy has been used to improve muscle function in several models, including the phosphorylase kinase deficient mouse, the mdx mouse, and the golden retriever muscular dystrophy model.[142,157,187,207] Based upon success in these animal models, attempts have been made to use myoblast transfer in Duchenne muscular dystrophy. The rationale is that genetically competent nuclei will either replace or augment dystrophic muscle nuclei that fail to synthesize dystrophin. Myoblasts derived from the parents of children with Duchenne muscular dystrophy can be incorporated into and improve skeletal muscle function,[156] al-

though the clinical efficacy of these studies has been seriously questioned.

The techniques that have been developed for systemic Duchenne dystrophy may, in fact, better serve the focal myopathies such as congenital ptosis. The unique properties of the oculomotor system, including the ease of vascularization of muscle grafts,[16] the relatively invariant load created by the globe, and the focal nature of strabismus and ptosis, support the notion that this system could benefit from myoblast transfer. Recently, we have demonstrated that transplanted myoblasts can be incorporated into existing and/or new muscle fibers within weakened levator palpebrae superioris muscles.[14] The unique fiber composition of the extraocular muscles may be an important consideration for myoblast transfer techniques that rely upon precursor cells derived from other skeletal muscles. Are precursor cells derived from any skeletal muscle capable of serving as an adequate structural and functional replacement or will only other extraocular muscles suffice as a myoblast source? The satellite cell population is not homogeneous,[89] and the fiber types that may be formed by myoblasts derived from other skeletal muscles and their functional contribution to extraocular muscle function represent significant questions that remain to be answered before this type of therapy can be exploited.

3. Muscle Extensions

Achieving an acceptable balance between correction of ocular deviations and reduction of function in the remaining active muscle is sometimes impossible with a simple recession procedure. A large retro-equatorial recession may seriously weaken the recessed muscle, particularly in the field of gaze toward the side of the recessed muscle, so that a limitation of ductions results. In an attempt to improve surgical outcome, natural or synthetic materials have been implanted to lenthen the tendon of an extraocular muscle. This procedure functionally lengthens the muscle, increases the arc of contact, and shifts the length-tension relationship (by decreasing the stretch on the contractile elements). Together, this lessens the force that the muscle exerts on the globe in the primary position, while still allowing rotation of the globe into the field of action of the operated muscle.

Bowen and Dyer[37] were the first to develop a dacron mesh artificial tendon for extraocular muscle. Ocular motility in animals receiving implants appeared normal but the authors commented that this was difficult to assess. However, they thought that the implant adhesions they observed might hinder function by limiting the range of ocular motion. More recently, Chekhova[52] has used dura mater grafts in convergent and divergent paralytic strabismus. Grafts (human dura obtained post mortem) were used to treat 26 patients over a 15-year period. Although graft efficacy was good, the authors did not specifically address the issue of amount of rotation in the direction of action of the lengthened muscle compared to that seen in a simple recession procedure. In summary, while muscle extension procedures may have value in a variety of clinical settings, it is not yet clear whether such implants perform as theorized.

4. Muscle Replacement

The strength and compliance characteristics of silicone make it potentially useful in the replacement of paralyzed extraocular muscles, as well as in the lengthening of overactive antagonist muscles. Collins and colleagues[67] investigated the use of silicone rubber bands for replacement of paretic lateral rectus muscles. They believed this would "permit less postoperative drift than the traditional resection of a paralyzed natural muscle." One prosthesis was substituted for a transposition procedure (insertion between the bodies of the superior rectus muscle and the inferior rectus muscle, passing beneath the paralyzed lateral rectus muscle). Another silicone prosthesis was used to connect the insertion site of the lateral rectus muscle and the lateral orbit, reportedly producing alignment, useful abduction, and fusion. Quantitative evaluations of the efficacy of this type of prosthesis on ocular motility have not been published.

