A CRITICAL REVIEW

PRIMARY DISEASES OF VOLUNTARY MUSCLES

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Introduction

THE voluntary muscular system forms in an average male about 43 per cent. of the total body weight. It is a very uniform system and is composed of aggregations of individual muscle fibres each of which are complex multi-nucleated cells, consisting of a sarcolemmal sheath and its nuclei, a motor end plate, and contractile substance. This system is affected by a large group of primary diseases, i.e. diseases in which the essential disturbance of function is most probably located in the muscle fibre or myoneural junction. The pathogenesis of all these diseases, which have been clearly recognized clinically for half a century, has so far remained obscure. In recent years, however, advances in the physiology of the muscle fibre, especially as regards the chemistry of muscular contraction and the transmission of normal excitation from nerve to muscle, have opened up new methods of approach to the study of muscular diseases and much work along these lines has already been done. The results so far are perhaps infinitesimal compared with the vastness of the problems awaiting solution, but it is to be hoped that they are only the first fruits of greater advances in the immediate future. The time now appears opportune to survey the work in this field, to evaluate the studies which have so far been published, and to discuss the lines along which further progress is likely to be made. It would not be possible in the compass of a short review to deal in detail with all aspects of primary diseases of voluntary muscle. Attention must therefore be specially directed to the results of recent biochemical studies and only such clinical, therapeutic, or histological details included as are necessary to make the review comprehensible.

It will also be necessary to exclude from consideration the large group of inflammatory diseases included under the term "myositis" and also such muscular abnormalities as cramp, myokimia, and the weakness in Addison's disease.

Progressive Muscular Dystrophy

Muscular dystrophy or myopathic atrophy is a disease in which large groups of voluntary muscles undergo primary degeneration. The age of onset

and the location of the affected muscles have led to the recognition of several clinical types of the disease, but as far as is known at present there is no essential pathological difference between these types. The histological features of the affected muscles have so far given no clue to the cause of the disease, but little attention has been paid to the anatomical changes since their first description. This is to be regretted, because it is clear that there is much to be learned about the appearance of the muscle fibre in the premyopathic stage, the sequence of changes in a degenerating fibre, and the variation of the histological picture with the rapidity of the degeneration. It is also possible that with the development of histochemical methods information may eventually be gained about the chemical process accompanying the degeneration. As far as one can see at present, however, this degeneration would appear to be secondary to alterations in the actual protoplasm of the fibre, about the nature of which we have no idea. The problem appears very difficult, but neither this difficulty nor the fact that the disease is hereditary and familial precludes the possibility that it might be possible to alter the course of the disease were the biochemical changes associated with the muscle degeneration discovered. For this reason the recent biochemical researches in this disease and the methods of treatment founded thereon have been followed with great interest. These researches have centred round the role of creatine in the metabolism of voluntary muscle and the discovery that the amino-acid glycine is a precursor of creatine in the human body.

Creatine-Creatinine Metabolism and the Changes produced by Glycine

It will be necessary right at the outset to call to mind some simple facts and chemical relationships with regard to creatine and muscle physiology. Creatine is a chemical constituent of striated muscle and 98 per cent. of the creatine in the body is to be found in this tissue. In muscle it is linked up with phosphoric acid in a highly labile compound usually termed phosphagen. The breakdown of this compound and its resynthesis play an important part in the chemistry of muscular contraction, which also involves other important reactions, namely the breakdown of glycogen to lactic acid through certain soluble carbohydrate esters and the breakdown of adenosine triphosphoric acid (adenyl pyrophosphate). The full details and significance of these changes are not fully understood. As a result of the endogenous muscle metabolism creatinine, which is the anhydride of creatine, is excreted in the urine to the extent of about 23 mg. per kilogram of the body weight in the 24 hours. This is the creatinine coefficient, and it is a fairly constant figure for each individual and is directly related to the total mass of voluntary muscle.

In the adult male no creatine is excreted in the urine, because it is all metabolized or stored in the muscles ; but in children up to seven years of age and periodically in some adult women some creatine is excreted in the urine. Although the origin of creatine in the body is not definitely known, this can only mean that in children more creatine is formed in the body than can be metabolized by the muscles at this stage in their development. The reason for the periodic excretion in women is not known.

In such conditions as diabetes, exophthalmic goitre, and during periods of fever and starvation creatine appears in the urine, so that increase in endogenous metabolism of muscle from different causes prevents the storage and conversion into creatinine of the normal amounts of creatine. This will also happen if a large amount of muscle tissue is lost, as through the amputation of a limb.

From these observations it is to be expected that in cases of muscular dystrophy where there is considerable loss of muscle tissue with impairment of function of the remainder, alteration would occur in the normal output of creatinine in the urine. That such is the case has been known for a very long time.

Rosenthal (1870) reported the occurrence of decreased excretion of creatinine in cases of muscular dystrophy, and similar observations were made by others. Spriggs (1907-08) noted that the diminution of creatinine output was proportional to the extent of the muscular wasting. Levene and Kristeller (1909) first reported the excretion of creatine in the urine of patients with muscular dystrophy, and later workers confirmed this finding and the diminution of creatinine previously recorded, (McCrudden and Sargent, 1918 ; Janney *et al.*, 1918 ; and Bürger, 1919). So far, no special interpretation was placed on these findings, and they were in fact rightly regarded as indicating that creatinine was a product of muscle metabolism and that in advanced muscle diseases there was impairment in the conversion of creatine into creatinine, so that creatine as such was excreted in the urine and the creatinine output diminished. Brand *et al.* (1929), working from the physiological standpoint on the origin of creatine, found that the constant creatinuria of muscular dystrophy could be increased 40 per cent. by the administration of the amino-acid glycine. This observation was confirmed by Thomas *et al.* (1932) and Milhorat *et al.* (1932), who found, however, that if the administration of glycine were prolonged for a period of 2-8 weeks, there resulted a considerable clinical improvement in the patients. In the last four years numerous workers have concerned themselves with the biochemical and therapeutic effects of glycine in muscular dystrophy. This work has resulted in the repeated confirmation of the changes in the creatine-creatinine excretion and the effect of glycine on the creatinuria in this disease. It has also been repeatedly shown that a lowering of the creatine tolerance also takes place. Normally in an adult if 1 gm. of creatine is administered by the mouth it is entirely stored in the muscles, and none appears in the urine. In muscular dystrophy, however, a large percentage of the ingested creatine may be excreted within 24-48 hours, and the greater the loss of muscle tissue the greater will be the lowering of the creatine tolerance. The reports in respect of the therapeutic effects of glycine are, however, very divergent, considerable improvement being reported by some (Kostakow and Slauck, 1933 ; Tripoli and Beard, 1934 ; Cuthbertson and Maclachlan, 1934) and no improvement by others (Brand and Harris, 1933 ; Mettel and Slocum, 1933 ; Börst and Moebius, 1936 ; and Bargi, 1937). Milhorat (1933) and Reinhold *et al.* (1934) have reported histological changes in dystrophic muscle following glycin therapy, which they considered indicative of improvement in the disease. These changes consisted in greater uniformity in fibre size, better staining reactions,

decreased numbers of visible nuclei, and decreased fat content of the muscle. Bargi (1937) has, however, not been able to confirm these findings.

