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Progressive pseudohypertrophic muscular dystrophy

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PROGRESSIVE PSEUDOHYPERTROPHIC MUSCULAR DYSTROPHY

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INTRODUCTION

Since Charles Bell (1) described in 1880 what appeared clinically to be a case of progressive muscular dystrophy in an eighteen year old boy, there have been many papers written on the myopathies and especially on progressive muscular dystrophy. However, in reviewing the literature on the topic, very few sources were found which give a complete picture as to the present status of this disease. It must be said at the outset that although an attempt will be made to summarize most of the published work, the picture will be far from complete.

Much information that has been amassed during the past forty years is being discarded now, and the separation of the wheat from the chaff will be most beneficial in searching a solution of this perplexing medical mystery.

The first cases of muscular atrophy or dystrophy mentioned in the literature were studied with no special reference to the condition of the spinal cord, peripheral nerves or of the muscles themselves, and the published reports have little validity in respect to progressive muscular dystrophy. Bell (1) was the first investigator who described what we now call progressive muscular

dystrophy. Bell reported a condition of "progressive spinal paralysis" in an eighteen year old boy. He found that all the muscles of the lower extremities, hips and abdomen were debilitated and wasted. There was no sensory defect, nor were the upper extremities affected, but the boy had a slight lordosis and scoliosis and complained of palpitation of the heart. There were also no genitourinary or bowel complaints. In reviewing the patient's history, Bell found that the onset of this malady was at the age of ten and began with a weakness of the thighs, which prevented him from rising. Bell described that "it was curious to observe how he will twist and jerk his body to throw himself upright from his seat. I use this expression because it is a very different motion from that of rising from a chair", a very striking description indeed.

In 1850, Aran (2) showed for the first time that there were changes in the spinal cord in the disease then known as progressive spinal paralysis, and this discovery proved that this disease was not, as previously believed, a primary myopathy. This was the beginning of the study of the myopathies. Meryon (3) in 1852 first demonstrated that in cases of pseudohypertrophic atrophy no microscopical changes are present in the spinal cord,

but that the muscles undergo a "fatty and granular degeneration".

Few cases were reported and almost no work was done on this condition until, almost twenty years later, Charcot (1872) (4) discovered Amyotrophic Lateral Sclerosis and pointed out the differences between it and progressive spinal muscular atrophy. Duchenne (5) in 1868 had previously recognized that his disease was independent of changes in the spinal cord and the central nervous system. He named this entity "pseudohypertrophic muscular atrophy". Friedreich (6) in 1873 discussed fully the reasons for separating the muscular dystrophies from the forms of spinal muscular atrophy. Dejerine and others in 1882 showed that many cases formerly supposed to be due to spinal lesions were really due to multiple neuritis, and Landouzy and Dejerine were also the first to recognize the facio-scapulo-humeral type of dystrophy in 1884 (7). Erb (8) in 1882 described the form of muscular dystrophy which he called the "juvenile" form and later (9) in 1884 he have a full account of this form of muscular dystrophy. Gowers (10) in 1879 collected and studied one hundred and sixty cases, the largest group of cases known up to that date. Later (1899) (11), he stated that the spinal cord was perfectly

normal in the majority of the cases studied. He noticed that although there were occasional hemorrhages and an increased number of neuroglia cells, the anterior gray matter was always unaffected.

It is obvious that up until the 20th century the studies of this disorder were mainly clinical and very few chemical and pathological studies were made. The lack of progress in the understanding of the condition led naturally to investigations along the paths of pathological and chemical research.

SOME ASPECTS OF MUSCLE METABOLISM IN THE NORMAL INDIVIDUAL

CREATINE AND CREATININE METABOLISM

Of approximately 120 grams of creatine contained in the human body, we find that 98% is contained in the muscles and 1.5% in the nervous system. The remaining 0.5% is distributed throughout the other organs of the body; of these, the testes contain it in the highest concentration. The skeletal and cardiac muscles and the gravid uterus contain a great deal more of this material than the smooth muscle of the gastrointestinal tract and elsewhere. Approximately 80% of the creatine in muscle is combined with phosphoric acid as phosphocreatine, the breakdown of which, it is assumed, provides energy for the contraction of muscle. Of the striated muscles, the rapidly contracting pale type contain more than the slower contracting red variety. (13)

Creatinine is present in muscle in much smaller quantities. One hundred grams of skeletal muscle, for example, contains 300 to 500 mg. of creatine and only 10 mg. of creatinine. The creatine of whole blood amounts to from 3.5 to 5.0 mg. and the creatinine

to less than 1.5 mg. per 100 cubic centimeters. By far the greater part, if not all, of the creatine is contained in the corpuscles. The creatinine is about equally distributed between the cells and the plasma.

THE EXCRETION OF CREATINE AND CREATININE

Whereas creatine is normally absent in the urine of the adult male, it is present in the urine of male and female children up to the age of puberty and frequently in the urine of adult women.

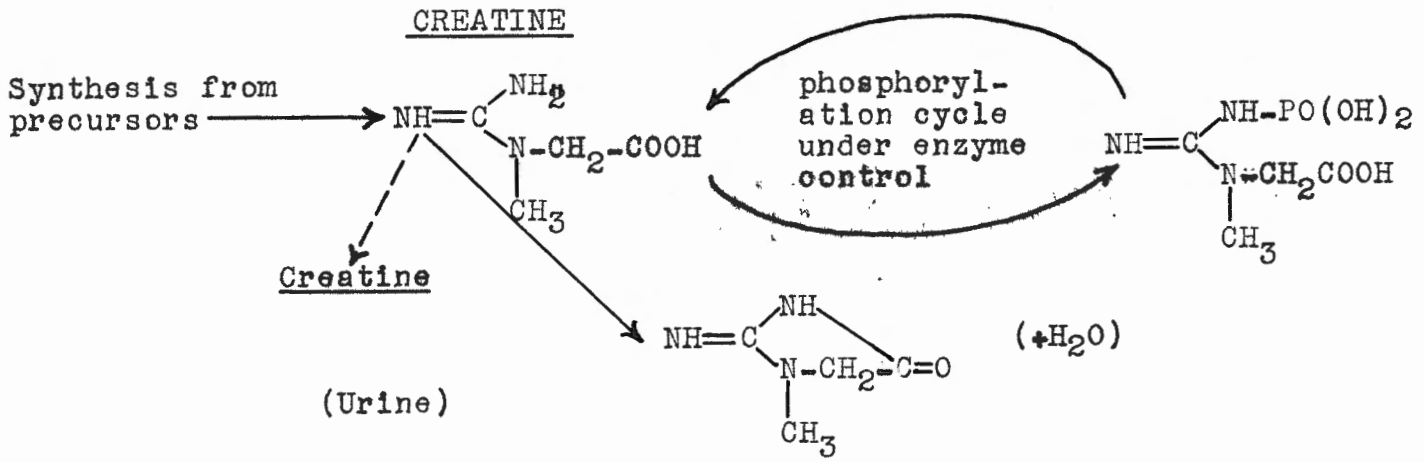
It has been shown repeatedly that creatine also appears in the urine of either sex under the following conditions: High protein diet, starvation, carbohydrate deprivation, diabetes, wasting diseases and fevers, exophthalmic goitre and in certain of the muscular dystrophies. We are particularly interested in the muscle dystrophies. In the other conditions, the increase is in all probability due to an increase in the normal catabolism of the muscular tissue, the liberation of creatine occurring more rapidly than its conversion to creatinine. Protein food, for example, has a stimulating effect upon metabolism, while in wasting

diseases, fevers, etc. tissue breakdown is accelerated. Carbohydrate deprivation probably acts indirectly in that its sparing effect upon the protein catabolism is absent. In the muscular dystrophies, e.g., myasthenia gravis, progressive muscular dystrophy, amyotonia congenita, anterior poliomyelitis, etc., the urinary creatine is probably derived from the degenerative muscle fibers; the muscles also appear to be defective in their power to store creatine. The creatinuria of normal children has received no satisfactory explanation; it is said to be due to an increased production of creatine, induced in some way by the growth process, and also probably by a low capacity of undeveloped muscles for creatine storage. Another possibility is that children have a relatively low power for converting creatine to creatinine. (13)

