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The next issue will treat of: HEADACHES

Editorial

A fines del siglo pasado comenzó a ser estudiada seriamente la miastenia como una entidad clínica. Sin embargo según lo expresa Guthrie, ya en 1685 Willis hizo una descripción que seguramente corresponde a esta afección.

Erb en 1879 se refirió a "un nuevo grupo de síntomas probablemente bulbares".

Como las necropsias realizadas dieron resultados negativos fue designada como "Parálisis bulbar sin cambios anatómicos".

El nombre de Miastenia Gravis Pseudoparalítica fue propuesto por Jolly en 1895.

En 1901 Oppenheim hizo una descripción de la enfermedad que ha quedado clásica.

Jolly y Oppenheim descubrieron la reacción miasténica que es la disminución progresiva de respuestas de los músculos afectados a la estimulación farádica repetida.

Los trabajos de Loewi y posteriormente de Dale en 1934 relativos a la importancia de la acetilcolina en la transmisión neuromuscular, han sido el origen de la discusión fisiopatológica y de la terapéutica moderna.

Walker por la misma época demostró la eficacia de las drogas anticolinesterasa en la miastenia.

Ultimamente fue introducido el concepto de que se trata de un desorden de autoinmunización.

La miastenia es una afección crónica con remisiones, cuyo síntoma fundamental, casi patognomónico, es la aparición de una debilidad muscular anormal y de intensidad variable, a continuación de movimientos voluntarios repetidos.

Las drogas colinérgicas producen un efecto benéfico dramático y bastante específico, hecho que para algunos autores reviste tal importancia que tienden a incorporarlo a la definición. Este criterio no es aceptado por otros especialistas.

El sueño es reparador. Sin embargo en los casos graves, los músculos que han sido afectados primero y en los cuales la enfermedad se muestra en su forma más severa, cesan de contraerse aún después de un reposo prolongado.

El corazón y los músculos lisos están respetados.

En el examen somático no se demuestran amiotrofias, ni fasciculaciones; la sensibilidad es normal lo mismo que los reflejos.

Al comienzo esta enfermedad suele hacerse evidente en los ojos. La ptosis palpebral es a menudo el síntoma inicial, aparece después paresia de uno o

más músculos extrínsecos, con la consiguiente diplopia, sin cambios pupilares.

También es frecuente aunque en un grado menor el comienzo por los músculos que tienen inervación bulbar y se produce disfagia, disartria, disfonía y parálisis palatina.

El paciente miasténico presenta un aspecto muy característico, los párpados bajos, la mandíbula caída, la cabeza se desploma vencida sobre el pecho, los brazos yacen a los lados del cuerpo.

El debilitamiento de los músculos intercostales y del diafragma puede acarrear consecuencias fatales, al producirse una perturbación respiratoria que lleva al paciente al exitus en forma repentina.

La electrofisiología ha estado siempre presente en el estudio de la miastenia, con la reacción miasténica de Jolly, el fenómeno de Wedensky y las manifestaciones electromiográficas.

Su causa es desconocida. Puede comenzar a cualquier edad desde la infancia a la vejez.

El embarazo a menudo mejora el cuadro clínico.

Algunos autores consideran que es un desorden metabólico secundario a una anormalidad del sistema endocrino. Con frecuencia aparece acompañado de un tumor o de lesiones microscópicas del timo, las relaciones entre la enfermedad del timo y la miastenia no son precisas. Esta última puede sobrevenir con una tirotoxicosis, aquí el vínculo parece ser más claro

A veces se asocia a otras enfermedades, lo que hace pensar de que quizás la miastenia sea un síndrome.

Evidentemente nos encontramos frente a un cuadro clínico de difícil explicación, dado que faltan evidencias que establezcan el sitio y las características del disturbio.

No han podido hallarse lesiones anatómicas en el sistema nervioso central, en los nervios periféricos, en el sistema autonómico, ni en los músculos (en éstos lo que se ha visto es de escasa significación).

Lógico es pensar entonces que lo anormal debe ocurrir en un sector sináptico, más precisamente en la unión neuromuscular.

Ciertos hechos apoyan este concepto, ellos son principalmente la semejanza de la miastenia con la intoxicación por curare y la acción farmocológica benefica de las drogas colinérgicas.

Esto ha llevado el problema al estudio de los ciclos enzimáticos que operan alrededor de la acetilcolina.

Estamos sumamente complacidos por haber podido reunir en este número autoridades tan brillantes sobre el tema como los que se han ocupado de los distintos problemas a que nos enfrenta esta intrigante enfermedad.

Nuestro más vivo reconocimiento a los autores Drs. Lewis P. Rowland, Henry Aranow y Paul F. A. Hoefer (New York); Robert S. Schwab (Boston); M. Montanari (Ferrara); J. Scherrer y A. Bourguignon (París); Kermit E. Osserman (New York), que hacen llegar a nuestros lectores a través de las páginas del International Journal of Neurology el fruto de sus experiencias sobre Miastenia.

VICTOR SORIANO.

Editorial

Myasthenia was first studied as a clinical entity at the end of the last century. However Guthrie affirms that a description coinciding with that of Myasthenia was made by Willis in 1685. Erb in 1879 spoke about a new probably bulbar group of symptoms.

As the necropsies performed didn't reveal any lesion it was called "Bulbar Palsy without anatomical changes". The name of Myasthenia Gravis Pseudo-paralytica was proposed by Jolly in 1895.

In 1901 Oppenheim made a description of the illness that remains as a classic one.

Jolly and Oppenheim discovered the myasthenic reaction which is the progressive failure of the muscles involved to respond repeated faradic stimulations.

The papers of Loewi and later of Dale in 1934 concerning the importance of acetylcholine in neuromuscular transmission have been the origin of a physiopathological discussion and of modern therapy.

Walter in the same period demonstrated the eficacy of the anticholinesterase drugs in myasthenia.

Later was introduced the concept that what was involved was an autoinmune disorder.

Myasthenia is a chronic illness with remissions, whose fundamental symptom and almost a pathonogmonic one is the appearance of a muscular weakness of variable intensity, following the performing of repeated voluntary movements.

The cholinergic drugs produce a dramatically benefical effect, and a rather specific one, to such a point that several authors considered it as part of its definition. This criterion is not accepted by other specialists.

Sleep is restorative. But in the serious cases the muscles that have been damaged first and in which the illness is most severe, cease their contractions even after a prolonged rest.

Cardiac and visceral muscles are not affected in this ailment. The somatic examination doesn't indicate any muscular wasting, or fasciculation, the sensibility is normal as are also the reflexes.

At the onset this illness is usually more evident in the eyes. Frequently the palpebral ptosis is the first symptom. Then the paresis of one or more extra-ocular muscles appears with diplopia, without pupilary changes.

Frequently but in a lesser degree though, the illness begins in the muscles

that have bulbar innervation and that produce dysphagia, dysarthria, dysphonia and palatal palsy.

The facial muscles particularly the retractors of the corners of the mouth are almost always involved.

Afterwards the neck muscles and the limbs are affected, the upper members being more damaged than the lower ones. The respiratory muscles also suffer.

The myasthenic patient presents a very typical aspect, the fallen eyelids, the hanging jaw due to lack of muscular support, the head drooping over the chest, the arms dangling loose at the sides of the body.

The weakness of the intercostal muscles and the diaphragm may cause fatal consequences when a perturbance of respiration brings about the death of the patient and in a very short time.

Electrophysiology has been always an important tool in the study of myasthenia with Jolly's myasthenic reaction, Wedensky's fenomena, and the electromyographic manifestations.

Its origin remains unknown. It may begin at any age from childhood to old age.

Pregnancy very often improves the clinical picture.

Several authors consider it brought about by some metabolic disorder secondary to an abnormality or the endocrinological system. Very often it is accompanied by a tumor or microcospic lesions of the thymus. The relationship betwen the diseases of the thymus and myasthenia are not very precise. The latter illness may occur with thyrotoxicosis, here the connection seems to be more evident.

Sometimes it is associated with another illness, which leads one to think that perhaps myasthenia is a syndrome.

Evidently we are confronting a clinical picture difficult to explain since there is a lack of information that would evidence the precise location and the characteristic of the disturbance.

Anatomical lesions have not been able to be found in the central nervous system, in the peripheral nerves, authonomic system, nor in the muscles (what findings have been made are of little meaning).

Then it seems logical to think that the abnormality must occur in a synaptic region more precisely in the neuromuscular connections.

Certain facts reinforce this concept. There are principally the similarity of the myasthenic symptomatology to those of the curare intoxication and the pharmacologic benefit experienced with the administration of colinergic drugs.

This has carried the study of this problem to the enzimatic cycles that operate around the acetylcholine.

We want to express our deep gratitude to the excellent collaborators who have enhanced this issue with papers so brillantly elaborated.

The topics treated by Drs. Lewis P. Rowland, Henry Aranov and Paul F. A. Hoefer (New York); Robert S. Schwab (Boston); M. Montanari (Ferrara); J. Scherrer and A. Bourguignon (Paris); Kermit E. Osserman (New York) will give to the readers an accurate picture of the latest knowledge on the puzzling problem of Myasthenia through the pages of the International Journal of Neurology.

VICTOR SORIANO.

Current Concepts of the Pathogenesis of Myasthenia Gravis

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INTRODUCTION

Twenty-five years ago, Dale, Feldberg and Vogt(21) indicated the role of acetylcholine in neuromuscular transmission, and the theory of neuromuscular transmission, has evolved since then. At about the same time. Walker(109, 110) demonstrated the therapeutic efficacy of anticholinesterase drugs in myasthenia gravis. Largely because of the conjunction of these events, myasthenia has been regarded as a disease of the neuromuscular junction. In 1960, the work of Strauss and Nastuk and their collaborators(96) provided the first tangible evidence of a new concept of myasthenia, when they demonstrated the presence of a "muscle-binding, complement-fixing globulin" in the serum of myasthenic patients.

Despite extensive study, however, knowledge of the following crucial aspects of the disease is incomplete: 1) the site of the lesion; 2) the role of the thymus; 3) the nature and significance of abnormal circulating substances; and 4) certain clinical features of the disease and its relationship to other syndromes. These deficiencies make it difficult to formulate a coherent theory of pathogenesis.

SITE OF THE LESION

Clinical Evidence: All of the symptoms of myasthenia may be explained on the basis of muscular weakness. Muscle wasting may occur, but is unusual. The deep reflexes are normal. There are none of the usual signs of disorder of either the central of peripheral nervous system, and autonomic function is normal. These facts suggest that the lesion may be at the neuromuscular junction or in the muscle itself.

The weakness is characteristically relieved, at least partially, by neostigmine and related drugs. This is so characteristic that it has been incorporated into a definition of the disease(83, 87), although this may be debated(105). These drugs have been thought to exert their pharmacological effects by virtue of their anticholinesterase activity(78). In addition, patients with myasthenia are usually much more sensitive to the paralytic action of d-tubo-curarine than normal individuals (1, 85); this drug presumably acts by competing with acetylcholine for the receptor substance at the motor endplate. The effects of these drugs on myasthenic individuals led to the belief that the disease is due to an abnormality of neuromuscular transmission.

Electrophysiological Evidence: In 1941, Harvey and Masland(48) showed that the response of myasthenic muscle to repetitive nerve stimulation was similar to that of partially curarized muscle and could be returned to normal by neostigmine. This could be explained by a deficiency of acetylcholine synthesis, a block of acetyl choline activity at the junction, or by excess activity of cholinestarase at the endplate. The latter possibility was not confirmed by

measurement of cholinesterase activity in myasthenic muscle(115), but there has been no definitive study of the activity of this enzyme at the endplate itself. (Cohen and Zacks(17), however, have shown by histochemical methods that the enzyme may be completely inhibited by neostigmine in fatal cases).