It is somewhat difficult to understand why so many papers have been published on this subject, unless it has been due to the possibility that the supposed beneficial effects of glycine administration corrected some underlying biochemical abnormality of the disease. It was not long after the publication by Thomas *et al.* (1932) of their findings that other workers suggested this possibility. Thus Kostakow and Slauck (1933) in their paper suggested that the underlying disturbance in muscular dystrophy might be the inability of the muscles to absorb and utilize creatine, and that this was corrected by glycine. Tripoli and Beard (1934) even wrote that in this condition after glycine treatment the creatine retained as creatine phosphoric acid in the muscles served over and over again to supply the energy for muscular contraction and the muscular efficiency increased at a remarkable rate. Also, more recently, Braestrup (1936) has stated that the facts with regard to the metabolic changes in muscular dystrophy indicate that the function of decomposition and re-composition of creatine phosphoric acid is radically impaired in this disease.

Unfortunately there is little justification for any of these statements, and it would seem that they could only have been suggested without due regard to all aspects of the question, and neglect of the obvious methods open for their confirmation or rejection.

In the first place the increased excretion of creatine following the administration of glycine does not necessarily suggest a fundamental defect in the creatine metabolism of the muscle, because, as is well known, the blood creatine in muscular dystrophy is normal and there is no evidence of any deficiency of creatine for the needs of the muscle. From the known physiology of creatine and creatinine already briefly stated it will be clear that criterion of an improvement of function in the muscles would have been a very definite increased excretion of creatinine, but such does not occur. Seeing that the increase is entirely in the creatine, this can only mean that glycine is a precursor of creatine and leads to the increased formation of creatine in the body, which is excreted and not stored owing to the widespread disease of the muscles, so that the administration of glycine is nothing more than an indirect creatine tolerance test. Thomas and his co-workers (1932) have stated that after prolonged administration of glycine the creatinine content of the urine does rise to some extent and the creatine content falls. These changes are, however, slight and are probably only expressive of general metabolic changes in the body following the administration of large doses of glycine. It is possible that the more normal muscles may come to metabolize slightly more creatine and that less creatine may be formed for some time after the discontinuance of an important precursor in the pure state. Apart from these considerations, the matter is put beyond dispute by the fact that in cases of extensive secondary wasting of muscles following disease of the nervous system, such as progressive muscular atrophy, similar changes in the creatine-creatinine excretion may be found and an increase of creatine output after the administration of glycine. This fact has been known since the intensive studies of creatine-creatinine metabolism in

muscular dystrophy began, but has been simply disregarded. Milhorat and Wolff (1937) in a recent paper confirm this fact and promise in a further paper details of the changes in cases of secondary muscle atrophy. It is only to be expected that in such cases the extent of the metabolic changes will be less, this being simply due to the more localized nature of the muscle disease in such conditions, as compared with muscular dystrophy, where practically the whole voluntary musculature may be wasted or abnormal. These observations also rule out the possibility of the effect of glycine on the creatine excretion being used as a method of differential diagnosis. It is not, however, to be denied that some information may be gained from its use, and also from the creatine tolerance, because in cases of muscular disease with only slight creatinuria a marked increase after glycine or the administration of creatine may occur and indicate a more widespread affection of the muscles and a greater inability to store creatine than was likely from the degree of spontaneous creatinuria or the degree of muscle-wasting. Milhorat and Wolff (1937) have reported the occurrence of the same degree of spontaneous creatinuria in a case of muscular dystrophy and myasthenia gravis, but in the latter the creatine tolerance was much higher, and the creatinuria following glycine less than in the case of muscular dystrophy. Such tests are, however, of little clinical value and would not repay the laborious chemical investigations necessary.

Direct Investigation of the Muscle Chemistry in Muscular Dystrophy

This brings us to the consideration of possible abnormalities in the important chemical compounds in muscle whose interreactions subserve muscular contraction. Observations have been made on the creatine phosphoric acid, the adenosine triphosphoric acid, the glycogen, lactic acid, and soluble carbohydrate, and the esters in dystrophic muscle removed at biopsy.

In an investigation of the phosphorus-holding compounds in muscle from patients with primary muscular degeneration, Nevin (1934 and 1936) found that there was present a considerable diminution of the total acid-soluble phosphorus expressed as milligrammes per gramme of wet muscle. This varied from case to case, and was considered most likely due to the varying fat and fibrous tissue increase in the muscle specimens. An individual examination of the various compounds making up this total showed some slight differences from the normal in the percentage of the total acid-soluble phosphorus of each compound. These differences consisted in a lowering of the creatine phosphoric acid and an increase in the soluble carbohydrate esters, but with no change in the adenosine triphosphoric acid. Debré *et al.* (1936) have also reported considerable diminution of the total acid-soluble phosphorus in the muscle from three patients, with a lowering of the total phosphagen and adenylypyrophosphate expressed as milligrammes P_2O_5 per gramme of wet muscle. The percentage of phosphagen of the total acid-soluble phosphorus was approximately normal in two cases, but lowered in the third, and the percentage of adenylypyrophosphate was lowered in all three. They apparently did not consider the lowering of the total acid-soluble phosphate as entirely due to the

increase of fat and fibrous tissue in the muscle, and they found the lactic acid and glycogen content of the muscles normal. Collazo *et al.* (1936) reported diminution of total acid-soluble phosphorus (expressed as milligrammes per 100 grammes of wet muscle), inorganic phosphate, phosphagen, and glycogen in the affected muscles in six patients with muscular dystrophy. The figures for lactic acid, on the other hand, approximated closely to normal and the percentage of phosphagen in the total acid-soluble phosphorus was also normal.

In the first place it will be clear that these observations lend no support to the theories which suggested that because glycine produced creatinuria a fundamental abnormality in the creatine phosphoric acid metabolism in the muscle existed. Such does not exist, and in one case showing a considerable creatinuria following glycine, Nevin (1936) found that the percentage of creatine phosphoric acid of the total acid-soluble phosphorus was normal.