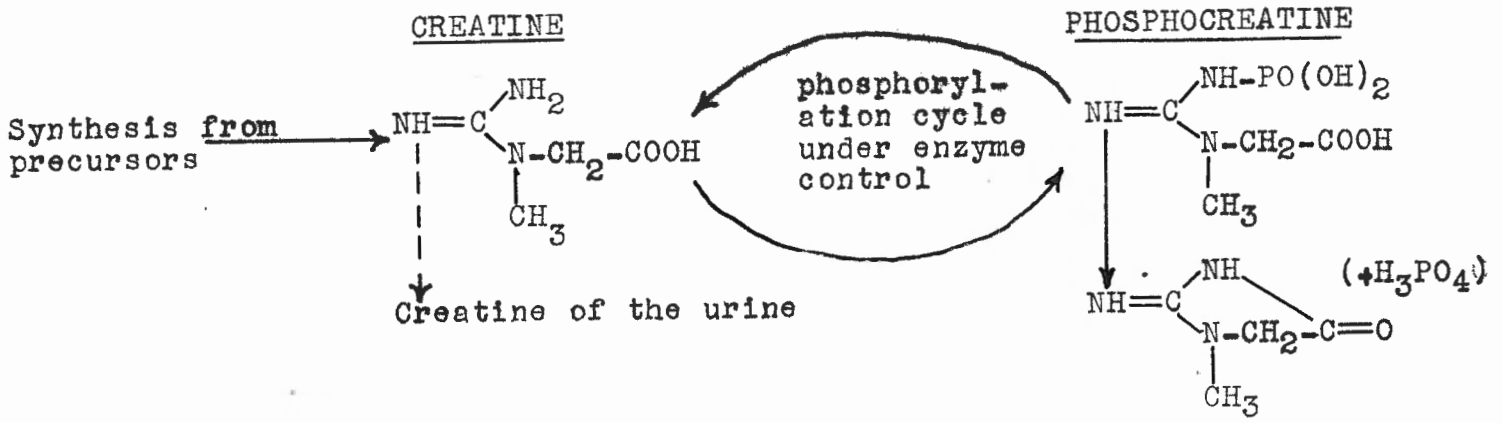
THE ORIGIN OF CREATININE

Creatinine is undoubtedly derived from creatine and it is generally accepted that this takes place by the removal of a molecule of water and the addition of the C-N linkage (Theory A, Wilkins and Fleishman (14)), though there have been a number of workers who have proposed that creatinine might be formed by the

THEORY A



THEORY B



dephosphorylation of phosphocreatine, as shown in Theory B. Boorsook and Dubnoff (15) found that in vitro at 38°C., without the intervention of an enzyme, phosphocreatine breaks down to creatine at the rate of 2% in 24 hours, which is faster than the formation of creatinine from creatine under normal conditions. Rosengart (16) working with minced muscle obtained similiar results and Lipmann (17) also suggested this possibility. Wang (18), as a result of extensive clinical investigation, stated that "the formation of creatinine may be somehow related to the amount of phosphocreatine present in the organism and not to the total creatine contents".

In certain of the muscular dystrophies there is a demonstrable diminution of the creatine output. Due to specific association of creatinine formation and excretion with the integrity of muscle processes, the urinary concentration of this material may, under certain conditions and in certain cases, give a more reliable indication of the disease than the urinary creatine.

Shaffer (19) suggested that creatinine is not derived from all tissues, but that it arises as a result of a special process of tissue catabolism taking

place "largely, if not wholly, in the muscles". Upon this hypothesis was based the belief that a large amount of creatinine excreted in the urine "bears a direct relationship to the potential efficiency of the muscles and is a reliable index of the muscular development of the individual". The belief originally stated by Folin, that creatinine represents a type of endogenous metabolism distinct from the exogenous metabolism of food protein is no longer tenable, as a result of the studies performed by Shoenheimer and his associates (20) with isotopic nitrogen. The constant daily excretion of creatinine in contrast to the highly inconstant excretion of other nitrogenous constituents of the urine, however, indicated that the formation of creatinine is an orderly and well regulated process, the biological significance of which is not entirely apparent. It has been proved that creatinine arises directly from creatine (Bloch, Shoenheimer and Rittenberg (21)). Moreover, it is also clear from the results obtained by numerous investigators that its origin from creatine is somehow associated with utilization of creatine by the muscles, and that the quantity of creatinine in the urine is a fairly adequate measure of the extent to which creatine is being metabolized.

The daily output of creatinine in the urine is constant for the individual, amounting to from 1.5 to 2.0 grams for men and from 0.8 to 1.5 grams for women. Unlike the excretion of urea, which is derived largely from exogenous sources, the creatinine output is practically independent of the protein level of the food. The creatinine excretion is, therefore, considered to be an index of the magnitude of the metabolism of the tissues and especially of the muscle. The daily output of creatinine is extraordinarily constant for the individual; it is not influenced by ordinary exercise or by the urine volume. The creatinine coefficient:

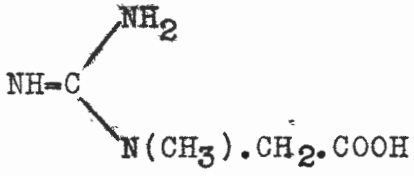
$$\frac{\text{Milligrams creatinine}^{*}\text{ excreted per day}}{\text{Body weight in kilograms}}$$

is from 20 to 26 for the majority of normal men and from 14 to 22 for women. Its value depends upon the muscular development of the individual, the sex variation being presumably due to the different relative amounts of fatty and muscular tissues in male and female bodies. Therefore, an athletic man of very slight build might have a coefficient higher than the very fat lady of the circus.

* Or creatine plus creatinine, when creatinuria exists.

ORIGIN OF CREATINE

Although there is some confusion as to the exact origin of creatinine, it is fairly well established that it comes from creatine. However, the origin of creatine is still a mystery. Many theories have been advanced, but there is still no definite conclusion made by the majority of the investigators. One or the other of the substances which has a similar chemical formula e.g., guanidine, glycine, arginine, histidine, betaine or choline, has been considered as a precursor. Creatine has the following structural formula:



It is, therefore, obvious that from a chemical standpoint creatine may be looked upon as a derivative of glycine, of guanidine, or of guanidino-acetic acid particularly. It is also related to arginine and probably to choline.

