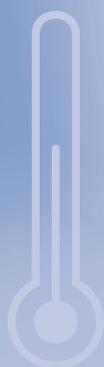


RAPPORT RAPPORT

Neuromuscular organisation of mammalian extraocular muscles

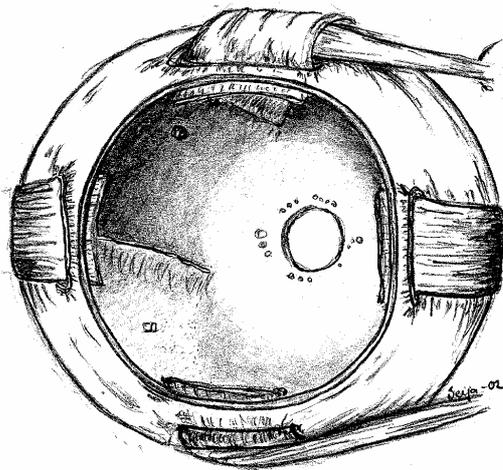
Inga-Britt Kjellevold Haugen (M.Phil)



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Neuromuscular organisation of mammalian extraocular muscles



Inga-Britt Kjellevoid Haugen (M.Phil)

Kongsberg 2002

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CONTENTS

<u>1.</u>	<u>PREFACE</u>	4
<u>2.</u>	<u>ACKNOWLEDGEMENT</u>	5
<u>3.</u>	<u>INTRODUCTION</u>	6
<u>4.</u>	<u>LITERATURE REVIEW OF MAMMALIAN EXTRAOCULAR MUSCLES</u>	10
<u>4.1</u>	<u>MUSCLE HISTOLOGY</u>	14
<u>4.1.1</u>	<i><u>Ultrastructure and physiology</u></i>	<i>14</i>
<u>4.1.2</u>	<i><u>Fibre classification and distribution</u></i>	<i>21</i>
<u>4.1.3</u>	<i><u>Motor innervation</u></i>	<i>27</i>
<u>5.</u>	<u>LIST OF TABLES AND ILLUSTRATIONS</u>	40
<u>6.</u>	<u>LIST OF SYMBOLS AND ABBREVIATIONS USED IN TEXT</u>	41
<u>7.</u>	<u>BIBLIOGRAPHY</u>	42

1. Preface

It is vital to be acquainted with the morphological and physiological features of all the various elements composing the oculomotor control system, in order to fully comprehend the fundamentals of binocular vision. As a consequence, the various aspects of this complex system have been given substantial attention for numerous years and many studies have been undertaken to increase the pool of knowledge.

This study has been undertaken to present an overview of the effector organs of the mammalian oculomotor systems. The morphological features of the extraocular muscles and their efferent innervation have been comprehensively covered in the document. Micrographs presented in the current study, illustrating some of these histological elements, were taken under light microscopic examinations of extraocular muscles. The tissues were obtained from various species within the animal kingdom and prepared for microscopy according to standard histological procedures.

This manuscript is hence a product of thorough reviews of the existing literature, as well as histological and gross-anatomical examinations of extraocular muscles from man, sheep, cat, monkey, rabbit, guinea pig and rat. The objective of the study has been to present data regarding extraocular muscle anatomy and motor innervation, with emphasis on the ultrastructural features. Most of the information presented in the current manuscript was obtained through previous research projects undertaken by the author (Kjellevold Haugen, 2001). Recently published information has been added to provide the reader with an updated literature review. The publication will hopefully be of good use for the reader as a reference manual and facilitate the understanding of extraocular muscle morphology. Remaining constituents of the oculomotor system, are not discussed in the current document and remain to be dealt with in future publications.

2. Acknowledgement

I wish to express my gratitude to Professor J. Richard Bruenech at Buskerud College, Norway, and to Professor Gordon L. Ruskell at City University, United Kingdom, for their skilful guidance and for placing their expert anatomical knowledge at my disposal.

The financial support provided by the Buskerud College, the Norwegian Optometric Society, the Norwegian Research Institute and J.H.& M. Jansons foundation is also gratefully acknowledged.

3. Introduction

Sight is thought overwhelmingly important in the intellectual life of man and in his existence as the supreme intellectual being on earth. Vision and the function of the visual system has hence been, and still remains, one of the mysteries that have challenged human thought since the beginning of civilisation.

Of all the organs by which we acquire knowledge of the external world, the eye is by many thought to be the most remarkable and the most important. The information we obtain by our other senses is comparatively limited. Touch and taste do not extend further than the surface of our own bodies. The sense of smell is exercised within a very narrow sphere. Recognition of sounds is limited by distance. Eyes, however, enjoy a more boundless range of possibilities in their observations. Apart from the reception of light and the transformation into visualised images, the visual system is sensitive to minute changes in luminosity and has a high ability to discriminate form, movement and colour. When necessary it even activates different somatic warning systems and for the mammals possessing overlapping visual fields, the visual system provides some degree of stereoscopic vision.

The exceptional function of the visual apparatus is understood to be an expression of its specific organisation and relationships - the structural elements constituting it, the way the elements are put together, how they relate to one another and to other structures, and the influences by which they are regulated or through which they influence other parts.

According to Polyak (1957) and Albert and Edwards (1996) the interest in vision, ophthalmology, ocular anatomy and physiology goes far back in time. In ancient medicine most of the illnesses were attributed to angry spirits, sins against the gods, or human sorceresses. Of the last, those with a notable eye disorder, such as squint, were considered particularly powerful, being able to send demons in to another person's eye. The god Hathor was thought to be the protector of the eyes, but when his protection failed numerous remedies were applied, both natural and supernatural, to cure the disease.

Human dissection was rarely practised in the ancient medicine and to some degree this explains the low number of surviving anatomical records compared to the number of documents related to physiological theories from this period. The Ebers papyrus (1550 B.C), somewhat a mixture of both of these types, includes a chapter of ocular disorders, which clearly show that not only were eye problems common, but they were also given some priority. The work of Susrutas (c.1000 B.C), yet extremely brief and inaccurate, was, however, the first to introduce an anatomical description of the eye. He claimed it to be made of 6 layers, two constituting the lids and the remaining four forming the eyeball.

A somewhat more detailed description of ocular structures was found in the writings of Hippocrates (c.460-375 B.C.), the father of medicine, whose teaching refused to accept the possibility of a mystical influence in the cause and treatment of a disease. He identified the structures that later were termed sclera, cornea, iris, the ciliary body, the pupil, and the retina, and mentioned that the eye contained water which he thought functioned as a photoreceptor and originated from the brain.

The first scientific description of eye structures was by Herophilos (344 -280 B.C) who, in contrast to Hippocrates' rudimentary understanding of anatomy and physiology, had gained his knowledge by dissecting animal eyes. He came from the first school of anatomy which was in Alexandria, and together with his colleague Erasistratos, he was considered the pioneer of Alexandrian anatomy and medicine. Herophilos and Erasistratos successively included systematic morphological investigations and dissections of human bodies. They wanted to replace the existing rather sketchy anatomical descriptions with more accurate information and it has even been said that they dissected hundreds of criminals alive, delivered to them by order of the king, to confirm their anatomical results physiologically.

The most influential anatomist in the ancient world was Galen (129-201 AD), a physician who also studied anatomy at Alexandria but later worked in Rome. His dissections were based on animals rather than humans and he investigated the organisation and physiology of the central nervous system as well as every other part of the body, under both normal and pathological conditions. Despite serious errors and misinterpretations, Galen's work became the unconquerable text for

anatomy and physiology, and kept its influence on the subject over the next 1300 years.

The foundation stone of the modern anatomy, however, is by many thought to be the work of Vesalius, published in 1543. Vesalius was born in Brussels, but gained his knowledge through studies in Louvain, Montpellier, Paris and Padua. The combination of his excellent illustrations and descriptions based on firsthand experience of human dissection made his book an epoch-making publication, which rapidly replaced Galen's work as the anatomical bible.

Since then, anatomical studies of the eye have proceeded and expanded in a number of directions and specialised areas of study have evolved. Through much of the ophthalmic history, the priority of the practitioners and researchers was to fight infection and do everything necessary to preserve vision. As the development of instruments and techniques advanced, however, more sophisticated areas of research were initiated.

The understanding of the extraocular muscles (EOM) and the oculomotor system, represent one such specialisation in ocular research. Although most of the knowledge within this field comes from the 19th century and thereafter, ocular muscle motor balance was mentioned as early as in the Ebers papyrus. Later Galen described the six muscles that move the eye, and subdivided them into four muscles for horizontal and vertical movements and two for rotation. His description of the oblique muscles were, however, extremely inaccurate and his dissections of animals led him to believe that retractor bulbi existed in humans as well. A more accurate gross anatomical picture of the ocular musculature was achieved when the researchers more easily gained access to human cadavers for dissection. Falloppio, a student of the great Vesalius who also included the EOM in his work, provided the first reasonably correct and detailed description of these muscles (1561), including the superior oblique (SOM) and the levator palpebrae superioris (LPS). Furthermore he contradicted the assumption that humans have a retractor bulbi muscle.

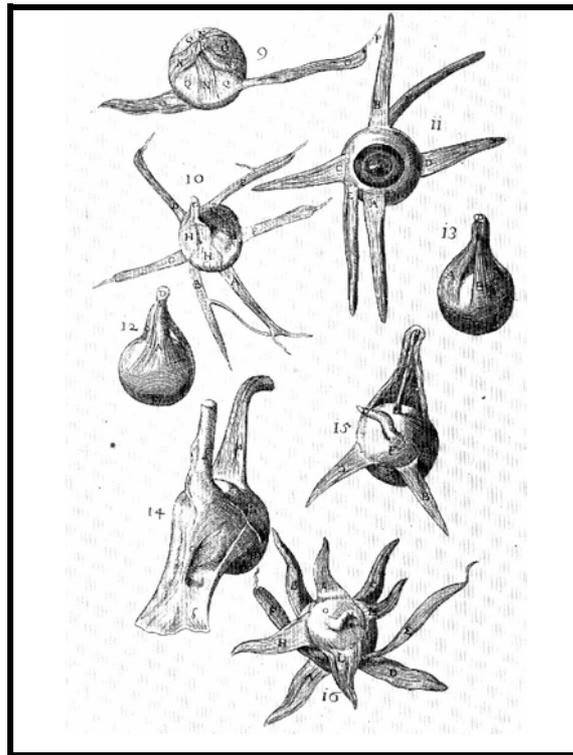


FIG. 3-1 MUSCLES OF THE EYE AS DRAWN BY FABRICIUS, A STUDENT OF FALLOPIO, IN THE 17 TH. CENTURY (THE HISTORY OF OPHTHALMOLOGY, ALBERT AND EDWARDS, 1996)

The gross anatomical observations of the eye were subsequently supplemented by histological studies as the microscope was introduced in the beginning of the 17 th. century. The study of ocular tissue under high magnification, the processes for embedding invented by Haensell around year 1860 and the application of the newly invented rotary microtome (Haensell, 1886), gave ocular research a whole new dimension; the researchers explored a novel world of minute structures never described before.

The extensive histological investigations of the mammalian oculomotor system that followed in the next centuries, and which to some extent will be presented later in this chapter, significantly increased the quantity of information available both in respect of structural and functional properties. Nevertheless, further detailed studies of the unique extraocular muscle component are still highly necessary to achieve a full comprehension of their function and the treatment of ocular motility disorders.