In 1952, Churchill-Davidson and Richardson(11, 12, 13) showed that myasthenics were more tolerant of decamethonium than normal individuals, and that in some myasthenics this drug acts like a non-depolarizing ("competitive") blocking agent such as curare, whereas in normal individuals it behaves like a depolarizing compound. This discrepancy, they stated, could be explained only if the lesion were due to an abnormal response of the endplate itself. Grob, Johns and Harvey(44) came to a similar conclusion from their studies of the effects of choline, injected intra-arterially, in normal and myasthenic individuals. They suggested that the disease is due to an abnormal response of the endplate to this normal product of acetyl choline metabolism.

Evidence against this hypothesis has been advanced by Desmedt(27), who maintains that the defect is presynaptic, not post-synaptic, and due to a deficiency of acetyl choline release. He bases his opinion upon the occurrence in myasthenics of "post-tetanic exhaustion"(25) and the similarity of the myasthenic block to that induced by hemicholinium in cats(26), both of which have been interpreted as being due to impaired synthesis of acetyl choline. Dahlbäck and his colleagues, studying intercostal muscle in vitro(20), came to a similar conclusion. In myasthenic muscle, they found a marked deficiency in the frequency of miniature endplate potentials, spontaneously and after the application of potassium chloride; post-tetanic facilitation was also lacking.

In this connection it is of interest that Riker and his colleagues(79) have presented evidence that both neostigmine and curare may exert their effects on nerve terminals rather than on the endplate. In addition, histochemical evidence(5, 17) has also suggested that the therapeutic effects of neostigmine may not be reflected by inhibition of cholinesterase at the endplate.

Further evidence for the possibility of a pre-synaptic defect is provided by the therapeutic efficacy of guanidine(24, 68), which is now thought to exert its neuromuscular activity by virtue of an effect on acetyl choline synthesis, rather than by cholinesterase inhibition(74).

There is also some evidence, however, that the muscle fiber itself may be abnormal. Bothelho(7) found a discrepancy between the electrical activity of myasthenic muscle and the force of contraction as measured by a strain-gauge manometer. Contraction might still be active at times when electrical activity was diminished. She suggested that there might be a defect in the muscle itself, rather than at the neuromuscular junction. These experiments have been criticized on technical grounds(27), but Hoffman has also stated that the ameliorative effect of veratrine on myasthenic muscle can be interpreted as an indication of a muscular defect(51).

The possibility of a muscular defect is supported by histological evidence (v.i.), and also by the neglected and unconfirmed report that the oxygen consumption of homogenates of myasthenic muscle, in vitro, is low, and is corrected by neostigmine(93).

In view of these contradictory findings, there is considerable uncertainty as to whether the myasthenic defect is presynaptic, synaptic, post-synaptic, or in the muscle fiber itself. These conflicts are perhaps not surprising; the mechanism of normal neuromuscular transmission is still a matter of debate. It is therefore difficult to deduce events at a diseased neuromuscular junction by analogy with the effects of pharmacological compounds which act in a manner which is not known precisely.

Histological Evidence: For many years, it was stated that the only lesions of the muscle in myasthenia were lymphorrhages, which by virtue of restricted number among normal appearing fibers, were innocuous. Because they might be present in other conditions as well, these lesions were not considered pathognomic. This belief was generally held despite occasional reports of pathological alteration of the muscle fibers or more marked inflammatory response(87).

In 1953, we reported evidence of polymyositis in 3 of 26 fatal cases(86), and Russell (88) presented evidence of significant muscular lesions in a more detailed report. Similar lesions were subsequently described by others(37, 87). These lesions do not necessarily refute the hypothesis of a basic defect in transmission, but any theory of the disease should take them into account.

In 1958, Coërs and Desmedt(15, 16) studied the neuromuscular junction in myasthenia by means of the intra-vital staining technique with methylene blue. They described abnormalities of the terminal arborizations of the motor nerves, supporting the hypothesis of a presynaptic lesion. These abnormalities have also been described by others(5, 61). Alterations of the nerve terminals, however, have also been described in other diseases (such as muscular dystrophies) which are believed to be myopathic in nature. Electron microscope studies have been few in number; in one case, no definite changes were seen(4), but in another there were abnormalities in both axon filaments and the sarcolemmal membrane(119).

Histological evidence has therefore failed to resolve the issue as to whether the lesion is pre or post-synaptic.

ROLE OF THE THYMUS

Thymomas occur in about 25% of myasthenic individuals above the age of 35; the tumor has not been reported in myasthenic children. A significant proportion (33-75%) of patients with thymoma also have myasthenia gravis(84). In myasthenic individuals who do not have a thymoma, the thymic tissue is abnormal in more than half the cases. These figures(30, 72, 86, 107) indicate a significant relationship, but the nature of this association remains obscure.

In some patients, removal of the thymus is followed by improvement of the myasthenia. However, there is no way of predicting whether any individual patient with myasthenia will improve after thymectomy. Age, sex, duration of disease have been found to be useful prognostic indicators by some workers but not by others. Most clinicians have felt that the presence of thymoma diminishes the chances of improvement after thymectomy, but this is not always the case(3, 6, 8, 72, 90).

The amelioration of myasthenia after the removal of the thymus in some patients led to the hypothesis that the gland produces some kind of toxic factor. Experimental studies of the results of injection of extracts of normal or pathological thymus in whole animals, in neuromuscular preparations or on acetyl choline synthesis, however, have been inconsistent(58, 113, 118); at best, it may be stated that no abnormal factor has been conclusively demonstrated (72).

Other facts suggest that there may be no causal relationship between the thymus and myasthenia. For instance, there have been many reports of fatal myasthenia in which no thymic tissue can be detected at autopsy, and there have been patients who have been in complete remission from myasthenia when the thymoma developed (cf. appendix, case 1) or spread(32). Furthermore there have been patients who were found to have a thymoma at a time when there was no evidence of myasthenia but who then developed myasthenia some years later(84). It is not possible to exclude the possibility that some thymic tissue remained after the operation, nor that inapparent myasthenia was present prior to thymectomy. Nevertheless, a reasonable explanation of these cases is that both the myasthenia and the thymoma were the result of some common cause. If this is so, it is difficult to understand why any patient should improve after thymectomy; yet some do. Viets and Schwab(107) have presented evidence that other major surgical procedures are not followed by similar improvement.

Thymomas have also been associated with aregenerative anemia, in a relationship which is similar to that of thymoma and myasthenia. In a few cases, removal of the tumor has been followed by hematological remission, but not in others(10, 47, 62, 66). In one case, the anemia appeared after the tumor had been excised(14). A few patients with thymoma have had anemia and myasthenia. Extracts of the tumors have not produced depression of the bone marrow when injected into experimental animals(53, 75) or humans(77).

ABNORMAL CIRCULATING SUBSTANCES

In 1942, Strickroot et. al.(98) reported that a child, born of a myasthenic mother, sucked poorly and had feeble limb movements. Within two weeks, the child moved normally. Since that time, 35 children have had a similar syndrome(42, 66). The most plausible explanation for this disorder is that some agent present in the mother's blood crosses the placenta, enters the fetal circulation and there exerts its effects on the child. After a period of time, this substance is either excreted or inactivated in some way and the child is normal thereafter.

The possibility that myasthenic muscle produces some noxious factor has also been suggested. When exercise of a myasthenic limb is performed under conditions of venous occlusion, and the circulation then released, there may be an increase of blepharoptosis(114). Many workers have sought to demonstrate blocking substances in the blood or urine (as well as the thymus) of myasthenic patients. Neither in humans, experimental animals, nor in nerve-muscle preparations have these studies been conclusive(2, 46, 58, 72, 89, 94, 101), but recent studies have again raised this possibility(97, 104, 116).

In searching for such a factor, Nastuk and his colleagues(71) found that serum of some myasthenics produced histological lesions in frog muscle (although this also occurred with some normal, too). They also found abnormal variations in serum complement activity(70). In 1960, Strauss and his associates showed, by means of fluorescein tagging, that there is a muscle-binding, complement-fixing substance in the serum of patients with myasthenia which is not present in normal individuals. This substance seems to label the A-bands of skeletal muscle, but not cardiac muscle(95, 96). It does not bind to thymus. There have not yet been studies of the specificity of this reaction, and in the original paper, similar results were reported in one patient with paroxysmal myoglobinuria; other conditions are in the process of study.

DISEASE OR SYNDROME?

The clinical features of myasthenia gravis are sufficiently characteristic that in most cases the diagnosis is not difficult. The clinical features are also sufficiently constant that it might be considered to be a disease, in the sense of having a single pathogenetic mechanism in all cases(91). The association of myasthenia with other diseases, and the existence of syndromes similar to myasthenia, however, have fostered the growing suspicion that myasthenia may be a syndrome due to more than one pathogenesis.

Myasthenia Associated with Other Diseases: Although myasthenia may occur fortuitously with a variety of other diseases, thyrotoxicosis seems to bear a special relationship. In various large series, 3-5% of myasthenic patients have had thyrotoxicosis at some time. The two conditions frequently occur at the same time, but often one may precede the other by months or years. The variability of this temporal relationship suggests, as in the case of thymoma, that both conditions result from a common cause, or at least a common susceptibility.

There are no other diseases which are commonly encountered in a myasthenic population. In some patients, the distribution of weakness is such that muscular dystrophy or some other myopathy might be suspected, and there may be electromyographic or histological evidence of myopathic disorder, but these patients might be considered to have "pseudomyopathic myasthenia". Whether those patients with marked histological lesions in muscle ("polymyositis") or those with thymomas should be considered separate categories is not clear. In our experience the clinical manifestations in the patients is not qualitatively different from the disease in patients without thymoma or myositis (cf. appendix, case 2).

It has been suggested that there is a special form of myasthenia which occurs in association with carcinoma. In our own series of more than 300 cases of myasthenia, we have encountered only one carcinoma (of the breast). In other series, the incidence of carcinoma has also been low enough to suggest that the association of

myasthenia and carcinoma is fortuitous(72, 87).

In our early series, there seemed to be a high incidence of epilepsy(50), but this has not been true in other series(72, 91) and seems to have been a local phenomenon, the cause of which is not clear.

Prostigmin-Responsiveness and Curare-Sensitivity in Other Syndromes: The beneficial effect of cholinergic drugs is so dramatic and sufficiently specific that it has been offered as part of the definition of myasthenia(87), although a vigorous dissenting opinion has been expressed by Viets(105). In our own experience, we have never seen an unequivocal and reproducible response to cholinergic drugs in any condition other than myasthenia gravis, alone or in combination with some other disease. Even Viets(105), who does not consider neostigmine-responsiveness part of the definition, has not seen it in any other condition.

Nevertheless, there have been reports of a beneficial response in a variety of other diseases. This problem has been discussed and the individual cases analyzed in some detail elsewhere(87). In some of these cases the proper diagnosis may have been myasthenia, alone or in combination with some other disease. In others, the improvement after neostigmine may have been more apparent than real, and it is noteworthy that in most cases the improvement has concerned the strength of arms and legs. In this situation it is frequently difficult to control subjective responses of patient or clinician. With the exception of exophthalmic ophthalmoplegia, there has been no documented (photographic) evidence of improvement of any cranial muscle function in any of these conditions. These objections do not, of course, refute the facts reported by several reliable observers, and electromyographic improvement has been reported in amyotrophic lateral sclerosis (69). On the other hand, these exceptions do not detract from the general utility of the response to cholinergic drugs as a diagnostic test for myasthenia.

Curare sensitivity in our experience has also been specific for myasthenia gravis (85). Eaton, Mulder and their colleagues, however, have reported similar responses in both the "myasthenic syndrome associated with mediastinal malignancy"(31, 57) and in amyotrophic lateral sclerosis(85). Croft(19) has also reported curare-sensitivity in patients with malignant disease of different kinds, but in his series exposure was not limited to the small amounts of d-tubocurarine used in the tests; rather, the patients failed to recover promptly from full curarizing doses given as an anaesthetic adjunct.

Syndromes Unresponsive to Cholinergic Drugs: In 1956, we described a woman who had a syndrome of fluctuating weakness affecting cranial, limb and respiratory muscles. There was no clearcut effect of cholinergic drugs and there was no histological evidence of disease of central or peripheral nervous systems or of muscle(83). It was pointed out that there was no satisfactory label for this syndrome other than myasthenia, but in the absence of pharmacological proof, this diagnosis cannot be established.