The greatest help in the search for a precursor of creatine has been the fact that in certain of the muscular dystrophies there is a great creatinuria. Brand and Harris (22) took advantage of this and fed dystrophic patients amino-acids in order to find whether or not there

was a lack of a precursor in this disease. They kept five patients with progressive muscular dystrophy on a standard purine and creatine-free diet of constant nitrogen, phosphorus and sulfur content for a year and a half. Their urine was analyzed daily for creatinine, creatine, urea, ammonia, uric acid, amino acid and total nitrogen, inorganic phosphorus, and total sulfur. During the experimental periods, amino-acids and other substances were given in addition to the basic diet. There were seventy-four experimental and sixty-six control periods varying in duration from one to three weeks. When glycine or gelatine were given there was an increased creatine excretion up to forty percent above the control level which increase was equivalent to a transformation of four to eight percent of the glycine. During these experiments the sulfur excretion dropped and the extra nitrogen eliminated was less than that given as glycine. This nitrogen and sulfur-sparing effect of glycine continued for more than a month after the period. The transformation of glycine into creatine was further confirmed by a drop in creatine excretion following benzoic acid and sodium benzoate feeding which calls on the body's glycine stores for detoxification purposes. The forty percent rise in the creatine excretion was not seen in

the normal patients studied. The proportion of ingested creatine which is retained is also much less than the normal as shown by the creatine tolerance test. It was also found that glycine plus d-arginine produced no greater creatinuria than the glycine alone. Guanidoacetic acid produced large amounts of creatine. There was a slightly diminished creatine excretion with sodium acetate and a slightly increased excretion with ammonium chloride, sarcosine, l-alanine, and d-arginine. Nucleic acid, urea, lactic acid, uric acid, d-glutamic acid, l-histidine, l-tyrosine, and l-cystine were practically without effect on creatine excretion. Betaine produced an increased creatine excretion for a few days, which dropped below the control level in spite of continued feeding. With the preceeding evidence in mind, on the basis of the cyanic acid theory of Salkowski-Werner-Fosse, Brand and his associates (23) proposed the view that creatine may possibly arise from a side reaction between cyanic acid and glycine.

$$(\text{CYANIC ACID} + 2\ \text{GLYCINE} \longrightarrow \text{CREATINE} + CO_2 + H_2O$$

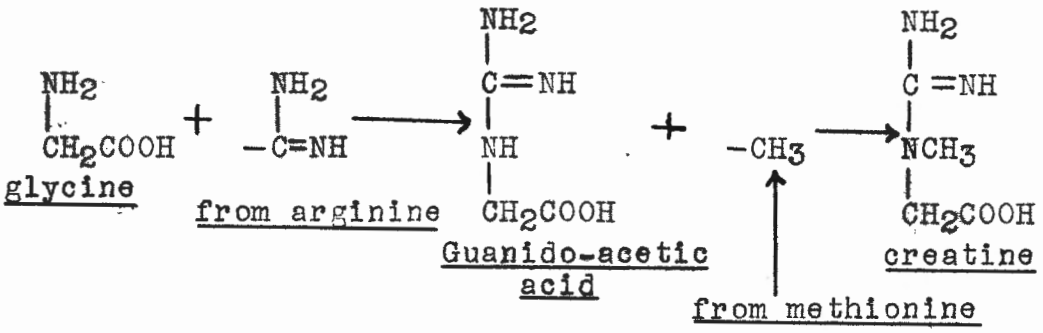
These results, aside from pointing to glycine as the logical precursor, also point to arginine and guanido-acetic acid as being instrumental of creatine

synthesis.

Recently, the subject of the synthesis of creatine has been somewhat clarified by the work of Block and Shoenheimer (24) with isotopes used as markers to identify the particular substance under investigation after it had been absorbed. They showed that the administration of isotopic glycine, consisting of heavy nitrogen (N^{15}) incorporated in the glycine molecule, gave rise to creatine with a high concentration of the nitrogen isotope. Of all the other amino-acids investigated by this method, arginine alone was found to be a primary precursor of creatine.

Although the views of Beard and his associates (25) have not been generally accepted, they maintain that almost any amino-acid as well as urea and other nitrogenous substances can give rise to creatine, and that creatinine is not derived from creatine but that the latter is formed by the hydration of creatinine. The first reaction, it appears, is between arginine and glycine with the formation of guanido-acetic acid, arginine furnishing the amidine group. The guanido-acetic acid then undergoes methylation by the transference of the methyl group from methionine.

Thus:



Wilkins et. al. (14) corraborates this view stating that creatine is synthesized by the combination of arginine and glycine to form guanidoacetic acid or glycocyamine which is methylated by some agent such as methionine or choline. New creatine is constantly being formed to replace the urinary loss of creatine and creatinine. In the muscle creatine enters into a rapid equilibrium exchange with inorganic phosphate. The enzymatic reactions necessary for this cycle involve the formation of adenosine triphosphate and the oxidation of carbohydrates. (26) The excretion of creatine is apparently influenced by factors different from those which govern the output of creatinine. It may very markedly in the same individual. It is high in childhood and low in adult life. It is increased by starvation, high protein diet, carbohydrate deprivation, fevers,

thyrotoxicosis, and by the administration of testosterone proprionate. The complete absence of creatine from the urine at times may be due to the fact that there is a renal threshold so that it is excreted only when the serum concentration exceeds o.58 mgm. percent. In marked contrast the excretion of creatinine is fairly constant for each individual. The relative stability of the output and the lack of effect of exercise and diet led originally to the concept that the total amount of creatinine excreted depended solely upon the total muscle mass of the body. The fact that changes sometimes occur which are greater than can be accounted for by alterations in the muscle mass makes it seem more probable that the creatinine output depends upon the total stores of creatine in the muscle which might be subject to variation, rather than upon the muscle mass. Bloch, Schoenheimer and Rittenberg (21) showed that the rate of excretion of creatinine corresponded to the conversion of two percent of the creatine in the body in twenty-four hours. There is no renal threshold for creatinine.

With the data collected so far, we can come to conclusions as to the different causes for the changes in excretion of creatine or creatinine. In the first place, changes in the rate of synthesis of creatine from

its precursors may affect the rate of excretion. It has been shown by Samuels and Henschel (27) that the synthesis of creatine is increased by the administration of methyl testosterone, and other factors may affect this synthesis in the same manner, although they have not been fully investigated. Secondly, there may be a change in the ability of the muscles to store or liberate creatine or phosphocreatine. Analysis of muscles have shown that the concentration of creatine is decreased in thyrotoxicosis (Wang, 18), in progressive muscular dystrophy (Nevin, 28) and in denervation atrophy (Tower, 29) Wang demonstrated increased creatine and phosphocreatine in the muscle of thyroidectomized animals and Williamson and Gulick (30) found an increased total creatine of muscle after the administration of testosterone proprionate. Thirdly, there may be changes in the rate or in the direction of the creatine-phosphocreatine cycle. Wang has suggested that the thyroid gland may have some bearing on this synthesis or breakdown of creatine.

PROGRESSIVE MUSCULAR DYSTROPHY

CONFLICTS IN DEFINITION

Progressive muscular dystrophy is a disease characterized by degeneration, weakness, and atrophy of various groups of voluntary muscles, notably those of the lower extremity, pelvic and shoulder girdle. Several clinical varieties based on the onset and location of the affected muscles have been suggested, but it is becoming increasingly clear that no sharp division can be made among many of the clinical types. (Hoagland, 31) It is also apparent that some fundamental defect common to the various syndromes may be responsible for the continuity and sequence of the phenomena observed in this group of muscle disorders.

The main point of differentiation is that between the primary and secondary myopathies. Wechsler (32) gives the following anatomical classification of the muscular atrophies which is probably as useful as any classification available:

GROUP I

A. PRIMARY MYOPATHIES

1. PRIMARY MUSCULAR DYSTROPHY
   (Usually of the lower limbs)
   a. Pseudohypertrophic type (Duchenne)
   b. Facio-scapulo-humeral type (Landouzy-Dejerine)
   c. Bulbar type (Hoffmann)
   d. Juvenile scapular (Erb-Zimmerlin)
   e. Infantile-hereditary (Leyden)
2. MYASTHENIA GRAVIS
3. AMYOTONIA CONGENITA (Oppenheim)
4. MYOTONIA CONGENITA (Thomsen)
   a. Early Life (Hereditary)
   b. Myotonia acquisita
5. MYOTONIA ATROPHICA

GROUP II

B. PROGRESSIVE NUCLEAR MUSCULAR ATROPHY

1. Mainly of the small muscles of the hand (Aran-Duchenne)
2. Hereditary, Familial, of infancy, childhood (Werdnig-Hoffman)
3. Sub-acute and chronic poliomyelitis
4. Bulbo-facial of Childhood (Fazio-Londe)
5. Progressive bulbar palsy (Glosso-labio-laryngeal, of Bruchard)

6. Chronic progressive ophthalmoplegia (von Graefe)

Lewin (33) states that the myopathies are primary affections of the muscular system, characterized by weakness and wasting, with or without preliminary enlargement of the muscles, and are not due to involvement of the nervous system.