The question remains, however, as to the significance of the alterations from the normal which have been recorded. Clearly the increase of fat and fibrous tissue must account in greater or less degree for the general diminution of the chemical compounds. This is borne out by the great variation in the analysis in different cases, probably related to the degree of atrophy in the muscle examined. The possibility of some diminution of the compounds in the actual muscle fibre is not excluded, and the increase of fat and fibrous tissue will not account for the lowered percentage of creatine phosphoric acid of the total acid-soluble phosphorus. This, however, has not been present in all the analyses reported, and it has been shown (Nevin, 1934) that creatine phosphoric acid breaks down during contraction of dystrophic muscle and is reformed during rest to an extent only slightly less than normal. A similar alteration in creatine phosphoric acid has been found in muscle undergoing atrophy secondary to nerve degeneration, so that it would appear that these changes are in some way secondary to the degeneration of the muscle in muscular dystrophy, and that they do not indicate specific chemical alterations in this disease.

Elkington and Goldblatt (1933) have found a diminished response in the rise in blood lactate on injection of adrenaline and no definite alteration in the hypoglycæmia in three myopathic patients. The resting values for lactate and glucose were within normal limits. These observations would correspond with the finding of a lowered glycogen content in the muscles by Collazo *et al.* (1936), because the lactic acid is derived from the muscle glycogen, but there is nothing to indicate that the changes from the normal are not due to the general diminution of muscle in which glycogen can be stored.

While concluding that so far the biochemical investigations, direct and indirect, in cases of muscular dystrophy have afforded results which can only be regarded as secondary to the muscle degeneration, it is clear that the question of the significance of abnormalities in the chemical compounds of dystrophic muscle cannot be considered closed. Further investigations of the chemistry of the living muscle removed at biopsy is clearly a fruitful line of research, and it may be that with advances in the normal chemistry of muscle, the introduction

of new methods may reveal for us at least the biochemical paths along which degeneration is taking place.

Therapeutic Effects of Glycine

Having found in the biochemical relationship involved no rational basis for the use of glycine as a therapeutic agent in muscular dystrophy, it remains to discuss the possible beneficial effects and their explanation. That the beneficial effects must be slight in degree and confined to special cases, such as those without advanced muscular wasting, follows from the numerous negative findings that have been reported. On the other hand, it can hardly be doubted that some improvement is experienced in suitable patients. Armstrong and Herbert (1935) have published their earlier results, and in a recent personal communication Armstrong states that advanced cases, especially of the pseudo-hypertrophic variety, do not benefit but become progressively worse, whereas those classified as Erb's Juvenile variety, and presumably less extensive and progressing less rapidly, do generally show improvement only while the administration of glycine is maintained. He has, however, noted that some patients seem to progress with extreme rapidity after the glycine is stopped, and in one such case he found the histological changes more intense than those present in a biopsy before the administration of glycine.

There can be no question of any specific effect of glycine in cases of muscular dystrophy, and there does not seem to be any explanation for the beneficial effects in some cases, other than that the specific dynamic effects of large doses of glycine leads to stimulation of metabolism in the muscles. This may act more through the healthy muscle fibres that remain than the actual degenerating fibres. The question as to whether this treatment may not be harmful in some cases has also to be considered, and it is doubtful if it should be used in other than selected patients who are still able to get about and take at least some active part in life. Here the increased feeling of well-being and slight general improvement may be important. Possibly small doses continued over monthly periods, with weekly free intervals and larger doses on special occasions, as advised by H. (1936), is the best way to use glycine in muscular dystrophy.

Further Theories and Methods of Treatment in Muscular Dystrophy

Kuré (1927) claims to have shown that voluntary muscle receives both a sympathetic and a parasympathetic nerve supply from the posterior roots, and that lesion of both these nerve pathways produces dystrophic changes in the muscles. On the basis that progressive muscular dystrophy is a disturbance of the autonomic innervation of voluntary muscle, Kuré (1930) has recommended treatment with injections of adrenaline and pilocarpine. He gives 0.2 c.c. of a 1 per cent. solution of pilocarpine and 0.2 c.c. of a 0.1 per cent. solution of adrenaline daily or every other day for 50 doses, and claims to have produced improvement in his patients and prevention of the progress of the disease. There is no scientific basis whatever for this theory, and it is not surprising that most reports record no beneficial results from the treatment

(Reese *et al.*, 1935 ; Paulian, 1934 ; and Curschmann, 1933). Hough (1933), on the other hand, reports benefit, but states that progression may occur while under treatment. This latter observation excludes the possibility of any specific effect from the remedies, and the benefit found was probably in large part psychological, as the author himself suggests.

Hirata and Suzuki (1937) have reported that in cases of muscular dystrophy they found a diminution of the output of vitamin C in the urine and also less of this substance in the cerebrospinal fluid. An analysis of diseased muscle showed a diminution in glycogen and creatine phosphoric acid, and it is claimed that the administration of vitamin C corrected those abnormalities and led to remarkable clinical improvement. The author's figures show a clear increase in the percentage of phosphagen in relation to the total acid soluble phosphorus after treatment. There are, however, no figures from control experiments, and the figures for the total acid-soluble phosphorus are so much higher than those recorded by other workers in normal muscle that it is very difficult to assess the value of his results. Also, it would appear unlikely that vitamin C deficiency could occur in such a manner as to cause only symptoms referable to the muscles.

In the recent Italian literature Meldolesi (1936) and Bompiani and Meldolesi (1936) have described defective proteolytic function of the pancreas in cases of muscular dystrophy. They have associated this with slight anatomical changes in the pancreas, and they record improvement in their patients by treatment with pancreatic extract. Barasciutti (1937) has, however, been unable to confirm these findings, so that the changes recorded were probably unrelated to the muscular dystrophy.

In concluding this section on muscular dystrophy it has to be observed that the biochemical researches of the last few years have led to little real advance in the knowledge of the disease. The alterations from the normal which have been recorded are entirely secondary or indirect effects of a pathological process the essential nature of which is still obscure. A great expenditure of time and energy has been wasted in repeatedly confirming these indirect results, to the consequent neglect of more fruitful lines of research. These clearly are to hand in histochemical and direct chemical investigation of degenerating muscle. Along these lines the paths of the muscle degeneration may be worked out, and it is not impossible that more beneficial methods of treatment may be evolved.