Do cases of this nature represent myasthenia gravis which does not respond to drugs? Or are they related disorders, in which the distribution of muscle weakness and the temporal characteristics of the disease are similar to myasthenia, but the basic pathogenesis is different?

There have been several cases of patients with thymoma and polymyositis who were either not tested with neostigmine, or in whom tests were said to have been negative (59, 87, 112). In most of these cases there would have been little difficulty in accepting them as instances of true myasthenia, had the pharmacological response been appropriate.

There are some disorders which are so like myasthenia in distribution of muscle weakness that they can be differentiated from myasthenia only because they do not respond to cholinergic drugs; thyrotoxic myophaty, exophthalmic ophthalmoplegia, ocular myopathy (chronic progressive ophthalmoplegia), any ophthalmoparesis in which the pupils are not affected, and any myopathy in which the reflexes are normal, including some cases of polymyositis (cf. Appendix, case 3).

Almost all patients with a past history of thyrotoxicosis who develop blepharoptosis prove to have myasthenia gravis. There are some patients, however, who do not respond to either cholinergic drugs or curare. Lack of pharmacological response is the only feature which critically differentiates this syndrome from myasthenia, and there is no appropriate name for it. Similar considerations may apply to patients with limitation of ocular movements in the absence of exophthalmos, although some may subsequently develop other evidence of "infiltrative ophthalmopathy"(22) (cf. Appendix, cases 4 and 5).

THE NATURE OF MYASTHENIA GRAVIS

In the past, no one has formulated a comprehensive theory of the pathogenesis of myasthenia. In many publications, however, many workers seemed to visualize the thymus gland as an endocrine organ, the secretion of which had a deleterious effect on neuromuscular transmission.

Attempts have been made to demonstrate some significant effect of other endocrine disorders on myasthenic symptoms, but except for thyrotoxicosis, no definite relationship has been seen. The symptoms of myasthenia may change during or after pregnancy, but not in any predictable way, and there has been no significant relationship between myasthenia and disease of pituitary, adrenals, gonads, or pancreas.

This concept of myasthenia as a distant relative of the better-known endocrine disorders was never accepted, because there was no positive evidence to support it, but the conceptual framework of modern medicine did not offer any better explanation. Although sometimes familial(41), there is no strong evidence that myasthenia is to be considered an inborn error of metabolism(56). Within the past years, a new concept of disease has been introduced and myasthenia is now regarded by several workers as an "autoimmune disorder"(73, 91).

This view was first expressed by Smithers (92) in 1959, who pointed out the similarity between the appearance of the thymus in myasthenia and the thyroid gland in Hashimoto's thyroiditis. The concept was then developed *in extenso* by Simpson(91). The strongest evidence in this direction has been provided by Strauss and Nastuk and their associates(95, 96), as cited above, and it is supported by the recent experimental production of lesions in the thymus similar to those found in myasthenia by the injection of typhoid-paratyphoid vaccine or diphtheria toxoid, as reported by Marshall and White(63, 64). The association of thymoma and agammaglobulinemia(36) is of interest because there seems to be an increased incidence of allergic reactions among patients with hypogammaglobulinemia(39, 41).

There is no clinical evidence to contradict this hypothesis. Burnet(9) has pointed out the variability of the course of those disorders currently considered to be auto-immune diseases, so the relapses and remissions so characteristic of myasthenia may be included. Burnet also emphasizes that diseases characterized by lymphocytic infiltration of tissues, without evidence of bacterial or viral invasion, should be considered as possibly auto-immune in nature, and myasthenia qualifies on this score. The high incidence of the disease in young women has also been cited(64). It might be objected that the peculiar tendency of myasthenia to remain localized in one or both eyelids, for instance, would be difficult to explain on the basis of a generalized disease, but even in these cases there may be evidence of myasthenic defect in asymptomatic muscles when tested by decamethonium(11, 12, 13) or curare(85).

Signs of systemic disease (arthalgia, fever, accelerated erythrocyte sedimentation rate, increased concentration of serum gamma globulin) which are frequently present in other auto-immune diseases, are not part of the usual picture of myasthenia, but concepts of this category of diseases are expanding. In Simpson's series(91), arthritis occurred in 16 of 440 patients, and there have now been 4 patients have had evidence of both myasthenia and lupus erythematosus(23, 49, 83, 85), although the clinical features may have been atypical. The possible benefits of steroid therapy in myas-

thenia remain inconclusive(34, 43, 67, 72, 102).

The concept of auto-immune disease is new, and no disease has been *proven* to occur by this mechanism. The most satisfactory demonstration of auto-antibodies which might be pathogenic has been in thyroiditis, but even here, similar antibodies have been demonstrated in some normal individuals(82, 108). In the case of myasthenia, the authors carefully refrained from calling the circulating globulin an antibody. The antigen has not been identified. The fact that it appears to bind to A-bands suggests that myosin may be the antigen (65); this would not explain the pharmacological features of myasthenia.

Furthermore, the identification of antigen and antibody does not itself provide evidence of the mechanism of disease. As Lumsden has stated(60), if this were so, then syphilis should be considered "a disease of man caused by antibodies to exheart". The only attempt to produce experimental polymyositis by sensitization to muscle extracts was followed by arthritis; there were no muscular lesions(76).

If there is a circulating antibody, it has not been demonstrated in all cases, nor has it been demonstrated to be the cause rather than the result of the muscular disorder, a possibility suggested by similar findings in myoglobinuria(96) and after cardiac surgery(54). In lupus erythematosus, several antibodies to different tissues and cell constituents have been demonstrated, but their relationship to manifestations of the disease is uncertain(52).

These reservations merely indicate that much work remains to be done and it seems very likely that immunological study of myasthenia will be important in the future. This approach may not be adequate, and the nature of myasthenia may not be encompassed by present concepts of disease. Nevertheless, this is the first important new lead in myasthenia in several decades. If the serological data can be explained and the pharmacological conflicts resolved, we will be closer to understanding this perplexing disease, in which there seem to be so many clues but no proof of its nature.

TABLE I

Date	Serum protein-bound iodine mgm. per 100 ml.	Radioactive iodine uptake % in 24 hrs
7/ 9 /60	10.5	
8/ 4 /60	8.3	
9/13/60	6.2	
11/ 9 /60		27
1/ 6 /61		34
1/14/61		34
3/ 9 /61	7.8	
5/10/61	8.1	
7/ 8 /61	8.1	

Table 1. — Thyroid function studies patient with probable Graves' disease following treatment of myxedema. Thyroid extract was discontinued on 8/19/60. The radio-iodine uptake on 1/14/60 was obtained after the administration of tri-iodothyronine, 50 mgm. daily, for eight days.

APPENDIX

Case 1.

Ocular myasthenia gravis at age 28, generalized at age 30. Complete remission at age 34; appearance of thymoma 8 years later without recurrence of myasthenia.

History:

R. O. (§ 85-97-76) began to have ptosis of the right eyelid at age 28 in 1944. This disappeared during a pregnancy shortly after the onset, but diplopia was present a few days postpartum and persisted thereafter. In 1946, she had ptosis, dysarthria, dysphagia, and difficulty in chewing. She was helped by neostigmine, 180 mgm. daily, and then became pregnant again. During the last 4 months she experienced a complete remission, but ptosis and diplopia recurred in the postpartum period. She was taking neostigmine, 45 mgm. daily.

She was examined for the first time in our Clinic in 1947. Except for weakness of the orbicularis oculi, no abnormalities were found. Posterior, anterior and lateral roentgenograms of the chest were normal (fig. 1a. b).

In 1948, medication was withdrawn but she experienced ptosis, dysarthria, and cer-

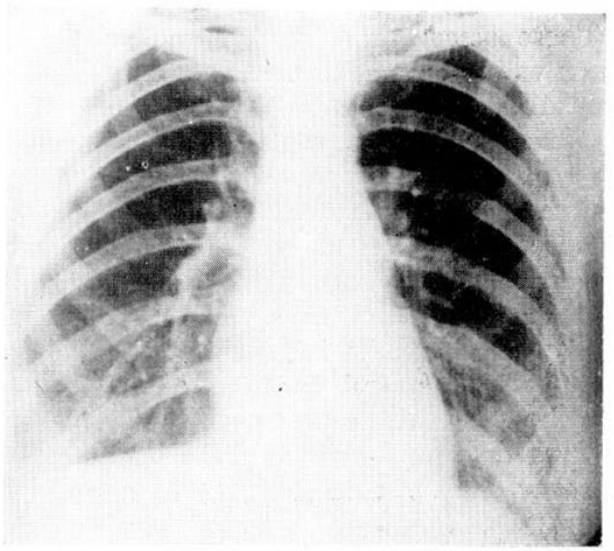

Figure a (Case 1)

vical weakness, and re-started medication. In 1950, medication was again discontinued and she remained symptom-free. During the ensuing years she had no myasthenic symptoms and no abnormalities were found in examinations performed annually.

In 1958, she began to have mild anterior chest pain and a mediastinal tumor was present in a roentgenogram of the chest (fig. 1, c, d, e). The tumor was visible, but smaller, in films taken the previous year.

Examination at this time was normal, but a curare test indicated sensitivity to the drug in cervical muscles. The tumor was completely removed by Dr. Robert Wylie and weighed 44 grams. It was a thymoma, predominantly epithelial in character, with some microscopic evidence of invasiveness.

The postoperative course was unremarkable. There have been no symptoms or signs of myasthenia in the three years since the operation was performed, nor has there been radiographic evidence of recurrence of the tumor.

Comment: This case illustrates the fact that the course of myasthenia is independent of the growth of a thymic tumor. There is no way of excluding the possibility that a tumor too small to be seen radiographically was present at the time of myasthenic symptoms.

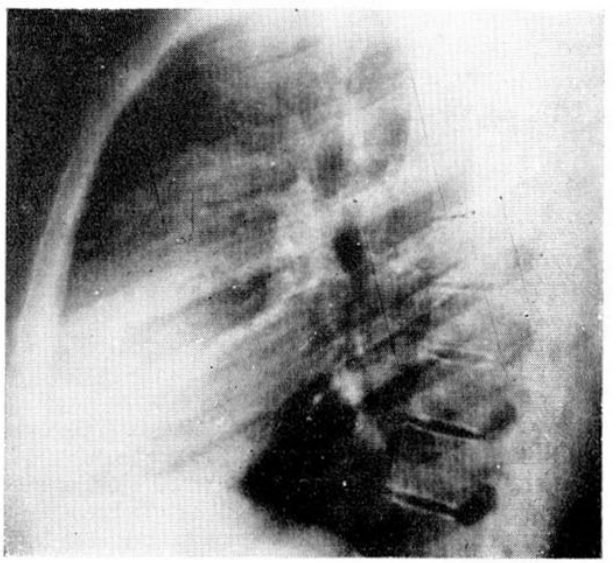

Figure b (Case 1)

Case 2.

Myasthenia gravis with thymoma at age 41. Thymectomy without improvement. Fatal exacerbation two months later. Myocarditis and polymyositis at autopsy.

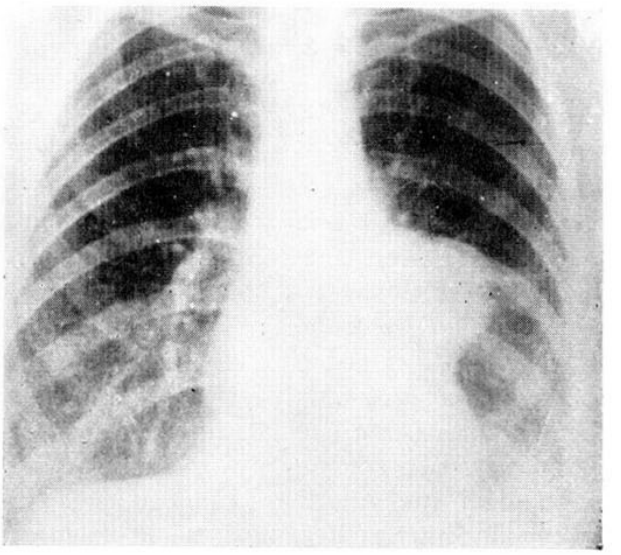

Figure c (Case 1)

History:

M. D. (§ 152-43-73), a 45 year old woman, noted occasional mild dysphagia after April 1960. Because of menorrhagia, a dilatation and curettage of the uterus was performed in December. The procedure itself was uncomplicated, but the following day she had marked dysphagia with nasal regurgitation, difficulty in chewing, and weakness of the arms and legs. Two weeks later she noted diplopia and in January 1961, she began to have ptosis of variable degree. She was admitted on April 24, 1961.