Barker (34) lists five points of differentiation between the primary myopathies and the progressive muscular atrophy of nervous origin. These points are summarized in Table I on the following page.

Of the various myopathies, the pseudohypertrophic muscular paralysis is the most outstanding. It is also referred to as pseudohypertrophic progressive muscular dystrophy, progressive muscular dystrophy, and idiopathic muscular atrophy. Hough (35) recognizes four distinct types of pseudohypertrophic muscular dystrophy which sometimes grade into each other. They are:

1. The Duchenne pseudohypertrophic type which is the most common variety.

2. A less common type, in which pseudohypertrophy occurs early in the alignment of the muscles of the shoulder girdle. Compared to the Duchenne type,

TABLE I

	PRIMARY MYOPATHY	NEURAL ATROPHY
AGE OF ONSET	Always early or before thirty	in middle or later life
SITES INVOLVED	Usually the trunk and pelvis or shoulder girdle	More distal extremities are involved first
FAMILY TENDENCY	Frequent	Seldom except in the Charcot-Marie-Tooth type.
FIBRILLARY TWITCHINGS	Absent	Almost pathognomonic of neural origin
SPASTICITY	None	Present, but may be combined with myopathy

this form has a later onset and/or a slower development.

3. The Leyden-Moebius type is similiar to, if not identical with the Duchenne type except for the absence of pseudohypertrophy.

4. The facio-scapulo-humeral type of Landouzy-Dejerine is a form characterized by early development and wasting of the facial muscles, with the appearance of the so-called "myopathic facies": apathetic, indifferent expression, loss of wrinkling of the forehead and lessening of the nasolabial folds. The lips are large, the upper lip projecting as the so-called "tapir lip". The power to whistle and pucker the mouth is lost. Labial letters are pronounced with difficulty. The affected child is unable to elevate the corners of the mouth, presenting the so-called "transverse smile". The eyes cannot be completely closed causing lagophthalmos.

Lewin (33) describes also about ten cases of another type: namely, the Endocrine type. Patients with this type of myopathy all look like brothers and sisters since they all have dystrophia adiposogenitalis or Froelich's syndrome.

These classifications are helpful for descriptive purposes, but they also have common characteristics:

they represent familial or hereditary conditions which develop early in life and usually are progressive. Therefore, the different types may be regarded as manifestations of the same disease entity.

There are many forms that cannot be sharply demarcated, such as the Distal Type of Gowers. Whether or not this type should be included in a classification of the primary myopathies is disputable. Batten (36) and Spiller (37) regard it as a primary myopathy. It does differ from the peroneal form of Charcot-Marie-Tooth since there are no peripheral sensory changes. Furthermore, facial involvement is not uncommon and, although atrophy begins in the distal parts, it soon spreads affecting also the muscles of the trunk.

ETIOLOGY

It has become increasingly apparent that progressive muscular dystrophy has a definite familial origin. Bramwell (38) reported that in all the cases diagnosed as progressive muscular dystrophy which later recovered there was no record of a family background for the disorder as far as he could ascertain. The family background is so much a part of the disorder that this statement would lead one to believe that the patients referred to by Bramwell were not cases of progressive muscular dystrophy, but rather of toxic influence of the nervous control of the muscles involved, with probably an endocrine basis.

Several members of the same family may be affected, brothers and sisters alike, but the disease is usually found in the male members. The following is quoted from Davison's review (39): "Bunting described one family in which three males were affected, while the females were not. Barnes found forty-two cases in five generations in a family of about three hundred to three hundred fifty individuals. Of the forty-seven who are living, the fifteen who developed muscular dystrophy were all males. In the first generation there

were six females and all transmitted the disease to eight of their male children (88 percent). The seven females of the second generation transmitted the disease to six out of eight males of the third generation. The children of the males who escaped the disease did not develop muscular dystrophy. The disease apparently is transmitted by the females and may appear in successive generations."

Hoagland (31) states that the disease occurs in a 6:1 ratio in males and females, and that males have the disease more severely. He also corraborates Davison in his belief that there is an hereditary and familial basis.

The etiology of progressive muscular dystrophy has been a mystery since its discovery, notwithstanding the fact that progressive muscular dystrophy has engaged the attention of the clinician, pathologist and neurologist ever since its discovery in the middle of the nineteenth century. The interest of the biochemist is traceable to the work of Levene and Kristeller in 1909 (40).

"Subsequently many studies have revealed a marked derangement in the metabolism of creatine exists in this disease. Endogenous creatine, formed from

amino acids, is not retained nearly as effectively as in normal subjects. When creatine is ingested by patients with progressive muscular dystrophy, much of it is excreted in the urine, the amount retained depending to some extent upon the severity of the disease. This observation has lead to the concept that there is in progressive muscular dystrophy a "diabetic-like" state with respect to the ability of the patient to retain either ingested creatine, or creatine formed endogenously from amino-acids. Whether or not this concept is true, the recognition of the biochemical abberation in creatine metabolism is perhaps the only truly significant contribution made in the last thirty years toward an understanding of the essential nature of this disease." (31)

THE CHEMICAL APPROACH

As already pointed out, the creatine metabolism is markedly disturbed in the muscular dystrophies. In 1925, Bramwell (38) said, "one is not likely to reach any rational conception of treatment of the myopathies from clinical investigation alone, and chemical investigation in these conditions is an uncultivated field which will repay any labor that is spent on it." It is hard to say

at this time whether or not this prediction has proved itself true, but in the past twenty years investigators have worked endlessly on the topic.

Evans and Burr (41) found in experiments with young rats, which were suckled by mothers deprived of vitamin E, that they not only showed decreased growth due to the vitamin E lack, but also displayed paralysis which developed about the twenty-first day of life. This was shown in forty-eight percent of their animals, while seventeen percent recovered and thirty-five percent died. It was shown beyond doubt that the condition was a vitamin deficiency and that the disease resembled an upper motor neuron lesion. They showed that in a great percentage of the affected animals the condition became arrested, the animals remaining normal. Among the affected animals, if the paralysis was not too far advanced the condition could be ameliorated by the administration of the lacking vitamin.

It has been found that histologically the myopathy caused by vitamin E deficiency resembles markedly the muscular dystrophies and amyotrophic lateral sclerosis as far as the muscular and the nervous system is concerned. This finding led

investigators to the assumption that the dystrophies in the human subjects might be the same as those resulting from nutritional deficiency in animals.

In 1939, Einarson and Ringstead (42), on the basis of experiments on rats, suggested that the muscular dystrophies, amyotrophic lateral sclerosis and tabes dorsalis are due to a deficiency of vitamin E.

In 1941, Morgulis and Eppstein (43) attempted to show the minimum requirements for dl-a-tocopherol in albino rabbits. They obtained successful cures in two-thirds of the 112 animals that they studied. They showed, however, that as the quantity of a-tocopherol fed increased beyond a certain limit it became progressively less effective in the protection against the dystrophy. The animal tissues soon became saturated with the vitamin and the excess was excreted. Another view put forth by these workers as to the cause of the excretion was that there might possibly be a greater rate of destruction occurring, but if that did take place, it took place only after the tissues became saturated. The rabbits were fed a synthetic diet lacking in the vitamin E. The control diet included the vitamins. Morgulis and Eppstein corraborated the evidence of Mattill (44) that

injections of dl-a-tocopherol acetate were inefficient in the cure of dystrophic rabbits. In these experiments they showed that the minimum requirements of dl-a-tocopherylacetate, as determined by the cure of dystrophic rabbits, is probably about 0.32 mg. for kilogram of body weight per day (calculated as free a-tocopherol). They also showed that the interval during which a supplement protects the animal against dystrophy is directly proportional to the total amount of a-tocopherol fed, provided the amount is below approximately 60 mg. The minimum requirement were not affected by sex or age.

