1933

Muscular dystrophies

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THE MUSCULAR DYSTROPHIES

By

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A THESIS

Presented to the Faculty of

The College of Medicine in the University of Nebraska

in partial Fulfillment of Requirements

for the Degree of Doctor of Medicine

Omaha, Nebraska

April 21st, 1933.

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INTRODUCTION

While associated with the Graduate College, the author was working continually on muscle histology and the histology of the neuro-muscular mechanisms. Under Dr. W.A.Willard, with whom the author was studying, opportunity to observe biopsy material from myopathic cases stimulated interest in the present subject. The step from normal to abnormal structure and function was a natural one to make.

Considerable space has been given to the questions involving muscle function. The author does not expect to escape criticism for this, yet practically every subject considered under this division has a vital connection to the problems arising out of the muscular dystrophies. In many instances these connections are not pointed out because they are so self-evident.

The author has three main objectives: 1) To determine what constitutes a careful and scientifically adequate study of a given case of myopathy. 2) To probe etiological, pathological, and therapeutic factors. 3) To learn the status in the hands of clinical observers of such unsolved questions as sympathetic innervation of striated muscle and muscle contraction.

MUSCLE PHYSIOLOGY

The Proteins of Muscle:

Muscle constitutes 42% of the body weight (Mathews). 50% of the metabolism during rest and 75% of the metabolism during work is that of muscle (Mathews). Muscle is composed largely of protein. It has been estimated and is standard teaching that 75% of muscle is water and 25% is solid, and of this latter amount 18 to 20% is protein. The chief protein constituents are myosin 70% and myogen 30%. The latter is water soluble. The work of Edsall, Muralt, Weber and Signer on the former constitutes a brilliant step forward in the knowledge of muscle composition (Parnas). The rod-like structural elements of the anisotropic discs can be correlated now on the basis of the above mentioned investigators' works as myosin. Extracted from freshground muscle with cold alkaline salt solutions 30% is recovered. Solutions of myosin are optically void and isotropic but when put in motion they are anisotropic. The double refraction means the presence of rod or needle shaped molecules and this must be the form of the myosin molecules.

The Carbohydrate of Muscle:

For recent developments of the knowledge concerning carbohydrate metabolism in mammalian muscle reference must be made to the admirable review by C. F. Cori. Glycogenolysis

in living muscle means, as the Coris and other workers have shown, the formation of lactic acid from muscle glycogen, with an intermediate formation of hexosemonophosphoric ester; this transformation is accelerated by epinephrine. The Coris have shown that muscle glycogen is not locked away, and that it does not pass through glucose when breaking down but is delivered into the blood as lactic acid. From the lactic acid, liver glycogen is built up; from glycogen of the liver, glucose can be formed and returns as blood glucose to the muscles. The effect of insulin is inverse; increased oxidation of sugar in muscle with no decrease but rather an increase in muscle glycogen, the liver glycogen being called upon to replenish the blood sugar which is withdrawn by the muscle (Parnas).

Phosphogen:

What A. V. Hill has termed the true revolution in muscle physiology was reported to the Biochemical Journal, December, 1931, by Egleton and Egleton. While working with the inorganic phosphate in muscle, they were impressed with the fact that only 25 mg. of phosphorus per 1 gram of muscle could be recovered by their method. All previous recoveries of inorganic phosphorus had totaled 100 mg. per 1 gram. of muscle. This discrepancy of 75 mg. is attributable to a phosphoric ester which is very unstable in acid solution, and which is estimated as inorganic phosphate by most methods. They called the new compound "Phosphogen". They reported that in rapidly induced fatigue, the true inorganic phosphate content is doubled at the expense of phosphogen, but considerably more phosphogen disappears than is necessary to account for the rise in inorganic phosphate. When a muscle goes into rigor the phosphogen disappears entirely, and the inorganic phosphate rises to about four times the resting value. Here the phosphogen is more than accounted for in the inorganic phosphate which appears.

As to the nature of the compound, these investigators gave no evidence, save that it is concerned in muscular activity and its disappearance coincides with fatigue.

A. V. Hill in January, 1932, summarizes the steps

by which phosphogen has become known to the physiological investigators concerned with muscle.

Thus in 1920, Hartree and Hill reported a delayed heat production in the three minutes following contraction; oxygen removed. Now this is recognized as the sign of a reaction whereby phosphogen is restored anaerobically at the expense of energy liberated by delayed lactic acid formation. In 1922, Embden found that phosphate diffuses far more rapidly into Ringer's fluid from a fatigued than from a resting muscle. Now this is known to be due to the new appearance of inorganic phosphate inside the muscle. He attributed it to change of permeability. In 1924, Embden reported that a considerable portion of lactic acid set free after tetanic stimulation may appear after contraction is over. Embden believed the immediate energy for anaerobic muscular work was derived from some unknown colloidal chemical reaction; actually it is derived from phosphogen. In 1925, Tiegs found that creatine diffuses far more rapidly from a fatigued muscle than from a fresh one, and that this excess diffusion was stopped by oxygen. In 1926, Hoet and Marks discovered that muscles rendered glycogen free by previous administration of insulin and thyroid may pass into a peculiar form of rigor, without lactic acid formation or increase in hydrogen ion concentration. He found the inorganic phosphate increased in blood. Creatine had been known to

be present in large amounts as was phosphorus. What had been called inorganic phosphorus proved to be creatine phosphoric ester. The organic phosphate was not the source of adenylpyro-phosphoric acid. In 1926, the Eggletons showed that when muscle was stimulated phosphogen breaks down, and in the presence of oxygen it was restored. Phosphogen in quick muscles is greater than in slow because there is more time for it to be restored. Its breakdown is greater, relative to lactic acid formation in the earlier than in the later stages. Fiske and Subbarow showed that the breakdown of creatine phosphoric acid affects the buffering power of the tissue. In 1927, Meyerhof had shown that the heat of hydrolysis of creatine-phosphoric acid is considerable. In 1928, Nachmansoha found that after activity a considerable part of phosphogen broken down is restored rather rapidly, even in absence of oxygen. In 1928, Lohmann proved that a considerable part of the supposed organic phosphate (other than phosphogen) was really pyrophosphate which later was found linked with adenylic acid. This compound is part of the co-ferment system in the hydrolysis of carbohydrate, and also to yield ammonia when it breaks down into inosinic acid and orthophosphate. If the muscle is poisoned with iodo-acetic acid there is no resynthesis of phosphogen because no lactic acid is formed. Lundsgaard proposed that "phosphogen is the substance directly supplying the energy of contraction, while lactic acid formation in

the normal muscle continually provides the energy for its resynthesis.

To summarize our present knowledge:

1. On stimulation phosphogen breaks down into creatine and phosphate with a liberation of 120 cals. per 1 gram of H_3PO_4; this is the primary change by which energy is set free.

2. The acid combining power of the tissue is increased, more at greater, less at lower hydrogen ion concentration, as a result of this breakdown.

3. (a) During contraction and relaxation and (b) in the next few minutes, lactic acid is set free. Lactic acid comes in (a) and (b) 50% each in five second tetanic contraction and in a twitch none in (a) and all in (b). When owing to the accompanying phosphogen change, there is no alteration of pH in the whole process, the heat liberated is about 200 calories per gram of lactic acid. When, in a more fatigued muscle, the pH decreases as a result of contraction, the heat liberated includes that due to the repression of the ionization of alkali protein, which in the extreme case may amount to 100 calories per one gram of lactic acid.

4. The restoration of phosphogen in anaerobic recovery is an endothermic process, masked, however, by the exothermic production of lactic acid. The energy liberated

by delayed lactic acid formation allows the resynthesis of phosphogen; this, however, does not occur if lactic acid formation is impossible, as in a carbohydrate-free muscle or in one poisoned with iodo-acetic acid.

5. The delayed anaerobic heat is the result of (a), the exothermic reactions of lactic acid formation and protein unionization, and (b), by the endothermic reactions of phosphogen resynthesis and protein ionization.

6. The heat in a series of twitches can be accounted for closely by the resultant phosphogen breakdown and the total lactic acid formation.

7. If the lactic acid formed in a slow series of twitches is continually removed by diffusion, the muscle can go on working for longer than if the lactic acid be allowed to accumulate (32). Presumably in the later stages, when there is little phosphogen left, the anaerobic resynthesis after contraction is very nearly complete.

8. In a muscle poisoned with iodo-acetic acid all the energy for contraction is derived from phosphogen breakdown. In the normal muscle the same is probably true, so far as concerns the energy alone, as distinguished from aerobic or anaerobic recovery. There is nothing inconsistent in regarding the whole of the lactic acid set free as being concerned with the resyn-

thesis of phosphogen broken down during activity.

Capillary Supply and Massage:

Krogh, Carrier and others have shown that large parts of the capillary system are normally closed and that a variety of stimuli may cause them to open. Among these stimuli light and heavy stroking are conspicuous, and it is also shown that following various degrees of such pressure the smaller vessels return with varying rapidity to their former state. It follows that an undoubted influence can thus be exercised by massage over large parts of the finer circulation in both superficial and deep structures. This is used in the treatment of extravasations following fracture. Massage of voluntary muscles, even though vigorous, is not accompanied by the evidences of lactic acid production, and acidosis which accompany relatively mild exercise of short duration, or by the evidences of loss of acid and alkalosis which follow exposure of the body to external heat. If massage produced additional amounts of lactic acid the benefits to over-exercised muscles would be difficult of explanation. Experience has shown that massage in the form of vigorous rub-down has a value after exercise. Massage is indicated in arthritis:

1. To prevent or delay atrophy of muscle tissue, and help in the restoration of atrophied tissue. The atrophy results from disuse or fibrositis incidental to the rheumatoid process.

2. To improve the local and general metabolism.
3. To improve the corpuscular elements in anemia accompanying infectious arthritis.
4. To aid venous return in edema in dependent parts and shiny trophic conditions of the skin.
5. To alleviate pain in myositis, as the pain is almost surely an expression of dysfunction of muscle bundles through faulty metabolism.

Muscular Contraction:

The Embden school of physiologists believed that the prime mover in the chain of reactions attending the muscular contraction was the liberation of phosphoric acid. The majority of investigators favor lactic acid and are strenthened in the fact that the amount of lactic acid found is proportional to the strength of the contraction.

Claude Bernard showed that when glycogen had all gone rigor set in. When the glycogen of muscles is all used up by large doses of insulin the animal's muscles pass at once into rigor as it dies.

But when lactic acid is added to plain muscle instead of contracting it relaxes. - Underhill and Evans.

If lactic acid production heads to contraction how are we to explain the fact that even in the absence of oxygen respiration, when the lactic acid is not removed, the muscle can still relax again. The explanation of this is that lactic acid is formed at certain sites in the muscle fibre (let us suppose in the anistroupous material) and at these sites produces the physical alterations which we know as contraction. This is momentary and soon diffuses away into the general substance of the fiber and is neutralized by buffers which are very abundant there. Consequently it is only after numerous contractions in the absence of oxygen that sufficient lactic acid has accumulated to affect the hydrogen ion concentration of the fiber permanently.

Theories as to how lactic acid produces contraction:

1. Surface tension theory. Raises surface tension at surfaces where produced; if these surfaces are not spherical already, they tend to become so and thus induce shortening. This is untenable.