4. Literature review of mammalian extraocular muscles

The term extraocular or extrinsic ocular muscles embraces the elevator of the upper eyelid as well as the six muscles capable of rotating the eyeball in different directions. The presence of six oculorotatory muscles is, with few exceptions, fairly constant across the vertebrate classes. The LPS, however, which is a later delamination of the SRM without any role in the positioning of the eye, does not make its appearance in phylogeny until the mammals (Spencer and Porter, 1988).

The structural arrangements, innervation patterns, and consequently the individual actions of the muscles, show interspecies variations. As demonstrated by the different eye positions in the heads of different species; whether they are directed forwards or laterally, the differences are associated with the mammals' visual requirements, their habits and activities, as well as their method of feeding. The higher animals, especially the hunting types, usually have the eyes set well forward in the head, equipping them with a field of binocular vision, binocular fixation and a visual concentration. They tend to have less prominent snouts and interpret their environment more through their vision than their olfactory sense. In contrast, the animals with their eyes laterally placed have two dissimilar visual fields with little or no binocular overlapping. This supplies them with a much wider panoramic visual field, but makes them less suited for visual concentration. Hunted species usually have such an eye position, since it augments their universal awareness and gives them a greater area of attention.

The cat, with an angle less than 20° between its two visual axis and a visual field of 250° , and the rabbit, which has approximately 160° between the eyes and a visual field of almost 360° , are good examples of the hunting and hunted animals, respectively.

Regardless of which cranial eye position the different mammals possess or to which animal family they belong, they all have their eyes protectively placed

within a bony, almost cone-shaped cavity in the head; the orbit. Within this orbital cavity the eyeball is surrounded by fat, which together with various ligaments and numerous radially running connective tissue septa, provide an important suspensory system. The EOMs equally contribute to this anchoring and supporting system of the eyeball through their muscle tonus.

Yet the bones of the orbital walls show interspecies variations as regards to presence, size and thickness (Prince et al., 1960), they all provide several pathways through foramina for the various nerves and blood vessels involved in the function of the mammalian eye. The optic nerve, sympathetic nerve fibres, and the ophthalmic artery, enter the orbit through one of them; the optic canal or foramen. The superior orbital fissure, which is separated from the more medial optic canal by a thin strip of bone, gives the superior ophthalmic vein access to the cavernous sinus; it also transmits autonomic nerves, the third, fourth, fifth and the sixth cranial nerves. In certain species two or three of the foramina combine into one larger foramen (Prince et al., 1960). In these species the nerves and vessels are described to enter the orbit through the orbitrotundum foramen, which merely is a fusion of the orbital fissure and the foramen rotundum. The inferior fissure in the orbital floor permits the inferior ophthalmic vein to exit the cavity and ascending branches of the sphenopalatine ganglion to reach their orbital destinations.

Gross anatomical descriptions of EOM can readily be found in standard anatomical text books such as «Gray's Anatomy» (1995) and review papers such as that by Spencer and Porter (1988). Of the six oculorotatory muscles, which anatomically and functionally are arranged into three pairs, five have their tendinous origin at the orbital apex, the most proximal end of the cavity. The sixth muscle, the inferior oblique (IOM), has its origin at the medial inferior portion of the orbital rim.

The superior (SRM), inferior (IRM), medial (MRM) and lateral rectus muscle (LRM) arise from a short, funnel-shaped tendinous ring. This common origin, called the annulus of Zinn, is oval in cross section and overlies the optic canal and the medial portion of the superior orbital fissure/orbitrotundum foramen. The dural sheath of the optic nerve fuses with the periorbita of the bony rim and the

annulus of Zinn, producing a thicker area of tendon from which the SRM and the MRM arise. The LRM originates as two distinct slips from the part of the annulus covering the superior orbital fissure and the IRM from the lower, slightly medial portion of the tendinous ring. The superior oblique muscle (SOM) has its origin a little superior and medial to the annulus of Zinn, and is slightly more displaced from the tendons of its neighbouring muscles than any other EOM. The LPS arises above the optic canal and the SRM.

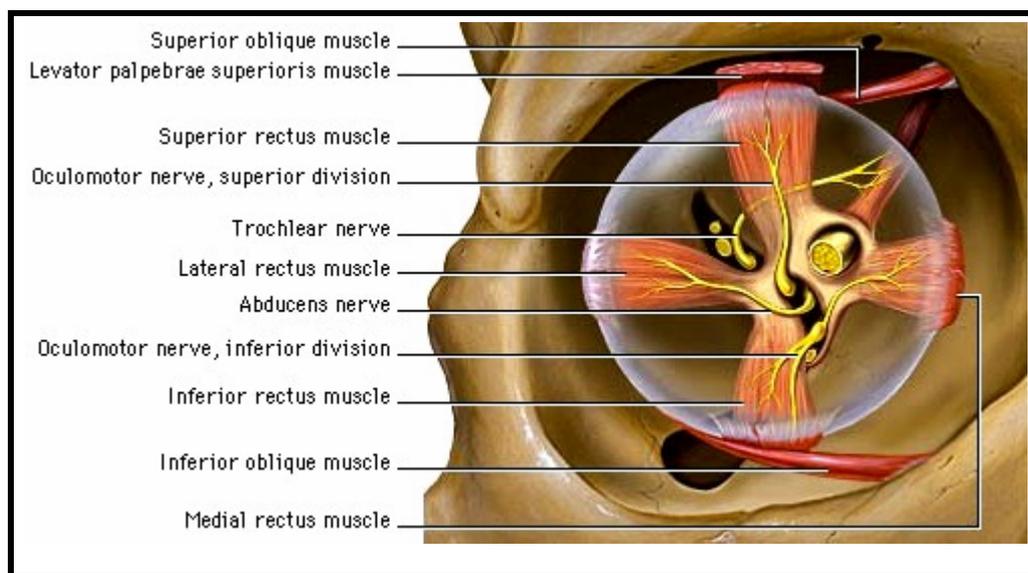


FIG. 4-1 THE ORBITAL APEX WITH THE EXTRAOCULAR MUSCLE ORIGINS (YALE CENTER FOR ADVANCED INSTRUCTIONAL MEDIA, 1998)

The recti, variable in length, course forward as rather flat narrow bands in a cone-shaped configuration. They insert at the globe with broad thin tendons, 5 to 8 mm behind the limbus, in a pattern called «spiral of Tillaux». Whilst the horizontal recti serve as the abductor and the adductor of the eye for all mammals, the vertical recti perform actions dependent upon the eyes position in the head of the animal. It is however only the secondary movements of the vertical recti that may be different in certain species. The primary actions, elevation and depression, are identical for both frontal and lateral eyed animals. The variations in secondary movements are corresponding to the interspecies difference in forward extension of the maxillary process, the angle of the visual axis and the spatial orientation of the canals (Spencer and Porter, 1988).

The slender SOM travels along the medial aspect of the orbital roof, converts into tendon as it passes through the anteriorly located fibro-cartilaginous trochlea, reflects at an angle of about 55°, and continues obliquely and laterally to insert under the SRM. As with the vertical recti, there are different arrangements and actions of the SOM in lateral- and frontal-eyed mammals. Certain lateral-eyed species have the muscle insertion anterolaterally to the central point rather than posterolaterally, which induces different secondary movements (Spencer and Porter, 1988). All species do, however, have intorsion as their predominant primary action of the SOM.

The rather thin LPS advances astride the medial edge of the SRM and ends as a broad aponeurotic expansion with insertions into the medial and lateral palpebral ligaments as well as into the upper lid. Having no insertion into the sclera, this muscle exerts no direct effect upon the globe. An indirect influence is, however, mediated by the partial blending of the levator aponeurosis and the tendon of the SRM.

The IOM, which is slightly shorter than the recti muscles, approaches the eye from the maxillary bone in the medial wall of the orbit, traverses the inferior orbit obliquely beneath the inferior rectus muscle, fans out and inserts directly or with limited tendon on the lateral aspect of the eyeball, close to the tendon of the LRM. The insertion of the IOM, like its antagonist, is posterior to the equator in frontal-eyed animals and anterior to the equator in certain lateral-eyed species. The primary action is hence extorsion for both groups, while the secondary actions vary.

The proximal tendons and the first centimetres of the muscle bulk are surrounded by thin transparent sheaths, which posteriorly, for the muscles advancing from the apex, blend with the dura of the optic nerve. A thick, opaque layer of connective tissue, continuous with the fascial sheath of the eyeball, then covers the remaining part of the muscle. Fibrous septa anchor them to the periorbita as they advance towards the globe and form an intermuscular membrane by interconnecting the various extrinsic eye muscles. All the insertions into the sclera are made by shiny tendon whose fibres run almost entirely parallel to the long axis of the muscle. The

fibres consist of collagen supported by thick elastic fibres, which in contrast to the resembling scleral fibres are well arranged in a longitudinal system rather than running in many directions. A similar organisation of the tendon fibres is present at the origins of the EOM as well.

4.1 *Muscle histology*

The microscopic appearance of the EOM is to some extent different from that of ordinary skeletal muscle tissue. This is not surprising in view of the unique and remarkable functional abilities of the ocular muscle group; the constancy of activity, their rapidity and the fine gradation of contraction. These muscles need to be more highly differentiated than any other muscle in the body, and have hence been equipped both with unique muscle fibres, a looser connective tissue envelope, a richer supply of elastic fibres, as well as a lower innervation ratio and greater vascularity than any other skeletal muscle (Gray's Anatomy, 1995).

4.1.1 *Ultrastructure and physiology*

The individual muscle is wrapped with a substantial quantity of fibrous connective tissue called epimysium, which separates the muscle from its neighbouring muscles and permits a more or less friction-free movement between them. Invaginations of the epimysium into the muscle bulk divide the muscle into bundles of muscle fibres, or fasciculi, of various sizes and patterns. These extensions of the epimysium, now called perimysium, encircle the individual bundle before they subsequently subdivide the muscle even further by penetrating into the interior of each fasciculus. These delicate invaginations, termed endomysium, finally surround and separate the multinucleated striated muscle fibres.

At the muscle origin and insertion, the muscle cells are gradually replaced by strands of tough fibrous tissue forming either closely packed bundles or sheaths of fibres.

The extensive connective tissue component of muscle tissue is essential not only in the aspect of assembling the muscle fibres into a muscle. The fibrous intercellular substance of the connective tissue also helps to transmit the force throughout the entire muscle during contraction. Furthermore, oxygen, nutrients, and innervation necessary for the vigorous function of the muscle cells, are brought by capillaries and nerves that lie between the muscle fibres in the endomysium. These were initially conducted into the interior of the muscle bulk through another part of the connective tissue; the perimysium.