Further studies have been made to secure information on the manner in which a-tocopherol intervenes in the biological processes of oxidation in muscle, on its relation to changes in the creatine and chloride in muscle, and on the enzyme systems. These studies were made on dystrophic rabbits, rats, hamsters and chicks, and both in vitro and in vivo experiments were carried out.

Morgulis and Osheroff (45) found that in dystrophic rabbit muscles there was a marked increase in the content of sodium and chloride, but this receded to normal within six to seven weeks when the deficient diet was supplemented with wheat germ. Hurwitz in 1936 (46)

had previously noticed in two patients with progressive muscular dystrophy a reduced blood chloride accompanied by an abnormal salt tolerance and retarded excretion of salt. Houchin and Matill (47) reported that there was no change in the chloride concentration of the muscle dystrophic rabbits, and it remained high during the parenteral administration of a-tocopherol phosphate.

DISTURBANCES IN THE METABOLISM OF THE OTHER MINERAL CONSTITUENTS

In the nutritional muscular dystrophy, as in many other conditions, we find that there is an antithesis of action of the sodium and potassium. Whereas there is a marked increase in the sodium and chloride content of dystrophic muscles, there is a concompetent decrease in the potassium content, but this increases again when the regenerative processes are initiated by proper dietary supplement. It is shown that the sodium and potassium changes almost compensate for each other. (Morgulis and Osheroff)

Morgulis and Osheroff (45) showed that there is an enormous increase in the calcium content of the dystrophic muscles in deficient rabbits, but this was

apparently quickly restored to normal on the curative diet.

In 1916 McCrudden and Sargent (48) noted and reported hypocholesteremia in the blood of dystrophic patients. Morgulis and his associates (49) showed in work with normal and dystrophic rabbits that the lipid content of the heart was not changed in nutritional muscular dystrophy, but that the skeletal muscles of the dystrophic animals have a very markedly increased cholesterol content. They came to the conclusion that there existed not only hypercholesterolemia, but also a specific and very striking rise in the cholesterol content in the skeletal muscles. The accumulation of the cholesterol raises the question as to its origin. We know that cholesterol can be synthesized in the organism of man and the higher animals as shown by Page 1937 (50), but neither the site of its formation nor its source is definite according to this author. Morgulis stated that we are dealing with an actual synthesis if cholesterol found in the muscles of dystrophic rabbits and not merely with a redistribution of cholesterol already present. Morgulis et. al. (49) have shown that the skeletal muscles alone manifest a greatly increased fat, lipoid phosphorous and cholesterol content, and that the

gastrocnemious was affected the most while the abdominal muscles the least.

Houchin and Matill (47) in their studies with dystrophic rats, rabbits and hamsters showed that the dystrophic muscles from vitamin E deficient animals, has a higher oxygen consumption, a lower creatine content, and a higher chloride content than the muscle from normal animals. The differences are great and hamster dystrophic muscle has an oxygen consumption of 250% greater and rat muscle 160% greater than normal muscle. They showed that the oxygen uptake appeared to increase with the severity of the dystrophic condition. Oral administration of a-tocopherol to the dystrophic hamster resulted in the lowering of the oxygen consumption of the affected muscles to a normal level within twenty-seven hours, whereas the administration by mouth of the a-tocopherol acetate lowered the oxygen consumption of the muscle within ten hours. Later, Houchin (51) showed that the high oxygen consumption of slices from dystrophic rabbit and hamster muscle was lowered 40% by the addition of a-tocopherol phosphate directly to the medium, while the oxygen consumption of slices from normal muscle was not affected. Later, it was shown that parenteral administration of a-tocopherol phosphate caused the high

oxygen consumption of the dystrophic rabbit muscle to drop to a nearly normal level. A sharp decline in the muscle creatine content accompanied the lowering of the oxygen consumption. Houchin was led to the conclusion that a-tocopherol phosphate is intimately connected with the complicated and yet unknown enzyme systems by which the physiological integrity of muscle tissue is maintained.

In the majority of the patients with progressive muscular dystrophy there is an altered carbohydrate metabolism producing a hypoglucemia. Janney and his associates (52) and Mc Crudden and Sargen (48) have reported this as early as 1918, but others deny that hypoglucemia is a constant feature.

Janney, Goodhart and Issacson (52) state that "the constant presence of hypoglucemia and the evidence of delayed glucose utilization in muscular dystrophy make it probable that defects in carbohydrate metabolism are intimately connected with, if not directly causative of, the metabolic picture of the disease. It seem likely that the muscles in this condition undergo weakness, atrophy, and degeneration as the supply of their carbohydrate pablum is interfered with".

McCrudden and Sargent (48) are of the opinion that the hypoglucemia may underlie the great fatiguability. Goodhart and Globus (55), who also emphasize the association of hypoglucemia with muscular dystrophy, hold similiar views. Bramwell (38) and Shrivastava (53) report that utilization of glucose is not always delayed and that in certain instances the utilization may even be rapid. Lewin (33) advocates the use of adrenalin to produce a hyperglucemia and an increase in the utilization of dextrose by mobilizing the stored glycogen. He also states that adrenal cortical extract increases glycogenolysis in the liver and should be beneficial.

ETIOLOGY----ENDOCRINE ?

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The etiology of the muscle dystrophies being uncertain, it is not surprising that the endocrine glands should have been incriminated. Practically no gland escaped being implicated, but the pineal and pituitary glands were particularly singled out because of a similiarity of symptoms in diseases of the ductless glands and those found in the dystrophic patient. Hoagland (31), studying the effects of the administration of certain hormones on creatinuria in progressive muscular dystrophy, found that testosterone proprionate, administered over varying periods of time, resulted in the retention of creatine both in normal male children and in male children with progressive muscular dystrophy. In normal children this caused diminished creatine output, and in both the normal and dystrophic child creatinuria was increased for variable periods of time following the withdrawal of the hormone. An increase in the excretion of creatine in progressive muscular dystrophy occurred following the administration of methyl testosterone; but neither testosterone proprionate nor methyl testosterone appeared to bring about any consistent change in the output of urinary creatinine.

Hoagland also studied the effects of concentrates of the hormones of the hypophysis on the excretion of creatine and creatinine in progressive muscular dystrophy. The results led him to believe that the essential defect is not found in the mechanisms which control the synthesis of creatine or in the mechanisms responsible for the transport of this substance, but rather in those systems which are linked with the production of creatinine in normal muscles.

There have been few autopsies on patients with pseudohypertrophic muscular dystrophy, but there are three cases that I could find in which there was found the presence of thymic tissue. (Bevans (54), and Goodhart and Globus (55)). Such findings, however, are not particularly significant, as the incidence of thymic tissue in normal persons is about the same.

Some relationship between pituitary dysfunction and progressive muscular dystrophy has been suggested by many authors, due to the more than casual occurence of pituitary adiposity and acromegaly in dystrophic patients. In fact, Lewin (33), as previously stated, goes so far as to define a type of dystrophy which he calls the Endocrine Type, associated with a pituitary gland dysfunction, but concrete evidence for a relationship

is lacking. Bramwell (38) admits that there appears to be a relationship between disorders of the pituitary gland and muscular dystrophies, but thinks that both conditions might be due to a common cause rather than that the muscular dystrophy is secondary to the endocrine disturbance.