2. Osmotic theory. Presupposes a semi-permeable membrane either at the surface of the fiber or somewhere within it. Production of lactic acid or other substances of low molecular weight would lead to the attraction of water from the surroundings and conceivably to shortening. In support of this is the alleged fact that under the microscope the clear stripe of the fiber is seen to diminish, while the dark stripe of the fiber is seen to increase in volume.

3. Swelling theory. Difficult to appraise. It is favored by Embden and his colleagues whose opinion it is that the production of lactic acid and phosphoric acid leads to an uptake of water by cell colloids while removal of these catabolities leads to shrinkage of the cell substance by a reversal of the process. They also believe that excitation of the muscle is accompanied by profound alterations in the permeability of the surface membranes.

4. Liquid crystal structure. If it be assumed that there is a film of liquid crystals in or upon the anisotropic substance, then the film might be caused to expand or contract by alteration in the angles of the lattice, which change if it occurs might be attributable to lactic acid.

Summary of Contraction. Study of the relationship

between lactic acid and contraction has not led to any satisfactory solution of the problem. It is not unthinkable that the physiological state of a muscle fiber depends upon the equilibrium conditions of a tissue complex of which glycogen is a component, and that the appearance of lactic acid is merely one of the outward signs of an alteration in the equilibrium condition of this complex.

Wright in his book, "Muscle Function", 1928, points out that the significant fact about muscles as regards leverage is that they are so attached that their power arm (the distance perpendicular from the joint or fulcrum to their line of action) is very short. This means that a muscle must have great strength to overcome a relatively slight resistance. A very little shortening of muscle will cause a relatively large excursion of bone. This means that the body is a machine for making quick movements against slight resistance. The actual power of a muscle is greatest when it is on stretch; i.e., at the beginning of a movement. In the transplantation of muscles it should be borne in mind that the actual strength of a muscle, in distinction from its real strength, can easily be increased by placing its insertion farther from the joint.

He defines synergists and antagonists:

> Synergist: - for the purpose of preventing undesired actions of a muscle other muscles may be used.
>
> Antagonists: - Sherrington has concluded that the voluntary performance of a movement inhibits the tone of the

antagonists. "The evidence does not seem to me to point to an increase in the tone of the antagonist muscles during an active movement, but rather to their inhibition. In cases of spastic paralysis it is possible to observe how movements are performed when the tone of antagonists is not inhibited."

Beevor came to the conclusion that muscles are innervated functionally, i.e., that each movement is initiated by one center of the central nervous system. Against this idea is the observation that a muscle may be transplanted from one group to another and trained finally to work with the new group after perhaps several months of training.

Innervation:

1. Sympathetic Innervation of Muscle:

The question of the sympathetic innervation of striated muscle is important with relation to the muscular dystrophies. Later in the paper suggestions of various authors as to the etiology of the dystrophies are recorded. And in these theories the sympathetic innervation of striated muscle is taken for fact. It is far from fact.

The case pro is admirably presented by Kuntz (1929) as follows:

Unmyelinated nerve fibers of small caliber exist in skeletal muscles (Terminaisons en groppe):

1882: Bumer -- three types of nerve fibers in striated muscle:

1. Coarse myelinated.
2. Fine myelinated
3. Unmyelinated.

He felt that the unmyelinated fibers are connected with the fine but not with the coarse myelinated fibers.

Huber and DeWitt observed fine unmyelinated fibers are within capsules of muscle spindles. They thought these were sympathetic and vasomotor.

Perroncito (1902): Unmyelinated nerves connected with motor end plates accompanying myelinated nerves and these latter ending the same place. In certain places he observed connections of these fibers (fine) with a perivascular plexus; he regarded them as sympathetic.

Gemelli (1905) maintained that the fine unmyelinated nerve fibers connected with the motor end plates are continuous with the arborizing filaments (terminal) of myelinated nerves.

Boeke (1909, 1911-1913, 1916, 1917): A system of fine unmyelinated fibers independent of myelinated fibers, terminating as end rings, end nets and end loops. Sometimes they were imbedded in the sarcoplasm of a motor end plate. The fact that they were hypolemmal and sometimes close to muscle end plates led him to conclude that they were autonomic and efferent.

After cutting nerve fibers to the extrinsic eye muscles and permitting degeneration to occur (3 to 5 days) the Bielschowsky method showed the non-medulated intact and the medulated and their terminal structures were undergoing degeneration. This meant according to Boeke that the fibers reached the muscle from the ciliary ganglion from the carotid

plexus.

But section of superior cervical ganglion still showed non-degenerated though fewer and therefore he concluded fibers supplied to eye muscles belong to the cranial autonomic system.

An experiment on the intercostals showed that after sectioning the dorsal and anterior roots six to nine thoracic nerves plus extirpation of their ganglia the intercostal muscle thirty days later showed nonmyelinated but no medullated.

Agduhr (1919) after 45 days found that same thing in the interossei after cutting lower four cervical and upper two thoracic.

Since then sympathetic innervation of skeletal muscle has been championed by Kulschetsky (1924), Hunter and Latham (1925), Kure' et al (1925) and Garven (1925). But this work was all on normal and is therefore not as conclusive as degenerated material.

Dissenters are Murray, Hinsey (merely regeneration), and Wilkinson.

The case con is presented by Wilkinson, the Australian who studied under Boeke (leading exponent of sympathetic innervation) and then writing from Northwestern's Department of Neuro-Anatomy under Ranson bitterly attacked the evidence of Boeke's work on sympathetic innervation.

Retzius ('95) called attention to fine epilemmal nerve endings of proprioceptive nerve fibers in eye muscles.

He called them "atypical motor endings". But Huber '98 and Dogiel '06 definitely established their identity as epilemmal afferent endings.

1. Fine nerve endings which Boeke mistook for sympathetic endings are sometimes found to arise from coarse medullated nerves at a node of Ranvier. These endings are always external to the sarcolemma and may lie in all possible relations to the muscle fibers.

2. No ganglion cells along the fourth cranial nerve but fibers from some external source join peripheral to dura.

3. Some of these are proprioceptive to the sup. oblique muscle but most of them pass thru or leave the fourth cranial nerve to become incorporated with another branch of the fifth cranial nerve to form the infratrochlear branch.

4. Those proprioceptive fibers from the external sources are traced to the semilunar ganglion.

5. Most of the proprioceptive fibers leave the brainstem by way of the trochlear.

Boeke (1930) replied spiritedly to Wilkenson: "But when Wilkenson goes on and writes, 'it has already been stated that no other investigator working on the muscles with the Bielschowsky technique has been able to confirm Boeke's observations', one reads this statement with astonishment for it reveals an entire ignorance of the literature bearing on the subject".

Woollard (1931) reported that section of the oculo-

motor nerve at the brainstem gave degeneration of motor and fine fibers alike. In addition he found chromatolytic changes in the cephalad part of the mesencephalic nucleus of the fifth cranial nerve suggesting a proprioceptive function for these fine fibers and not a sympathetic function.

Tower (1931) concluded: Applying three techniques methylene blue, Bielschowsky's silver, and Ranvier's gold chloide, to limb muscle of three mammalian species, cat, dog, and goat, the innervation of the skeletal muscle fiber was studied in normal material, sympathetically senervated material and in material in which each of the three compenents of innervation had been isolated by degenerative section of the other two.

Without exception, every ending seen on a skeletal muscle fiber was formed either by a myelinated nerve fiber or by a non-myelinated branch of such, and degenerative section demonstrated the somatic origin of these fibers. Endings of sympathetic nerve fibers or of non-myelinated fibers of independent or of untraceable origin were in no instance observed. Muscular and vascular innervations were separately derived from the larger intramuscular nerve trunks and at no point communicated in their peripheral distribution.

In conclusion it may be said that sympathetic innervation of striated musculature is not established.

2. Pleurisegmental Innervation:

Cattell and Stiles (1924) observed that the tension developed on stimulating separately each of the nerve roots to the frog's gastrocnemius expressed as the sum of tension developed in an isometric tetanus, exceeded in the ratio of 1.7 to 1 the tension developed when the entire sciatic nerve was stimulated. Anatomically Agduhr has demonstrated by differential nerve degeneration with histological study of the muscle using the Bielschowsky technique that plurisegmental innervation is a reality. Cuajuneo (1932) concluded that differential nerve degeneration of the three nerve routes (seventh and eighth cervicals and first thoracic) shows that neuromuscular spindles in the flexor digitorum sublimis and profundus muscles of the cat may be mono-, bi-, and trisegmentally innervated.

3. Muscle Tonus:

Within recent times regarded as a phenomenon of sympathetic innervation, muscle tone now is identified with the proprioceptive reflex by the word of Sherrington. The receptors which lie in the deep tissues appear adapted for excitation by changes going forward in the organism itself. These changes work, it appears, largely through the agency of mass with its mechanical consequences of weight and innertia, and also largely through mechanical strains and alterations of pressure resulting from contractions and relaxations of muscles.

The repeated demonstrations of loss of tone in de-

afferented limbs of monkeys by Sherrington, 1931, establishes the question of tone on a somewhat firmer foundation. Sherrington points out that the monkey realizes the limb is useless under voluntary effort and make attempts to tear it away from its body.

Histological Changes in Striated Muscle following nerve section:

While perhaps not in the strict sense a part of true muscle physiology, this subject is mentioned because microscopic findings in dystrophic diseases will be mentioned and a basis of comparison is afforded. The conclusions of Eugene C. Grau, 1923, studying the muscles of the lower vertebrates following nerve section, present a definite picture of histological sequence. According to his work there is a progressive reduction in size of the denervated muscle. During the first two months the reduction in size is due to a uniform reduction of the constituent fibers. After two months the reduction in size of the fibers isirregular in character. The first reduction in size of the fibers is due to a loss of sarcoplasm followed later by reduction in the number of myafibrils. The denervated muscle is lighter in color in the gross and less acidophilis in staining reaction indicating a chemical change. There is no proliferation or degeneration of nuclei but there is an orderly reduction in size of nuclei which is not as great as the reduction in fiber size. Mitochondria are particularly prominent in the normal muscle in the sarco-

plasmic bands adjacent to the capillaries. In the early stages of atrophy there is slight increase of mitochondria between the fibrillae, as the bands with their mitochondria disappear, but in the later stages there is a disappearance of mitochondria throughout the fiber. Atrophy after demobilization is similar but not identical with atrophy following nerve section. There is a reduction in fiber size but not the reaction resulting in the cohesion of the fibers within the fasciculi. The relative rate of atrophy in the two cases was not determined. The above factors indicate that inactivity is a predominant factor in muscle atrophy, but that there is an intrinsic chemical or metabolic change accompanying atrophy of denervated muscle not present in simple atrophy of demobilization.

Experimental Nutritional Muscular Dystrophy:

In the work of Goettsch and Papenheimer, 1931, a diet is described which leads to a progressive, highly selective, and ultimately fatal dystrophy of the voluntary muscles. Guinea pigs and rabbits are susceptible, rats resistant. The diet used is complete in known requirements, except for vitamin E; the addition of this factor, however, does not prevent the development of the disease. The lesions are not due to inanition, infection or scurvy and must be referred to some still unknown factor. These muscles with replacement fibrosis and lipomatosis closely resemble those of progressive muscular dystrophy in man.