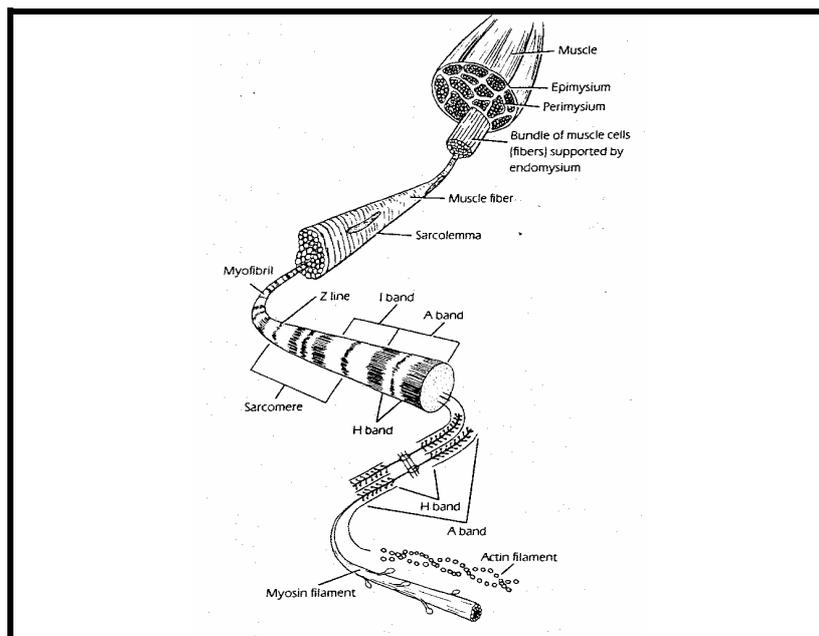


FIG. 4-2 THE STRUCTURAL ORGANISATION OF A MUSCLE (CLINICAL ANATOMY OF THE EYE, SNELL AND LEMP, 1989)

When investigated with light microscopy (LM), the immense number of cross-striated muscle fibres composing extrinsic ocular muscles, appear as closely packed cylinders, 3-50 μ m in diameter (von Noorden, 1990), with circular profiles. The individual muscle fibre may stretch from one end of the muscle to the other, but

many of them traverse only part of the length. Studies of mouse, rabbit, rat and sheep EOMs have indicated that such short fibres only are found at the end of the muscles, in the vicinity of the myotendinous regions (Pachter, Davidowitz and Breinin, 1976; Davidowitz, Philips and Breinin, 1977; Mayr, 1971; Harker, 1972). The work of Alvarado and Van Horn on cat (1975), however, revealing a higher number of muscle fibres in the central part of the muscle than in the proximal and distal portion, indicates that many of these shorter fibres terminate or arise along the course of the muscle as well, linking through so-called myo-my contacts. All muscle fibres are multinucleated and enveloped by a cell membrane, the sarcolemma, which fuses with tendon fibres at the end of the muscle cell. The nuclei are flat and elongated, up to 11µm in length, scattered in the peripheral cytoplasm, just beneath and with their long axes parallel to the cell membrane.

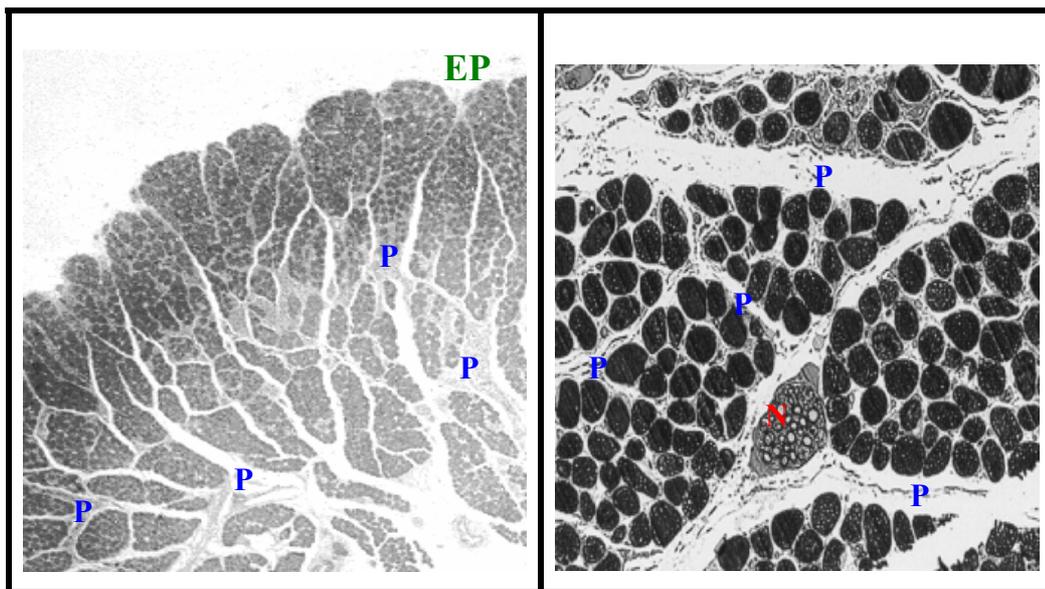


FIG. 4-3 MICROGRAPHS OF THE STRUCTURAL ORGANISATION OF HUMAN AND SHEEP (HIGHEST MAGNIFICATION) EOMS, LM/TRANSVERSE SECTION. STAINED WITH TOLUIDINE BLUE.. “E” – REPRESENTS ENDOMYSIUM, “P” PERIMYSIUM, “EP” EPIMYSIUM AND “N” NERVE

Most of the space within the muscle fibre is occupied by longitudinal and parallel running threads, myofibrils, approximately 0,1-0,5 µm diameter (Eggers, 1982). They are evenly suspended inside the muscle fibre in granular sarcoplasm, the counterpart to cytoplasm. High resolution and magnification provided by the electron microscope (EM), reveals that the individual myofibril consists of a

number of fine and longitudinally disposed elements called myofilaments. These filaments are distributed over the entire muscle length, only divided transversely into serially repeated compartments, by dark zones of dense material; Z-bands. The portion of the myofibril located between two successive Z lines is called a sarcomere.

Two types of myofilaments, chemically characterised as actin and myosin, are distinguishable in each sarcomere, the former being thinner than the other; 6 and 16 nm respectively. Their interactions and regular arrangement creates the characteristic pattern of cross striated muscles; darker and lighter transverse lines and bands along the length of the myofibril, striations that seem to continuously traverse the myofibrils across the entire muscle fibre. These dark and light stripes correspond to the regions containing thick filaments and areas containing thin filaments only. The dense band in the sarcomere, called the A band, represents the total length of the thick myosin filaments, including the parts at each end which are overlapped by actin filaments. The area in the middle of the A band; the H-zone, appearing relatively less dense, is exclusively occupied by myosin elements. A dense central line called the M-line, sometimes appears in this H-zone due to a slight increase in the diameter of each myosin filament, probably caused by a series of fine threads interconnecting the middle parts of adjacent thick myofilaments.

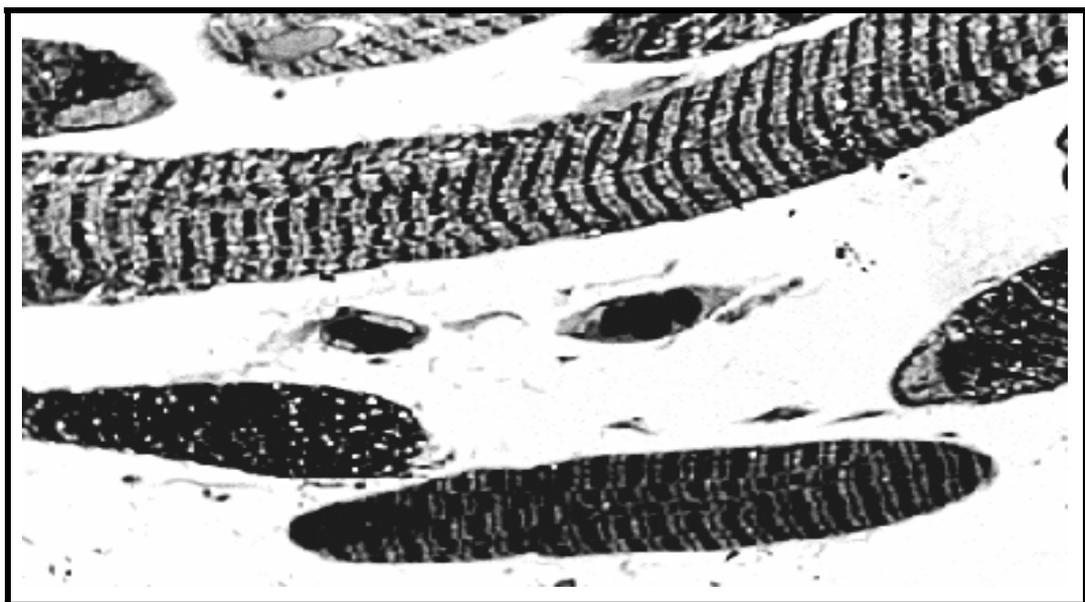


FIG. 4-4 MICROGRAPH SHOWING A LONGITUDINAL SECTION OF CAT EXTRAOCULAR MUSCLE FIBRES , LM, STAINED WITH TOLUIDINE BLUE.

The light areas in the sarcomeres, the I bands, divided by the Z-lines, are composed of thin myofilaments only. These actin filaments are anchored in the Z lines and extend on either side of it to interdigitate with the myosin filaments, which they surround in a hexagonal pattern.

The myosin filaments are large, polymerised contractile protein molecules consisting of tail, and head regions. The tails aggregate to form the thick filaments, while the heads project laterally, in a spiral pattern, to extend towards the actin filaments. In a contracting muscle these projections gain contact with the adjacent actin strands and pull the thin protein filaments between the thick ones toward the sarcomere centre by making and breaking of the interfilamental cross-connections in a cyclical fashion (Eggers, 1982; Jacobiec, 1982).

The thin but ubiquitous actin filaments, are composed of two longitudinal contractile actin threads twisted around each other in an extended helix, with subunits of globular proteins attached end to end. A second type of protein, tropomyosin B, is wound around the two strands of the helix, lying in the spiral grooves between them. At regular intervals an additional protein, troponin, is bound to the long tropomyosin B and together they exert a regulatory effect on muscle contraction, by preventing the myosin processes from interdigitating with the actin in a resting muscle. Calcium ions, which are liberated during contraction from adjacent cytomembranes, in contrast, cause the troponin to push away tropomyosin B from the actin filament, allowing the myosin to bind.

In addition to the myofibrils, the sarcoplasm of the cross-striated ocular muscle fibres contains vital organelles and cytomembranes (Eggers, 1982). Ribosomes and clusters of small glycogen granules are scattered in between the myofibrils, as are Golgi bodies, lysosomes and lipid vacuoles. A high number of mitochondria occur under the sarcolemma, between and parallel to the myofibrils, under synapses and aggregated around nuclei. An extensive intracellular system of channels; the sarcoplasmic reticulum (SR) and the T-system, is also present. The sarcolemma sends narrow, tubular invaginations to the interior of the muscle fibre, which run perpendicular to the myofibrils, branch and anastomose amongst them. These

transverse tubules forming the T-system, extend across the muscle cell at a location along the sarcomere that is species-specific; in humans it is at the junction of the I and A bands, and they contain extracellular fluid that is continuous with the fluid outside the cell. The SR consists of an abundant system of branching and anastomosing channels and sacs which fill most of the space between the myofibrils.

At the A-I junction, these irregular tubules forms small cisternae that closely abut the transverse tubular invaginations of the sarcolemma. The T-tubules and the cisternae on each side of them form muscle triads (Porter and Palade, 1957), a membranous system of channels which are thought to play a vital role in the initiation of a contraction. The close relation of the cytomembranes allow extracellular space to communicate with the intracellular channel systems. When the sarcolemma is stimulated, the T-system conducts the contraction-eliciting impulses into the depth of the fibres. The SR, which is highly developed in the more rapidly contracting types of muscles and capable of binding calcium ions to its constituent membranes, consequently releases these contraction mediating ions into the sarcoplasm surrounding the myofibrils and action potentials are propagated.