A relationship between the pineal gland and muscular dystrophy has been suggested by Timme (56) who, in reporting four cases of "a somewhat atypical muscular dystrophy rather resembling Erb's infantile type," states that, "the probability approaches pretty closely to proof that the disturbances of pineal gland play an important role in the pathogeny of progressive muscular dystrophy". He puts forth some proof that there is a real correlation between the glandular pathology and the dystrophy.

ETIOLOGY----NERVOUS ?

Kure (57) suggested that progressive muscular dystrophy was caused by lesions of the autonomic nervous system. This was based upon the experimental fact that dystrophy of the leg muscles could be produced in dogs by extirpating the abdominal sympathetic chain. Furthermore, by cutting the corresponding posterior nerve roots at the same time, the dystrophic changes could be accellerated, and this was found later to be due to the parasympathetic innervation of the muscle. In six patients out of twenty-one, whose cervical sympathetic had been severed for therapeutic purposes, Kure found that there was marked atrophy of the trapezius, deltoid, and pectoralis major several months after the operation, and histological examination revealed typical dystrophic changes. Occasionally the upper arm muscles were involved, but the forearm and hand were always free from change. He suggested that the reason why muscular dystrophy did not appear in all the operated cases may be due to a difference in the muscular innervation in different individuals, whether they are vagotonic or sympathicotonic. In sympathicotonic individuals, since their muscles are chiefly under the trophic influence of the sympathetic system, the resection of this

supply would induce muscular dystrophy. As further evidence that muscle dystrophy is an autonomic nervous system disease, he showed that both sympathectomized and dystrophic muscles have a decreased tone and reflex patterns which are almost identical. Besides, both react to adrenalin upon fatigue, which is not characteristic of normal muscle. Kure also pointed out in his paper that there were varying amounts of sympathetic fibers going to the different muscles, and that the phrenic, intercostal and muscularis nerves contained many sympathetic fibers which innervated the pectoralis major, gluteus maximus and quadriceps femoris, while there were extremely few sympathetic fibers to the policus brevi and the lumbricales in the hand, which is seldom involved in muscular dystrophy. A falacy in his theory seems to be that, although the heart and the muscles of the respiratory system are extensively supplied with autonomic fibers, these muscles are among the last to be affected in progressive dystrophy.

Bramwell (38) also postulated a sympathetic nervous system lesion as one of the causes of muscular dystrophy, and presented considerable evidence suggesting that the skeletal muscles in man have a dual innervation; a somatic supply concerned with movement and a

sympathetic supply concerned with fixation. He stated that the gradual loss of power and wasting may be determined as either a direct consequence of interference with the sympathetic innervation or as a consequence of secondary involvement of the somatic nerve fibrils to the changes in muscles and interstitial tissue which result from disease of the sympathetic nerve supply.

HISTOLOGIC CHANGES IN PSEUDOHYPERTROPHIC MUSCULAR DYSTROPHY

In progressive muscular dystrophy changes occur in the muscle fibers themselves which accounts for the weakness and paralysis of the muscles in the presence of a motor nerve which, to all appearances, is perfectly normal. This is in contrast to the secondary myopathies, where the basic lesion is in the spinal cord or in the peripheral nerve, while the changes in the muscle are due to the alteration in the lower motor neurons rather than to loss of integrity of the muscle tissue *per se*.

In the pseudohypertrophic form of muscular dystrophy the muscles are enlarged and are firmer than normal, which makes a bizarre picture considering the profound weakness exhibited by the muscles. These changes are most often seen in the gastrocnemius, deltoid, supraspinatus and infraspinatus muscles. The "infant Hercules" is the common term used to describe the appearance of these children.

The microscopic findings vary in the different muscles involved and even in different parts of the same muscle. In some muscles, especially in the early stage, the muscle fibers are swollen and

rounded, with loss of the characteristic transverse striations. The nuclei of the sarcolemma are more numerous, but there is no increase in interstitial tissue. In other muscles, especially in the later stages, many of the fibers are smaller than normal, with marked increase in the interstitial tissue and thickening of the walls of the blood vessels. This interstitial increase is greater than can be accounted for by a mere replacement fibrosis, and is much more marked than that seen in progressive muscular atrophy. It has been suggested that the changes in the muscle and the interstitial tissue are due to some common cause.

In the pseudohypertrophic form, the enlargement of the muscles is at first due to the large size of the muscle fibers. Later, a great deposit of fat occurs between the fibers, thus making the enlargement greater. In a number of patients, the pseudohypertrophy is associated with an endocrine disorder of pituitary gland origin. It is thought by some that the deposition of fat in pseudohypertrophic muscular dystrophy is due to this pituitary dysfunction, but there are no actual pathological observations to corraborate this idea.

Bevans (54) in a recent review of the

literature states that the changes of smooth muscle in the gastrointestinal tract and elsewhere had not, in the study of progressive muscular atrophy, received adequate attention. He reviewed the histories of four patients (ages 14 to 20 years), and necropsy findings showing that all of these patients presented myocardial lesions of varying severity. The lesions were similar to but not identical with the changes seen in the skeletal muscles. One of the four patients died of cardiac failure and the others showed symptoms of disturbed cardiac rhythm. The tongue and the upper esophagus presented changes differing only in degree from those seen in the skeletal muscles, but these changes were not accompanied by symptoms, except in one patient. The changes in the gastrointestinal tract were remarkable. The smooth muscle of the gastrointestinal tract showed edema, variation of size, atrophy and disappearance of cells and, occasionally, small areas of necrosis. Gross lesions included marked dilatation of the stomach (in 2 cases) and perforation (in one), dilatation of the colon (in 2 cases) and fecal impaction (in one). The changes in the smooth muscles were not considered specific, although it was suggested that, in many ways, they were comparable to those seen in the skeletal

muscles. No outstanding abnormalities of the endocrine system were found, in these four patients, and there were no lesions of the smooth muscle, of the vascular system or of other organs.

Globus, studying the heart muscle in progressive muscular dystrophy (59) also found that the heart was involved in a great number of patients. While observing the clinical course of several cases of progressive muscular dystrophy he noticed that patients who had remained in statu quo for fairly long periods of time, would, suddenly and without warning, develop in rapid succession hypostatic pneumonia, pulmonary edema, hydropericardium and hydrothorax, culminating in death. It was natural to suppose that some cardiovascular disturbance was involved in this condition.

Globus collected all the case histories found in the literature and discovered in all of them fairly definite indications of myocardial disease of varying degree. Although acute infection was present in three patients, this was not sufficient to explain the diffuse nature and the morphologic character of the myocardial involvement. He found in the intercurrent diseases causing terminal illness that there was one case of pulmonary tuberculosis, a "pulmonary condition", two cases of

pneumonia and the balance of the group were classified as pulmonary edema and grave gastrointestinal disturbances. There is little reason to suppose that the terminal acute pulmonary conditions or the gastrointestinal disturbances accounted for the chronic lesions of the heart, and he concludes that probably the cardiac insufficiency was responsible for the development of the conditions leading to death.

In studying the reports on the findings in organs other than the heart, Globus found few pathologic changes which could in any way suggest an etiologic factor responsible for the heart lesions other than the primary myopathy. The character of the lesions which he found lent further support to his views. He explained the decreased pathology in the microscopic examination of the heart as being due to a certain degree of resistance or partial immunity to the morbid process on the part of the heart muscle. This resistance or immunity prevents the heart muscle from going beyond the stage of fibrosis.