"The earliest change in the fiber is shown in the appearance of transverse ridges or contraction bands, in which the striations are brought more closely together. The discs become disarranged and lose their individual identity to fuse into a swollen hyaline mass. Fibers cut in their long axis may show a succession of more or less globular hyaline masses, between which the sarco lemma is collapsed containing only granular detribies. The sarcolemma nuclei are displaced and distorted and tend to become oriented at right angles to the long axis of the fibers; subsequently they undergo karyorrhexis and may disappear completely. In most instances, however, side by side with the necrobiotic changes, there was found an active multiplication of cellular elements with numerous mitoses. The cells have deeply staining oval nuclei, and a rather small amount of purplish cytoplasm. They lie in clefts in the coagulated and necrotic muscle substance, and may completely fill the sarcolemma sheath. The cylindrical columns of closely packed cells constitute the "Muskelzellenschlauche" of Waldeyer. The origin of these cells, whether from invading histiocytes or from the division of the uninjured muscle nuclei with their surrounding sarcoplasm, has been often discussed. Reference may be made to the excellent studies of Forbus who by means of preliminary vital staining was able to distinguish the invading phagocytic histiocytes, which aid presumably in the removal of the necrotic material from the proliferating

muscle nuclei which are concerned in the regeneration of new fibers.

It has seemed to us that the majority of the mononuclear cells making up the "Muskelzellenschauche" were derivatives of the muscle cells themselves, although we have occasionally observed the invasion of the dead fibers by polymorphonuclear leukocytes. Many of the, as Forbus and others have pointed out, undergo subsequent degeneration, but others assume a spindle shape, align themselves in rows and by the development of myofibrils on their surface, give origin to regenerating muscle fibers. Because of their basophilic staining, such young regenerating fibers are easily distinguished from the persistent original fibers which have escaped destruction. In many of our preparations, there is a conspicuous formation of large multinucleated plasmatic masses, lying against the necrotic remains of the muscle substance. Calcification of fibers is occasionally seen".

The diet:

Rolled oats (Quaker)	355	parts
Wheat Bran (Pillsbury)	180	"
Casein (Merk technical)	75	"
Lard	80	"
Cod Liver oil (Mead, Johnson)	10	"
Salt	10	"
Calcium carbonate	15	"

W. M. Rogers (1931) studied the nervous tissues and found no visible alterations in the above animals.

Traumatic Degeneration of Muscle:

Fishback and Fishback, 1931, produced degeneration of skeletal muscles by different types of trauma - physical, chemical, bacterial, parsitic and pharmacological. The stages of muscle degeneration produced were:

a. Slight granular clouding with swelling and dimming of cross striations.
b. Edema of fibers with prominent longitudinal fibrils.
c. Vacualization.
d. True granular degeneration
    a. albuminous
    b. fatty
e. Waxy degeneration, with further
    a. lumpy disruption
    b. granular disruption.

The extent depended upon the amount of trauma but when the trauma was of sufficient strength all types of trauma gave similar results.

THE DYSTROPHIES

Progressive Pseudohypertrophic Muscular Dystrophy:

History:

The recognition of this syndrome dates back about a hundred years, for although Duchenne (Etude comparee des Lesions Anatomiques dans l'Atrophie Musculaire progressive et dans la Paralysie generale. L'Union Medicale, VII:51,202, Apr. 30, 1853.) is commonly credited with the original description, he was really antedated by Semmlo in 1834 and Costa and Giorja in 1836. Twenty years after his original work Duchenne gave a more complete work pronouncing the disease a myosclerosis.

Leyden (Klenik der Ruckenmerkskrankheiten. Berlin, A. Hirschwald, II,2 Abth., 1876) and Mobius (Uber die, Hereditairen Nervenkrankheiten. Volkmann's Samml. Klin. Vortr., No. 171, 1879.) described certain hereditary forms.

In 1883 Erb (Discussion. Neurol. Centralb., II:452 1883) clarified the knowledge of the condition by differentiating the atrophies of nervous origin from the primary myopathies , described the microscopic pathology of the muscles and presented the juvenile type which has since been known by his name.

In 1884 Landouzy and Dejerine (De la Myopathie atrophique progressive. Compt. Rend. Acad. d. Sciences, I:53, 1884.) described the facioscapulohumeral type, which has since been known by their names.

Incidence:

Hough, 1931, found an incidence of 27 cases out of 2800 admissions at the Shriner's Orthopedic Hospital. He estimates that there were six cases per 100,000 of population. Males are more frequently afflicted than females by a ratio of 4:1. Hough had no females in 27 cases.

Clinical Picture:

Ordinarily this is clear cut and definite. The parents seek medical attention when the child is from 4 to 7 yrs. of age. The history is one of disturbance of gait--strutting, waddling, or steppage--which has gradually been increasing. Occasionally the onset is somewhat later and may take place at puberty or adolescence but rarely after 30. The physical examination reveals a child which stands with exaggerated lumbar lordosis and abdominal protuberance. The calves and less constantly the glutei and quadriceps, show a characteristic enlargement termed pseudohypertrophy. The shoulders fall forward and the scapulae are apt to be prominent. There is more or less weakness of the lower spinal and pelvic muscles which with advancing disease progresses towards the extremities. In sitting down the child is noted to fall rather heavily upon the chair, and to use hands to arise from a sitting position. Standing from recumbency the child proceeds through a characteristic and pathognomonic series of maneuvers, commonly spoken of as climbing up the legs. This was described by Gowers and is known as Gower's sign. After getting on hands and knees, the child extends legs fully using the hamstrings to assist in stabilizing the knees. The hands are then brought back

toward the feet and the shin grasped with one hand, the weight is thrown backward over the hips and the opposite leg caught below the knee. By alternately advancing the hands up the legs the trunk is raised into the erect position. Another characteristic phenomenon is associated with atrophy of the shoulder girdle---loose shoulders. The examiner places his hands in the axilla and lifts. The examiner gets the impression that the child is falling between his own scapulae. Sometimes the acromions reach the level of the ears.

Diagnosis:

Barker lists five points of differentiation between myopathy and progressive muscular atrophy of neural origin:

	Primary Myopathy	Neural Atrophy
Age of onset:	Early before 30	Middle or later life
Site of involvement:	Trunk, pelvic and shoulder girdles	More distal
Family tendency:	Frequent	Except for Charcot-Marie- Tooth peroneal palsy there is no familial tendency.
Fibrillary twitchings:	Never	Practically always
Spastic phenomena:	Rare to be combined with true myopathy	Primary central lesion always indicated.

Classification of types:

1. Duchenne's pseudohypertrophic (most common).

2. Less common type with pseudohypertrophy occuring early in the muscles of the shoulder gridle. Apparently this form is rather of later onset, or slower development, or both than the typical Duchenne type.

3. Leyden-Mobius type. This is very similar to the Duchenne type if not identical with itexcept for the absence of pseudohypertrophy.

4. Facioscapulohumeral type of Landouzy and Dejerine. This form is characterized by the early involvement of the face muscles, with the appearance of the socalles "myopathic facies" with apathetic, indifferent appearance , loss loss of wrinkling of the forehead and lessening of the nasolabial folds. The lips are large with the upper lip projecting and the power to whiste or pucker the lips lost. Labial letters are pronounced with difficulty. The child is unable to elevate the corners of the mouth, presenting the so-called "transverse smile." The eyes cannot be completely closed, causing lagophthalmus. Secondary to the facial change there is progressive loss of power in the shoulder girdle and upper arms.

5. Juvenile form of Erb. This is similar to the facioscapulohumeral type but without the typical facies and it usually develops somewhat later in life.

Clinical Course:

The cases progress to loss of ability to walk. This is commonly associated with a temporary confinement in a fourth of the cases. The weakness of the arms in-

creases and finally reaches the hands. Flexion deformities of hips and knees and equinus of the feet increase markedly. The literature is scant on the actual duration of the disease but Hough estimates about 7 yrs. following the inception walking is impossible. In 4 to 6 yrs. more the arm power is lost. Death takes place in 2 to 3 yrs. from intercurrent infection.

Pathology:

Erb in 1883 describe microscopic alteration in the muscle fibers consisting of true hypertrophy, subsequent atrophy, splitting of muscle fibers with proliferation of nuclei, connective tissue proliferation, vascular hyperplasia, fat between muscle bundles.

Rocaz and Cruchet (Arch. de Med. d. Enf., IX, 344, 1906) discovered a localized lesion of the midbrain, to which they attributed the origin of the disease . Westphal, Foix, Nicholesco all found basal lesions. Henke and Seeger (Biol. Centralbl., XLVII:727, 1927) also found similar lesions.

Hough describes a biopsy from one of his cases: Sample was taken from the gastrocnemius. It was pale grossly. Microscopically showed fat and fibrous tissue mostly. The fat appeared normal but the connective tissue consists of coarse fibers and the nuclei are more abundant than one would expect. The muscle fibers were normal in size. The fat infiltrated the muscle. The muscle nuclei were normal in number and appearance. Striations were not well defined. And in areas the fibers are smaller and the nuclei are more numerous.

The pathologist, Dr. Key, reported to Hough:" In some places the muscle fibers are widely separated and the spaces between them contain a coarse basophilic precipitate as though the tissue were edematous and the fluid contained some albuminous material which the fixative precipitated. Blood vessels were of normal size and number. Walls of the vessels are thicker than usual and in some places show degenerative changes of perivascular infiltration with leucocytes or round cells. There was no evidence of infection."

Endocrinology:

Goldstein regards pineal gland as the etiological factor. "The early involution of the pineal gland gives rise to muscular fatigue, asthenia, and even dystrophy. Quite a number of children suffering from muscular difficulties have shown evidence of glandular dysfunction. Some of these cases which have been to autopsy show atrophic areas, tumors, infection, or inflammation of various ductless glands, particularly the thymus, pineal, adrenals, parathyroid, thyroid, and to some degree dyspituitarism."

Goldstein's statement seems to be a very loose one particularly because he is so sure in the face of so much doubt, and also because his statments are so all-inclusive. However there is some evidence for endocrine imbalance. Chvostek reported myopathies due to parathyroid disturbance. Friedericksen reported two cases with adrenal apoplexy. Marie and Boultier reported a case of Erb's type of dystrophy which improved with the use of injections of whole adrenal. Sprunt refers to the unusual fatty deposits in mammary and inguinal

regions. Janney, Goodhart and Isaacson pointed to changes such as dryness and abnormal pigmentation, acromegalic features, brittleness of hair, trophic changes of the nails, regressive osseous changes, marked retardation of growth, hypoglycaemia, delayed glucose utilization, creatin and creatinine changes in the urine.

Mustafaeff (Vroch. diels, Kharkow, XII, 530, 1929) states that all endocrines may be involved to a certain extent. However, he does not consider this derangement to be the primary causative factor, but rather as a result of the disturbance of the higher vegetative centers controlling the glands. Hough observed no stigmata of endocrine imbalance in 27 cases. His case were all of the early or Duchenne's type and he believes that the endocrines are more apt to be brought up in connection with the later types.

Blood Chemistry:

In questionable cases there has been reported a low carbohydrate reserve in the blood. Subscribing to this viewpoint are the names of Barker, Goldstein, and particularly Moren.

Heredity:

It is not uncommon to see 2 or more cases in the same family. Characteristically it occurs in brothers. Occasionally it occurs in cousins. But there may be no history of the disease in preceding generations. Minkowski (from Hough) (Arch. de J. Klaus- Steft. f. Verer bungsforsch., III,239, 1928-28) studied the hereditary nature of the disease in a secluded Swiss valley, where family records were available as far back as the sixteenth centruy. No cases occurred for many gener-

ations, when there was a sudden explosive outbreak of muscular dystrophy in the descendents of R. and H. among whom there had been many intermarriages. These studies lead to the conclusion that inheritance of the disease occurs according to the recessive mode in the mendelian sense. Homogametes (i.e. cases of disease) would appear only from hetero gametic marriages . The anlage or geneotypic rudiment of the disease apparently must be present in both parents, for they found the disease only where each parent had been derived from both the H and R strain indicating a double mendelian recessive process. Further it seemed certain that the pathologic gene must have been present in these strains for at least 300 yrs. They found no evidence of a sex-linked inheritance.