Myotonia and the Diseases in which it occurs

Myotonia is a clinical condition characterized by delay in relaxation of voluntary muscle after natural, mechanical, or electrical stimuli. It is found predominantly in two diseases, dystrophia myotonica and myotonia congenita, but in the latter the myotonia is generally more marked and more widespread.

It has been known for many years that both electrical and mechanical myotonia can occur in myotonic muscles following blocking of the motor nerve. This naturally led to the view that the essential functional abnormality

in the phenomenon was peripherally situated. Gregor and Schilder (1913) and Bürger and Schellong (1923) found that myotonia was associated with action currents. With the less sensitive methods of examination then available it was not always possible to demonstrate the occurrence of such action currents, but in recent years this observation has been confirmed by Delmas-Marsalet and Bague (1934) and Lindsley and Curnen (1936).

The association of characteristic action currents with the delayed relaxation in myotonia indicates clearly that the phenomenon is in some way an abnormality of excitation of the muscle fibres, and there is furthermore no evidence that it could be purely myogenic in origin.

Lindsley and Curnen (1936) consider that myotonia is reflex in origin, and is due to the persistent discharge of hyperexcitable sensory end organs in the muscle. These workers leave out of consideration entirely the occurrence of myotonia after block of the motor nerve, so that while it is impossible to say that reflex action may not play some part in the production of myotonia under natural conditions, it is obviously no explanation of the phenomenon. Clearly some abnormality at the neuromuscular junction must be present.

Recent observations on the effects of drugs in myotonia lend support to this view. Lanari (1936) has found that, while the intra-arterial injection of 0.04 gm. of acetylcholine produced no motor effect in normal subjects, in patients with myotonia it gives rise to a painful reversible muscular contracture lasting about 30 seconds. This does not occur if the acetylcholine is injected into the muscle directly. There is now clear physiological evidence that acetylcholine plays some part in the transmission of the motor impulses from nerve to voluntary muscle (Dale *et al.*, 1936), so it is legitimate to conclude that the abnormal action of the intra-arterial injection of acetylcholine in myotonia is produced at the neuromuscular junction. Furthermore, Russell and Stedman (1936) have found that myotonia can be increased by the administration of prostigmin and large doses of potassium chloride or potassium citrate, and both prostigmin and the potassium ion are known to potentiate acetylcholine transmission at nerve junctions. Russell and Stedman suggest that myotonia may be due to an excessive production or accumulation of acetylcholine at the motor nerve-endings. They also found that ethyl alcohol temporarily relieves myotonia, and Kennedy and Wolff (1937) have found that quinine hydrochloride has a similar effect. There is no evidence to show that ethyl alcohol and quinine act at the neuromuscular junction, but their effect is most likely to be produced at this site.

It seems most probable, therefore, that myotonia is produced by some abnormality at the neuromuscular junction, but as regards the cause and nature of this abnormality nothing is as yet known. It may be primarily dependent upon a hyperexcitability of the nerve ending to the chemical transmitter, or it may be due to excessive accumulation of acetylcholine at some stage of contraction and relaxation, with which may be associated an abnormal esterase function. The clinical and physiological facts available do not permit of any definite statement. It is also probable that the full development of myotonia clinically is dependent upon the way the muscle is innervated. If a muscle is

directly innervated it may be absent and yet appear when the muscle is contracted to a similar extent synergically.

It has also been observed clinically that the myotonia following the movement of grasping is in reality an addition of contraction in some muscles rather than a delay in relaxation. Future investigation must therefore be directed to the nature of the peripheral abnormality and the nature of the central innervation which combines with it to produce voluntary myotonia.

Diseases in which Myotonia occurs

In dystrophia myotonica the predominant features of the disease are the muscular dystrophy and the general endocrine changes. No definite relationship has been established between these changes, and their relation to the myotonia is also unknown. It might seem likely that the dystrophic changes in the muscles led to abnormalities in the nerve-endings which gave rise to the myotonia, but Devry and Everard (1936) have described members of families in which myotonia was present without muscular atrophy or endocrine changes. On this account it would seem probable that the myotonia was not secondary to the muscular atrophy or the endocrine changes. The muscular aspect of dystrophia myotonica consists, therefore, in a primary degeneration of the muscle fibre and an abnormality at the neuromuscular junction, resulting in delayed relaxation. This is in contrast to myotonia congenita, where there are probably no primary changes in the muscle fibre and the neuromuscular abnormality constitutes the disease. The only constant histological change in the muscles in the latter disease is the hypertrophy of the individual fibres. This is most probably secondary to the myotonia, because if during voluntary movement each contraction is followed not by relaxation but by a varying degree of additional contraction, hypertrophy of the muscle fibres might be expected to result.

It is interesting to compare the creatine-creatinine metabolism in dystrophia myotonica and myotonia congenita. In the former the changes are similar to those found in muscular dystrophy, but in the latter no creatine is excreted in the urine, there is an increased creatine tolerance, and the creatinine content of the urine is a high normal. These findings in myotonia congenita are exactly what one would expect to occur, because the muscular hypertrophy leads to greater ability to store creatine and convert it into creatinine, the natural end-product of muscular metabolism. Poncher and Woodward (1936), who have reported the increased creatine tolerance in myotonia congenita, state that in a patient with this disease they found that creatine administration accentuated the myotonia. It is difficult to suggest an explanation of this observation on the basis that the myotonia is primarily an abnormality situated at the myoneural junction, but it is equally difficult to explain it as a direct effect on the contractile substance of the muscle fibre. In this connection reference must be made to another case described by Poncher and Woodward (1936). This was a male infant of 5 months in which there was present marked hypertrophy of all the muscles of the body. The muscles showed a localized

dimpling and sustained contraction on percussion. The child was subject to generalized muscular spasms which were regarded as myotonic in nature. There was an absence of the physiological creatinuria of infancy and childhood. Creatinuria was produced by the administration of thyroid extract, and at the same time the myotonia and muscular hypertrophy disappeared. Myotonia could, however, be produced by the ingestion of creatine. The authors took the view that the patient was not suffering from hypothyroidism and that the case was one of myotonia congenita, in which the symptoms were relieved by thyroid medication. They suggest that some abnormality in the intrinsic chemical mechanism of muscular contraction may account for the abnormal metabolism of creatine in this case of myotonia congenita, and that the beneficial effects of thyroid may result from alterations in this abnormal metabolism. It is admitted, however, that no explanation is available as to why adults with myotonia congenita are not benefited by thyroid extract. The case cannot, however, be easily accepted as a case of myotonia congenita. The age of onset of the symptoms, the enlargement of the tongue, the lack of spontaneous movements, and the atypical nature of the myotonia all suggest strongly that thyroid deficiency was present in the patient, and that the case really falls into the group of muscular hypertrophy and myotonia associated with hypothyroidism. The authors, however, reject this explanation of the case. There are no analyses recording changes in the muscle chemistry in myotonia congenita, and this case cannot be taken as evidence that such are likely to be found. Morgulis and Young (1931) have also suggested that in dystrophia myotonia there is a failure of the muscle to synthesize phosphagen. There is no evidence for this statement, and the chemical changes in the muscle in this disease are similar to those in progressive muscular dystrophy. It cannot, therefore, be accepted that abnormalities in the intrinsic chemical mechanism of muscular contraction are of primary importance in myotonia congenita or dystrophia myotonica.