There was bilateral ptosis of the eyelids; oropharyngeal and limb weakness were prominent. The responses to Tensilon and d-tubocurarine were characteristic of myasthenia gravis. There was no laboratory evidence of thyrotoxicosis, but roentgenograms indicated the presence of a thymoma.

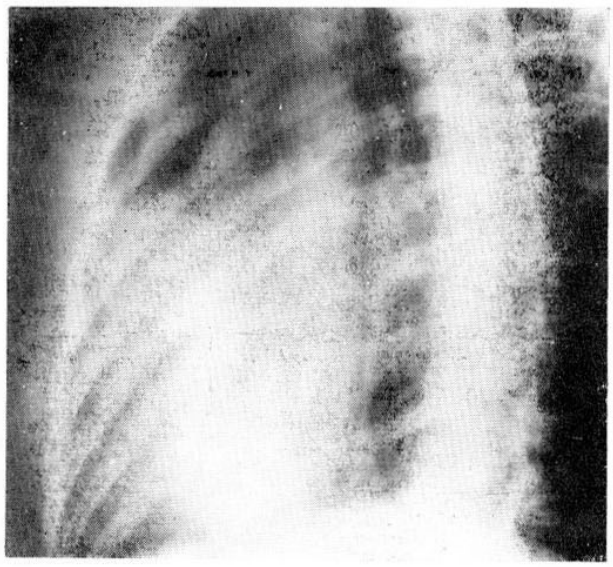

Figure d (Case 1)

She was discharged on April 29, taking Mestinon 120 mgm., 5 times daily. She improved considerably and only the ocular symptoms remained.

She was re-admitted on May 7 for removal of the tumor. In addition to the ptosis there was also overt ophthalmoparesis, almost complete. Thymectomy was performed by Dr. Robert Wylie on May 15 and the postoperative period was uncomplicated. She was discharged on June 6, taking Mestinon 750 mgm. daily.

On July 7 she was re-admitted because of increasing dysphagia and exertional dyspnea. There was complete ophthalmoplegia, facial, masticatory, oropharyngeal, respiratory, and limb weakness.

A tracheostomy was performed and she was placed on intermittent positive pressure respiration. Medication was discontinued but she showed no spontaneous improvement.

On July 8 she became oliguric. The blood pressure could be maintained only with administration of intravenous levarterenol. An electrocardiogram indicated the signs of recent anterolateral myocardial infarction. Her critical condition did not improve and she died on the 6th day after admission.

Postmortem Examination: There was no gross or microscopic evidence of residual thymoma. There was a diffuse myocarditis, with fragmentation, loss of striation and some basophilia of muscle fibers, accompanied by discrete and diffuse areas of infiltration by round cells and histiocytes (fig. 2a). A similar process was evident in skeletal muscle (fig. 2b). In addition, there was bilateral lower lobe atelectasis of the lungs and an agonal duodenal ulcer.

Comment: The clinical features of this illness were those of myasthenia gravis. In cases of this kind, there is no method of predicting the appearance of histological changes in the muscles.

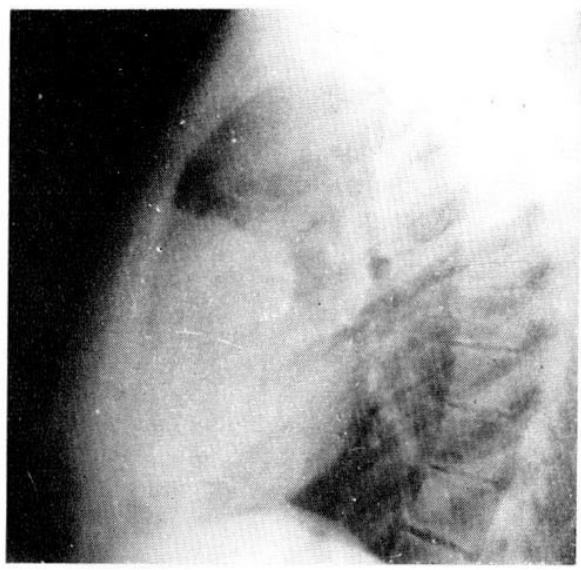

Figure e (Case 1)

Roentgenograms of the chest. In 1947, when myasthenic symptoms were prominent, no tumor was visible. (a, b). In 1958, while patient was in complete remission, a large thymoma was evident (c, d, e).

Case 3.

Transient syndrome of oropharyngeal and limb weakness simulating myasthenia gravis but pharmacologically unresponsive. Histological evidence of polymyositis.

History:

A. J. (§ 75-87-64), a 58 year old woman, had pain in all joints in December 1960. During the next few weeks she was treated with cortisone, penicillin and bed rest without improvement. The joints were said to have been swollen, but she had no fever. During March she remained in bed the entire month because of inability to walk. She was admitted on March 28, 1961.

She was febrile (102°F.) but did not appear to be in distress. There were no visible abnormalities of the joints, although she was reluctant to move all limbs. The only weakness recorded was in the hand grips, and this was attributed to arthritis. There were a few rales at both lung bases but the remainder of examination was normal.

The following laboratory tests were abnormal: 1) Hemoglobin, 10.3 gms. %; Red blood cells, 3.4 million per cu. mm.; 2) White blood cells, 14,800 per cu. mm., with normal differential count; 3) Erythrocyte sedimentation rate - 130 mm./hr.; 4) Roentgenograms

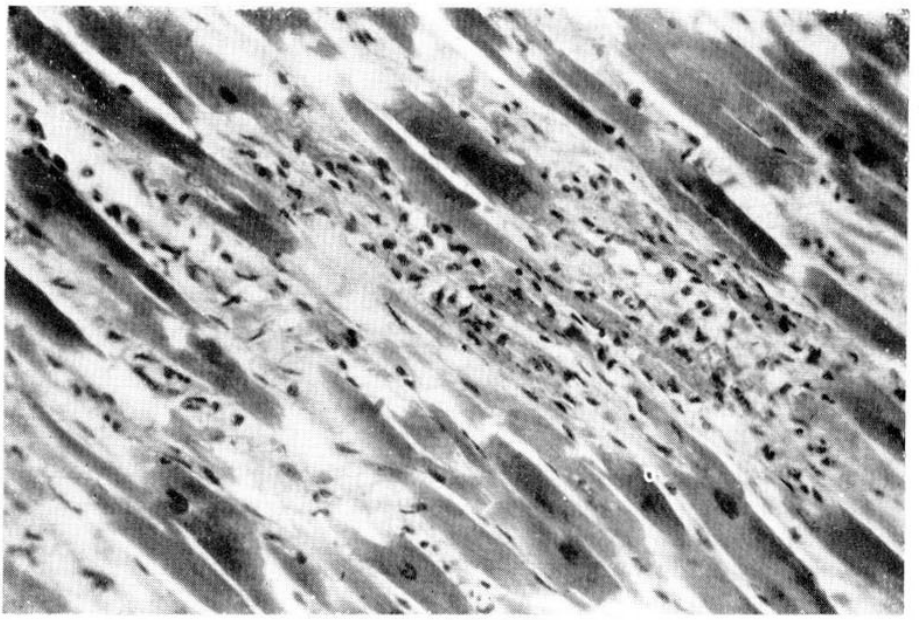

Figure a (Case 2)

of chest - pneumonitis, left lower lobe; 5) Serum protein electrophoresis - increased globulin concentrations; alpha-2, 1.0; beta, 1.2, gamma, 2.8 gms. %; 6) Roentgenograms of joints - moderate hypertrophic arthritis, both ands, knees, ankles; 7) moderated albuminuria; 8) Muscle biopsy; degeneration of fibers with inflammatory exudate (fig. 3); 9) Creatinuria - 166 mgm. in 24 hours.

The following laboratory studies were normal: serological tests for syphilis, lupus erythematosus, infectious mononucleosis, and toxoplasmosis (serum for viral studies was contaminated); serum urea nitrogen, cholesterol, calcium, phosphorus, sodium, potassium, uric acid, alkaline phosphatase, antistreptolysin, cephalin floculation, thymol turbidity, carotene, vitamin A, protein-bound iodine, transaminase and lactic dehydrogenase; bromsulphonphthalein excretion; roentgenograms of esophagus. Electromyograms were not performed.

During the next few days she became dysarthric and dysphagic. On April 3, there was no ptosis or limitation of ocular movements; but there was marked weakness of jaw and facial muscles. She was unable to protrude her tongue and saliva pooled in her mouth. There was diffuse limb weakness, but no muscular atrophy or tenderness. The reflexes and sensation were normal. A tracheostomy was performed.

On April 5th, there was marked improvement of oropharyngeal symptoms, but respiration was weak and she was assisted with intermittent positive pressure respiration. Tensilon (10 mgm. intravenously) and neostigmine (1.5 mgm. intramuscularly) had no effect. Nasogastric intubation was necessary for nutrition.

On April 6th, neostigmine (2.0 mgm.) and Tensilon (10 mgm.) again had no definite effect. She was given d-tubocurarine (1.2

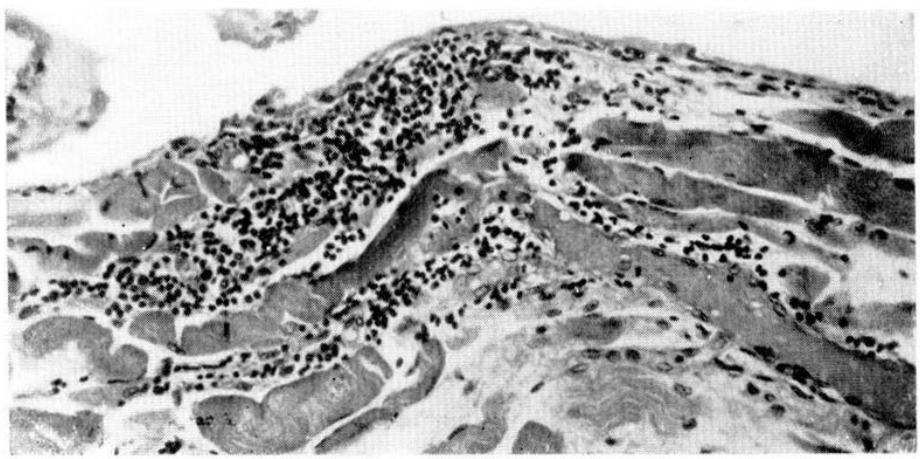

Figure b (Case 2)

Degeneration of muscle fibers and inflammatory cellular infiltration in heart (a) and skeletal muscle (b) in patient with thymoma and myasthenia gravis. (H. & E., X280).