Contrary evidence appears in certain genealogical trees of families with the Landouzy-Dejerine type in which the disease exhibited a mendelian dominance. Barker in discussing these facts, presents this as proof that the Duchenne type and the Landouzy-Dejerine type are totally different diseases though clinically similar.

Associated Diseases:

No single disease is in constant association. Hereditary syphilis is definitely established in some. Central nervous system lesions are definitely established in some. Extrapyramidal lesions , idiocy, epilepsy, anterior poliomyelitis have all been mentioned as associated occasionally with the disease.

Pathogenesis:

Erb's original assumption that the primary lesion

was in the trophic center of the central nervous system was subsequently abandoned, but recent theories are returning to a similar assumption. Adami and McCrae,(1914), state,"The condition is thought to be an example of abiatrophy in which the muscle starts life with less than the proper molecular energy. It has little bearing upon the pathological condition that the disease in its early stages shows hypertrophy, for this is only apparent, occasioned by the intramuscular fatty infiltration."

For the endocine theory refer to the previous heading: "Endocrinology."

Barker states that there is a primary defect in the sympathetic innervation of the sarcoplasm of the muscle fibers, which might be due to insufficiency of the internal secretion of the suprarenal capsules. Gerstle and Goddard reported a case with acute meningeal symptoms and suggest but do not prove a midbrain lesion of trophic centers. Kure and Okinaka (Klin. Wchnschr. IX:1168, 1930) believe that the basic disturbance is an alteration of the autonomic innervation of the muscles. (Refer to previous heading of "Sympathetic Innervation" under MUSCLE PHYSIOLOGY" for the precarious position of the assumption that muscle of the voluntary type has a sympathetic innervation)

Treatment:

In the past treatment has been of no avail. Orthopedists have endeavored to correct the equinus but the burden of these procedures often makes the patient immeasurably worse in a very short time. Moren mentions that Weimer reported a

cure in a boy 22yrs. old by the systematic use of gymnastic exercises, after other therapeutic measures had failed. This would appear to be a very unusual case and, as Moren points out, apparently cases developing later in life offer a better prognosis. Goldthwait (1922) attributed good results to the correction of lordosis and enteroptosis. Moren quotes Oppenheim and Gordon as considering galvanic stimulation of benefit, but expresses his own opinion that massage is more useful, although its benefit is insufficient to really check and improve the condition. Moren also mentions the high carbohydrate diets of Eaton and Barnell who claim to increase activity, improve function and delay the onset of fatigue. Calcium has been advocated but Barker thinks more experimentation is necessary. Herrmann and Kral (from Hough) (Med. Klin. XXXII:1890, 1927.) reported several cases showing marked improvement following t the use of hyperthermin injections combined with extracts of testis and ovary. This substance was claimed to act as an altering principle producing an allergic condition. Mustafaeff contributed the most recent study on the use of adrenalin. In 6 cases he could find no evidence of adrenal involvement. He reports that adrenalin has a symptomatic effect, stimulating the sympathetic nerve endings and thus increasing tone of the muscles (Again the idea that sympathetics innervate striated muscle and are responsible for its tone---refer to Muscle Tonus and Sympathetic Innervation under MUSCLE PHYSIOLOGY) He concludes that adrenalin therapy is not very effective in spite of some temporary improvement.

Kure and Okinaka (from Hough) (Klin. Wchnschr. IX:1168 1930) used subcutaneous injections of .2 to .3 cc. of 1% adrenalin plus .1 to .2 cc. of 1% pilocarpin hydrochloride

given daily or every second day up to fifty or sixty doses without interruption. There series of 12 cases showed increased strength in dystrophic muscles persisting for about 12 hours noticed 2 to 3 hrs. following the injection. Repeated doses gave increasing strength . Improvement lasted for months. In two cases astonishing results were obtained. A girl who who could walk but 100 meters with crutches after 40 injections subcutaneously, walked 4 to 5 kilometers without crutches. A boy had no recurrence 3 months after discharge. Use of the affected muscle during the injection is necessary for the proper restitution of the muscle. The only undesirable reaction is palpitation. But 120 injections will not cause cardiac hypertrophy or increased blood pressure. These authors do not believe that dystrophy can be permanently or completely cured.

Hough's personal experience with the Kure and Okinaka method used in 27 cases leads him to conclude that it is attended with symptomatic temporary benefit in each case. And in a comparatively early case a symptomatic and functional recovery has been obtained. Permanency of the treatment is being carefully checked by this author.

Myasthenia Gravis:

History:

In 1877 Wilkes described the first case. In 1887 Oppenheim described a case of "chronic progressive bulbar paralysis without anatomic findings" and regarded it as a neurosis. This view was held by many until cases were reported with definite pathologic findings and it was then abandoned. In 1891 Goldflam observed no actual paralysis but only a too ready exhaustion. In 1894 Jolly investigated the muscle exhaustibility in great detail, and described the myas thenic reaction (the rapid tiring of muscle by the faradic current). Buzzard 1905 found lymphocytic changes in the muscles. He didnot ascribe the functional changes to these infiltrations however. He also noted that proliferative and degenerative changes in the thymus are frequent but not constant. In 1912 Markeloff (quoted by Keschner and Strauss) reported the abnormal fatigue was not confined to striated muscle but involved the smooth and cardiac muscle and even the psychic lives of these individuals.. In 1928 Foxe contrasts the ready exhaustibility of the somatic musculature in myasthenia gravis and reports a case with marked palpitation and dyspnea. Bowel atony studied fluoroscopically gave rise to incontinence of feces when a laxative was given. A slight urinary retention appeared in the evening and disappeared in the morning. The visceral symptoms were better with rest.

Clinical Picture:

The disease begins insidiously and the most common early symptoms are those arising from weakness of the ocular and facial muscles and the muscles of mastication, so that diplopia, ptosis, and difficulty in chewing are very common early symptoms. The facial expression is characteristic with unilateral or bilateral ptosis, the corners of the mouth down and the smile has a peculiar nasal snarl. The voice is nasal because of tongue and palatal weakness. The mouth hangs open because of weakness of the masseter pterygoid and temporal muscles. The reflexes are normal and there is no twitching. These last two findings serve to differentiate myasthenia gravis from pseudobulbar palsy. Dyspnea from respiratory muscle weakness is common and causes death. Remissions frequently occur.

Females are involved more frequently than males. It may occur in childhood or in senility but the usual ages are between 20 and 50. It may occur after pregnancy or after an acute infection. It is most often unrelated to any other condition. The muscles used most are frequently first involved, such as the muscles of mastication, eye muscles, the fingers (of a pianist).

Rapid flushing points to the unstable vaso-motor system. Quinke's edema and urticaria are often present. Limitation of ocular movements is frequent and subject to great daily variation. Emotional upsets make the symptoms more severe.

Myasthenic Reaction: The myasthenic reaction is not pathognomonic. It may occur in physiological and other pathological conditions. (Keschner and Strauss) The rapid tiring of the muscle to the faradic current has never been satisfactorily explained. Because of the fact that the reaction can be obtained on direct stimulation of the muscles, Lewandowsky believes that the cause of the reaction must be sought in the muscle fibers and not in the nerve endings. He suggests two possibilities: 1) a toxic effect---a toxin circulating in the blood which paralyzes the muscle, or an accumulation in the blood of fatigue products which inhibit further muscular contraction; 2)a change in the muscle chemistry in consequence of which the substance that is the immediate source of muscular contraction either ceases to be stored in the muscle or, if present, is too quickly used up, so that further contraction becomes impossible. Jolly (Berl. Klin. Wchnschr. 32:1, 1895) in his original description of the myasthenic reaction expresses his belief that the direct cause is a change in muscle substance, but that this muscle change is remotely influenced by the central nervous system. Salmon (Policlinico 14:157, 1913) attributes the phenomenon to a functional fatigue of cortical sensory centers.

Sensation: Although there are reported cases with subjective and objective sensory disturbances these have not been common enough to be included as a part of the symptomatology of the disease.

Psychic: Keschner and Strauss (1927) state, "We

believe that the psychic symptoms are merely the normal mental reactions of a person affected with a chronic disease of such disabling character.

Blood: In uncomplicated cases this is normal.

Metabolism: Almost all investigators agree that in myasthenia gravis there is a low creatine and creatinine excretion. The normal creatinine Nitrogen per kilo of body weight is 8 mg. for men and slightly less for women. Creatinine is a normal urinary constituent and remains constant as long as an individual is on a creatine-free and creatinine-free diet. Creatine is normal up to the beginning of the second decade after which its appearance in the urine is usually pathologic. Curshmann, and Keschner and Strauss do not believe that there is any disorder of metabolism. Others have blamed low carbohydrate tolerance, hypermetabolism, among other disorders of metabolism.

X-ray: Negative except for an enlarged thymus in some.

Differential Diagnosis:

The early appearance of weakness in levator palpebrae, orbicularis oculi, muscles of chewing, swallowing, and speech, trunk and back, and extremities; the absence of atrophy; the absence of the reaction of degeneration; the presence of general weakness following exertion; the myasthenic reaction; rapid recuperation with rest; lymphorrhages in excised muscle; X-ray shadow in the mediastinum--a-- serve to differentiate myasthenia gravis from hysteria, neurasthenia, polyneuritis, post-diphtheritis paralysis, lues, acute Landry's syndrome, chronic poliomyelitis.

Etiology:

Myasthenia gravis has been reported following flu, typhoid, diphtheria, scarlet fever, rheumatism, lead poisoning, strenuous physical exertion, and pregnancy. Lindenmulder 1932, regards the etiology as a matter of speculation but mentions auto-toxemia in certain types of constitutions, chronic infections, tumor, toxins, or persistent thymus as possible etiological factors. Abraham (1932) lists the theories as: abiotrophy, toxin, heredity, infection, endocrine dysfunction, disturbed vegetative nervous system. In support of the last mentioned theory he refers to the work of Marinesco , Sager, and Kreindler(Ztschr.f. Klin. Med. 113:404, 1930) who reported that ergotamine aggravated the condition. Abraham then goes on to say that" if one accepts the dual innervation of muscle as established, it could well be that the contracting stimulus via the spinal or cranial motor nerves reaches the muscle normally and the muscle contracts as it should (the contractile part of the sarcoplasm is normal) but that the necessary stimulation to relaxation (via the sympathetic ?) is not normal or does not reach the muscle(the reflex inhibitory pathways are not functioning normally). If this view is correct it would fit in with the well supported view that myasthenia gravis is due to pathologic changes primary in the vegetative nervous system".