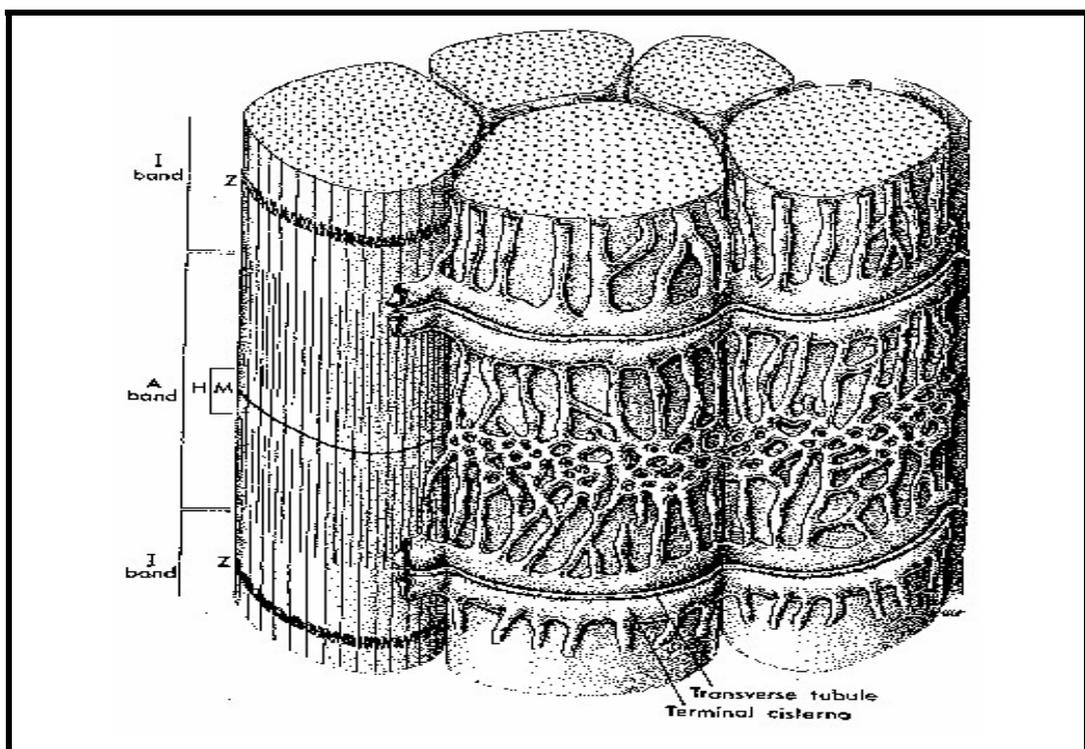


FIG. 4-5 THE MYOFIBRILS AND MEMBRANE SYSTEMS OF A MUSCLE (HISTOLOGY 8TH.ED , HAM & CORMACK)

As electrical stability returns to the sarcolemma at the end of contraction, calcium is re-bound to the SR and consequently the cross-bridges are cut between the actin and myosin filaments. Due to the presence of T-tubuli, the electrical changes are provided both along and into the fibre, enabling all parts of the fast muscle fibre to contract more or less simultaneously.

During muscle contraction the actin filaments slide in relation to the myosin towards the centre of the sarcomere, bringing the anchoring Z-bands closer together and changing the striation pattern (Eggers, 1982). The H-zone closes as the actin move over the myosin, and a new dense zone develops in the centre of the A band when approaching actin filaments overlap. As the Z lines are approaching each other, the sarcomeres and the muscle shortens, but the lengths of the thin and thick myofilaments remain the same.

The overlap between the actin and myosin filaments changes proportionally to the shortening of sarcomere length during contraction. The number of cross-links, and hence muscle force and tension, are equally dependent upon the overlap between them (Eggers, 1982). Isometric contractions, contractions without shortening of the muscle, therefore generate different tensions when performed at different sarcomere lengths. Minimal tension is generated where there exist little or no overlap of actin and myosin. The tension rises to a maximum value when the H-bands are at their minimum width, and there is a maximum overlap between the myofilaments without distortion of their arrangement. Striated muscles may, however, perform in at least three ways. Apart from the contraction at a fixed length where great tension is created on the muscle, a muscle may also effectuate an isotonic contraction and generate tension whilst being stretched. During isotonic contractions, where the muscle shortens under constant load and performs positive external work, the tension remains constant and lower than in isometric contractions. Muscle tension even decreases with increasing speed. The actin-myosin cross-bridges are the basis for a sliding of the filaments, which results in fewer active cross links and lower tension. When the filaments are stationary, as in isometric contractions, a larger number of cross-bridges make and break repetitively to maintain length of the sarcomere.

The extraocular muscles, which are exposed to a constant load, follow the same contraction patterns when moving the eyes in different directions, effectuating isometric contraction to maintain muscle tonus.

The number of muscle fibres contracting simultaneously and the tension developed within a given muscle is highly dependent upon the degree of stimulation and demand of contraction force. The sarcomere lengths and myofibrillar overlap will hence vary between the individual muscle fibres, giving identical muscle cell types quite different appearances when examined with LM.

4.1.2 Fibre classification and distribution

The wide and well described variations of the structural and functional properties in somatic musculature have generated several muscle cell classification systems. Most of them agree on the existence of three to four fibre types in typical skeletal muscle; 1) slow twitch, fatigue resistant 2) fast twitch, fatigue resistant 3) fast twitch, fatigable; and 4) fast twitch, intermediate (Gray's Anatomy, 1995). No existing classification system, however, has been able to place every single fibre in a given mammalian muscle into different categories. Intermediate variations are frequently observed, and a few muscle groups even encompass muscle fibre categories only described in sub-mammalian musculature. The extraocular muscles, which are unique both in their cellular organisation and constituent muscle fibre types, are included in this latter group.

LM examination of the unique extrinsic eye muscle fibres reveals intercellular structural differences both with respect to innervation, arrangement of myofibrils, content of organelles and amount of SR. Since functional characteristics are believed to be recognisable in the muscle cell structure, these variations indicate a presence of multiple muscle fibre types as well as cells with dissimilar physiology. The quantity of T-tubuli and SR are known to correlate with characteristics like contraction speed. The mitochondrial content and the capillary network associated

with the individual myofibres are related to fatigue resistance. Since these features are abundantly distributed in specific extraocular muscle fibres, this suggests some of the extrinsic ocular muscle fibres to be faster and able to perform longer lasting contractions than others.

Based on the structure and innervation pattern, the muscle cells fall into two basic classes. Mammalian skeletal muscles consist generally of muscle fibres that undergo an all-or-none contraction. As indicated in all four previously mentioned categories, they respond to neurotransmitter release from a single motor neuron with a rapid contraction or twitch. Acetylcholine (ACh) interacts with receptors located on the postsynaptic muscular surface, which result in a sarcolemmal depolarisation, a propagated action potential along the fibre surface with the succeeding transfer of signals into the inner cell via the T-tubular system, and finally a muscle contraction.

The twitch fibres of the EOM, representing the largest group of the extraocular muscle cells, approximately 80 %, resemble those of the skeletal muscles. They are usually large cells with a prominent SR, a well developed tubular system (Hess, 1960) and they receive their innervation from one large, heavily myelinated, rapidly conducting motor nerve. The neuromuscular junction consists of a typical motor end plate or «en plaque» ending with numerous post-junctional folds and many synaptic vesicles in the terminal axon.

The second basic type of extrinsic ocular muscle cells, the remaining 20 %, are fibres which are rarely found in general mammalian musculature. They are rather thin, with more centrally placed nuclei (Locket, 1968) and in contrast to the twitch fibres, they have multiple nerve contacts or «en grappe» endings distributed along their length. They do not fall into any of the general categories mentioned and lack the ability to propagate action potentials (Hess and Pilar, 1963). Instead of twitches, these muscle fibres undergo slow, graded contractions at each synaptic site. They exhibit the morphological and physiological properties of the multiply innervated, slow fibres more commonly found in skeletal muscles of amphibians and avians (Morgan and Proske, 1984). In mammalian muscle they are extremely rare; only demonstrated in the stapedius and the tensor tympani muscle of cat (Fernand and

Hess, 1969) as well as the oculorotatory muscles of several species, including rabbit (Krüger, 1949; Kern, 1965), guinea pig (Hess, 1961), cat (Cheng and Breinin, 1965; Hess and Pilar, 1963), monkey (Cheng and Breinin, 1965-66; Miller, 1967), sheep (Harker, 1972) and man (Dietert, 1965). These slow fibres are supplied by small diameter, unmyelinated or myelinated motor nerves (Teravainen, 1968; Pilar and Hess, 1966) with nerve terminals that in general appear to be less specialised. The bouton formed by the terminal is not as conspicuous as in the fibrillar fibre (Pilar and Hess, 1966; Hess, 1967). Post-junctional sarcolemmal folds are virtually absent or show only a few rudimentary invaginations, giving a smooth myoneural junction (Couteaux, 1955; Hess, 1960; Page, 1965). In several species the M-band is absent (Hess, 1960; Page, 1965), their fibrils are irregularly arranged and the SR as well as the T-system is less abundant compared to the twitch fibres (Krüger, 1949). The presence of multiple end plates indicates that the fibre is innervated by either multiple branches from the same nerve or by more than one nerve fibre. Since polyneuronal innervation does occur in other vertebrate musculature, and remains undemonstrated in EOM (Kupfer, 1960; Bach-y-Rita and Lennerstrand, 1975), the slow fibres are assumed to be supplied by multiple branches from one single nerve fibre.

Due to the presence of multiply innervated muscle fibres, the classification systems for somatic musculature have been found inapplicable in the description of EOM. New categorising systems have hence evolved throughout the years. Thulin (1914) was the first to describe multiple muscle fibres types in his work on human and monkey EOM. The original subdivision of the EOM fibres, however, was by Kato (1938), who divided them into large and small diameter fibres. Based on the light microscopical appearance of their myofibrillar arrangement and their resemblance to already well described muscle cells, Siebeck and Krüger (1955) elaborated the classification system further and named the large and small extraocular muscle fibres *fibrillenstruktur* and *felderstruktur* fibres respectively. Hess (1961) was, nevertheless, the first to actually confirm the presence of two distinct morphologic fibre types by studying extrinsic eye muscles of guinea pigs using the electron microscope. In 1963 Hess and Pilar observed them in cat and correlated the

anatomic findings with the physiologic evidence of the fast and tonic contractile activity in EOM. The fibrillenstruktur fibres were associated with the rapid phasic movements, and the felderstruktur fibres to the tonic type of sustained contraction. The EM work by Peachey and Huxley (1962), and Page (1965) emphasised the physiologically important intercellular differences and confirmed that the transverse system and the triads are absent in the latter muscle fibre type.

Further ultrastructural studies on rabbit (Kern, 1965; Cheng-Minoda et al., 1968), cat (Pilar and Hess, 1966), humans (Dietert, 1965) and monkey (Cheng and Breinin, 1966; Mayr et al, 1966), demonstrated that EOM fibres are not so easily divided into two morphologic groups as these earlier studies suggested, neither can function be so easily correlated with anatomy. The fibrillenstruktur fibres and the felderstruktur fibres were hence subsequently subdivided further, according to their various parameters of internal cell structure and in terms of topographical localisation within the oculorotatory muscles. Peachey (1971) suggested a classification system, largely based on descriptions of EOM in monkey (Miller, 1967) and rat (Mayr, 1971), which still is frequently applied. He divided the oculorotatory muscle fibre population into five or six types; three singly innervated muscle fibre types and two multiply innervated types, with an additional intermediate singly innervated fibre as a tentative sixth category, and used parameters like innervation pattern, location (orbital or global layer) and colour (red, intermediate or white) for identification.