Muscular Hypertrophy and Myotonic-like Symptoms associated with Hypothyroidism

In recent years several cases exhibiting these features have been described in the literature. Weitz (1931) described a 44-year-old man who developed myxœdema after operative treatment for exophthalmic goitre. In this patient the muscular system throughout showed increased tonus and sudden movements led to painful cramp in the muscles, which became very hard and boardlike. Percussion of the muscles caused localized contractions which lasted some seconds and slowly relaxed. Movements became quicker on repetition. Electrical hyperexcitability of the nerves and muscles was also present. The author considered the symptoms as closely related to myotonia and secondary to the myxœdema. He refers to descriptions in the older literature of spastic muscles and myotonic reactions in myxœdematous patients. Garcin *et al.* (1935) have reported in great detail the occurrence of Thomsen's syndrome in association with myxœdema in a young man of 28. In this case the myotonic disturbances

of voluntary movement were associated with hypertrophy of the muscles. Bourguignon and Garcin (1935) noted that the myotonia was of shorter duration than occurs in Thomsen's disease. Histologically there was found a variable hypertrophy of the muscle fibres which might not involve the whole length of the fibre. There was some increase of interstitial tissue, and in places accumulations of histiocytes between the muscle fibres. The authors consider that possibly both the myotonia and myxœdema were secondary to some central nervous disturbance. Debré and Sémelaigne (1935) and Eckerström (1936) have described patients with somewhat similar features, the former in infants and the latter in an adult. In Garcin's case no record is given of the effect of thyroid medication, but in the others this led to a disappearance of symptoms, which shows clearly that the condition is quite distinct from myotonia congenita. It is probable, therefore, that careful clinical and electrical analyses of the myotonic-like reactions in the muscles will show that these are essentially different from true myotonia. It is clear, however, that in some patients hypothyroidism may be associated with hypertrophy and myotonic-like symptoms affecting the voluntary muscles. The muscular symptoms are directly related to the hypothyroidism, and it is very difficult to suggest an adequate explanation for their occurrence. It does not appear very probable that changes in the muscle chemistry can be the primary cause, because it is difficult to see how slowness of relaxation from this cause could lead to the muscle hypertrophy. Some abnormality of excitation would seem necessary to account for the very great tension which develops in the muscles after contraction. It is possible that in these cases some chemical abnormality is present at the myoneural junction which linked up thyroid deficiency can give rise to the myotonic-like symptoms and muscular hypertrophy. In Poncher and Woodward's (1936) case, which was considered to belong to this group, the administration of creatine produced myotonia at a time when the patient was free from symptoms. This observation may hold a clue to the underlying chemical changes which produce the abnormal muscular reactions.

Myotonia Acquisita

Myotonia acquisita is a condition very similar to myotonia congenita, but differing from it in not being congenital or hereditary, and developing later in life, after infection or trauma or without recognizable cause. Krabbe (1934) considers that true muscular hypertrophy and myotonia acquisita are variations of the same abnormality, namely, an abnormal regeneration after neuritic processes, and that hypertrophy of the muscle sarcoplasm results in the myotonic condition. Cases of this nature are rare, and consequently there are no reports of the effects in this condition of drugs known to influence the myotonia in Thomsen's disease. The myotonia in the two conditions is, however, very similar clinically, and it is possible that also in myotonia acquisita some abnormality at the neuromuscular junction constitutes the major pathology of the disease. If the myotonia in myotonia acquisita were primarily dependent on an abnormality of the sarcoplasm it must be considered quite distinct from

that associated with Thomsen's disease. The cases of muscular hypertrophy without myotonia which Krabbe considers related to myotonia acquisita may possibly be examples of muscular dystrophy in which a preatrophic stage of generalized muscular hypertrophy is a very prominent feature.

Myasthenia Gravis

Myasthenia gravis is a disease characterized by weakness and rapid fatigability of the voluntary muscles. The clinical features of the disease have been known for over half a century, but the nature and site of the loss of function have always presented most baffling problems to the clinical investigator. It is, however, clear from the spontaneous remissions, in some cases approaching practically complete recovery, that a remediable cause underlies the pathology of the condition. The anatomical changes in the disease have been fully investigated with the following results. Slight changes have been found in the nervous system in some cases, but these have never been accepted as being causally related to the disease. The affected muscles show no abnormality except the presence of lymphorrhages, which consist of small collections of lymphocytic cells between the muscle fibres. Such collections of cells are also found in other organs as well as in the muscles. Hyperplasia, or a tumour of the thymus gland, is the only other abnormality reported. The significance of this finding has been disputed because it is not constantly present, but in reference to this point Greenfield (1923) stated that unless the mediastinum was carefully searched the presence of abnormal thymus tissue might be easily overlooked.

The biochemical investigations in the disease have so far yielded negative results. The earlier studies were conflicting and they will not be described as details are to be found in an article by Keschner and Strauss (1927). Marburg (1931) reported that he found the magnesium in the blood abnormally high (6 mg. per cent., the normal being 2–3 mg. per cent.) in a case of myasthenia gravis. He considered it possible that this increased concentration of the magnesium ion might be secondary to thymus hypertrophy and act by producing a curare-like action on the nerve endings of the voluntary muscle.

Boothby *et al.* (1932) have found, however, that the blood magnesium was normal in six cases and they also found no abnormality in the other inorganic or nitrogenous constituents of the blood. In this paper Edgeworth reported that in a detailed chemical examination of the urinary, blood, and faecal constituents in her own personal case at a time when she was physically prostrate the only abnormality found was a slight creatinuria and lowered excretion of creatinine. A lowered creatinine excretion had already been reported by Spriggs (1907) and some degree of creatinuria with a low muscle content of creatine by Williams and Dyke (1922).