F. MUSCLE NEUROTIZATION AND ELECTRICAL STIMULATION

1. Re-establishment of Muscle Innervation

Under normal circumstances, complete recovery from paralytic strabismus occurs only following nerve regeneration. For this reason, techniques designed to establish reinnervation where it has not occurred naturally have attracted attention. Two methods of reinnervating paretic extraocular muscles have been attempted: secondary muscular neurotization and secondary neural neurotization. Secondary muscular neurotization inserts the cut edge of a muscle, with its intrinsic nerve fascicles, into a denervated muscle. The severed, preterminal motor nerves of the anastomosed muscle are intended to grow

into and reinnervate the paretic muscle. Secondary neural neurotization involves the reinnervation of paretic muscle by implantation of a neuromuscular pedicle from a nearby, expendable and healthy muscle. The transposed muscle segments degenerate, leaving the intact nerve terminals, rather than severed axons, to sprout and innervate the palsied muscle.

Aichmair[4] reported successful reinnervation after muscle anastomosis into denervated rabbit extraocular muscle, but the extent to which recovery was the result of secondary muscular neurotization or simply the recovery of the original nerve is unclear. In patients, limited success was obtained with transposition of a healthy inferior oblique muscle to a paralyzed lateral rectus muscle.[4] Experimental preparations in our laboratory that better controlled for regeneration of the original innervation showed only limited reinnervation in the vicinity of the anastomosis site only.[62] The failure to detect motor end plates more than a few millimeters from the attachment site and atrophic appearance of most muscle fibers together suggest that muscular neurotization procedures require further refinement.

Secondary neural neurotization may have the theoretical advantage that sprouting, rather than axon regeneration, is required for reanimating a paretic muscle. Experimental studies suggest that this procedure might be effective in restoring function to paretic eye muscles.[107]

In summary, at this time, secondary neurotization cannot be recommended as a therapeutic alternative in paretic strabismus, but the idea has merit and further work may demonstrate a role for this procedure.

2. Restoration of Function with Implanted Stimulators

Electrical stimulation has been studied as a means of providing muscle contraction to produce purposeful eye movements. Such an approach is difficult to implement because it requires a sophisticated servomechanism with eye position feedback. However, electrical stimulation of the extraocular muscles might be used to induce tonic contraction and muscular hypertrophy in paretic muscles. Chen et al[53] suggested that electrical stimulation of extraocular muscle might produce anatomical changes that, in turn, restore a more normal muscle balance in the strabismus patient. There is, however, little experimental evidence to support the possibility that electrical stimulation will affect atrophy in denervated muscle. Two recent attempts to explore the utility of implanted stimulation devices are discussed below.

Robins[233] has evaluated electrical stimulation techniques for the production of eye movements. Isotonic displacement and isometric force changes were evaluated in cat extraocular muscle during variation of the stimulation parameters of electric pulse rate and width, time, current, and preloads. Large saccadic eye movements could be produced in cats with intact innervation under ketamine anesthesia.[232] This research demonstrated that a fairly large range of ocular motion is possible with electrical stimulation. Friedman[94,95] developed an electro-ocular stimulation unit. This unit uses an external loop antenna positioned over a radio frequency receiver implanted subcutaneously at the temple. The receiver is connected to platinum/iridium electrode disks which conform to the shape of the extraocular muscle. This type of unit was intended for muscle exercise in cases of pediatric strabismus with intact innervation but decreased motility. Further research possibilities include the development of a smaller implantable electronic chip receiver/stimulation unit.