The suggestion that the skeletal muscle changes are different in primary and secondary myopathies led Bowden to investigate this in an endeavor to find diagnostic points in the differentiation of cases of these

similar disorders. In a recent paper (58) Bowden described extensive studies of biopsy material from a case of progressive muscular dystrophy, from which he came to the conclusion that the early changes consisted in a reaction of the nuclei and the granular constituents of the sarcoplasm, but that there is complete dedifferentiation of the striated material leading to fragmentation of the muscle fibers, accompanied by a breakdown of the chromatin of the nuclei. He thus showed that the late changes in dystrophic muscle fibers are identical with those observed in the final stages of denervation atrophy. He found, as had been previously noted, that in progressive muscular dystrophy the fibers in the nerve trunks remained intact, but that degeneration of the muscle fibers apparently led to loss of contact at the myoneural junction, which was followed by an abortive regeneration of the terminal nerve fibers. From such evidence he concluded that examination of biopsy material of muscle in suspected cases should afford valuable evidence for diagnosis.

SYMPTOMS AND SIGNS

The symptoms of progressive muscular dystrophy are so striking that the condition can hardly be overlooked. The symptoms come on early in childhood, nearly always before the tenth year, and generally between the second and seventh years. The disease represents an atrophy and pseudohypertrophy, usually first noticed in the muscles of the pelvis, thigh, and the extensors of the spinal column, resulting in general weakness of the lower extremities accompanied by a marked increase in the size of certain muscle groups, usually those of the calves. But pseudohypertrophy may affect any muscle group of the lower extremity. The muscular weakness results in a waddling gait which consists of an excessive raising and lowering of the pelvis in walking. Or with involvement of other muscle groups, the patient experiences difficulty in getting up from the sitting or reclining position. The manner of rising from the reclining position is almost pathognomic for the dystrophies. If the patient is lying on his back, he rolls over on his face and abdomen, rests the hands upon the ground and raises the trunk until he is in a kneeling position, lifts

the knees from the ground and supports himself only with his hands and feet on the ground. Then, by placing one hand on the knee of the same side, he brings the body up with a jerk or he places both hands at successively higher levels on the thigh until he assumes the erect posture. This latter method of "climbing up his own legs" is one of the most common symptoms described in the literature. With progression of the disease, the patient can no longer rise from the ground unless assisted or unless he can grasp a stationary object. Children walk very unsteadily and fall easily; this may be one of the first signs noticed in the very young child.

The weakness of the abdominal muscles and of the muscles producing extension of the hip joint causes a lordosis. A scoliosis may also be observed. The classical "loose shoulders" or "winged scapulae" result when the disorder involves the muscles of the shoulder girdle. The weakness or falling in of the abdominal muscles causes, on deep inspiration, almost an hour-glass constriction of the waist, the "taille de guepe", or "wasp waist".

The atrophy usually begins in the proximal parts of the body and in the trunk muscles. The distal musculature of the hands and feet is usually spared.

Instead of atrophy, there may be pseudohypertrophy and this may be noticed in the muscles of the calf or arm and the posterior muscles of the thigh. The pseudohypertrophy of the upper extremity is usually seen in the triceps and deltoid muscles. The combination of atrophy and pseudohypertrophy causes an alteration in the configuration of the muscles. But in spite of the hypertrophy, the muscles have less power. The most frequently enlarged is the infraspinatus, next the supraspinatus and the deltoid. The pectoralis and the latissimus dorsi are not enlarged but, on the contrary, are generally markedly wasted. Bramwell (38) states that the muscles especially predisposed to dystrophy are: (a) those which develop early (with the most rapidity) in the foetus; (b) those which are regressive (in the sense that they no longer fulfil such an important function as in an earlier stage of evolution) as opposed to those which have been acquired at a later date or have taken on new functions; and (c) those especially associated with the function of fixation. The weakness of the shoulder muscles produces the characteristic condition that, when the affected children are picked up by grasping them by the arms, they slip through the hands. The rhomboids and the levator anguli scapulae,

the biceps and the triceps are gradually involved, and later in the disease there is such extensive atrophy, with corresponding weakness, of all the affected muscle groups that the patient may be unable to walk or even stand, and is absolutely helpless except for the use of his hands. Dystrophy of the orbicularis oculi and oris and of the muscles of mastication has been described. In case the orbicularis oris muscles are involved there is usually pseudohypertrophy and, the lips being swollen, the patient is unable to pout the mouth or whistle. The affection of the muscles of the neck and face results in the myopathic facies ("facies of a sphinx"). Atrophy of the muscles of respiration of the heart and of the visceral muscles has also been demonstrated. The dystrophy is always bilateral.

Fribrillations due to anterior horn cell disease, as in the ordinary atrophies, are not found in this order. Cases with fibrillations reported belong possibly in the group of neural disorders. The electrical reactions show lessened response to faradism and galvanism but no reaction of degeneration. (Bowden and Gutmann, 58)

The tendon reflexes of the atrophic and pseudohypertrophic groups of muscles are diminished or absent depending upon the degree of atrophy. The ankle jerk

remains the longest.

Contractures of the tendons are known to take place, and permanent contractures of the biceps, flexors of the knees and calf muscles are known as dystrophia myoscleratica. Atrophy of bones, arthropathies and scleroderma have been recorded. In some instances, disturbances in the endocrine glands as manifested by scantiness of hair, female distribution of pubic hair, atrophic genitalia and hypopituitary obesity are not unusual. Apparently the mental status of these people is perfectly normal although due to their disability they are somewhat retarded.

As for the other forms of the muscular dystrophies, there is little to be said. In the juvenile form, the symptoms do not make their appearance until between the tenth and sixteenth year, and in the facio-scapulo-humeral form the disability is confined chiefly to the upper extremities and the process begins in the muscles of the face.

THE TREATMENT OF PROGRESSIVE MUSCULAR DYSTROPHY

The treatment of progressive muscular dystrophy has only been able to follow the lines of research on the etiology of the disease. Since the etiology is unknown, the only logical approach to treatment is to follow the various leads given by the biochemist working with laboratory animals. This has lead to more or less a "faddish" treatment cycle, with the various endocrine preparations, amino-acids, vitamins, etc. The results, so far, have been inconclusive, but in certain cases some progress has been made. It is difficult to evaluate the methods of treatment since the patients have not been observed for long enough periods, and it is hard to tell whether remissions have been spontaneous or therapeutic.

Brand, Harris, Sandberg and Ringer (23), who were the first to suggest the relationship of glycine to muscle metabolism, found that the ingestion of this amino-acid was followed by a large increase in urinary creatine. Such increased excretion of creatine after administration of glycine occurs not only in progressive muscular dystrophy but in a variety of other conditions in which the muscles are involved. The normal

person can readily synthesize glycine. The relationship between glycine and creatine seem to play an important role in muscle function. The daily ingestion of 5 grams of glycine is followed by a definite rise in the creatinuria; ingestion of 15 to 20 grams, however, is generally advocated and this amount will increase the daily excretion of creatine 300 to 500 mg., the more advanced cases excreting larger amounts. After a period of from two to eight weeks, the creatinuria begins to decrease in spite of continued rise of the glycine, until it falls to the control level. A rise in the creatinine output coincides with the decrease in the creatinuria and an improvement in the patient's ability to retain ingested creatine. These changes in the metabolism disappear in the course of a few weeks after the cessation of glycine ingestion, but return when the administration is resumed. While these changes in metabolism are taking place, the patients improved remarkably. However, none of the patients with muscular dystrophy treated with glycine showed such striking improvement as those reported by Thomas, Milhorat and Techner. (60)

Thomas, Milhorat and Technor found that discontinuence and resumption of the glycine therapy were

followed by retrogression and improvement, respectively. The first symptoms reported in half of their patients was a feeling of crawling or rumbling sensation in the muscles which in one cases was so severe that it interfered with the patient's sleep. The muscle groups most affected were those whose function was the most impaired. This curious feeling appears some days before the creatinuria begins to fall and disappears in two to fourteen days after further administration of glycine. Fatigue, which frequently constitutes a prominent and distressing symptom in this disease, also disappears. Gradually the function of certain groups of muscles improves to such an extent that stair climbing, rising from the floor and bicycle riding are carried out more effectively.