With the discovery of the effect of glycine on the creatine output in muscular dystrophy, Boothby (1932) studied the effects of glycine on myasthenia gravis, and reported clinical improvement possibly explained by the building up of the amount of creatine phosphoric acid in the muscles. In a fifth report Boothby

(1934) states that the fact that glycine decreases the fatiguability of the disease can no longer be questioned. Remen (1932) also found benefit from glycine in myasthenia gravis, and considered that this substance corrected abnormalities in the creatine-creatinine metabolism in the disease. It is definitely known that some degree of creatinuria which can be increased by glycine does occur in myasthenia gravis, but this affords no justification for the above assumption, as will be seen from the previous discussion in this review in relation to the creatinuria in muscular dystrophy. Furthermore, the chemical constituents of myasthenic muscle have been investigated and found normal both as regards the phosphorus-holding compounds at rest and on contraction (Nevin, 1934) and the glycogen and lactic acid content (Collazo *et al.*, 1936). Also Elkington and Goldblatt (1933) have found that the rise in blood lactate derived from the muscle glycogen after injection of adrenaline is normal. These findings also negative the suggestion by Costedoat and Aujeleu (1934) that the underlying fault in the disease may be the failure of the reconversion in the muscle of lactic acid into glycogen. This suggestion was based on the observation that in rabbits, muscles rendered poor in glycogen gave a myasthenic reaction. It follows from these observations that there is no definite evidence in myasthenia gravis of a primary chemical abnormality in inorganic or organic chemical constituents of blood, urine, or faeces; nor in the intrinsic chemical mechanism of muscular contraction.

The beneficial effects of glycine have not been confirmed, and it is more than probable that it has no place in the treatment of myasthenia gravis. As repeated investigations failed to show any fundamental histological abnormality in the nervous or muscular systems or any biochemical alteration in the blood or muscle fibres, attention became directed to the myoneural junction as the probable site of the disturbance of function in the disease.

Holmes (1923) stated that the site of the lesion was peripherally situated and that disturbances of thymus function must play an important part in the pathogenesis of the disease. Support for this conception has been afforded by the discovery that two drugs, ephedrine and eserine, have a very beneficial effect on the disease and by experimental work on the relation of the thymus to muscular weakness.

The use of ephedrine was discovered by Edgeworth (1930), and although its effect is not so striking as that of eserine sulphate, it is more gradual and can be maintained over long periods, if no intolerance exists, by oral administration. The drug is very similar in its action to adrenaline, and McAlpine (1934) suggested that the explanation of its therapeutic effect might be related to the relief of fatigue in voluntary muscle which follows sympathetic stimulation. Corkell and Tiegs (1933) have shown that this effect is due to the transfusion of an adrenaline-like substance from the sympathetic nerve-endings to the neuromuscular junction. Injection of adrenaline has a similar effect, so it is very probable that ephedrine acts at the neuromuscular junction in myasthenia gravis, although the mechanism of its action is still obscure.

The beneficial effects of eserine sulphate in myasthenia gravis were first reported by Remen (1932). This worker, however, disregarded the observation

on account of the excessive vomiting produced by the drug and devoted his attention to studying the effects of glycine, as already described. Walker (1934) independently observed the effects of eserine in this disease, and by giving atropine controlled the unpleasant gastro-intestinal symptoms. She later reported that even better results could be produced with a related drug, prostigmin (1935), and since these observations the remarkable effect of these drugs in causing a recovery of function in the affected muscles has been repeatedly confirmed. Pritchard (1936) has also shown that it causes a return to normal in the form of the myasthenic myogram produced by high rates of stimulation. The effect is, however, entirely symptomatic, and leads to no maintained improvement in the patient's condition. In bulbar cases as the effect of the drug wears off aggravation of symptoms may occur. The introduction of oral administration (Everts, 1935), giving a more prolonged and gradual effect, seems to have increased the therapeutic value of prostigmin, but it would appear that its use must be guided by a careful study of the response of the individual patient. Apart altogether from its therapeutic value, there can be little doubt that its action is produced at the myoneural junction, thus indicating the site of abnormal function in the disease. It has been established that peripheral parasympathetic effects are transmitted by the liberation of acetylcholine, which is rendered inactive by an enzyme in the blood and tissues called choline esterase. The activity of this esterase is inhibited by prostigmin and analogous drugs. As already stated, Dale (1936) has furnished evidence that acetylcholine is also liberated at the myoneural junction in voluntary muscle during excitation, and the remarkable effect of prostigmin can therefore be explained by supposing that its action in delaying the destruction of acetylcholine corrects some abnormality of neuromuscular transmission at this point. The nature of this abnormality is still entirely obscure.

An attempt has been made to gain some information thereon by estimating the choline esterase in the serum. Stedman and Russell (1937) have found that the average content of the esterase in the serum is lower than normal. Pilcher (1937) in seven cases also reports a similar finding. McGeorge (1937) has considered, however, that in his three cases the esterase content fell within normal limits. Even if it be accepted that a slight lowering of the serum esterase is present in myasthenia gravis, its significance is difficult to assess because the relation of the serum esterase to that in the tissues is not known. It might be taken to indicate a tendency for the esterase in the muscles to be low and this again might indicate a diminution of acetylcholine activity, as the amount of esterase in a tissue and its acetylcholine activity are roughly parallel. The low value for serum esterase seems, however, to exclude excessive destruction of acetylcholine as the abnormality at the myoneural junction.

It is possible that this abnormality consists in defective formation or mobilization of the chemical transmitter. Fraser *et al.* (1927) interpret the beneficial effects which they have observed in myasthenia gravis following the subcutaneous injection of acetylcholine, carbaminoylcholine and acetyl-beta-methylcholine as most likely indicating a defect of this nature. Briscoe (1936)

has, however, shown that mild curarization experimentally can produce a myogram very similar to that found in myasthenia gravis with a fast rate of stimulation, and which similarly returns to normal with prostigmin. Now curarization does not affect the liberation of acetylcholine (Dale *et al.*, 1936) so it would seem more probable that the threshold of excitation was in some way abnormally raised. This is not likely to be due to any anatomical change at the neuromuscular junction, as the variability of the condition and the absence of muscular wasting show. It is more likely to be due to some chemical change, and this may be the presence of some substance foreign to the neuromuscular junction, or on the other hand some product of the destruction of acetylcholine, the removal of which is impaired. This latter possibility would seem a fruitful line for investigation, because prostigmin in large doses in normal muscle can have a depressant effect on rapid stimulation of the nerve, presumably due to accumulation of excess of transmitter (Briscoe, 1936). If this is so, then the retention of a breakdown product of acetylcholine, normal or otherwise, might produce a curare-like effect. The presence of large amounts of choline are known to raise the threshold for acetylcholine excitation experimentally, so that it is quite possible that an abnormal balance between production and removal of acetylcholine may be the basis of the defect in neuromuscular transmission. Study, therefore, of the actual nature of the chemical abnormality at the neuromuscular junction is a primary consideration in the further investigation of myasthenia gravis, but it must be remembered that the cause of this abnormality may arise from pathological changes outside the muscular system, and this leads to further consideration of the relationship of thymus hypertrophy to the disease.