VII. Conclusions

The extraocular muscles are not typical skeletal muscle (for a summary comparison of the two muscle groups, see Table 2). For example, not all fiber types propagate action potentials and highly fatigue-resistant fiber types also may have fast twitch characteristics. Thus, the traditional fiber type classification schemes cannot be applied to these muscles, nor can assumptions regarding their structure and function be based solely upon data from other skeletal muscles. The extent to which differences between extraocular and typical skeletal muscle result from genetic or epigenetic factors is not yet clear. The unique muscle fiber types in the eye muscles and the timing of their differentiation and maturation do require careful consideration in the development and implementation of treatments for strabismus and amblyopia. In addition, the properties of extraocular muscles and motoneurons may explain the predisposition or sparing of this muscle group in disorders such as Duchenne muscular dystrophy, myasthenia gravis, and Graves' disease. The determination of mechanisms that are responsible for differential involvement of extraocular muscle in various neuromuscular disorders or clinical/experimental manipulations may contribute to knowledge of the etiology and treatment of both ocular and systemic disease.

TABLE 2

Key Differences Between Oculomotor and Skeletomotor Muscle Systems

Characteristic	Extraocular Muscle	Limb Muscle
Embryonic origin	Prechordal/somitomere mesoderm	Somite mesoderm
Fiber types	Atypical, six types that are unique to this muscle group	Three traditional types that are seen in most muscle groups
Innervation pattern in adult	Singly and multiply innervated	Singly innervated exclusively
Mode of contraction	Twitch and non-twitch fibers	Twitch fibers only
Fatigue resistance	Highest of any skeletal muscle	Varies from muscle to muscle
Stretch reflex	Absent	Present
Functional diversity[a]	Individual muscles have a wide dynamic range	Individual muscles serve either postural, gross movement, or fine control functions
Response to axotomy	Limited atrophy, type grouping not seen	Severe atrophy, type grouping with reinnervation
Botulinum toxin denervation	Mild atrophy, lasting fiber type-specific effects	Severe atrophy, completely reversible
Local anesthetic toxicity	Mild, fiber type-specific response	Degeneration of all fiber types
Changes in:		
Muscular dystrophy[b]	Refractory	Cyclic degeneration/regeneration
Myasthenia gravis	Earliest affected muscle group	Become involved later, if at all
ALS[c]	Spared until late	Severe, hallmark of the disease

[a]Indicator of the diversity of functional tasks assigned to individual muscles.
[b]Duchenne muscular dystrophy; eye muscles are specifically targeted in oculopharyngeal dystrophy.
[c]Amyotrophic lateral sclerosis; involvement of extraocular versus limb muscles reflects different sensitivity at the motoneuron level.

Taken together, the singular properties of the extraocular muscles should be regarded as an opportunity for specificity in targeting treatment of neuromuscular diseases that affect ocular motility. Such an opportunity for therapeutic breakthroughs can be exploited only if based upon a thorough understanding of the structure and function of this unique muscle system.

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Outline

I. Oculomotor physiology
   A. Basic concepts of the motor unit
   B. Functional types of eye movement
   C. Brainstem physiologic correlates of eye movement
   D. Feedback control of eye movement
II. Extraocular muscle anatomy
   A. Gross anatomy
   B. Cellular organization
      1. Introduction
      2. Traditional muscle fiber type classification
      3. Extraocular muscle fiber types
      4. Accessory extraocular muscles
III. Embryology
   A. Muscle origin
   B. Myogenesis
   C. Genetic regulatory factors
   D. Epigenetic regulatory factors
IV. Specificity of function in extraocular muscle
   A. Division of labor among extraocular muscle motor units

B. Operational properties of extraocular muscle
V. Pharmacology and toxicology
A. Botulinum toxin
B. Succinylcholine
C. Calcium channel blockers
D. Local anesthetics
VI. Response to disease and manipulation
A. Myasthenia gravis
B. Muscular dystrophy
C. Thyroid disorders
D. Changes as a consequence of strabismus, muscle denervation and strabismus surgery
E. Muscle replacement and augmentation
1. Muscle grafts
2. Myoblast transfer
3. Muscle extensions
4. Muscle replacement
F. Muscle neurotization and electrical stimulation
1. Re-establishment of muscle innervation
2. Restoration of muscle function with implanted stimulators
VII. Conclusions

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