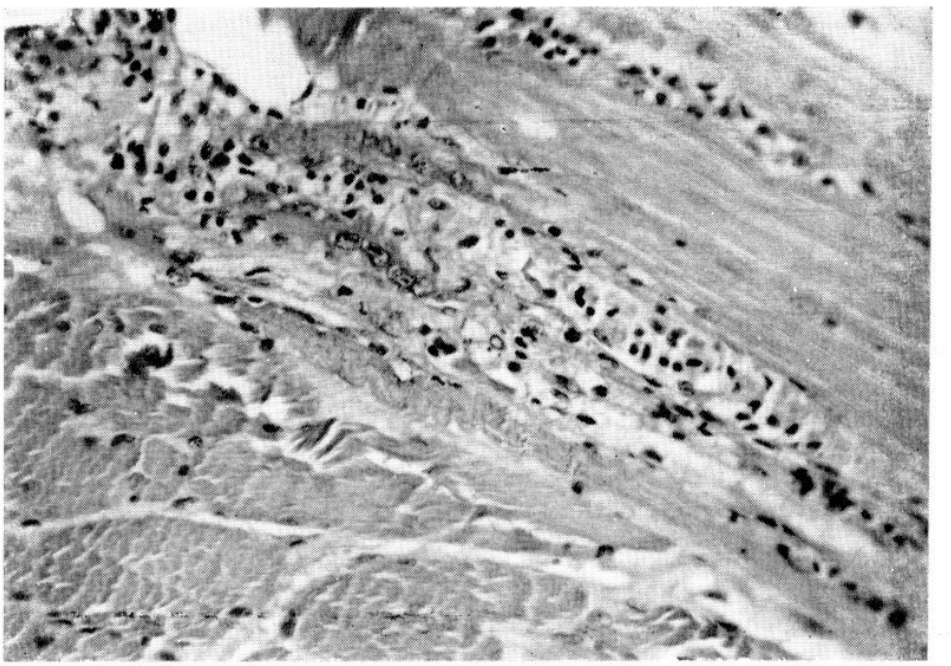

Figure 3 (Case 3). — Necrosis of muscle fibers and inflammatory exudate in syndrome simulating myasthenia gravis, but unresponsive to cholinergic drugs or d-tubocurarine. (H. & E., X280).

mgm., weight 158 lbs., 1/10th of a curarizing dose) without definite effect.

Her subsequent course was one of progressive improvement. On April 10th, both the nasogastric and tracheostomy tube were removed. The fever gradually subsided and she was discharged on April 28. There has been no relapse during the six-month period of observation and there has been no residual weakness.

Comment: The rapidity of onset, the distribution of muscular weakness (face, oropharynx, neck, limbs), lack of clinical or laboratory evidence of neural disorder, and variable course were all consistent with myasthenia gravis. The lack of pharmacological response, however, made it impossible to prove this diagnosis. The fever could have been due to pneumonitis. Only the history of arthralgia (without objective evidence of arthritis) and the abnormal serum proteins gave evidence of systemic disease. The muscle biopsy was compatible with polymyositis.

Case 4.

Thyrotoxicosis and ophthalmoparesis without exophthalmos in a 40 year old woman. No response to cholinergic drugs, equivocal response to curare. Subsequent development of infiltrative ophthalmopathy.

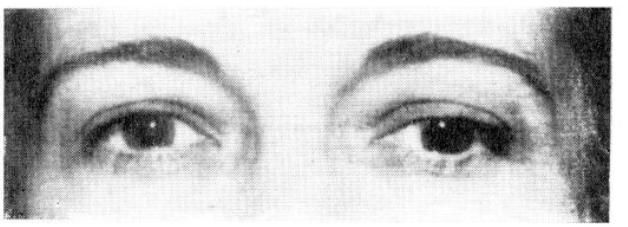

Figure a (Case 4)

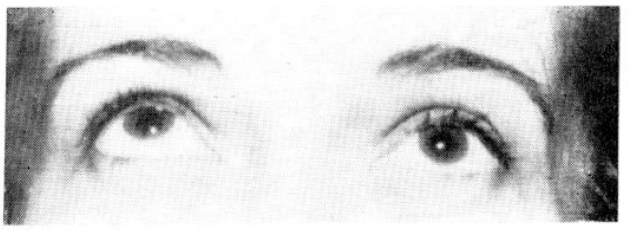

Figure b (Case 4)

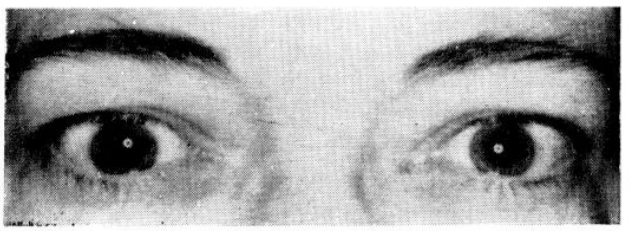

Figure c (Case 4)

Ophthalmoparesis without exophthalmos in patient with thyrotoxicosis. When first examined there was no exophthalmos (a) but patient was unable to elevate the right eye (b). Subsequently lid retraction became evident (c).

History:

H. F. (§ 145-21-72), a 40 year old woman, was admitted to the care of Dr. Robert A. Fishman in November 1959. Seven months previously she began to have diplopia in all directions of gaze. Concomitantly she felt nervous, menstrual flow decreased, she was intolerant of heat, and lost 20 pounds.

Her skin was warm and smooth. The pulse rate was 120 per minute. The thyroid was diffusely enlarged. There was a tremor of the outstretched hands.

Dr. Robert Day saw the patient in ophthalmological consultation. There was slight retraction of both upper lids but lid-lag was only inconstantly present. The left lacrimal gland was palpable, but there was no fullness of the lids or congestion of the conjunctivae. There was no exophthalmos but there was 20° right hypertropia, with the left eye in the primary position. Ocular movements were grossly normal except that she was unable to elevate the left eye (fig. 4a, b). There was diplopia in all directions of gaze on red-glass testing.

There was slight weakness of eye-closure against resistance and slight proximal limb weakness, but other cranial muscles and the reflexes were normal.

The diagnosis of thyrotoxicosis was substantiated by abnormalities of serum protein-bound iodine (16.1 micrograms %), basal metabolic rate (plus 59 %) and radioactive iodine uptake (72 % in 24 hours).

There was no response to Tensilon (10 and 15 mgm. intravenously). She was given d-tubocurarine (weight 135 lbs., 2.1 mgm., 1/5th curarizing dose) in 8 fractional doses at 2-minute intervals. Prior to the test she was able to raise her head from the bed in supine position for 30 seconds without difficulty. This deslined progressively and at the end of the test she could raise her head for only 5 seconds. There were no changes in eyelids, ocular movements, facial or oropharangeal muscles or in limb strength. Tensilon (15 mgm.) did not reverse the cervical weakness and the test was considered equivocal.

She was treated with propylthiouracil. By January 1960 her general symptoms had receded, and she had gained 10 lbs., but the ocular signs were not changed. Limb strength was normal. In February, however, toxic symptoms recurred. In addition, she noted swelling of the eyelids and lacrimation. There was now bilateral lid retraction and pigmentation of the lids (fig. 4c). Hertel exophthalmometer measurements increased 1 mm. but there was no frank exophthalmos. These signs again receded with further treatment and return to erthyroid state. She has not developed evidence of myasthenia during the past two years.

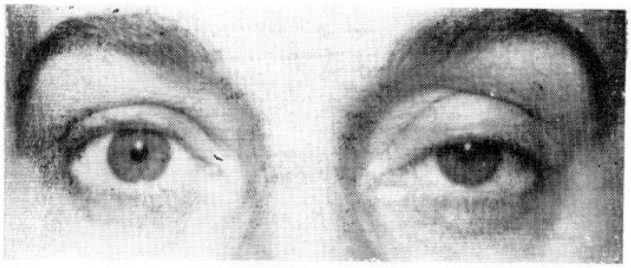

Figure 5 (Case 5). — Ptosis of the left eyelid was the presenting symptom and most prominent sign in patient with probable Graves' disease. Lid retraction on the opposite side was inconstantly present and there was no exophthalmos. There was no response to cholinergic drugs or d-tubocurarine.

Case 5.

Myxedema treated with thyroid extract. Development of ptosis during probable thyrotoxic state but no response to cholinergic drugs or d-tubocurarine.

History:

F. B. (§ 98-04-18), a 50 year old biochemist, was admitted to the care of Dr. Robert A. Fishman on July 9, 1960.

In December 1958, while serving as a control subject for a new method of measuring serum cholesterol concentration, her own value was found to be 435 mgm. %. Upon inquiry, she realized that during the preceding year her eyelids felt swollen in the morning, her voice seemed very hoarse and her skin drier than usual. In May 1959, the basal metabolic rate was 30 %, radioiodine uptake, 9 % in 24 hours, and serum protein-bound iodine was 2.1 micrograms percent.

She was treated with thyroid extract in gradually increasing amounts, up to 150 mgms. daily. She was then asymptomatic until July 1960, when she noticed ptosis of the left eyelid. One week later she became aware of a pulling sensation in the right eye, the palpebral fissure of which seemed wider. These symptoms were constant; there was no diplopia and there were no other symptoms.

Examination was normal except for ptosis on the left (lid at upper margin of pupil) (fig. 5). Lid retraction on the right (lid above iris) was inconstantly present. Ocular movements were normal.

Neostigmine (0.75 mgm. and 1.5 mgm. intramuscularly) and Tensilon (10 mgm. intravenously) had no effect. There was no sensitivity to d-tubocurarine (1/5th curarizing dose). Thyroid function studies: serum cholesterol 233 mgm. %, basal metabolic rate

minus 8 %, serum protein-bound iodine 10.5 micrograms %. Subsequent studies are recorded in table 1. After thyroid extract was discontinued, the serum protein-bound iodine returned to normal, but even without resumption of treatment, has once again reached elevated values. There has been no change in the ophthalmological abnormalities.

The failure of the radioactive iodine uptake to be depressed by the administration of tri-iodo-thyronine is also consistent with Graves' disease (113).

SUMMARY

1. For many years, myasthenia gravis has been regarded as a disease of the neuromuscular junction, although no precise formulation could explain all features of the disease.

2. It is not yet possible to provide a coherent theory of the pathogenesis of myasthenia gravis for the following reasons:

a) Neither clinical, electrophysiological nor histological evidence has unequivocally defined the site of the myasthenic defect.
b) The role of the thymus remains uncertain.
c) The possibility that circulating autoantibodies or neuromuscular blocking substances play a role in the disease has to be elucidated.
d) It is uncertain whether myasthenia should be regarded solely as a disease (implying a single pathogenesis) or a syndrome of more than one etiology.

RESUMEN

1) Por muchos años la miastenia gravis ha sido enfocada como una enfermedad de la unión neuromuscular, aunque ninguna fórmula precisa pudo explicar todos los aspectos de la enfermedad.

2) No es todavía posible establecer una teoría coherente de la patogenia de la miastenia gravis por las siguientes razones:

a) Ninguna evidencia clínica electrofisiológica e histológica ha definido en forma inequívoca el asiento del defecto miasténico.
b) El papel del timo permanece incierto.
c) La posibilidad de que anticuerpos circulantes o sustancias que bloqueen la unión neuromuscular desempeñen un papel en la enfermedad tiene que ser dilucidada.
d) Hay incertidumbre con respecto a si la miastenia debe ser vista como una enfermedad única (implicando una simple y única patogenia) o un síndrome de más de una etiología.

RÉSUMÉ

Pendant de nombreuses années, la myasthénie grave a été considerée comme une maladie de la jonction myo-neurale, sans qu'il soit possible d'expliquer ainsi tous les aspects de son évolution d'une manière précise.

Il n'est actuellement pas possible d'établir une théorie cohérente de la pathogénie de cette affection pour les raisons suivantes:

a) Aucune preuve clinique électrophysiologique ou histologique n'a précisé jusqu'a présent et sans équivoque, le siège du défaut myasthénique.
b) Le rôle du thymus parait incertain.
c) La possibilité d'un blocage de la jonction myo-neurale par des anticorps circulants ou d'autres substances, reste à démontrer.
d) Un désaccord subsiste sur le fait de savoir si la myasthénie doit être considérée comme una maladie unique, (comportant une pathogénie simple et unique) ou comme un syndrôme de plusieurs étiologies.

ZUSAMMENFASSUNG

1. Viele Jahre hindurch wurde die Myasthenia gravis als eine Erkrankung der neuromuskulaeren Uebergangszonen angesehen, obwohl es keine exakte Formulierung gab, die alle Eigentuemlichkeiten der Krankheit erklaeren konnte.