The ideas of Buzzard are extremely interesting and will be cited at some length. To him the exhaustion of a muscle is a relative phenomemon and bears a definite relation to the nature and strength of the stimulus employed. The liability to exhaustion is much more pronounced in the case of tetan-

izing stimuli such as are employed in voluntary action and faradism, than in the case of stimuli producing single sharp contractions such as direct percussion, indirect excitation through the tendon and galvanism. Buzzard refers to the work of Botazzi (Arch. f. Anat. u. Physiolog. 1901, S. 377) supported by Jatezko (Jour. de Neurolog., 221, 1904) that develops the idea that in muscle there are two contractile substances, a fibrillar and a protoplasmic. The fibrillar contraction is the short sharp response as produced by the make or break of the galvanic current. The protoplasmic contraction is slow and resembles that seen in the reaction of degeneration. They may both be produced by the galvanic current but the protoplasmic reaction requires a stronger stimulus than the fibrillar. After nerve section the muscle tends to return to an embryonic stage in which the fibrillar substance diminishes and the sarcoplasm relatively increases. Assuming these views to be correct, they would help to explain the paradoxical condition observed in the myasthenic reaction, and Buzzard suggests that in the disease under consideration , some agent is at work which reduces the excitability of the protoplasmic more than that of the fibrillary constiuents of the muscle. Buzzard thinks that the inconstancy of the findings of abnormalities of the thymus is a bar to attaching too much importance to them.

Pathology:

Marked symptoms may show nothing at autopsy. The main, though not consistent observation (Abraham) is that of round cell infiltration around blood bessels, chiefly in muscles but also in central nervous system, endocrines and

elsewhere. These were called "lymphorrhages" by Buzzard. Muscular atrophy is found only in the extremely chronic case and is from disuse (Abraham). Occasional changes in the central nervous system are reported by McAlpine (1930). He found mucoid degeneration , cortical atrophy, and chromatolysis of the ganglion cells

Regarding the lymphorrhages described by Buzzard, that author states, "The impressions gained from examining a large number of these cell deposits inclines one to the view that they arise in some way from the capillary blood vessels. Close association of the lymphocytic exudation with a small blood vessel has been noted repeatedly. With regard to the fate of the lymphorrhages we can only suppose that they are transitoru phenomena, since they are not more numerous, if as numerous, in long standing cases as in those which run an acute and rapidly fatal course." He could not form any opinion on the relationship between the prevalence of lymphorrhages and the functional activity of the muscle because of inadequate data. He found lymphorrhages in a case of amyotrophic lateral sclerosis but on another case couldn't find them.

Hun,Blumer and Streeter (Albany M. Ann. 25:28,1904) believed that these masses were a response to chronic inflammation. Link (Deutsche Ztschr.f. Nervenh. 23:114, 1902) is of the opinion that the lymphorrhages prevent the neutralization of the hypothetical fatigue products by interference with the circulation of the lymph. Changes such as fatty degeneration , vacuolization, granulation, plasmoid degeneration are frequently reported in the literature (Keschner, M. and Strauss). Knolblauch (from Keschner and Strauss) (Frankfurt. Ztschr.f.

Path. 2:57, 1908) pointed out the frequent occurrence of muscle fibers whose nuclei are deposited in the inner part of the fibers and away from their margins. From his study of the muscles he concludes that two kinds of muscle fibers exist in myasthenia gravis: 1) pale, rapidly exhausting fibers and 2) red, fatigue with-standing fibers which are in the minority. The myasthenic reaction according to him is the normal reaction of the pale muscle fibers. Knoblauch's ideas do not find expression in recent work.

Treatment:

The disease has a tendency toward remission. Therefore any reported efficacious therapy must be scrutinized carefully. Another point that must not be overlooked and which Keschner and Strauss (1927) mention is the extreme suggestibility of these people. Complete physical and mental rest for weeks and months is an essential part of the treatment. Feeding should be done one spoonful at a time with sufficient intervals between spoonfuls to rest the muscles involved in swallowing. There is to be no glass or cup drinking--all by spoon. If masticatory symptoms are present, then the diet must be liquid. Absolute rest would seem to contrindicate strychnine yet good reports are frequent in the literature. Dana (1922) reported good results with enormous doses of strychnine--1 to 3 grs. t.i.d. High carbohydrate diets, calcium ion and organotherapy of all sorts have been used with varying results. Thorium has been used in malignant thymic tumors and one investigator reported by Keschner and Strauss used intravenously 1000 and 1500 electrostatic

units of Thorium X with no results. Mella (1923) reports improvement following irradiation in two cases. One wonders if this too is but the psychic benefit and remission.

Lindemulder (1932) summing up the literature gives the treatment as rest, removal of foci of infection, rectal or intravenous glucose, ephedrine sulphate grs. three-eighths to three-fourths t.i.d.

Bayha (1931) mentions that Swingle and Pfefner's new cortical suprarenal extract which is so good in relieving the asthenia of Addison's disease has failed to do the same in myasthenia gravis.

Boothby (1932) utilizing the known facts that little creatine is excreted in myasthenia gravis cases and that glycine which is 25% of the amino acids of gelatin increases better than anything else this excretion in cases of progressive muscular dystrophy , administered glycine in 15 gram doses b.i.d. for several weeks. He hopes to build up the phosphocreatine content of the muscles, which is thought to play such an important part in the mechanism of the contraction. His work is still in experimental stages but he definitely regards glycine as the cause of the improvement shown by three patients who were given the amino acid. To quote Boothby,"Case 2.--The second man, aged thirty-five years, had been well up to within ten days or two weeks before he came to the Clinic. Weakness of the muscles of the eyelids, throat, arms and legs then suddenly developed. On admittance to the Clinic he could walk only a block or two, needing assistance to prevent

falling; he had much difficulty in swallowing and opening his eyelids. He excreted about .1 gm. of creatine nitrogen and .6 g. preformed creatinine nitrogen daily. A diagnosis was made of typical myasthenia gravis. Within a week after being given 15 gm. of glycine twice daily he was much stronger and in two weeks he could walk nine blocks. Today he can walk fourteen blocks easily without help, and in the last week has shown rapid improvement in all muscles affected. He has practically no difficulty in swallowing or keeping his eyes open."

Another remedy , already mentioned, with specificity for myasthenia gravis is ephedrine. Results have been only fairly satisfactory.(Wilder discussing Boothby's paper). The discovery of and a patient's experience with ephedrine for myasthenia gravis is recorded by the patient who was a laboratory worker. (Harriet Edgworth, 1930)

Amyotonia Congenita:

History:

This rare disease was first described by Oppenheim in 1901 (Monatschr. f. Psychiat. u. Neurol., Berl., 1900, VIII, 232) under the heading of "myatonia congenita." It has also been called "congenital hypotonia" or "amyoplasis" by Coombs 1907. Batten spoke of the disease as " myopathy, infantile type" in 1903.

Clinical Picture:

Amyotonia congenita is characterized by a condition of extreme flaccidity and smallness of the muscles without local atrophy, and with loss of deep reflexes. The disease is usually present at birth but may not be discovered until about the time for the baby to begin to walk. The flaccid paralysis is mainly of the lower limbs. The mentality is not affected, the sphincters are not involved. The child learns to walk in several years. The muscles are very flaccid and the hands and feet can be bent at unusual angles. The amyotonia progresses to amelioration. Deep reflexes may return even after years of absence. Amyotonia never hits regions previously unaffected. It thus differs from the myopathies.

It is debatable whether an acute disease such as bronchitis, pneumonia, diarrhoea, causes a latent condition to assume acute form in amyotonia. Quite possibly this is the case (Spiller, 1913).

The muscular weakness is symmetrical and widely spread but in differing degrees. Final stages show atrophy. It is impossible to palpate the muscle from the subcutaneous

tissues even when the muscle is contracted. No fibrillations are present. Collier and Wilson (1908) referred to the long and narrow hands and feet.

Spontaneous improvement is the rule, but the individual may be so weak during the acute stages that he might succomb to intercurrent infection. Long continued cases frequently show contractures, chiefly of the knee (flexion0 and ankle (extention).

Diagnosis:

Anterior poliomyelitis is differentiated by the strict symmetry of the amotonia and the absence of local atrophy and complete paralysis in amyotonia.

Post diphtheritic palsy may very closely simulate amyotonia. In general the above pointw will be of value in differentiating the conditions however.

A differential diagnosis may have to be made between Werdnig-Hoffmann infantile spinal atrophy and amyotonia. Spiller (1913) lists the differentiating features:

Infantile Spinal atrophy	Aymotonia
Last half of the first year. More gradual destruction of nerve cells	Spinal process has reached its height at birth and improvement depends upon the condition fn the ant. horn cells.
Marked degree of flaccid paralysis.	All movements feeble.

Acquired	Congenital
Usually familial	Usually a single case.
Atrophy easily recognized.	Atrophy concealed
Tendon reflexes in proportion to the atrophy	Loss of tendon reflexes.
R-D	Electrical irritability ? Amyotonic reaction (faradic lost, galvanic normal).
Progression with constant impairment	Improvement

Etiology:

The etiology of amyotonia congenita is unknown. Suggestions include acute disease (Spiller, 1913), multiple neuritis or an arrest in the nerve's development (Berhardt, see Spiller) or tissue arrested in development. Males form a slight majority of the cases reported (Barnes). Rarely two cases have been found in one family (Sylvestri, see Barnes).

Pathology:

Spiller (1913) reports Finkelnburg in a case which went to biopsy. That investigator found fields of very small muscles fibers without increase of connective tissue between them. Finkelnburg thought these small fibers

could not be considered as normal fibers in a state of development, as they were much smaller than they should be in a child of the age of his patient. Councilman and Dunn (see Spiller) have shown that muscle fibers vary greatly in size in children of the same age. Finkelnburg concluded that the small fibers were not atrophied fibers, but fibers arrested in their development and their tendency toward dystrophic change was shown in the presence of hypertrophied fibers among the small fibers. No changes in the nerve cells were found.

Holmes (Rev. Neurol. and Psychiat., Edinb., 1908, VI:138) reported that the ventral roots were smaller and the ventral horn cells less numerous than in the normal.

Treatment:

The natural spontaneous improvement is helped by generous diet, cod-liver oil and malt, iron and strychnin, massage, passive movements of contracted joints, faradism, and avoidance of splints and supports (Barnes).

Myotonia Congenita (Thomsen's Disease):

History:

Jacoby (1887) reviewed the historical features up to that date. He described the myotonic reaction in a most thorough way and his remarks on the probable presence of embryonic sarcoblasts is of considerable interest in view of later theoretical considerations. He writes: "In Thomsen's disease the motor nerves and motor endplates do not show any deviations from the normal. The nerve impulse, therefore, is transmitted into the muscle fiber in the same manner as in the normal condition."

Toomey (1916) reported up to that time four hundred cases listed in the index catalogue of the Library of the Surgeon General's Office and Index Mediens.

Thomaen, himself, classed myotonia congenita with the psychoses -- "When a psychic impression awakens the muscular cramp, whether it is fright, a friendly blow on the shoulder from behind, or when the foot strikes against an unexpected stone, or when a sudden noise reaches the ear; a painful feeling shoots through the entire voluntary musculature, like an electric current. Every affect is exaggerated in the susceptible disposition, fright and anger as well as joy".

Brissaud and Bauer (Rev. Neurol., 17:600, 1909) cited synergic contraction of antagonists as the seat of difficulty. Jaquet (La Semaine Med. 23:381, 1903) believed that there was an irradiation of nervous impulses to opposed

muscle groups. Johnson and Marshall (1914) considered the myotonia a function of the blocking of the pyramidal system.

Rosett (1922) wrote an article describing how the finding of the disease in one individual led to its definite establishment in seven others of the same family. His study of the inheritance features is quite likely to remain classic.

Clinical Picture:

Inhibition of voluntary movement through the sudden contraction of a group or several groups of muscles and their failure to relax properly. Voluntary effort is effectual only after repeated slow attempts.