Studies that followed on sheep (Harker, 1972), rabbit (Chiarandini and Davidowitz, 1979), cat (Alvarado and Van Horn, 1975) and monkey (Spencer and Porter, 1981) not only consistently demonstrated five to seven fibre types with distinctive ultrastructural features, but also introduced other classification systems. These systems are current and use cellular characteristics like size, mitochondrial number, fibrillar size, banding pattern, and development of SR to define the EOM cell type. Some of them even include parameters from the longitudinal plan (M and Z lines) and histochemical profiles (Lennerstrand, 1981) in the attempt to

categorise the various extrinsic ocular muscle cells. Age-related variations (Miller, 1975), differences between species (Barker, 1974), and reports of systematic morphological variations along the length of some rat and rabbit muscle fibres (Mayr, 1971), have been arguments for the need of additional sub-groups. The systems using five to six categories for muscle cell identification are, nevertheless, still found sufficiently applicable and represent the most used systems today.

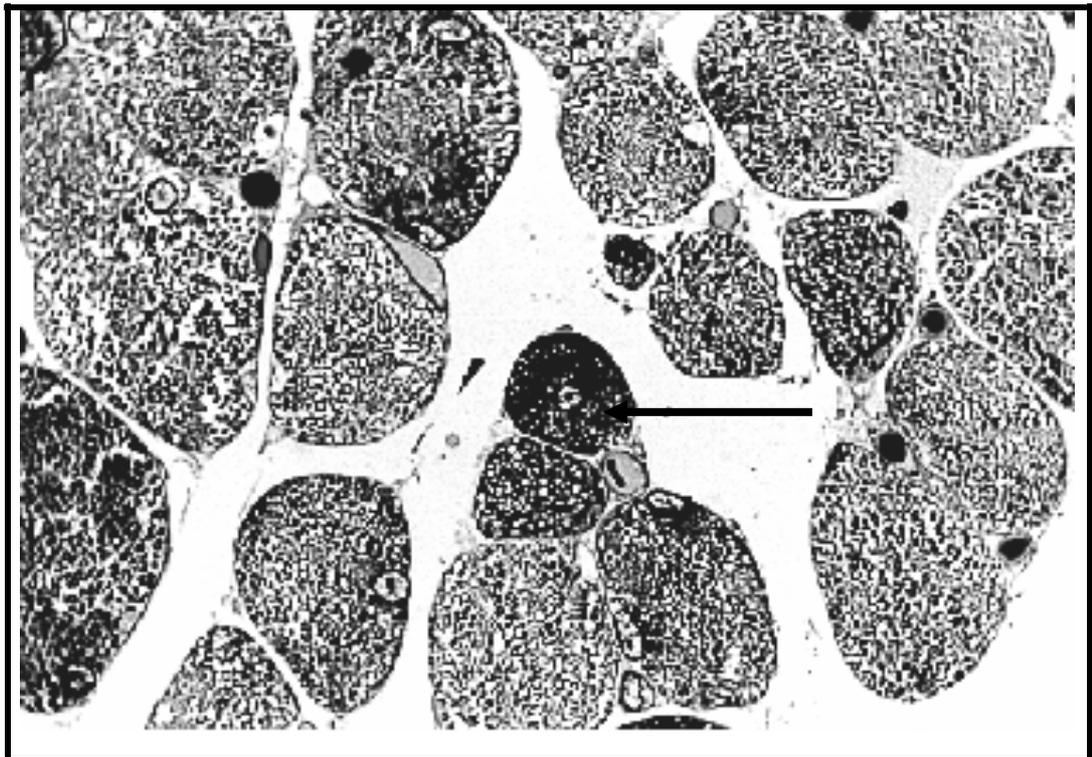


FIG. 4-6 MICROGRAPH OF FELDER- AND FIBRILLEN-STRUKTUR FIBRES FROM CAT EOM. ARROW POINTING TOWARDS FELDERSTRUKTUR FIBRE. LM/TS. STAINED WITH TOLUIDINE BLUE.

The oculorotatory muscles of most mammals exhibit two distinct regions; a peripheral orbital layer (OL) facing the periorbita and orbital bone, and an inner global layer (GL) adjacent to the optic nerve and bulbus. They reveal differences both in fibre type content and area extensions. The OL is made of a sheath of smaller diameter, mitochondrien rich muscle fibres covering the orbital surface of the muscle. At the level of the nerve entrance in the recti muscles it has a C-shaped in appearance, overlapping the muscle edges. In the oblique muscles the OL is more concentrically organised. The underlying main body of the muscle, the GL, is composed of a mixture of small but mainly large diameter fibres, with variable

mitochondrien content. While the global region extends the full muscle length, inserting via a well-defined tendon, the fibres of the orbital region tend to be shorter, usually leaving a staggered arrangement of muscle-tendon junctions (Mayr, 1975; Alvarado and van Horn, 1975). At the origin and insertion of the EOM in sheep, the orbital rim is also surrounded by an additional peripheral patchy layer, which contains medium diameter muscle fibres (Harker, 1972).

Multiply and singly innervated muscle cells occur in both muscle regions, yet with an invariably higher percentage of multiple innervated muscle fibres in the OL than in the GL of most species. The majority of the muscle fibre types are conserved across the mammals, but there are, nevertheless, some significant interspecies variations when it comes to morphology and muscle fibre distribution (Mayr, 1971; Harker, 1972; Peachey et al, 1974; Davidowitz et al., 1976, 1977). The twitch fibres and tonic fibres vary in diameter; from 10-40 μm and 5-25 μm in rats (Mayr, 1971), 10-35 μm and 5-20 μm in rabbits (Davidowitz, Philips and Breinin, 1977), 15-35 μm and 15 μm in cats (Peachey, 1974), to 15-29 μm and 13-32 μm in sheep (Harker, 1972). The areas occupied by thin fibre types, as seen in many sections, also varied between species; many mammals have the orbital and the bulbar zone distinctly separated from each other, sometimes even by an internal perimysium (Kato, 1938; Mayr, 1978), whilst others have a transition zone with intermediate sized muscle fibres (Peachey et al, 1974) or a mixture of muscle cell types from either zone.

The majority of mammalian OL of the EOM do consist of two small fibre types, one with multiple and one with focal innervation, and the central mass of the muscles of three larger fibre types, two of which are singly innervated and one which is multiply innervated (Miller, 1967).

The arrangements described do not, however, apply to the LPS. This muscle does not show any sort of layer organisation in practically any subhuman species. Dietert (1965) and Harker (1972), who included the LPS in their fibre system studies, found no fibres of the Felderstruktur type either, despite the muscle's close relation to the oculorotatory muscles and the innervation from the same oculomotor nerve.

4.1.3 Motor innervation

The speed and precision of eye movements are, as previously mentioned, partly results from the unique structure and function of the extrinsic eye muscles. They are unique not only in respect of their constituent muscle fibres, but also when it comes to the number of nerves and elastic fibres that they accommodate. Each extraocular muscle receives a nerve which is very large compared to the size of the muscle it supplies. Consequently the muscles have an extraordinarily high density of nerve fibres amongst the muscle fibres and an enhanced possibility to control muscle activity. The abundant elastic tissue is, however, of mechanical reasons, also considered a generous contributor to the unique delicacy and smoothness of ocular movements. Elastic fibres are believed to help the contracting muscle, as well as to regulate the give of its antagonist. Of the two, the rich nerve supply is, nonetheless, undoubtedly the main source. Despite the frequently reported structural and functional variations of the EOMs between species as well as a large difference in the need of eye movements, it is correct to say that no other muscle is so richly innervated, nor are there cross striated muscles with finer motor control.

Eye movements are accomplished through contractions and interactions of all six oculorotatory muscles. The individual muscle contractions are initiated by impulses conducted through their respective motor nerve fibres. Muscle stimulation does not, however, merely change the tone and length of the contracting muscles. The remaining EOMs are affected as well. As the globe moves, the positions of their insertions relative to their origins changes and accordingly the actions of the unstimulated muscles are altered too. Descriptions of the independent actions of the different extrinsic eye muscles usually found in the literature are hence strictly a hypothetical convenience to enhance the understanding of ocular rotation.

Comprehension of eye movements through analyses of antagonistic muscle pairs is, yet still simplified, a more realistic model. In order to accomplish a purposeful movement of the eyeballs and obtain the important alignment of the foveae of both eyes toward targets of visual interest, the neural control system obviously plays a very important role in this intimately connected muscular arrangement.

In contrast to the optic and olfactory nerve, which in fact is a fibre tract of the CNS, the cranial nerves in charge of eye movements are classified as parts of the peripheral nervous system. Their cell bodies reside in the brainstem, clustered together in distinct groups called oculomotor nerve nuclei. From this site the nerves advance via the cavernous sinus into the orbit where they subsequently take different routes towards the various EOMs within the orbital cavity. In their course outside the CNS, the oculomotor nerve fibres show a broad range of diameters, from less than 1 μm up to 21 μm in man (Spencer and Porter, 1988). They are associated in fascicules, which vary in size, number and pattern at different levels along their course. The axons are classified as motor, sensory and possibly autonomic EOM fibres.

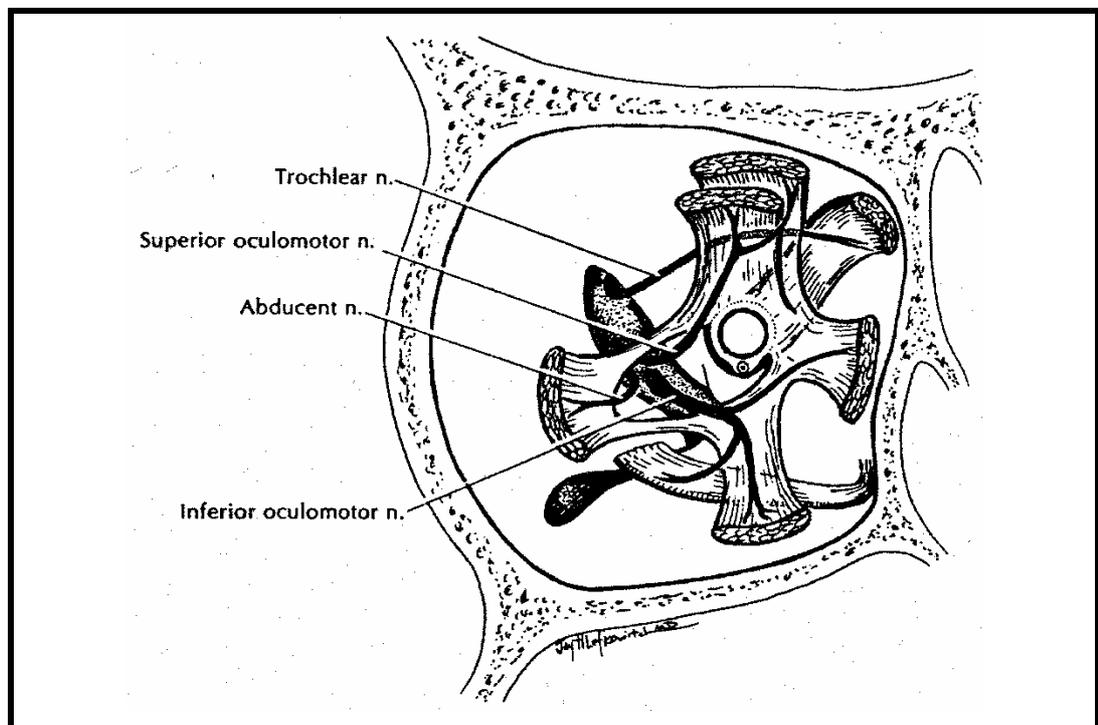


FIG. 4-7 OCULOROTATORY NERVES (JACOBIEC, 1982)

All nerves entering the orbit, with exception of the optic nerve, traverse the orbital fissure or its counterpart in certain mammals, the orbitorotundum foramen (Prince et al., 1960). Three of them are in collaboration controlling the extrinsic eye muscles; the oculomotor nerve (III), the trochlear nerve (IV), and the abducens nerve (VI). Part of a fourth nerve, the ophthalmic division of the trigeminal nerve, seemingly conducts their sensory information toward the CNS in certain species.