2. Es ist noch nicht moeglich, eine zusammenhaengende Theorie ueber die Pathogenese der Myasthenia gravis zu geben, aus folgenden Gruenden:

a) Es gibt weder klinische, noch elektrophysiologische noch histologische Befunde, die eindeutig den Sitz der myasthenischen Laesion definieren.

b) Die Rolle des Thymus bleibt ungewiss.

c) Die Moeglichkeit, dass zirkulierende Autoantikoerper oder neuromusklaere Hemmstoffe eine Rolle bei dieser Krankheit spielen, muss noch weiter geklaert werden.

d) Es ist ungewiss, ob die Myasthenie nur als eine Krankheit (mit nur einer einzigen Pathogenese) oder als ein Syndrom mit mehr als einer einzigen Aetiologie aufgefasst werden muss.

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Basic and Clinical Concepts in Myasthenia Gravis

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The clinical syndrome known as myasthenia gravis was first described in 1671 by Willis.[1] The classic descriptions by Erb[2] and Goldflam[3] in the latter part of the nineteenth century emphazised the lack of any gross or microscopic findings at postmortem examinations of brain, muscles, and nerves. As a result there was no specific part of the body that suggested therapeutic attack. Indeed, until 1930, treatment was unsuccessful.

In 1930 Harriet Edgeworth,[4] who had myasthenia, by chance found that ephedrine sulfate taken for a sinus infection relieved her symptoms partially.

Mary Walker in 1934,[5] hearing that myasthenia resembled curare poisoning whose antidote was physostigmine, injected this drug into some of her patients. Her remarkable success with the natural alkaloid (physostigmine) and later the use of the synthetic analogue Neostigmine (Prostigmine) began both practical therapy as well as understanding of the disease.

It was known from the experiments of Claude Bernard[6] that curare produced a chemical disturbance at the myoneural junction, blocking a normal nerve impulse from reaching a normally responsive muscle fiber. J. Pal[7] had found that physostigmine corrected this in some way and identified this alkaloid as an antidote for curare poisoning in 1900. The disease now had a site at the myoneural junction even if it had no gross or even microscopic pathologic lesions in this area.

It might be well at this point to define and describe the symptoms of this disease of the myoneural junction. The outstanding and constant finding is a pathologic and rapid exhaustion of voluntary muscular contractions. After the initial contraction occurs, the second, third, and fourth ones are reduced in amplitude steadily until they are no longer possible. If the contractions are measured by means of an ergograph, this steady decrement in amplitude constitutes the characteristic fatigue curve of this disorder. While it is true that the normal muscle, if it is given a *heavy* task of work to perform, shows a similar-appearing fatigue curve, the difference between normal fatigue and that of the myasthenia patient is very great. The loss of amplitude as the voluntary act is continued reaches the zero point *10 times as fast* in the patient with myasthenia as in the normal subject.

Sixty-five years ago Jolly,[8] demonstrated this rapid exhaustion of the muscle by using a faradic stimulating current and rapidly stimulating the muscle to contract at a rate of 90 times in a minute until no further response was visible. In myasthenia this occurred in a fraction of a minute where at this rate it could go on indefinitely in the normal person. The Jolly reaction, at it is called, is essentially the basis for the more complicated and advanced electrical stimulation and recording that are used today. These will be described later in this article.

After a pathologically long period of

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rest, however, the myasthenic muscle can again contract, and the fatigue curve is repeated. The second characteristic of myasthenia gravis is a pathologically slow return to the previous state after a certain period of rest. Again, we must look at the normal recovery of a muscle after heavy work on a voluntary basis, and see that, in myasthenia gravis, not only is there rapid exhaustion or fatigue of the muscle under either voluntary or electrical stimulation, but an unusual or pathologically long period of time is also required for the muscle to recover its original ability to contract. A voluntarily driven bulb ergograph, —(Fig. 1)— which has been in use in our laboratory since 1951, has been so constructed that the squeeze of the bulb at an interval of 1 second produces only slight fatigue in the normal person at 100 to 120 squeezes. Thus, it is possible for him to squeeze the bulb 120 times with little drop in amplitude (Fig. 2-C). In order to produce a similar curve of *no fatigue* with the bulb ergograph in a patient moderately afflicted with myasthenia gravis, it is necessary to provide an interval of rest between each voluntary contraction of 6 to 20 seconds (Fig. 2-D). Greene[9] using this same apparatus in London reported recently (1961) that the shape of the myasthenic fatigue curve is diagnostic of the condition. He found that less than one-half of the initial amplitude is reached before 1 minute or 60 squeezes occur. This is so in most myasthenics with involvement of limb muscles but it is also seen in many patients with Parkinson's disease with akinesia. The differential diagnosis in such cases is rarely a problem.

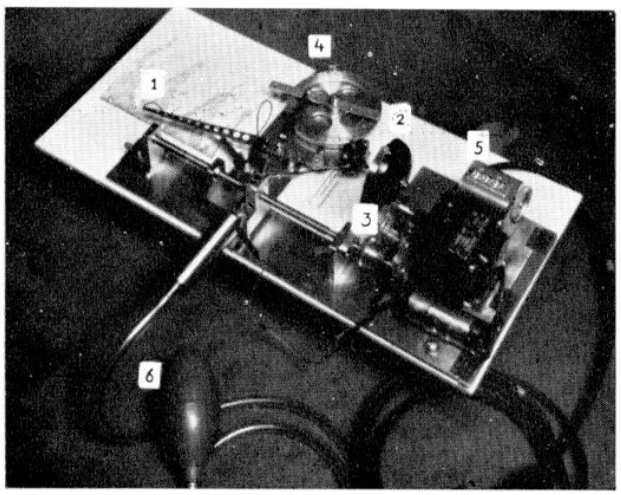

Fig. 1. — Bulb ergograph designed by author and made by Mr. Fred J. Christensen of Watertown, Massachusetts. Note (1) write out pen (2) signal bell; patient squeezes when he hears this. (3) gear shift that slows it to 1 revolution every 4 seconds (every other bell gives the 8 second interval) (4) integrator wheel, (5) counter of centimeters of pen distance travelled. (6) rubber bulb that patient squeezes.

The disorder is essentially in the recovery phase of the muscle action cycle. The rapid fatigue is simply due to inadequate time for this recovery to take place before the next impulse is received. For example, the levator oculi muscles holding the eyes open in the normal subject have every 3 or 4 seconds a brief rest resulting from the spontaneous blink. An 0.5 second rest is all that is needed for complete recovery of the normal muscle. In myasthenia gravis, where 3 to 10 seconds rest may be needed, the muscle is rapidly exhausted, resulting in the ptosis so common in this disease. This is illustrated diagrammatically in Fig. 3. A further example that fits Figure 3 would be the speech of a lecturer. He slowly exhales through his vocal apparatus, throwing some 8 to 15 words at his audience in 5 seconds — inhales quickly over 3/4 second (work 8 rest 1). The respiratory rate is reduced to 12 per minute but the minute respiratory volume is unchanged or increased. Long before there was any specific drug therapy for myasthenia gravis, Monrad-Krohn[10] in Oslo, Norway, instructed his patients to rest before eating, to take one mouthful, to chew it, to swallow it, and to rest for 15 to 30 seconds, and to continue in this pattern. Nutrition can be maintained in this way. Even with the fair therapeutic success we have in this disease today, following brief action with a long rest, as in the curve at the bottom of Fig. 3, is helpful to some patients. Furthermore it does help patients better to understand the nature of their troubles and as a result to manage the residual symptoms that modern therapy sometimes fails to overcome.

Normal activity such as standing, keeping the head erect, walking, all involve alternate

periods of muscular activity with brief but adequate periods of rest or inactivity. Where this normal ratio of activity to rest (8 to 1) becomes altered, as in holding the head in a rigid, fixed posture where there is no rest, the normal muscle soon develops marked signs of fatigue. In Parkinson's disease, too, these necessary periods of muscular rest are lost so that fatigue, weakness, and reduced muscular performance are conspicuous symptoms.[11]

One might well define myasthenia gravis as fatigability of those muscles which are not fatigued in normal activity, as the muscles used in moving the eyes, swallowing, talking, and in breathing. This difficulty can become extremely serious; thus a tenfold recovery time of the diaphragm is incompatible with survival.

We may now turn to the basic problem of transmission at the myoneural junction. The work of Loewi[12] and Dale[13] in identifying a substance similar to acetylcholine in the frog's heart after stimulation of the vagus nerve began the long and controversial explanation of neuromuscular

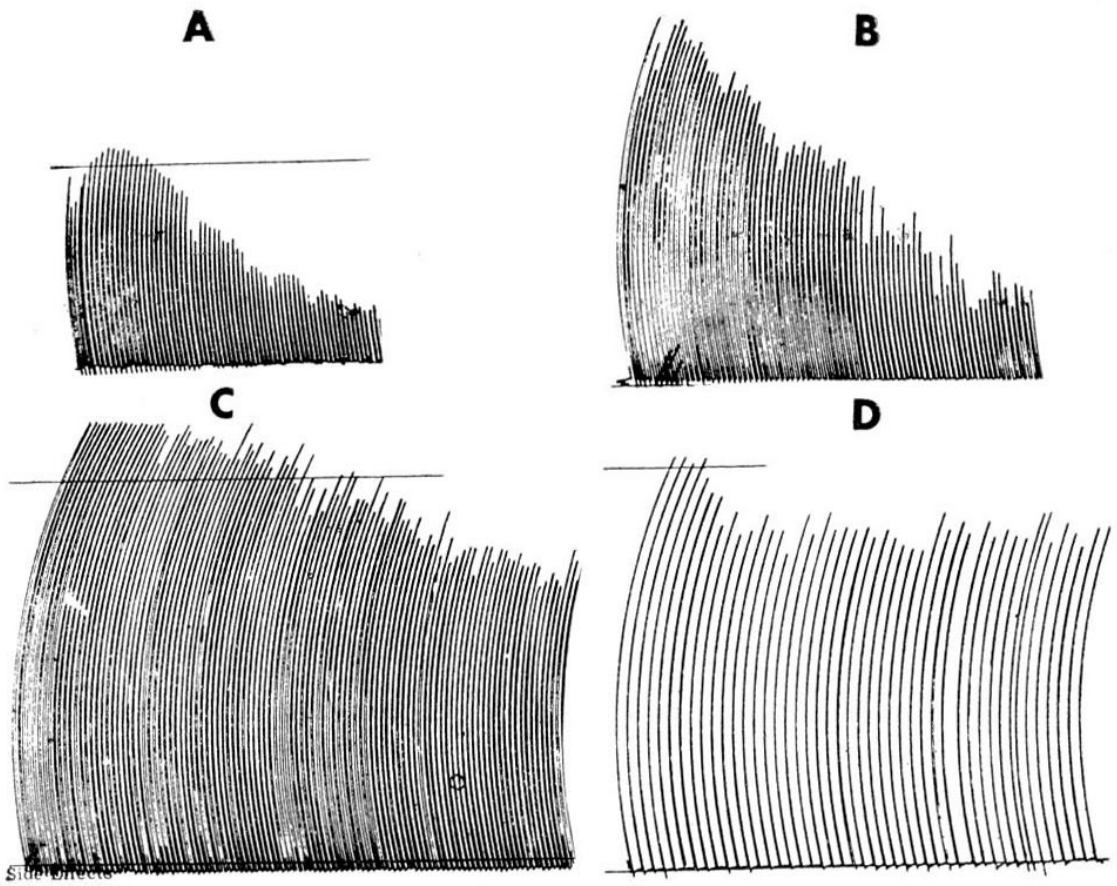

Fig. 2. — These are all bulb ergograms. A is a bulb ergogram at 1 per second in a patient with myasthenia gravis of moderate severity, off all medication. Note the steady drop in the fatigue curve at 1 squeeze per second.

B, A voluntary ergogram in the same patient when regulated on oral medication and reporting a 65 per cent level of motor activity. There is still a considerable amount of fatigue at 1 per second although there is no question that on medication the ergogram is better than A.

D, On this same amount of medication at another time the patient is allowed to squeeze the bulb ergograph with a rest of 8 seconds between squeezes. On this amount of rest there is almost no fatigue in the curve and it resembles the normal one at 1 per second (C).

C, The normal curve of a 51-year-old woman is shown to the left. The bulb ergograph was squeezed at the rate of once per second for a duration of 2 minutes. There is only slight fatigue at the end of this period.