Myotonia is precipitated by fear, strong emotion, fatigue, sudden arresting of their attention, cold. Practically every muscle may be involved. These individuals fall to the groung on attempting to stand or to walk. The tongue or larynx may be involved. There is heightened mechanical and eletrical contractility. Striking a muscle gives a slow, prolonged tonic contraction with a groove or furrow developed. Repeated tapping of patellar tendon may give tonic extension of the knee. Farodic and galvanic currents give prolonged contraction up to tetanization. Hypertrophy is frequently present.

Males are more frequently involved than females. The disease is rare. It appears in childhood usually. The facial, ocular, or laryngeal muscles are rarely implicated. Arm, hand, and leg muscles are most frequently involved. The size of the muscles is a poor guide to the force of the

muscles. These individuals appear muscular. The myotonic reaction of Erb is present. Contractions caused by either current attain their maximum slowly and relax slowly, and vermicular, wave-like contractions pass from the cathode to the anode. Remissions are common. The onset is insidious but may be sudden. The mentality and sensory systems are normal and the reflexes as a rule are unaffected. The disease is slowly progressive and often ceases to extend after reaching a moderately advanced stage. A large number of cases show atrophy of muscles.

Etiology:

Rosett (1922) discussed some of the factors possibly involved in the myotonic spasm. He pointed out that it made no difference by what stimulus the action of the muscle was evoked, whether by tapping with a hammer, or by electric current, or by volition or emotion, the resulting abnormal phenomenon was always the same - a persistence of the contraction beyond the duration of the stimulus and, in the case of a stimulus repeated in rapid succession, a simple summation of the residual contractions.

He considered the manner in which the residual contractions are summated in the biceps and triceps in the alternate contractions of these muscles. The greater the amount of residual contraction of the triceps, the greater must be the contraction of the biceps in order to move the forearm through a given angle. The subsequent residual contraction of the biceps is greater, therefore, in amount than

it was in the case of the triceps. When the triceps is now called upon to extend the forearm, the amount of force which it must exert is greater than that exerted by the biceps in flexing it, and the subsequent residual contraction greater now than at the beginning. The amount of force which the biceps must exert in flexing the forearm the second time, therefore, must be greater than that exerted in flexing it the first time.

The result of the geometric summation of the residual contractions of opposing muscle groups is that after a few movements of flexion and extension the entire musculature of the limb is contracted to its utmost capacity. Every segment then remains in a position between flexion and extension.

It is almost certain, however, that if the patient could overcome the rigidity and flex and extend the forearm a few more times, the succeeding movements would become easier and finally normal.

In view of the ignorance of the ultimate causes of muscle contraction, he felt it would be useless to speculate upon the reasons for the diminution and the final disappearance of the residual contraction of the myotonic muscles upon the repitition of the movement in which they are engaged. He points out that Thomsen ascribed the abatement of the rigidity upon repetition of the movement to a concomitant rise in the temperature of the active muscle. Considering the effect of temperature upon the phenomena of osmosis, and of surface tension, as well as the fact that all conditions of

muscular rigidity, are lessened under the influence of a higher temperature. He states, "Thomsen's assumption may not be far from the truth."

Heredity has been associated with the disease since Thomsen described his own family with a history of the existence of the disease over five generations. Rosett (1922) states, "After a careful consideration of the facts in connection with this family, the suspicion has been forced upon the writer that myotonia congenita is caused primarily not by an inherited abnormality of muscular structure or function, but by an inherited sub-lethal factor which exerts an injurious action upon the neuro-muscular system." This might help to explain existence of psychoses.

If myotonia congenita is caused by an inherited abnormal content of body fluids, then a temporary myotonia might be caused by a temporary alteration of the contents of the body fluids of a certain kind.

Jelliffe refers to Jacoby's ideas about the cause being sought "in the nerves themselves, and not in the muscles, probably a change in their molecular arrangement, for microscopically the nerve terminations appear normal and it is after all possible that later observations may discover changes either in the peripheral or central nervous system which will take this peculiar affection out of the domain of the primary muscular disorders to which it now appears to belong."

With such a divergence of opinion no conclusion as to etiology can be made but the hereditary nature is strongly urged upon us.

Pathology:

Jacoby (1887), Johnson and Marshall (1914), and many other investigators (Schifferdecker - Deutsch. Zeitschr. f. Nervenh., 1904, 25:1) (Dejerine and Sottas, Rev. de Med., 15:241, 1895) (Pelz, Arch. f. Psychiat. 42:704, 1901) agree that the pathology consists of great thickness of size of voluntary muscles, great number of nuclei within sarcoplasm, and increase of interstitial tissue. Jacoby said, "It is obvious that a considerably larger number of embryonic sarcoplasts must have entered into the construction of each individual fiber than is the case of normal development."

Occurrence of Thomsen's in people with average size musculature is infrequent. Nearly all writers agree that the muscular strength of persons affected with Thomsen's disease, in relation to the size of muscles, is below normal. Atrophy occurs in twelve percent of cases. This is not due to stretching because atrophy is present in facial muscles which are too weak for stretching action.

Treatment:

There is no treatment other than clearing up of foci of infection, massage and active and passive movement of the affected muscles. To the extent that cold has a tendency to aggravate and increase the condition, a warmer climate is indicated.

Dystrophia Myotonica (Myotonia Atrophica):

History:

The history starts in 1886 with Erb's monograph on Thomsen's disease which stimulated interest in atypical Thomsen's which we now call myotonia atrophica.

Symptoms described first by Deleage in 1890, and effectively by Batten and Gibb, 1909, and Steinert. These men pointed out that the face is uniformly involved.

Time has shown us that far from being an affection of the muscular system alone, myotinia atrophica is now known to be a general dystrophic disorder with diverse and widespread manifestations. The finding of cataract as a frequent symptom led to this. Other extramuscular symptoms developed: - atrophy of testicles, baldness, loss of body weight.

Fleischer (1918) proved the familial tendency of the disease and called attention to the slit lamp examination of the lens in the disease. He described a typical star-shaped opacity in the posterior cortex with punctate opacities in all layers. This feature has been developed into a definite point in diagnosis by Vogt (Klin. Monatsll F. Argenh 72:421, 1924). Gifford, Bennett and Fairchild (1929) add an excellent description of the lens findings.

Numerous Syndromes resembling myotonia have been described in the literature. Most of these cannot be properly classified. There are rported numerous cases of tetany, epilepsy, tabes, amyotrophy, syringomyelia, multi-

ple neuritis, etc., in which the myotonic reaction could be elicited in some of the muscles. This has always led to a discussion whether, in these instances, the myotonia is a symptom or a complication of the principal disease, or whether it is a distinct clinical entity associated with the disease in question. Some writers regard myotonic atrophica as a clinical type of myotonia congenita or Thomsen's. It presents some clinical features which distinguish it from Thomsen's. Lewandowsky regards myotonia atrophica as merely an atypical form of myotonia congenita and according to Belz 12% of all cases of myotonia congenita show muscular atrophy. There have been two hundred cases in the literature since 1912 up to 1923. Adie and Greenfield state that there is a need for autopsies and biopsies and that new cases are not devoid of interest.

Clinical Picture:

Age of onset is between 20 and 35, and it may be earlier. In a surprisingly large number there has been proficiency in athletics. Mode of onset--insidious. In some a feverish illness precedes. Myotonia first in majority (debated) and no proof at present that it is preceded by atrophy. Course is slow. Life is rarely prolonged after the 45th year. Death is from asthenia.

Myotonia and muscular atrophy: At one end of the series there are cases in which atrophy is widespread and severe and many muscles are myotonic; in an intermediate position there are many in which one is severe whilst the other is slight, or both are present in a minor degree, and

every gradation is encountered until we come to the rare cases in which one or the other is absent. Hence, although a bare knowledge of the facts that muscular atrophy is usually found in the face, neck and forearms, and that myotonia is usually present in the hand-grasps, will enable one to recognize typical cases, a much more profound knowledge is necessary if the numerous cases that diverge widely from the classical Batten-Curschmann type are not to escape detection. It might be thought that the severity of the symptoms would depend upon the duration of the disease, but this is by no means the case.

All writers agree that active myotonia is shown most frequently by difficulty in relaxing the hand-grasps; in many cases it is confined to this feature; but this has been given undue prominence (Adie). Difficulty in relaxing grasps, buckling up of feet on beginning to run, stiffness in the knees after squatting, stiffness in jaws after mastication. By appropriate tests wider distribution is encountered. Myotonia is greatest in cold weather. Delay in relaxation diminishes usually with succeeding efforts. The "falling like a log" is also similar to Thomsen's disease. This is explained by weakness causing a patient to stumble and then the effort to prevent falling causes a generalized spasm. Acceleration of movements leads to myotonia. Acceleration exerts greater force and relaxation is not complete when contraction begins in another group. Striking a myotonic tongue with a small percussion hammer leads to dim-

pling at the point struck.

Electrical: Qualitative changes are identical with those which are present in Thomsen's disease. In weak muscles and muscles showing active or mechanical myotonia, the reaction to direct faradic stimulation is often diminished. To direct galvanism the reaction of the atrophic muscles is sometimes increased, but it is more often diminished. In many respects the reactions resemble the reaction of degeneration, for apart from the changes just mentioned A.C.C. is often greater than K.C.C. and slow worm-like contractions are sometimes observed on direct galvanic stimulation.

In most cases the classical myotonic reaction is found in very few muscles or in none at all, but is usual to find minor modifications of it. Many modifications of the classical reaction have been described, indeed it seems as if every observer who directs his attentions to the electrical reactions in these cases finds something that has not been described before, but it is not yet possible to say whether any one of them are constant or peculiar to this disease (Adie).

If the cases described by Curschmann (Deut. Zeitschr. f. Nervenheilk., 1922, 74, 157) of dystrophia myotonica without myotonia are to be admitted as pos sibilties special investigations must be made to show that cataract does not occur in other muscular dystrophies. The combination of presenile cataract with muscular atrophy but without myotonia does not justify a diagnosis of this disease although it

certainly makes it probable.

Myotonia is notoriously variable in distribution and intensity in the same case at different times. It tends to disappear and reappear.

Muscular Atrophy: Batten and Gibb suggested that a characteristic distribution may exist in this disease and they differentiated a distinct clinical group in which weakness was confined to the facial muscles, the muscles of mastication, the sternomastoids, the vasti of the thighs and the dorsiflexors of the feet.

Steinert differentiated three stages; the muscles of the forearm are first attacked, then those of the face, the sternomastoids and mastication, then a later stage where the peronei and other groups may be hit. According to Adie the sequence described by Steinert is not the constant or average finding. The forearms are spared in many cases when atrophy in some or all of the head and neck group are severe. Atrophy of the forearm muscles alone is rare.

Within the head and neck group it is usual to find some weakness of all the muscles, but one pair often suffers more than another and atrophy may be extreme in one, in the sternomastoids for example, before the others are attacked. In the forearm the supinator longus is picked out first and it may waste greatly before other muscles in the forearm group are attacked. The statement has been made that the

extensors are more often hit than the flexors but on this point the author can give no rule.

From the sites of election already mentioned atrophy may spread to adjacent muscles, or pick out individual muscles at a distance. The rate at which atrophy progresses is extremely variable. In one of our patients with wasting of the sternomastoids and facies myopathica the limbs retain their bulk and power seven years after the onset.

As in other types of myopathy, the loss of power in some of the muscles is often greater than the degree of atrophy would suggest.