Using dogs, Adler (1937) states that he has produced experimentally muscular weakness resembling clinical myasthenia by repeated transplants of thymus tissue from young animals. The symptoms so produced were completely relieved by prostigmin. Injections of thymus extracts also produced muscular weakness. Adler suggests that the enlarged thymus produces some substance which leads to an abnormal breakdown in acetylcholine at the myoneural junction. It is not likely that the explanation is so straightforward as this, because such a substance would be present in the serum, and the values for blood esterase would be likely to be higher instead of lower than normal.

If this work is confirmed it is clearly of very great importance, because it will enable a local disturbance at the myoneural junction at least analogous to that present in myasthenia gravis to be investigated experimentally. Details of the experiments and also the method of preparation of the thymic extracts are unfortunately not published. Rowntree *et al.* (1936) in their large number of experiments with injections of extracts of thymus and also transplants into rats did not record any muscular weakness in the experimental animals. Also Asher and Scheinfinkel (1929) claim to have separated two fractions in watery extract of thymus gland, one alcohol-soluble which relieves fatigue in muscle and the other alcohol-insoluble which accelerates growth in young rats. It may quite well be that different animals react differently to the thymus transplants, but clearly Adler's work must be repeated and extended.

Obiditsch (1937) has studied histologically a series of nine thymus tumours, and has found that those consisting of small round cells were associated with myasthenia symptoms, while those with epithelial and malignant cells were not. It is not known yet whether the pathological changes occurring in myasthenia gravis with thymic hypertrophy are the same as those occurring in thymic tumours with myasthenia, but they must be very closely related. Also Stern (1937) has described the recovery of a case of myasthenia gravis following the combination of prostigmin and irradiation of the thymus. He quite admits that the recovery may only have been a spontaneous remission, but clearly it is possible that irradiation combined with prostigmin may be effective, whereas the results from this treatment previously were inconclusive. Surgical removal of abnormal thymus tissue should also be considered in suitable patients.

There are some isolated observations in regard to myasthenia gravis which are interesting in their possible relationship either to the local abnormality at the neuromuscular junction or to the possible general pathological changes. It is known that thyroid extract in large doses produces temporary benefit followed by aggravation of the disease. The initial benefit may be due to increased metabolism at the neuromuscular junction, and as thyroid extract leads to thymus hypertrophy in animals the aggravation may be secondary to such a change. Injections of thymus extracts (Allen and Hanbury) have been observed to produce aggravation of symptoms in some cases (personal observation). Other observations clearly related to endocrine changes are the occurrence of remissions of the disease in association with pregnancy, and Simon (1935) has stated that improvement can be produced by treatment with anterior pituitary. On the other hand, potassium chloride in large doses (Laurent, 1936) and Veratrine (Kroll, 1936) produce beneficial effects in the disease, and the action of these drugs most probably takes place at the myoneural junction. The intolerance of myasthenic patients for large doses of local anæsthetics such as novocaine is probably also a direct effect of the drug at this junction.

Familial Periodic Paralysis

In this disease, which is most frequently familial but may be sporadic, attacks of muscular weakness varying in severity up to complete paralysis occur in otherwise healthy individuals. The paralysis, which may last many hours before complete recovery takes place, is rarely fatal from respiratory failure, and is associated with loss of deep reflexes and electrical inexcitability of the muscles.

Although the pathogenesis of the disease has remained obscure, it has been generally considered as most likely due to general metabolic disturbances of a temporary nature producing in some way a loss of muscular function. The results of recent chemical investigation in cases of the disease support this conception and indicate the lines of research along which a full explanation of the disease is likely to be found. The most important aspect of these investigations is the observation, to which attention was first directed by Allott (1935),

that a marked lowering of the serum potassium occurs during an attack. Aitken and Allott *et al.* (1937) showed that this could be produced by the administration of large amounts of glucose by mouth, by the injection of insulin, and more easily by both these procedures together. Allott and McArdle (1938) have extended these observations. They found that the potassium is not excreted during the attack and must therefore accumulate in some tissues and that the serum inorganic phosphate shows parallel variations to the potassium, only slighter in degree. Adrenaline also reduces the serum potassium and inorganic phosphate and may sometimes produce an attack. The normal serum potassium is 16–20 mg. per cent. and the level at which paralysis occurs is usually 10–12 mg. per cent., but in one case weakness developed with the potassium content just below 16. Administration of large doses of potassium citrate or potassium chloride cuts short the attack. How the paralysis arises from these chemical alterations is not clear. The fall in serum potassium is not the only factor, because by repeated adrenaline injections in a normal person the serum potassium can be lowered to a figure which would be associated with paralysis in a patient subject to these attacks, and very low figures have also been observed in diabetics under treatment with insulin without symptoms. As glucose and insulin administration normally gives rise to a slight fall in serum potassium, it would appear that in this disease an abnormal mobility of this ion exists with some phase of carbohydrate metabolism, so that potassium is removed not only from the serum but also from some part of the motor unit where its presence is necessary for the transmission of the nerve impulse or the excitation of the muscle. The inability of nerve or muscle to retain the necessary potassium concentration when abnormal metabolic variations occur may be the essential abnormality in the disease.

The main site of the lesion, if such it might be called, is probably in the muscle fibre distal to the nerve ending, because the paralysed muscle is inexcitable to direct electrical stimulation, though at present it is impossible to exclude simultaneous involvement of nerve.

Earlier observations in the disease are interesting in view of the more recent work. Shinosaki (1925) had observed in his cases that the administration of glucose and insulin and also adrenaline could precipitate attacks, but he did not correlate these observations with alteration in the potassium content of the serum. Biemond and Daniels (1934), on the other hand, recorded a lowered potassium content of the serum in one of their cases during an attack, the full significance of which they did not, however, appreciate; and more recently Herrington (1937) has used therapeutically repeated 5-gm. doses of potassium citrate with very beneficial effects. Also some of the clinical features of the disease, such as precipitation of the attacks by excitement or their nocturnal occurrence after a late heavy meal, or the ability to avert attacks by exercise, can be considered as producing alterations in adrenaline output or carbohydrate metabolism and thereby correlated with the known chemical alterations in the disease. Another interesting feature of the disease is the fact that muscular atrophy sometimes supervenes. Biemond and Daniels (1934), while regarding the atrophy in their cases as neural in origin, held that it also was hereditary,

and not a secondary effect of the attacks because it bore no constant relationship to the number and severity of preceding attacks. It has not, however, as yet been definitely established that the wasting is neural or dystrophic in origin, a point of considerable interest in the classification of the disease.