The most recent apparatus has an integrating device (See Fig. 1). The work done is squeezing the bulb and driving the pen and counter is, of course, a constant and the comparative sums of the line lengths of all the squeezes is what is of interest. This can be expressed in centimeters per minute.

In the normal ergogram shown at C this is 750 centimeters for the 107 squeezes. For the untreated myasthenia at A its is 80 centimeters for only 53 squeezes. B is 206 centimeters for 90 squeezes and D, 208 centimeters for 44 squeezes, requiring at slow speed over 352 seconds. It should be noted that although it takes over three times as long at D, a bit more work is done and the patient is left in an unfatigued state to continue some other task or activity. Note that in both A and B less than one-half of the initial contraction is reached before a minute or 60 squeezes occur, which Greene feels is diagnostic of myasthenia gravis.

transmission. It is still not fully resolved in spite of hundreds of papers, arguments, and experiments in neurophysiology and pharmacology. There are still some who feel that the essential event is the electric action potential; the chemical changes are secondary to this. The other school which seems now to be triumphant, and is headed by Nachmansohn,[14] holds that the chemical changes, particularly those involving enzyme cycles with acetylcholine as the essential activator are the critical events, with the electrical discharge as a secondary concomitant. Colloquially the two groups are represented by "sparks" and "soup" for the chemical transmitters.

Chemical transmission makes more practical sense than a straight electrical one. The action potentials become smaller and smaller in amplitude, and slower in velocity as motor nerve fiber diameter is decreased on its way to its particular muscle. At the terminal points where the fine threadlike branches reach the various motor points of the muscle, the action potential will be of very small amplitude and have a relatively sluggish velocity. It is difficult to see how such attenuated and diminishing electrical events could by themselves get across these tiny gaps and stimulate the muscle into sustained and reliable activity without some help. The critical part of the transmission of the signal from the alpha motor cell in the anterior horn of the spinal cord to the muscle cell is *the bridging of this tiny myoneural gap.* It is the only spatial break in the continuity of the motor nerve-muscle system. Granted that where the fiber diameter is greatest the large initial neural impulse can move by purely electrical spread, how can such an attenuated voltage of the terminal fiber jump any gap at all, even a minute one? The concept of chemical transmission is, therefore, a logical one, and the transmitting substance as it is formed at the terminal branch of the nerve would act as an amplifier or catalyst in making the final physiologic activity more certain. At any rate, we are now sure that acetylcholine is the transmitter of the myoneural junction and activator of the motor end plate of the muscle. It may also be essential in the billions of synapses in the spinal cord and brain itself.

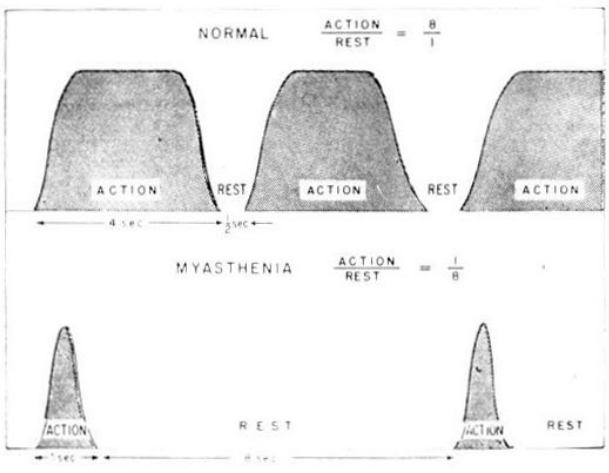

Fig. 3. — Diagram of the normal pattern (top) of the 8 - 1 work rest ratio compared to the 1 - 8 work rest ratio of the myasthenic. Note the amplitude in the work is higher in the normal as well as many times longer.

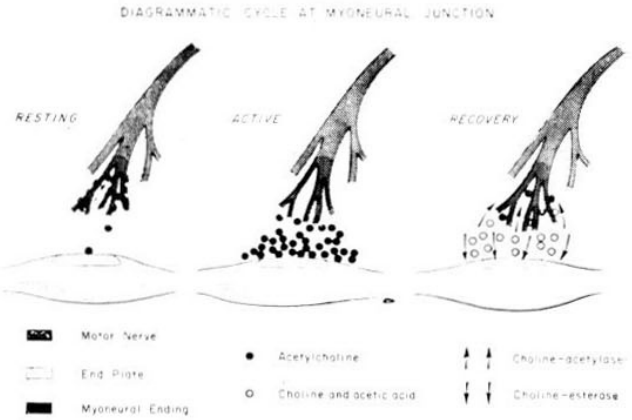

Fig. 4. — The normal branched motor nerve ending showing during resting phase a small quanta of acetylchonine steadily going across the gap to the muscle end plate.

When the nerve impulse arrives, 100 times the amount of acetylcholine is discharged in a volley towards the end plate, firing it off as this transmission agent combines with the protein molecule of the plate.

The recovery phase depends on the hydrolysis of the acetylcholine by the enzime cholinesterase shown by ↓ ↓ which as choline and acetic acid drift away from the plate. Later these two resynthesize to acetylcholine by choline-acetylase ↑ ↑ recharging the motor ending. Nachmansohn in his most recent paper calculates the cycle takes well under 100 microseconds.

The concept of chemical mediators requires a series of balanced equilibria that

work in a cycle which is vulnerable to the presence of excesses in the various chemicals involved and which may reverse or stop the smooth and efficient chemical cycle from continuing. In natural processes involving chemical mediators a certain amount of waste is obvious. This is typical of nature; thus, in order to make certain of the fertilization of an ovum, many millions of spermatozoa are produced. At the terminal ending of the motor nerve the formation or ejection of the quanta of acetylcholine molecules must be in excess

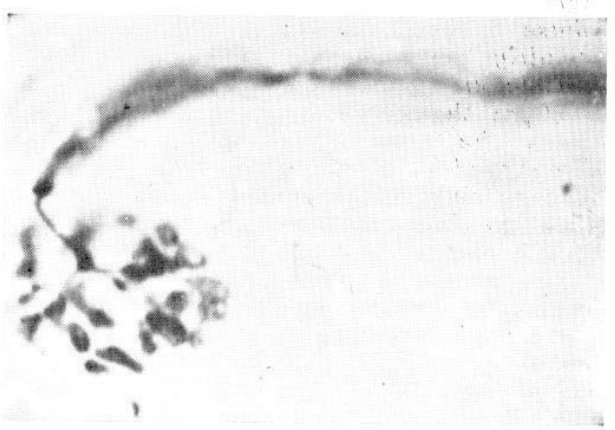

Fig. 5A. — A photomicrograph of the normal motor nerve ending. Both Fig. 5A and 5B were obtained through the courtesy of Prof. C. Coërs Laboratoire de Medecine Experimentale, Hopital Brugmann, 4 Place Van Gehuchten, Brussels, Belgium. Note the even branch-like structure covering a circular area.

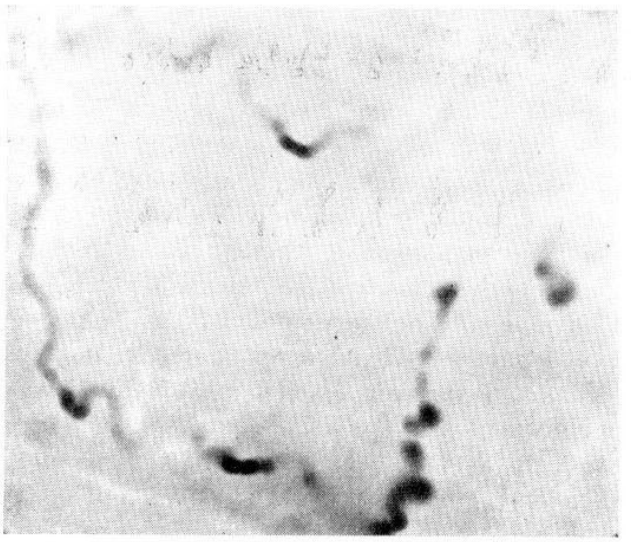

Fig. 5B. — A photomicrograph of motor nerve ending in a patient with myasthenia gravis. Note the multiple, deformed, irregular ending quite different from the normal of Fig. 5A.

of the few that are required to depolarize the minute receptor membrance or end plate on the muscle fiber. Fatt[15] first showed the resting motor nerve terminal tip is continually "squirting" or "oozing" out small quanta of acetylcholine. These are not enough to "fire" the end plate but may help maintain its special sensitive property that is not found anywhere else in the muscle fiber. When the motor nerve ending fails to produce this resting acetylcholine, as in denervation from cutting the nerve, the end plate's specific properties eventually disappear. Even though the distance between the terminal nerve bouton and the receiving end plate on the muscle is ultramiscroscopic (200 Angström units) according to Lehrer,[16] the dispersion of molecular substances which would move about by diffusion in all directions is obviously wasteful in this respect and many molecules will be left that are not attached to the sensitive membrane area. These must be cleaned up also at each cycle.

The Normal Cycle

The normal cycle in a healthy person or animal as understood today in this chemical system is as follows:

1. The nerve impulse reaches the terminal bouton which then discharges about 100 times the resting quanta of molecules of acetylcholine. A certain number of these molecules reach the sensitive membrane receiving area of the muscle fiber, the end plate, and combine with its structure in a way that is not yet clearly understood. This combination alters the properties of this receptor membrane. Potassium ions move out. Sodium ions move in. The special membrane of the end plate loses its charge of polarization which immediately creates the muscle fiber impulse that rapidly spreads throughout the entire fiber and is associated with a muscular contraction.

2. Cholinesterase which has been concentrated in this area* as a concomitant event associated with these membrane changes now removes by hydrolysis the acetylcholine

* Blood levels of cholinesterase bear little if any relation to the concentration of this postsynaptic enzyme, although drugs such as neostigmine reduce both.

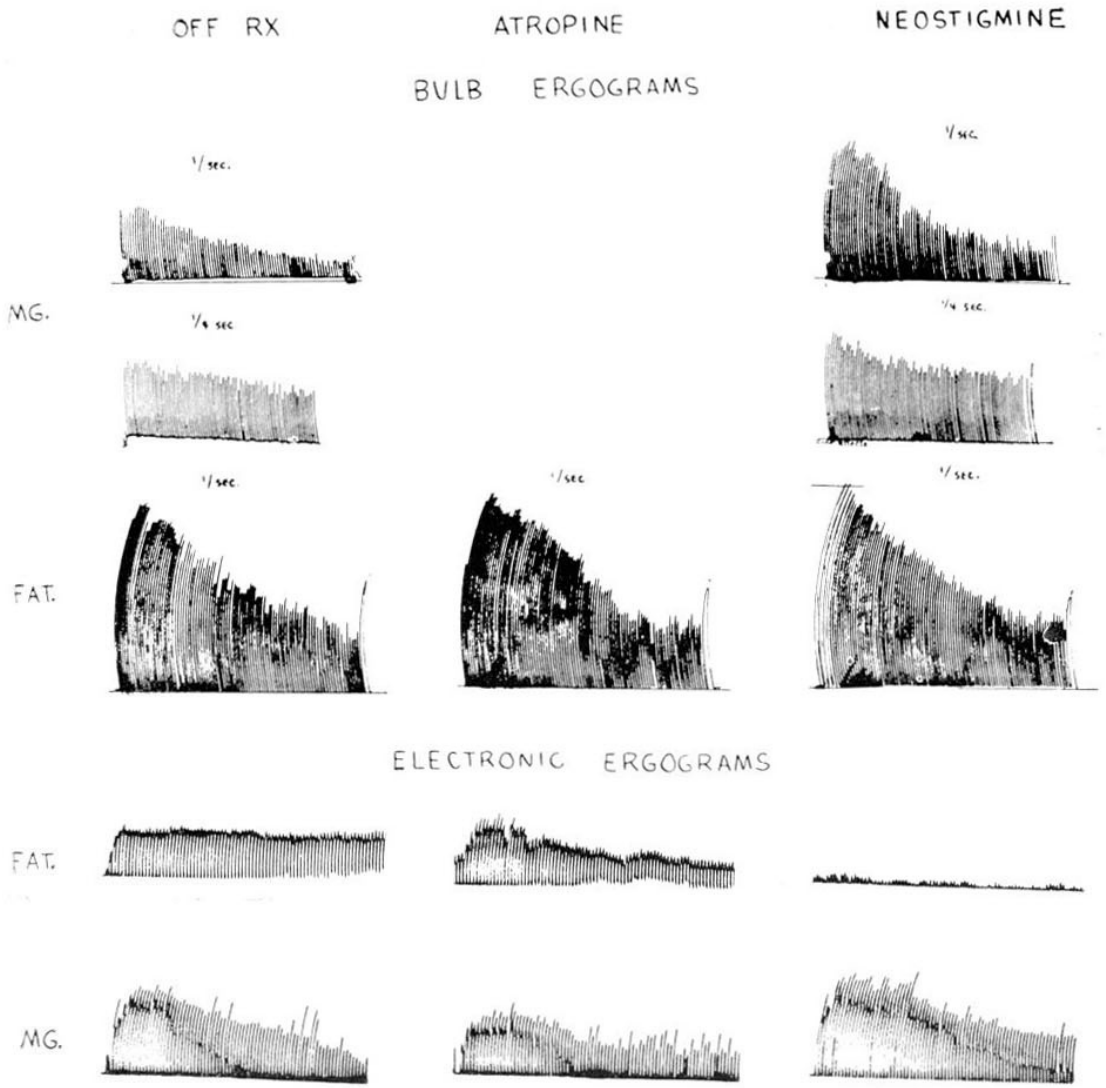

Fig. 6. — Comparison of both electronic and bulb ergograms in a patient with myasthenia gravis and psychogenic fatigue.