Cataract: This occurs in less than half of the cases. Greenfield (1911) suggested "that the degenerative conditions in the lens and muscles may be due to a deficient vitality of the tissues showing itself in these somewhat specialized structures".

In patients with dystrophia myotonica and in their brothers and sisters, cataract, if it occurs at all, appears at an early age; in the members of the earlier or preceding generation it appears later but is still presenile in most instances, while in earlier generations it comes on in old age as ordinary senile cataract.

In its typical form the presenile cataract of the dystrophic generation begins as a star-shaped opacity first in the posterior and then in the anterior cortical lamellae, with or without very fine punctiform opacities scattered throughout the lens. It ripens quickly to a total soft cat-

aract with a small nucleus, at about the same time in both eyes. In the preceding generation its characters are much the same except that consistent with the more advanced age at onset the nucleus is larger and harder. In earlier generations it comes on in old age and has the characters of ordinary senile cataract.

Gifford, Bennett and Fairchild (1929) describe the eye findings in a case as follows: Right eye 20/20, left, hard movements with good projection. Left eye showed a mature cataract with a brownish nucleus. The right eye showed a layer of opacities best seen with a slit lamp. They were just under the anterior and posterior capsules, composed of dots and flakes, giving a play of color. Inside of the thin layer the lens was normal.

Atrophy of the testicles: Varies with the observor, experience and judgment but there is no doubt that the sexual functions are arrested sooner or later in a very large number of cases of both sexes, and it is reasonable to connect the almost constant loss of desire and power in males with changes in these organs. Infantilism may exist but it is more common to have normal sexual life up to 25 or 30 years. One of the cases described had a healthy child four years after onset. (Adie)

Baldness: This is especially noticed in the frontal region and is very frequent. In some cases the growth of hair on other parts of the body is scanty. A general wasting of all tissues of the body and a loss of the body weight much greater than can be accounted for by muscular

atrophy is seen in many cases. It has been stated that this is due in part to a diminution in the calcium content of the bones, and it is probable that this defect plays a part in the production of the spinal and other bony deformities that are sometimes present in advanced cases.

Reflexes: Loss or diminution of the tendon reflexes in the upper extremity and lower limbs has been noted in a large number of cases. Indeed it is extremely rare for all of them to be present. That this should occur when atrophy of the muscles is severe is not surprising, but it often happens that the knee jerks are absent when the muscles concerned appear to be healthy. A ready explanation for this was found in the degeneration of the posterior columns described by Steinert in his case which remained for many years the only one that had been examined after death. But this degeneration was absent in all the cases that have come to autopsy recently, and it seems as if the cause for the loss of reflexes must be sought in the muscles themselves.

Psychic: In many cases, however, the temperament shows a peculiarity that is rather difficult to define. Dulness and lack of interest are perhaps more apparent than real in the majority of cases, and the expressionless face is apt to be misleading. The patients are often suspicious and mistrustful, resenting examination and refusing to submit themselves to special tests.

Stigmata of degeneration are often present. We have been struck by the almost constant presence of a very high, narrow, hard palate in these cases.

Cardiac: Extreme slowness of the heart has been observed in isolated cases.

Etiology:

The generally accepted view as to etiology is that it is a heredo-degenerative disease. Findley (1912) believes that the disease is primarily in muscles but that the nervous system plays an important role in its production because:

1. Creatin and Creatinine ~~metal~~ points to an unusually efficient muscle and not a degenerated one.
2. No myotonic reaction during involuntary movements.
3. Condition gradually disappears on repetition of movements, but not on repetition of a direct electrical stimulus.
4. Mental state a decided influence on the condition.

Soderbergh saw in the tonic spasms which preceded active movements in Wilson's disease a close resemblence to the dystrophia myotonica. He thinks the central nervous system is hit by a toxin.

Earlier writers said it was a myogenic disease. Later writers hold that it is neurogenic.

Gregor and Schilder (Zeitschr. f. d. gesl Neur. ul Pschul. 1913, 17, 206) used a string galvonometer and reported an oscillation of 50 per minute during the myotonia after contraction. They regarded this as evidence of central origin of the myotonia. They regarded this myotonic reaction as a myotonic reflex. The voluntary contraction produced a stimulus within the muscle which called forth another con-

traction, etc. Schaffer (Deut. Zeitschr. f. Nervenheilk., 1921, 67, 225) failed to find oscillations suggestive of a neurogenic origin. He showed that myotonia persists when the nerves are blocked. Grund (Deut. Zeitschr. f. Nervenheilk, 1919, 64, 102) had previously reported persistence of myotonia in limbs paralyzed with intra thecal injections of stovaine. Adie found no oscillations suggestive of neurogenica theory.

No changes have been found in nervous structures to account for the weakness and wasting. In other words the atrophy is not neurogenic in the ordinary sense and does not depend upon a lesion of lower motor neurone.

But it has been suggested that the atrophy may be due to the loss of a hypothetical trophis influence that normally reaches the muscles through sympathetic fibres. This hypothesis has received warm support from Naegeli and his co-workers, who maintain that the primary defect in this disease is a pluriglandular disorder of internal secretion. To explain the muscular symptoms they assume that the functions of voluntary muscles can be influenced by the sympathetic system and therefore indirectly by the ductless glands. Striped muscle, they say, identifying themselves with the views of Frank (13) and others, has a double innervation of ordinary motor fibers which supply the fibrils, the part of the muscle concerned in phasic contractions, and by sympathetic fibers which supply the sarcoplasm, the part of the muscle concerned with tonic contractions, and it is to dis-

turbance in the innervation of the sarcoplasm that atrophy and myotonia in this disease are said to be due. (Refer to previous sections on Innervation.)

Pathology:

Muscles in general show three stages of pathology. The first stage is characterized by merely an excess of sarcolemma nuclei which have very little tendency to invade the muscle fibers. The next stage shows sarcolemma nuclei more numerous and many had invaded the muscle fibers producing chains of central nuclei. Muscle fibers varied greatly in thickness. The contour of some was irregular and showed signs of longitudinal division. The longitudinal striation was exaggerated and the transverse striation less definite than normal so that it was impossible to say which of the two was the more obvious. And in cross sections the individual muscle fibrils could be clearly distinguished. The sarcolemma nuclei had proliferated enormously, giving rise to dense chains of nuclei both within and along the border of the muscle fibers. And many heaps of sarcolemma nuclei lay between muscle fibers. There was however little evidence of disappearance of muscle fibers. The intramuscular connective tissue showed only a slight increase.

Slauck considers that there is considerable similarity between Erb's classic muscular dystrophy with a greater tendency for the formations of chains in myotonia dystrophica.

Adie and Greenfield claim a characteristic fea-

ture is the chain of nuclei. This is so in the early and middle stages of the atrophic process. The disease hits whole muscle substance picking out a few fibers particularly. Thick and thin may be seen lying together. Muscle fibers lose polygonal shape. Sarcoplasm disintegrates leaving sarcolemma nuclei. Central nuclei become surrounded by clear haloes. Disintegration starts at the periphery. There is some fat deposition. Fatty connective tissue eventually replaces muscle. An increase of longitudinal striation was very striking in not a few of their cases. It was always associated with a diminution in the intensity of the cross striation.

It is suggested that both in muscular atrophy following loss of nerve supply and in dystrophia myotonica the overgrowth of connective tissue is purely secondary and is largely proportional to the degree of atrophy of the muscles.

Dr. Willard reports the biopsy findings in one of the cases of Gifford, Bennett and Fairchild (1929): "Anterior tibial muscle, frozen section, was stained with haemotoxylin and congo red. Increase of connective tissue was noted along with extreme variation in size of fibers. There was great increase in the numbers of nuclei. Longitudinal section showed well marked striations of normal fibers. There was no uniformity in character of nuclei. Pronounced atrophy was found but large fibers were larger than in normal muscle. The elongated clusters of nuclei had arisen apparently from the long nuclear chains. On disintegration of

the fibrils, the nuclei remained."

Treatment:

The prognosis as to life is good but as to cure and helping atrophy, it is very poor.

Treatment consists of exercise of the will, gymnastics and massage (not strenuous), and avoidance of cold baths. Good results have followed thymus administrations. Some use strychnine.

A typical statement is that of Finesilver, "We ourselves have had occasion to treat these cases in the wards of the Montefiore Hospital with all measures advocated but, unfortunately, we could find no method of treatment that has had the slightest effect on the progress of the disease."

CASE HISTORIES

Pseudo-Hypertrophic Muscular Dystrophy:

Number 5098. A.H., 10 years of age, American, entered the University Hospital 11-23-20 complaining of difficulty in walking, curvature of the spine.

History: At three years of age it was noticed that the boy did not walk as the other children. His condition for three years was not bad enough to see a doctor about. At six years of age he began to get worse and became somewhat sway-back. The boy did not sit until nine months. He did not walk until twenty-one months. He had chicken pox at five years of age.

Examination: The following muscles showed atrophy: pectoralis major; pectoralis minor; supra-spinatis; infra-spinatis; rhomboidei; erector spinae. In the upper extremity the muscles were very small. Wing scapulae were present. The lower extremities show thigh muscles very small and atrophic. The calf muscles are large and appear hypertrophic. Measurements of the mid-thigh give the right 26 cm. and the left 26½ cm. Measurements of the calf give the right 22 cm. and the left 22 cm. When lying on the back and told to get up he first rolled over on the abdomen and raises upon the elbows and knees and then goes to the squatting position. From here he must be lifted or have something to pull himself up with. The head and neck muscles are weak. His gait is a rolling gait and the feet are wide apart.

Course: The boy was observed for a short space

of time. He was treated with thyroid extract, gr. 1/10, and pituitary, gr. ½. These alteratives were administered t.i.d. a.c. The boy was dismissed unimproved.

Number 27584. S.A., male, ten years of age, white, entered the University Hospital 2-2-29, complaining of weakness of both legs, inability to walk without falling down.

History: Three years ago when the patient was seven years old he had diphtheria for two weeks. His legs have become progressively weaker since. He now has difficulty in getting up out of bed. First he would use his "fours" then put his hands over the knee, then up to the thigh and around the hip to raise himself. He walked with wobbling gait. He has not been confined to bed but went to school. He walked to school, a half a block, until now (entrance). Boy had tonsillectomy two years ago.

Examination: There is marked hypertrophy of the gastrocnemius muscles. The boy cannot stand. The knee jerks are absent. He could not lift his legs while lying in bed. The upper extremities are normal.

Laboratory: Blood: Hb. 90%, R.B.C. 6370000, W.B.C. 10800. Polys 57%, lymphs 40%, Eosinophils 2%, Basophils 1%. Baso metabolic rate; / 8. Sugar tolerance test; 66.5 grams of glucose given.

	Blood	Urine
7:15	99 mg. %	19 mg. in tot. sam.
7:45	148 "	
8:15	109 "	26.3 "
8:45	70 "	
9:15	84 "	16 "
10:15	86 "	22 "
11:15	79 "	56 "

Course: This boy was treated with whole pituitary gr. 1, and thyroid extract gr 1/2, three times a day. He was dismissed unimproved.

Number 41410. K.L., eight years of age, female, entered the University Hospital 11-25-32 complaining of weakness and inability to walk.