The effects of glycine feeding were studied by Lewin (33) for periods of up to fourteen months, but he found little tangible evidence of improvement in the muscular function. However, muscle biopsy specimens removed after treatment were distinctly better in quality, chemically and histologically, than similar specimens taken before treatment. Regeneration of the muscle fibers was accompanied by restoration of various characteristic muscle components.

Hurwitz (46) states that the opinion regarding the value of glycine is divided. Milhorat (60) and Tripoli (61), and their co-workers, reported definite improvement on this therapy, but Brand (62) reported no striking benefit with this therapy in 46 patients studied. Boothby (63) and Cheney (64) also share this opinion. Hurwitz treated 12 patients with 4 to 30 grams of glycine daily for 6 to 35 months. He found subjective improvement in 7 patients; increased appetite, gain in weight, a feeling of well being, and greater endurance due to the decreased fatiguability of the muscles involved. There were no parasthesias in this group. Hurwitz believes that in two of his patients treated with glycine the disease was arrested.

The mode of action of glycine is still unsettled but it is believed that in dystrophy the muscles are unable to retain creatine. Within the body the glycine forms creatine which is retained in the muscles for a short time, at least; and clinical improvement results. Furthermore, the glycine increases the specific dynamic action of proteins, it forms glutathione with cystine and glutamic acid, and it also has a sparing effect on nitrogen and sulfur metabolism. The stimulation of metabolism with glycine probably accounts

for the subjective improvement of the patients.

In 1938, Einarson and Ringsted (42) suggested that the muscular dystrophies, amyotrophic lateral sclerosis and tabes dorsalis were due to a deficiency of vitamin E in the diet. Bicknell (65) and Stone (66) were strongly in favor of supplying vitamin E, and Bicknell reported that twelve out of thirteen patients with progressive muscular dystrophy improved on a diet including 14 grams of whole wheat germ fed twice daily. The believed that normal diets are deficient in vitamin E, but did not think that the anti-sterility factor (alpha-tocopherol) was identical with the myotrophic and neurotrophic factors.

Hafner and his associates (68) claim that the pathologic change in vitamin E deficient animals (degenerative changes in the central nervous system and in the striated muscles) bear a marked resemblance to those present in certain human neuromuscular diseases, particularly progressive muscular dystrophy and amyotrophic lateral sclerosis. Although the possible relationship between vitamin E deficiency and the pathogenesis of these human disorders was apparent, it was not until 1940 that the first reports were published of clinical observations on the use of vitamin E in these conditions.

Wechsler (67) found some improvement in patients with amyotrophic lateral sclerosis feeding wheat germ and a-tocopherol acetate both orally and intramuscularly. In a recent paper, Hafner (68) reports nine patients treated with 75 mg. of synthetic-dl-a-tocopherol (ephynal acetate) daily over periods of three to twenty-seven months, in which he determined muscle strength as well as urinary creatine and creatinine excretion. Four showed objective evidence of an increase in strength in certain muscle groups, together with some subjective improvement; two remained stationary and three became progressively weaker. There were no changes in the urinary excretion of creatine and creatinine. Hafner found it impossible from his observations to draw definite conclusions as to the efficacy of synthetic dl-a-tocopherol in the treatment of progressive muscular dystrophy, although about half of the patients showed some improvement even though the disease usually runs a progressively downhill course.

However, the failures in the treatment of progressive muscular dystrophy with vitamin E preparations have just begun to be reported. Since 1942, Schwarz, Gammon and Masland (69), Pohl and Baethke (70), Alphers, Gaskill and Cantrow (71), Zech and Telford (72),

Lubin (73) and Davison (39) all agree in their reports that the treatment whether with wheat germ or with the synthetic tocopherol prepatation is of little or of no value.

Antopol and Shotland (74) advocated the use of pyrodoxine (vitamin B_6) in the treatment of progressive msucular dystrophy and reported considerable improvement in six patients. However, the use of this vitamin has not been extensive and does not seem to be of much value.

The failure of alpha-tocopherol in the form of wheat germ or as the synthetic acetate ester has been one of the strongest arguments against the idea that progressive muscular dystrophy in man is similar to the nutritional muscular dystrophy in animals. Blinn (75), in 1946, reviewed the relationship between these two disorders.

No report has been found in the literature on the use of the water soluble phosphate ester of a-tocopherol in human subjects. This ester was used by Houchin (51) in hamsters and rabbits, and earlier, by Morgulis and Eppstein with admirable results, and whether or not there is a correllation between the nutritional dystrophies and the human myopathies, it would

be of interest to try this preparation on human subjects.

In 1930, Kure and Okinaka (76) expressed the belief that the basic disturbance in progressive muscular dystrophy was an alteration of the autonomic nervous system, and they advocated the use of from thirty to fifty injections daily or on alternate days of from 0.2 to 0.3 cc. of a 1:1000 solution of epinephrine hydrochloride and from 1.0 to 2.0 cc. of a 1% solution of pilocarpin hydrochloride. Hough (35) studied the effect of this treatment in 38 patients. Hurwitz, in similar studies agrees with the claim that this treatment causes symptomatic relief and may slow the rate of progress of the disease, but does not cure it or alter the mortality.

Many other therapeutic measures have been tried, but there is little to indicate a curative action on the disease. The patient is helped symptomatically and for this reason they should be employed. In 1914 Parhon (77) fed preparations of fetal muscle and reported improvement in two cases, but other reports on this therapy are lacking. Some have reported that calcium lactate is of value, but Hurwitz (46) had poor results. Many investigators recommend a high vitamin diet

consisting of an abundance of fresh fruits and vegetables, etc.

Endocrine therapy should be used whenever tenable, especially in cases resembling what Lewin calls the endocrine type of the disorder. The chief glands used are the thyroid, pituitary, parathyroid and adrenals. The therapy with the adrenal medullary and cortical hormones has already been discussed. Hurwitz used all the glandular products without apparent benefit, but it seems that they should not be overlooked where there is any indication of a possible need.

Other general measures consist in avoidance of overexertion, moderate massage and physiotherapy, especially in the early stages of the disorder, at which time galvanic stimulation amy also be of some value. Orthopedic appliances have been advocated by some, but Davison (39) doubts their value. He also decries the use of tenotomy in cases where there has been a contracture, because this operation merely increases the patient's disability.

SUMMARY AND CONCLUSIONS

1. Although there is considerable confusion as to the origin of creatine, it appears that this substance is synthesized from amino-acids, by a reaction between the amidine group of arginine and glycine forming glycocyamine which, in turn, is methylated by the transference of methyl groups from methionine.

2. Due to the fact that human progressive muscular dystrophy does not behave like the muscular dystrophy in animals of nutritional origin (vitamin E deficiency) it should be regarded a dissimilar process.

3. It is apparent that although the theories of nervous and endocrine origin of progressive muscular dystrophy have more or less fallen into disrepute, the points in favor of a sympathetic, or at least an autonomic nervous system lesion in muscular dystrophy are too important to be disregarded completely; and it appears that more work should be done along these lines.

4. With the information at hand, it appears that we cannot place the etiology of muscular dystrophy

into any single category, and it must be said that the etiology of this disease is still not understood.

5. There is, as yet, no satisfactory treatment for muscular dystrophy.

6. There is excellent evidence for the presence of a family diathesis, and the hereditary nature of the disease is fairly certain.

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