The oculomotor nerve is not only the most complex of the cranial nerves supplying the EOMs, but also the nerve innervating the majority of the muscles; the MRM, IRM, IOM, SRM and LPS. As it proceeds through the orbital fissure/orbitorotundum foramen and the tendinous ring of Zinn, the nerve divides or is already divided into a superior and an inferior branch. The former advances towards the SRM and the LPS, while the latter take a path beneath the optic nerve to innervate the MRM, IRM and IOM. Prior to entering the individual muscles the nerves often re-divide. The efferent impulses hence usually access the muscle through several, fairly parallel nerve branches rather than one single nerve trunk. The nerves enter the rectus muscles from the inside of the cone, approximately at the junction of the middle and posterior thirds of the muscles. The IOM is supplied at a slightly more proximal site, around the middle of its posterior part. The LPS is innervated by a division of the superior branch. The nerve fibres reach this muscle by either penetrating the medial edge of the SRM, and concurrently form a link between the two muscles, or by winding around the medial border of the SRM for then ultimately to enter the LPS.

The oculomotor division, advancing toward the inferior oblique muscle, also carries parasympathetic fibres. These fibres leave the IOM branch in the posterior orbit to subsequently enter the lower part of the ciliary ganglion. At this site they synapse with postganglionic neurons, whose fibres advance in the short ciliary nerves and finally supply the ciliary muscle and sphincter pupillae.

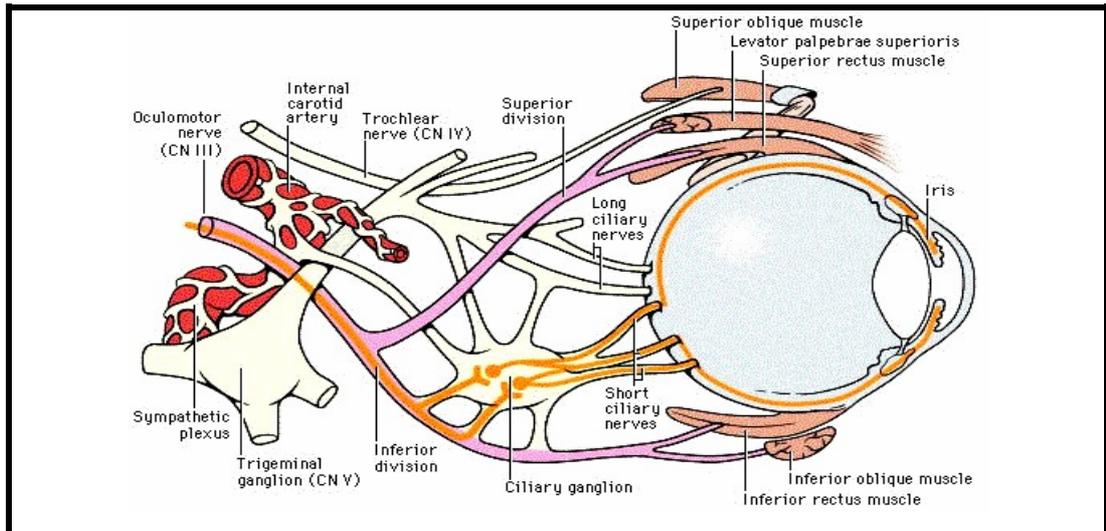


FIG. 4-8 THE OCULOMOTOR NERVE (YALE CENTER FOR ADVANCED INSTRUCTIONAL MEDIA, 1998)

In contrast to the oculomotor nerve, the trochlear nerve supplies only one oculorotatory muscle; the SOM. This rather thin nerve passes through the lateral aspect of the orbital fissure/orbitorotundum foramen, just outside the fibrous ring, and then runs outside the muscular sheath of the eyeball towards the SOM. After crossing the muscle from the medial side the nerve enters the SOM at the outer orbital surface, near the lateral border. The nerve divides into 3-4 branches just prior to entering the belly at the anterior half of the posterior third of the muscle.

The abducens nerve also supplies one single extraocular muscle; the LRM. It enters the orbit through the superior orbital fissure/orbitorotundum foramen, runs inside the fibrous ring and innervates the muscle from within the muscular sheath. Like the other oculomotor nerves, it splits into multiple branches just prior to entering through the medial muscle surface. The insertion point is slightly posterior to the middle portion.

Apart from carrying efferent stimuli from the various ocular motor nuclei to the neuromuscular junctions of the EOMs, the distal aspect of all extraocular motor nerves probably also accommodate afferent fibres with sensory information for the CNS (Porter, 1986). The specific course of afferent EOMs axons has, however, been debated for several years. As many as three possible routes have been suggested (Carpenter, 1988). They may either run straight from the muscle to a

branch of the trigeminal nerve or simply travel together with the motor nerves towards the CNS. The third possibility, a hybrid model of the two former paths, suggests the sensory fibres exit the EOMs as a fraction of the rotatory motor nerves, then subsequently cross over to the ophthalmic division of the trigeminal nerve via small communicating branches. The literature refers to the course as species dependent (Eggers, 1982). Tozer and Sherrington (1910) claimed to have evidence for the second model when they found the majority of the nerve fibres to degenerate in cat, monkey and rabbit EOMs after cutting the oculorotatory nerves in the brainstem. The few remaining fibres that were still intact were only briefly mentioned. These were suggested to run within the trigeminal nerve and argued to be of little significance in the afferent system. They expected the sensory fibres to represent a much larger portion of the nerve fibres. Some years later, when repeating the investigations of cat EOMs, Tarkhan (1934) found the same results, which in fact are evidence in favour for the hybrid model. Yet the sensory fibres run within the oculorotatory nerves for a part of their course, they were traceable in the trigeminal nucleus. Manni and Bortolami (1979) even more convincingly exposed a similar path in sheep. Communicating branches between the oculorotatory nerves and the ophthalmic division of the trigeminal nerve were clearly visible in the cavernous sinus. Comparable communicating pathways have also been exposed in degeneration studies of guinea pig (Manni et al, 1981).

All nerve fibres of the peripheral nervous system (PNS), including the oculorotatory nerves, are enclosed by a sheath of glia cells, Schwann cells, which invest the axons almost throughout their entire course. Many of the fibres are also surrounded by a myelin sheath, which is composed of spirally wrapped membrane layers of the same Schwann cells. The smallest axons of peripheral nerves are commonly lacking this latter wrapping and hence referred to as unmyelinated axons. A few minute nerve fibres with myelin are nonetheless also present in the nerve. One Schwann cell, when not forming myelin, may embrace as many as a dozen axons. The unmyelinated axons are occupying deep depressions of the cell surface and completely surrounded by the plasmolemma of the Schwann cell. In contrast, when forming myelin, the Schwann cell includes only one single axon.

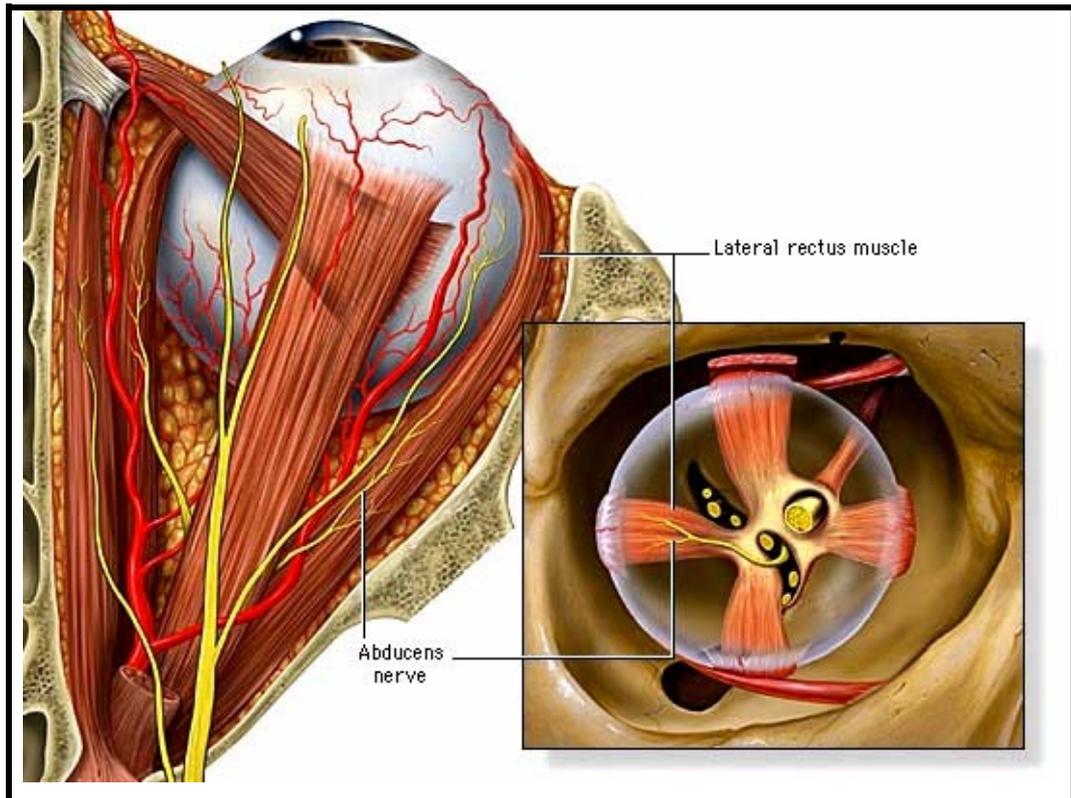


FIG 4-9 THE ABDUCENS NERVE (YALE CENTER FOR ADVANCED INSTRUCTIONAL MEDIA, 1998)

The glia cells are interrupted at regular intervals by structures called nodes of Ranvier. These formations mark the beginnings and ends of the Schwann cells that successively are covering the length of the axon. Here the nerve fibres are only incompletely enclosed by a complex arrangement of Schwann cell processes. The internodal segments tend to be shorter in the terminal portions, but generally the size of the Schwann cell varies according to the fibre size. Nerve fibres surrounded by the largest cells most commonly convey the fastest signals.

The myelin sections are occasionally interrupted by discontinuities; Schmidt-Lantermann clefts. These oblique gaps represent separations in the plane of the myelin sheath filled with Schwann cell cytoplasm.

The motor nerves of the EOMs are larger than any other motor nerve in the body when compared to the size of the muscle it supplies. Fibres of varying diameter are enclosed by epineurium and separated by endoneurium.