History: The child had been normal until three years of age. At that time she started to falling over backwards. The onset was insidious. Could walk only by holding on to chairs. The atrophy began in the hips, then down to the feet. It extended up the trunk to the shoulders and down to the hands. Child is nervous, has no appetite. There has been no history of alteration of sleep. Lately she has had frontal headaches. There has been no fibrillating twitching. The child has had whooping cough after the onset of the present illness. She has been in the Orthopedic Hospital in Lincoln for one year with no help. She has had many colds, but no sore throats. The family history is negative. The child was a normal delivery. She is normal intellectually but unstable emotionally.

Examination: A poorly nourished, poorly developed, anemic appearing, little white girl. Unable to stand alone. When the child is held erect marked scoliosis of lumbar and lower thoracic vertebrae to the left is noticed. The pectorals are atrophied and weak. The back shows prominence of the musculature on the left and lack of prominence on the right due in part to posture and part to atrophy. There is mild systolic blow heard at the apex. Extremities: show

marked atrophy of all muscles with weakness. The feet are held in a position suggesting foot drop but she is able to correct this voluntarily. Touch is normal. There is a questionable hypalgesia over lower extremities. Reflexes: abdominal, present; knee jerks, absent; ankle jerk, absent; no Babinsky, Klonus or Hoffman. The patient can get up by climbing on her knees.

Laboratory: Urine, negative. Blood, negative. Blood creatinine, 1.2 mg. %. Blood creatine, 14.2 mg. %. Two weeks later these figures were .8 and 9.9 mg. % respectively. Glucose tolerance test:

	Blood	Urine
7:15	72 mg. %	9 mg. per hour
7:30	137 "	
8:00	115 "	7 "
8:30	88 "	
9:00	89 "	7 "
10:00	73 "	6 "
11:00	84 "	4 "

Course: On January 7th, 1933, the child was dismissed as unimproved. Efforts were made to initiate glycine therapy but arrangements could not be made to procure the drug in suitable form.

Myasthenia Gravis:

Number 16892. W.B., eighteen years of age, male, farmer, single, white, entered the University Hospital 5-22-25, complaining of double vision, difficulty in swallowing and talking, weakness in all skeletal muscles.

History: Two years ago the patient was entirely well. He noticed weakness of the eyelids shortly afterwards.

Eyelids dropped nearly shut during the latter part of each day. He easily held his eyes open in the morning. Soon the eye balls became set. One year ago he had a gradual weakness develop in the right then in the left hand. He could not grip anything. In December 1924 a stiffness developed in both shoulders hindering the lifting of the arms higher than horizontally. "When I'd start to walk, I'd feel like I could walk a mile, but the legs would give way--right worse." Five months ago a weakness in his lower extremities made stepping upwards difficult. Later his knees began to give way unexpectedly, the right worse than the left. His back was weakened and it became progressively more difficult to get in an erect position. Three months ago he first had difficulty in swallowing, and in a short time he had difficulty in chewing as well. At first it was less marked in the mornings. The last two months he has had difficulty in speech. He talks with a slurring, nasal twang. Now he is able to walk if helped to get erect. He walks as if he was weak with no ataxia or spasticity. He cannot rise to a sitting position from a reclining one. At times he cannot close his teeth without using his hands to help. It is difficult for him to hold his head up. He is at his best mornings and at his worst at night. His speech is hard to understand, lacking articulation. Ptosis has disappeared from the lids and the eye ball movements have improved, but are limited. He is very restless. His childhood diseases were measles at 8, diphtheria at 6, and frequent tonsillitis. His tonsils were

removed three months ago. Six years ago he was kicked by a horse and was unconscious. He had a headache for a day. He was thrown from a run away and his back was hurt at one time. The family history reveals that his father died of alcoholism. His mother died of Bright's disease. One brother is dead, cause unknown. A sister was a still-birth. An uncle was feeble minded all his life (mother's brother). The maternal grandfather died of alcoholism.

Examination: Exophthalmos-some. Slight lid ptosis. External strabismus. Limitation in rotation in both eyes upward. Fifth motor, weak. Masseters, atrophic. Inability to close teeth in contact. The facial movements are limited. The lingual muscles are weakened. There is impaired movement of soft palate. Shoulder and neck muscles are weak but symmetrical. Upper extremities: extensors, very weak on both sides, worse on the left. Flexion is weak on both sides, worse on the left. The grip is negligible. Interosseous muscles are weak, most pronounced in abduction. The reflexes: right biceps, absent; no tactile; thermal; vibratory nor pain sensation. Muscles, flacid but not markedly atrophic. There is marked impairment of flexion and extension of the knees and adduction and abduction of the thighs, and in dorsal flexion of the feet. Vertral flexion of the feet is good on both sides. Lower extremities, reflexes are normal. There is a positive Babinsky. There is no mental deterioration.

Laboratory: N.P.N. 34. Creatinine, 1.2. Blood

sugar, 80 mg.

Course: Various lines of therapy were carried out including strychnine, calcium chloride, adrenalin. No improvement was obtained. He was in the hospital 232 days and was a difficult nursing problem. Biopsy of the left pectoral muscle was performed. Typical lymphorrhages were found. Toward the end he became restless, the respirations became difficult. He became cyanotic. Red spots appeared on face and neck. Respirations became shallow. Perspiration was marked. Pulse was 148 and very weak. Temperature was 100° rectally. He gasped for breath and died. Autopsy showed an enlarged thymus with petechial hemorrhages. The pericardium showed petechiae. The spleen was enlarged and softer than normal. The meninges were rather hemorrhagic.

Number 37140. Mr. A.O., American, white, farmer, 45 years of age, entered the University Hospital 11-29-31, complaining of difficulty in swallowing, change in voice, weakness and loss of weight, numbness of all extremities, occasional attacks of dizziness.

History: This began one and a half years ago as numbness in the hands and feet. He lost weight gradually, but he continued to work. The disease has shown slow progression with remissions. Six weeks ago, he had a change in voice, dysphagia, choking on food and peroxysms of coughing. In the past few months he has had attacks of dizziness, the last one was two weeks ago which lasted one week. He has had impotence one year, has lost weight from 220 pounds to 150

pounds in two years. He is too weak for light labor. There has been no change in numbness in the last six months. All teeth were removed in 1931 because of pyorrhea. A complicating factor has been a fracture of the second lumbar spine which was treated by cast with good results. The fracture occurred when the patient fell off a hay stack.

Examination: A patient of large stature. Shows considerable loss of weight. He looks older than the stated age. The skin is atrophic, the hair grey, the face sunken, and there is an arcus senilis. The laryngeal pharynx is flooded with mucous. The mucous membrane is of normal color. The muscles of deglutition are deficient in their action. Laryngeal or vocal cords are slightly thickened. The arytenoids are in a continuous state of approximation. In phonation the vocal cords show limited motion (typical of myasthenia gravis). The patient is apethetic and appears depressed. He shows loss of interest. He is unable to converge the left 4th nerve. He shows general wasting and atrophy. It is most marked inthe hands--thenar and hypothenar eminences. He has subjective numbness of hands and feet. The girdle muscles are atrophied. There is weakness of the arm and hand muscles and flexors of the neck. Reflexes: biceps, triceps present; Hoffmann, negative; abd. absent; cremasteric absent rt. sluggish rt.; K.J. sluggish with reinforcement; Achilles absent bilaterally; Babinski and Oppenheim, absent; Ankle clonus absent; heel to knee and finger to nose tests, O.K.; Adiodoko kinesis absent; Vibration , O.K.; position, O.K.; slight un-

steadiness; Romberg, absent; no muscular twitchings or fibrillations. The Jolly myasthenic reaction: no marked fatigue after 20 to 40 stimulations. No marked fatigue of muscles to muscular action.

Laboratory: Glucose tolerance test:

	Blood	Urine
F	81 mg. %	14 mg. %
½	106 "	
1	126 "	11 "
1½	143 "	
2	107 "	12 "
3	106 "	11 "
4	74 "	18 "
5		13 "

Urine, negative. Blood, negative. Spinal fluid, negative. N.P.N. 28.5 mg. %. Creatinine, .96 mg. %. Creatine, 5.9 mg. %. Baso metabolic rate, plus 14. X-ray; the heart is globular in contour of a type commonly associated with thymicolymphatic constitution. No gross widening of the upper mediastinal shadow.

Course: He was treated with strychnine, biopsy was done, typical findings reported, and discharged on 1-10-32 as unimproved.

Myotonia Atrophica:

Number 38396. J.R., American, white, single, farmer, 46 years of age, entered 10-7-31, complaining of nervousness for fifteen years. Pain in the precordium and post sternal area after exertion, ten years duration. Tiredness, loss of interest, palpitation.

History: In 1918 the patient had the flu and he has been weak ever since. In 1907 he had an appendectomy.

In childhood he had measles, diphtheria and whooping cough. Cataracts were removed from the right eye in 1922 and from the left eye in 1923. He has had frequent colds. His palpitation has not been association with edema. He has been in the habit of working 16 hours a day on his farm. He eats well. He has a constant aching in the right shoulder. The family history reveals a feeble minded brother.

Examination: The patient is tall, thin and emaciated. Blood pressure 128/64. The testicle atrophied. Extremities: weakness in both upper and lower extremities. Atrophy of muscles of hand and deltoid. Reflexes exaggerated. The neck muscles atrophic. Marked myotonic reaction in the upper extremities. The lower extremities show bilateral distral atrophy with myotonic reaction.

Laboratory: Urine, negative. Blood, negative. Wassermann, negative. N.P.N., 28.5 mg. %. B.M.R.-11%.

	Blood	Urine
F.	82 mg. %	16 mg. per hr.
1/2	88 "	
1	91 "	20 "
1½	96 "	
2	97 "	20 "
3	67 "	4 "
4	70 "	19 "
	With Adrenalin	
F.	79 mg. %	27 mg. per hr.
1/2	124 "	
1	230 "	97 "
1½	164 "	
2	166 "	408 "
2½	105 "	408 "
4	52 "	196 "

X-ray: Substernal thyroid and evidence of old tuberculosis

in the left. Biopsy was done.

Course: On a ketogenic diet the patient gained strength. Strength was increased in the pectorals particularly. He was dismissed in this condition.

CONCLUSIONS

1. An adequate study of a given case of myopathy should include accurate history with a well worked out family history, complete physical including an ophthamoscopic, electrical reactions, naming of affected muscles and their degree of affection. additional laboratory work of creatine and creatinine determinations in blood and urine, sugar tolerance test, and biopsy where-ever permissable.

2. Sympathetic innervation of striated muscle cannot be taken as established, but lacking in demonstration by many of the best research histologists.

3. Muscle tonus does not depend upon a sympathetic innervation nut rather upon a proprioceptive reflex.

4. Nutritional muscular dystrophy has been produced in animals which closely simulates progressive pseudo-hypertrophic muscular dystrophy in man.

5. There is much correlation in the effect on muscle of various types of trauma.

6. There is a treatment for Duchenne's progressive pseudo-hypertrophic muscular dystrophy which has been meeting with success particularly in early cases.

7. Aside from ephedrine in myasthenia gravis, glycine holds out considerable hope in the treatment. Boothby of the Mayo Clinic is doing work on this treatment.

8. Etiological factors are but poorly understood in the muscle dystrophies. Best evidence points to a strong heredo-degenerative factor in most dystrophies.

9. The findings of a particular type of cataract in

a myopathic individual establishes the diagnosis of myotonia dystrophica. Biopsy material is fairly constant here, showing long chains of nuclei as an outstanding characteristic finding.

10. The exact meaning of the lymphorrhages of myasthenia gravis are still unknown. They are being regarded more and more as a perivascular disturbance.

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