Muscular Weakness and Hyperthyroidism

It is well known that in exophthalmic goitre muscular weakness is a prominent symptom, so much so that weakness of the quadriceps muscle has been recognized as a test for myasthenia in hyperthyroidism. It is significant that in exophthalmic goitre there is hyperplasia of the thymus and lymphorrhages have also been found in the muscles. Further, the full clinical picture of myasthenia gravis is not infrequently associated with exophthalmic goitre (Cohen and King, 1932), and the improvement in the muscle function following ephedrine and prostigmin leaves no room for doubt regarding the diagnosis. It is not likely that such an association is merely fortuitous, but rather that the hyperthyroidism has predisposed in susceptible individuals, possibly through the thymus hyperplasia, to the development of the pathological changes which constitute the disease of myasthenia gravis. Sauerbruch (quoted Adler, 1937) has removed a hyperplastic thymus gland from a patient with exophthalmic goitre and severe myasthenia. There followed a gradual disappearance of the myasthenia but no alteration in the thyrotoxicosis. The minor degrees of muscular weakness found in exophthalmic goitre probably depend on closely related if not identical pathological changes.

This leads to the consideration of exophthalmic ophthalmoplegia to which Brain (1937) has recently drawn special attention. The condition is characterized by ophthalmoplegia of varying degree and sometimes œdema of the eyelids associated with thyrotoxicosis. The degree of thyrotoxicosis is usually slight and the condition may occur after thyroidectomy for hyperthyroidism when the basal metabolic rate is normal or even subnormal. œdema of the orbit and enlargement of the ocular muscles has been observed at operation. Histologically the muscles show œdema with foci of lymphocytic infiltration, while fibrosis and enlargement of fibres have been reported. Prostigmin in such cases has no effect on the ocular movements, so that the condition is not the simple association of myasthenic symptoms of the ocular muscles with hyperthyroidism. Also the ophthalmoplegia does not appear to be entirely mechanical and due to the exophthalmos, because decompression may relieve the exophthalmos but not the muscular weakness. It has frequently been suggested that the thyrotropic hormone of the pituitary may play some part in the development of the condition, and recent experimental work supports this view. Smelser (1937) has injected extracts of the anterior pituitary into thyroidectomized guinea-pigs and has produced exophthalmos and œdema of the retrobulbar connective tissue, fat, and muscles indistinguishable from that found in clinical exophthalmos. There was also some round cell infiltration in the fat and muscles, but the degeneration of the latter was less than has been reported in clinical exophthalmos with hyperthyroidism. No reference was made to ophthalmoplegia in this work, but it would appear

from it that the exophthalmos in exophthalmic goitre and exophthalmoplegia are closely related.

How the thyrotropic hormone acts in the production of the exophthalmos and the lesions in the muscles is obscure. The muscle changes can, however, be regarded as a toxic myopathy secondary to metabolic abnormalities and they are probably responsible for the ophthalmoplegia, although mechanical alterations may accentuate the defects of movement. It is interesting that some cases of exophthalmic ophthalmoplegia are associated with generalized muscular wasting. The nature of the changes affecting the limb musculature is not known, but it is probable that they are similar to those affecting the eye muscles, and should also be regarded as a toxic myopathy of metabolic origin. Cases of muscular wasting occur, however, without ophthalmoplegia, so that comparison of the histological changes in the eye muscles and the limb muscles must be made before the two can be grouped together under the heading thyrotoxic myopathy.

Exophthalmic goitre is not only described in association with myasthenia gravis but also in association with periodic paralysis (Shinosaki, 1925 ; Dunlap and Kepler, 1931 ; Morrison and Levy, 1932). There is, however, generally an absence of a family history of the disease. Owing to the fact that in Dunlap and Kepler's patients thyroidectomy cured the attacks, the association of the two diseases cannot be regarded as fortuitous. Shinosaki (1925) has observed that the administration of thyroid extract may produce slight attacks in typical familial periodic paralysis. It would appear, therefore, that exophthalmic goitre can predispose in susceptible individuals to the development of pathological alterations similar to those occurring in this disease. The investigation of how these changes are brought about and also whether the attacks are accompanied by a fall in the serum potassium will be of great interest in regard to the pathogenesis of familial periodic paralysis.

Classification of Primary Diseases of Voluntary Muscle

The following classification of primary diseases of voluntary muscle is appended as a brief summary of the review. It is based on an attempt to assess the site and nature of the pathological changes responsible for the loss of function in each disease. Few, if any, of the complex problems presented by these diseases have been settled, but fruitful lines of investigation based on sound physiological and biochemical knowledge have been opened up, and it can confidently be expected that the future will show great advances in this field.

(1) Progressive muscular dystrophy.

Primary degeneration of the contractile elements of the muscle fibre. Nature entirely obscure.

(2) Dystrophia myotonica.

Primary degeneration of the muscle fibre closely allied to that in the first disease, with an added abnormality at the myoneural junction giving rise to myotonia.

(3) Myotonia congenita (Thomsen's disease) and myotonia acquisita.

Primary abnormality at the myoneural junction resulting in myotonia and secondary hypertrophy of the muscle fibre. Pathological physiology still obscure.

(4) Myasthenia gravis.

Essential lesion at the myoneural junction, but probably conditioned by pathological changes in the body generally.

(5) Familial periodic paralysis.

Essential lesion in the paths of excitation distal to the nerve ending. Associated with general metabolic abnormalities involving the potassium ion.

(6) Muscular disorders related to disease of the thyroid gland.

(a) Muscular hypertrophy and myotonic-like symptoms associated with hypothyroidism (rare).

(b) Myasthenia and occasionally the full clinical picture of myasthenia gravis complicating exophthalmic goitre.

(c) Periodic paralysis complicating exophthalmic goitre (rare).

(d) Thyrotoxic myopathy (rare). Weakness and wasting of voluntary muscles, probably dependent on toxic changes of metabolic origin affecting the muscle fibre. Associated with hyperthyroidism. Here may be grouped exophthalmic ophthalmoplegia as the changes in the muscle are also indicative of a toxic process.

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