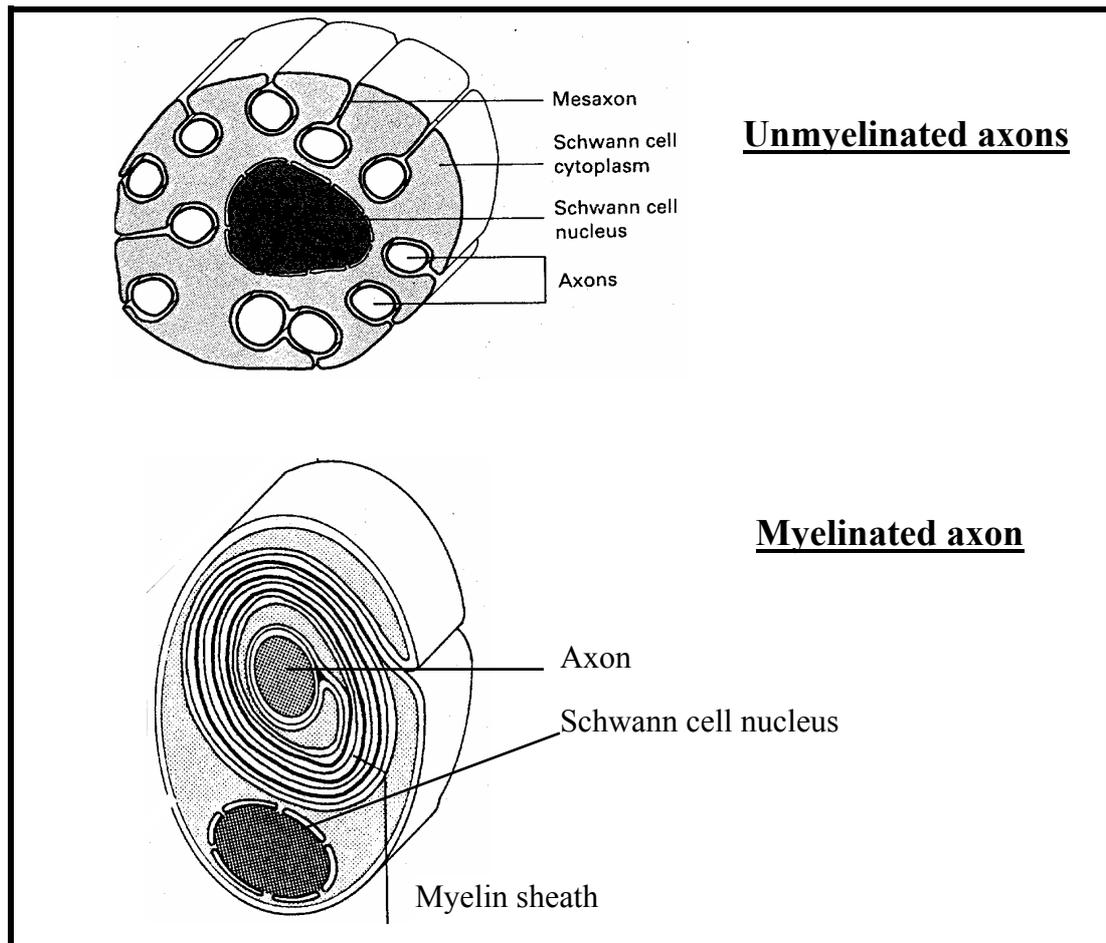


FIG. 4-10 UNMYELINATED AND MYELINATED AXONS (FUNCTIONAL HISTOLOGY 3.ED, BURKITT, YOUNG AND HEATH)

Both myelinated and unmyelinated fibres are numerous present in the nerve trunks, yet with a much higher incidence of the former. The nerve fibre diameters vary from one EOM to another as well as between species (Batini et al., 1979; Steinacker and Bach-y-Rita, 1968). The size of the nerve fibres found in rat and monkey EOMs show a bimodal distribution (Kerns, 1980; Ruskell, 1983). Most of them have diameters of approximately 2,5 μm and 7-11 μm . Similar bimodality is also described in sheep (Browne, 1976), with peaks at 3-6 μm and 9-13 μm . Unmyelinated fibres with very small diameters, 1 μm and less, are present as well, probably representing sensory and sympathetic motor innervation of the muscle (Buisseret-Delmas, 1976; Ruskell, 1983). The latter nerve fibres are derived from the superior cervical ganglion and almost exclusively associated with muscular blood vessels (Hines, 1931).

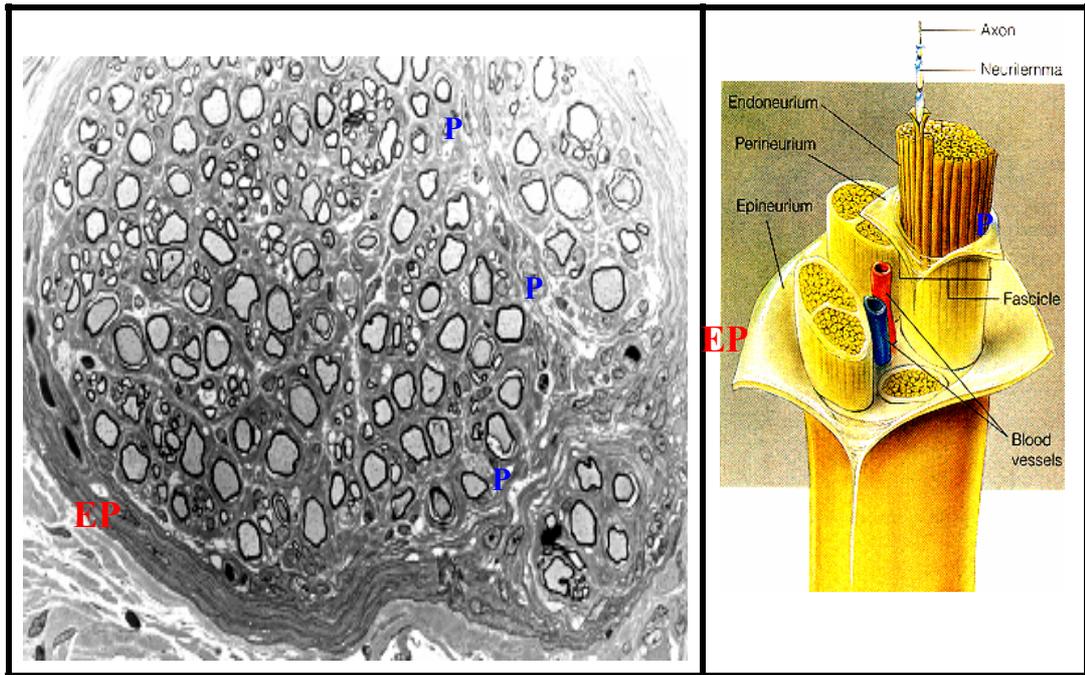


FIG. 4-11 MICROGRAPH OF A HUMAN NERVE TRUNK. LM/TS. STAINED WITH TOLUIDINE BLUE .
DRAWING (ESSENTIALS OF HUMAN ANATOMY AND PHYSIOLOGY 6.ED, MARIEB) . “E” REPRESENTS ENDONEURIUM,
“P” PERINEURIUM AND “EP” EPINEURIUM

Liddell and Sherrington (1925) introduced the term motor unit, which is defined as a motor neuron and the muscle fibres that it innervates. It represents the basic functional unit of a muscle and the unit size, number of muscle fibres per motor neuron, determines the fineness with which the muscle force can be increased or decreased.

The size of the motor unit is muscle and specie dependent, ranging from nearly 1:1 in cat EOMs (Alvarado and van Horne, 1975) to over 1000 in human gastronemius muscle (Salpeter, 1987). Smaller motor units allow a gradual increment of muscle force, and are hence frequently found where precise control is required, as in the EOMs. The force generated by each unit, consequently, is inversely related to the precision of motor control. Most muscles contain motor units that differ in contraction speed. All muscle fibres of a given motor unit, however, share the same physiological and histochemical characteristics. They are often widely spread within the muscle (Burke and Tsairis, 1973), which results in a rather diffusely generated force when only a few motor units are active.

Adjustments of the number of active motor units will vary the tension in the musculature. A system of asynchronous firing prevents muscular fatigue and allows

the contraction to be sustained for long periods. A muscle is never fully at rest; it always has a muscle tone.

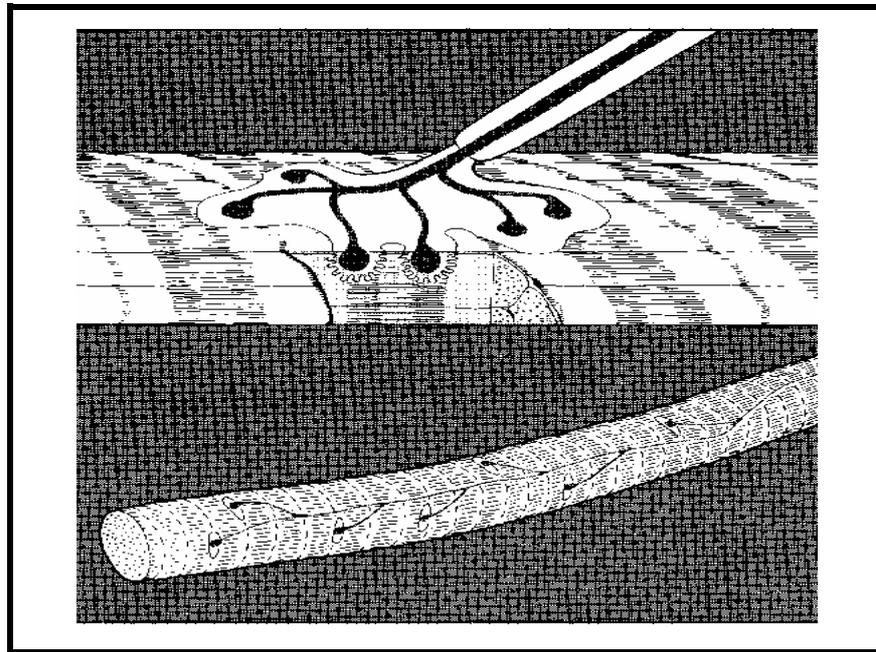


FIG. 4-12 "EN PLAQUE" AND "EN GRAPPE" ENDINGS (OCULAR ANATOMY AND PHYSIOLOGY 1993, SAUDE)

Once the nerve enters the muscle it breaks up into a network of smaller branches, which run in the epimysium and perimysium before advancing into the endomysial spaces around the muscle fibres. Within this inner level of connective tissue the autonomic fibres ramify throughout the whole muscle to supply the blood vessels. Efferent fibres break up into a number of branches and lose their myelin as they terminate on a variable number of muscle fibres.

Two structurally different types of neuromuscular junctions are found and thoroughly described in mammalian EOMs; «en plaque» and «en grappe» endings (Eggers, 1982; Salpeter, 1987). The former, which corresponds to the typical single endplate described in skeletal muscles, are exposed on muscle fibres which propagate action potentials and respond to impulses with a rapid twitch; Fibrillenstruktur fibres. They were given the name by Rouget (1862), who related it to the mitochondria and clusters of nuclei he found in their postsynaptic cytoplasm (Salpeter, 1987). The «en grappe» endings resemble efferent nerve terminals found in slow musculature of amphibians, avians and muscles in the inner ear of

mammals, as well as in the larynx of man and cat (Salpeter, 1987). In EOMs they are located on the unique slow Felderstruktur fibres, which are multiply innervated and incapable of generating action potentials (Stefani and Steinbach, 1969). These muscle fibres undergo a graded contraction dependent upon the degree of local membrane depolarisation induced by the multiple «en grappe» stimulations. The grape resembling endings were named by Tschiriew in 1879 and described in EOMs for the first time by Retzius in 1892 (Salpeter, 1987, Sadeh and Stern, 1984). Many years later they were also identified in many other species, including man. Hess (1961) was, however, the first to associate this type of neuromuscular junction to a specific type of ocular muscle fibre. Due to the lack of Felderstruktur fibres, which are the fibres associated with these endings, the LPS only contains “en plaque” terminals (Dietert, 1965; Namba et al., 1968; Harker, 1972).

Histochemical examinations, applying cholinesterase stains on teased extraocular muscle fibres or large bulks of muscle, display the same two categories of motor terminals. They were exposed in several animal groups, including man, guinea pig, cat, monkey and man (Kupfer, 1960; Hess, 1961; Hess and Pilar, 1963; Cheng, 1963; Zenker and Anzenbacher 1964; Dietert, 1965).

One type of terminal is revealed as an irregular band of dense staining in the middle third of the EOMs, just distal to the nerve entry. Each ending is large, compact and intensively stained. The other type of terminal consists of light speckled staining distributed over the full length of some muscle fibres. These endings are smaller, lighter stained and arranged in chains or loose clusters. The former structure clearly represents «en plaque» endings, whilst the latter represents the multiple “en grappe” endings supplying tonic muscle fibres.

Histological studies confirm the results from the histochemical investigations. Endplates are confined to a fairly narrow transverse motor band in the middle third of the muscle. Dietert (1965) exposed one «en plaque» ending on each human ocular Fibrillenstruktur fibre although Kupfer (1960) found the majority of human ocular Fibrillenstruktur fibres to possess two or more. In SOMs of rodents more than one endplate have also been found (Teravainen, 1968; Salpeter et al., 1974).

“En grappe” endings, in contrast, are numerous distributed along Felderstruktur fibres. The distances between them vary considerably. Dietert (1965) examined human EOMs and found them to occur with intervals from 10µm to 2-3 mm. Endplates in human EOMs are often seen covered by a sheath formed from the perineurium of the terminating nerve (Ruskell, 1984). Nerves associated with endplate endings are occasionally also found spiralling around the muscle fibres before attaching to its surface. The latter structures have been found in the EOMs of several species, including man, cat and monkey (Daniel, 1946; Sas and Appeltauer, 1963; Ruskell and Wilson, 1983; Ruskell, 1984). They form a small minority, amounting to 5% of the motor endplates in humans, and the majority of them are partly covered by a perineural sheath (Ruskell, 1984).

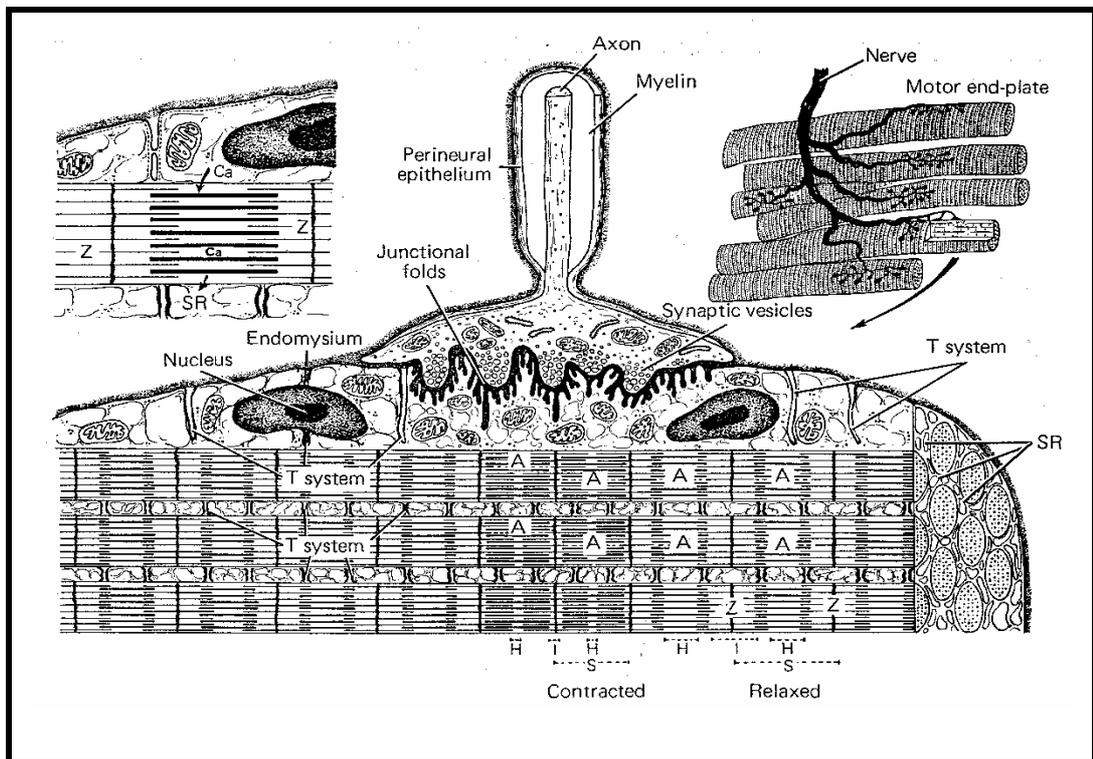


FIG. 4-13 THE MOTOR ENDPLATE AREA (BASIC HISTOLOGY 1989, JUNQUIERA, CARNEIRO AND KELLEY)

«En plaque» endings are generally innervated by thick myelinated axons, while «en grappe» terminations are supplied by thin myelinated or unmyelinated axons (Pilar and Hess, 1966; Teravainen, 1968; Teravainen and Huikuri, 1969). The difference in size and myelination indicates a disparity in impulse speed, the thinner unmyelinated fibres being the most slow conducting axons.

At the neuromuscular junction of “en plaque” endings the axon slightly expands to enclose accumulations of synaptic vesicles and mitochondria. The muscular part of the endplate is called sole plate. The muscle surface is here somewhat elevated due to accumulated granular sarcoplasm, mitochondria and sole plate nuclei beneath the sarcolemma (Cheng and Breinin, 1965). The expanded axon lies in a groove on the muscle fibre surface and the terminal are hence often referred to as hypolemmal endings. The synaptic clefts of these endings are well developed, and their postsynaptic membranes hold deep and numerous folds (Cheng and Breinin, 1965). Certain structural variations between muscles have been found in cat EOMs, where these motor terminals tend to be smaller and more irregular in SOMs (Hess, 1967). Structural variations between the individual endings are found in sheep (Harker, 1972), implying a subdivision or different types of “en plaque” endings.

The Schwann cells do not enter the synapse, but function as a cover over the junction. The axonal vesicles are filled with the transmitter substance acetylcholine (ACh). As the depolarisation of the axon reaches the terminal a change in permeability, induced by the depolarisation, gives intercellular calcium access to the vesicles. The calcium interacts with the vesicles, which as a consequence empty their content into the synaptic cleft. The amount of released transmitter substance varies according to the size of the depolarisation. The ACh diffuses across the synaptic cleft. Receptors, which attract the transmitter substance, occupy the postjunctional membrane on the opposite side of the cleft. A binding of the two components depolarises the sarcolemma and, if its threshold is exceeded, initiates an action potential along the muscle fibre. The transmitter substance is rapidly degraded into choline by AChE, an enzyme present in the synaptic cleft, to avoid excessive muscle contractions.

“En grappe” endings are less complex motor terminals (Pilar and Hess, 1966; Hess, 1967). They are distributed along a muscle fibre, presumably derived from a single nerve. The elevation of the muscular membrane found in endplate terminals is not present, nor does the nerve ending lie in a groove. The “en grappe” terminations are hence often referred to as epilemmal endings. Distinct synaptic gaps are not revealed and their postsynaptic folds, if any present, are rudimentary (Cheng and Breinin, 1965; Pilar and Hess, 1966; Pilar, 1967; Harker, 1972). The minute

synaptic gap occasionally causes the nerve and muscle membranes to make contact (Cheng and Breinin, 1965). Acetylcholine is, however, still found in the junction (Couteaux, 1955; Salpeter et al., 1974). The neural endings contain synaptic vesicles, which are similar to those of “en plaque” endings (Pilar and Hess, 1966).

5.List of tables and illustrations

<u>FIG. 3-1 MUSCLES OF THE EYE AS DRAWN BY FABRICIUS, A STUDENT OF FALLOPIO, IN THE 17 TH. CENTURY (THE HISTORY OF OPHTHALMOLOGY, ALBERT AND EDWARDS, 1996)</u>	9
<u>FIG. 4-1 THE ORBITAL APEX WITH THE EXTRAOCULAR MUSCLE ORIGINS (YALE CENTER FOR ADVANCED INSTRUCTIONAL MEDIA, 1998)</u>	12
<u>FIG. 4-2 THE STRUCTURAL ORGANISATION OF A MUSCLE (CLINICAL ANATOMY OF THE EYE, SNELL AND LEMP, 1989)</u>	15
<u>FIG. 4-3 MICROGRAPHS OF THE STRUCTURAL ORGANISATION OF HUMAN AND SHEEP (HIGHEST MAGNIFICATION) EOMS. LM/TRANSVERSE SECTION. STAINED WITH TOLUIDINE BLUE.. “E” – REPRESENTS ENDOMYSIUM, “P” PERIMYSIUM, “EP” EPIMYSIUM AND “N” NERVE</u>	16
<u>FIG. 4-4 MICROGRAPH SHOWING A LONGITUDINAL SECTION OF CAT EXTRAOCULAR MUSCLE FIBRES , LM, STAINED WITH TOLUIDINE BLUE.</u>	17
<u>FIG. 4-5 THE MYOFIBRILS AND MEMBRANE SYSTEMS OF A MUSCLE (HISTOLOGY 8TH .ED, HAM & CORMACK)</u>	19
<u>FIG. 4-6 MICROGRAPH OF FELDER- AND FIBRILLEN-STRUKTUR FIBRES FROM CAT EOM. ARROW POINTING TOWARDS FELDERSTRUKTUR FIBRE. LM/TS. STAINED WITH TOLUIDINE BLUE.</u>	25
<u>FIG. 4-7 OCULOROTATORY NERVES (JACOBIEC, 1982)</u>	28
<u>FIG. 4-8 THE OCULOMOTOR NERVE (YALE CENTER FOR ADVANCED INSTRUCTIONAL MEDIA, 1998)</u>	30
<u>FIG. 4-9 THE ABDUCENS NERVE (YALE CENTER FOR ADVANCED INSTRUCTIONAL MEDIA, 1998)</u>	32
<u>FIG. 4-10 UNMYELINATED AND MYELINATED AXONS (FUNCTIONAL HISTOLOGY 3.ED, BURKITT, YOUNG AND HEATH)</u>	33
<u>FIG. 4-11 MICROGRAPH OF A HUMAN NERVE TRUNK. LM/TS. STAINED WITH TOLUIDINE BLUE . DRAWING (ESSENTIALS OF HUMAN ANATOMY AND PHYSIOLOGY 6.ED, MARIEB) . “E” REPRESENTS ENDONEURIUM, “P” PERINEURIUM AND “EP” EPINEURIUM</u>	34
<u>FIG. 4-12 ”EN PLAQUE” AND ”EN GRAPPE” ENDINGS (OCULAR ANATOMY AND PHYSIOLOGY 1993, SAUDE)</u>	35
<u>FIG. 4-13 THE MOTOR ENDPLATE AREA (BASIC HISTOLOGY 1989, JUNQUIERA, CARNEIRO AND KELLEY)</u>	37

6. List of symbols and abbreviations used in text

#	Number of
μm	Micron
ACh	Acetylcholine
AChE	Acetylcholinesterase
CNS	Central nervous system
EM	Electron microscopy
EOM	Extraocular muscle
GL	Global layer
GTO	Golgi tendon organ
IOM	Inferior oblique muscle
IRM	Inferior rectus muscle
LM	Light microscopy
LPS	Levator palpebrae superioris
LRM	Lateral rectus muscle
MRM	Medial rectus muscle
MS	Muscle spindle
MTC	Myotendinous cylinder
nm	Nanometer
OL	Orbital layer
PE	Palisade ending
PNS	Peripheral nervous system
SOM	Superior oblique muscle
SR	Sarcoplasmic reticulum
SRM	Superior rectus muscle
T-system	Transverse tubule system
TS	Transverse section

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