The left-hand column represents the ergograms before any drug is given. The middle columns are ergograms after 0.6 mg. of atropine intramuscularly. Tests were done 15 minutes after the injection of the atropine. Figures on the right of the illustration are all done 20 minutes after the intramuscular injection of 1.5 mg. of neostigmine methylsulfate.

The two ergograms at the upper left are of an untreated 22-year-old patient with a moderate case of myasthenia gravis. The upper voluntary bulb ergograph was done at a squeeze rate of 1 per second and shows a steady and rapid decrement of the fatigue curve. The last squeeze made under strong urging was no higher than the one preceding it. The ergograph directly below, made about 1 hour later, was at the rate of one squeeze every 4 seconds. There is only slight fatigue in this curve indicating that a period of rest of 4 seconds between each squeeze was of considerable benefit to this particular patient.

On the upper right is the ergogram after the injection of neostigmine at a squeeze rate of 1 per second. Note that the amplitude is higher but there is a steady fatigue curve, just the same, and there is a slight increase about 35 per cent on the last squeeze over the one preceding it, under strong motivation. The curve directly under this was done 20 minutes later at one squeeze every 4 seconds showing again an increase in amplitude, a reduction in fatigue with this period of rest, and very little increase on the last squeeze under strong urging.

The curves marked "Fatigue" (FAT.) are the voluntary ergograms of a psychoneurotic patient who complained of being tired all the time. Without medication she showed a steady, decreasing fatigue curve and the last squeeze under strong urging was about 100 per cent greater than the preceding one. The rate of squeezing here was 1 per second. After the injection of atropine sulfate there was an essentially similar curve, and after the injection of 1.5 mg. neostigmine sulfate the curve was not altered significantly, even though the patient had some fasciculations in the tongue and some slight salivation and cramps.

The bottom six curves are electronic ergograms of the left hand. The muscle used was the interosseus muscle of the index finger. The stimulation voltage was 20,000. Duration of the pulse was 7 microseconds. The stimulation rate of the complex was once per second. The fatigue curve of the psychoneurotic patient showed nearly no decrease in amplitude at this rate. There was little change, if any, after the injection of atropine, but after the injection of 1.5 mg. neostigmine methylsulfate there was a marked drop in amplitude and failure of that segment of the dorsal interosseus muscle to move with the stimulating current, showing the presence in the muscle of a considerable amount of depolarizing block from the anticholinesterase injection.

The bottom three electronic ergograms are of the same patient with myasthenia gravis shown in the upper four curves. There is a steady fatigue before medication and there is almost no effect from the atropine, but there is an increase in amplitude and performance after the injection of neostigmine. The weight used in the six electronic ergograph tests was a 4 ounce weight and all stimulations were at 1 per second.

FAT. = Fatigue.

MG. = Myasthenia gravis.

molecules from the end plate and environs, breaking them into choline and acetic acid. With the sensitive end plate freed of its acetylcholine it can repolarize to a level that permits it once more to receive its acetylcholine and discharge a second time.

3. The choline and acetic acid must now be resynthesized and made once more available as acetylcholine to the bouton of the motor nerve ending. A synthesizing process involving the presence of adenosinetriphosphate and a second enzyme called choline acetylase complete the cycle. Nachmansohn[17] deserves full credit for identifying this final enzyme in 1943. Fig. 4.

The Abnormal Cycles

Competitive block. In partial curarization, as well as in myasthenia gravis, the cycle is interfered with by the presence of a molecule which has a greater affinity for the receiving muscle cell end plate membrane than acetylcholine, and therefore successfully competes for this minute space and also combines chemically with the membrane. Therefore, the acetylcholine molecules cannot discharge the end plate of the muscle fiber and *chemical transmission* is blocked.

Depolarized block. If the second stage of the cycle is interfered with so that the cholinesterase is strongly inhibited or removed, the acetylcholine molecules remain on the receiving membrane area of the end plate of the muscle fiber so that repolarization is impossible and this membrane remains *depolarized.* This also produces a state of complete interference with chemical transmission and is called depolarized block. Substance which, like neostigmine, remove the cholinesterase, chemically produce in the normal muscle fiber this type of depolarized block, which is just as lethal as the competitive block.

Characteristics of Myasthenia Gravis

The first classical paper on the identification of the dynamics of myasthenia gravis and its relationship to partial curarization was published in 1941 by Harvey and Masland.[18] Recording the electromyogram from the small muscles of the hand as the ulnar nerve at the elbow was stimulated electrically, they had an excellent system in the human to investigate the effect of drugs in myasthenia and in normal subjects. At rates of stimulation of from 1 to 50 per second, in normal individuals, they showed that there was no diminution of the second or subsequent electromyographic responses to the stimulating shock, indicating that the myoneural junction chemical cycle which we have described was exceedingly rapid and efficient. In patients with myasthenia gravis, however, the second discharge was smaller than the first, and the third, fourth, and fifth became increasingly smaller until there was no response at all. This decline in the electromyogram was a classical finding in myasthenia gravis, and has been used repeatedly by others to identify the disease and study its characteristics pharmacologically. A nearby identical response was obtained when the normal human being was partially curarized with tubocurarine. This led Masland to conclude that myasthenia gravis was some direct form of poisoning with a curare-like substance that pharmacologically and neurophysiologically resembled curare poisoning. Both of these conditions could be restored to what they called a completely normal level by the intra-arterial injection of small amounts of neostigmine methylsulfate so that the effect, reported by Walker[19] seven years before, could now be demonstrated in this exquisitely sensitive human pharmacologic preparation.

As important as this work was at the time, it unintentionally misled many clinicians, including the author, into believing that the correct amount of a suitable anticholinesterase drug would restore each patient to a normal state. Even with the most careful, deliberate, and repetitive juggling of doses of neostigmine we found it quite impossible to restore some of our patients to even half the normal level, and a number died in spite of anticholinesterase treatment.

Grob and Johns,[20] working with Harvey in the early fifties with normal subjects and patients with myasthenia gravis, repeated much of the work of Masland,

emphasizing the competitive type of block in myasthenia and in curare poisoning. They added, however, critically important data about the other type of block due to excessive cholinesterase depression, the *depolarized block.*

If an anticholinesterase compound such as neostigmine is given to a normal subject, acetylcholine remains in excess at the myoneural junction. The end plate area of the muscle remains depolarized after transmission of the action potential and does not recover so that it can respond again. This depolarized block remains until the cholinesterase builds up once more to release the end plate of the acetylcholine molecules. According to Nachmansohn[21] the inhibition of the esterase from neostigmine slowly reverses as the drug diffuses (reversible inhibition), which is in contrast to the permanent inhibition from the alkyl phosphates which require a chemical like 2 PAM to restore the esterase. If neostigmine is given to a normal person this type of depolarized block always results. To complicate the picture further, in 1956, Grob[22] reported that in normal subjects if intra-arterial acetylcholine was given, there was a short increase in the action potential at the muscle followed by a reduction in the height of the discharge in a few seconds, due to the depolarizing block, and some 20 minutes later there was a second reduction in the muscle potential which he felt was due to the presence of one of the breakdown products of acetylcholine, namely, choline. He showed that acetic acid when injected did nothing, but that choline produced a decrease in the second, third, and fourth discharges, similar to the action of curare, suggesting that the mechanism in myasthenia gravis was possibly due to the choline itself.

Churchill-Davidson and Richardson[23] from St. Thomas's Hospital, working with myasthenia gravis patients and normal subjects, showed that the response to decamethonium iodide intravenously was quite different and puzzling. The normal person shows to 2.5 mg. intravenously of this substance an increasing block of the depolarizing type that is aggravated by the injection of anticholinesterase substances such as neostigmine. The myasthenic patient, on the other hand, shows a surprising tolerance to this substance so that 10 mg. intravenously produces no augmentation in the weakness of the patient. If the drug is continued, however, an increase in the myasthenic weakness then occurs which strangely enough is reversed, partially at least, by the injection of the intravenous neostigmine. This suggests that in myasthenia the end plate response first was that of a depolarizing block, and later showed a competitive block responses as acetylcholine does in the normal person. This emphasizes the extreme complexity of the myasthenia process.

Bennett and Cash[24] reported on the exquisite sensitivity of the patient with myasthenia to curare as a diagnostic test. With one tenth to one twentieth of the curarizing dose, marked weakness is brought out in cases of doubtful and suspected myasthenia. Such exceedingly small doses do not affect in any way the normal subject.

In Belgium, Coërs[25] has recently worked out a technique for intravital staining at biopsy of a piece of muscle from a myasthenia patient, using a presurgical stimulation and electromyographic test to identify the myasthenic response in that segment of the muscle to be removed. Then the specimen is removed and processed according to his technique. His sections show clearly that the myoneural junction in myasthenia gravis is quite specifically abnormal. Fig. 5-A, 5-B. Instead of the round bouton of the normal motor ending he finds elongated endings with various curled types of processes not seen in normal subjects or in other abnormal conditions. Various degrees of abnormal forms are seen and others in the same slide will show normal endings. In severe myasthenia nearly half of the endings will be abnormal and in milder cases only 1 in 10. This technique is of great interest to the neuropathologist because in many other diseases such as progressive muscular dystrophy, amyotrophic lateral sclerosis, pathologic muscle or nerve cells are present alongside normal ones, and this scatter of abnormality from extreme levels of involvement through perfectly normal ones is a characteristic find-

ing in diseases of the neuromuscular system. This work of Coërs further helps us understand myasthenia gravis as a more complicated condition than chemical poisoning by a curare-like substance.

The most important clinical difference is that in curare poisoning all of the motor end plates will be uniformly affected by the substance and respond in the generalized manner of pathologic involvement according to the level of the curare given. In myasthenia, on the other hand, the abnormality would be scattered in an unpredictable way in various muscles. In the same muscle there would be abnormally acting nonmyasthenic terminal motor fibers and severely affected myasthenic ones with abnormal responses. Intermediate levels would, of course, be found. This immediately presents an answer to the tremendous difficulties of pharmacologic balance in adjustment of these patients. Removal of the cholinesterases such as neostigmine produces favorable effects or repair, as it is called, in the abnormal myasthenic nerve endings, as shown by Coërs, but the same drug produces a depolarizing block in the remaining normal myoneural junction. Thus there will be pharmacologic improvement in motor performance in some muscle fibers and early depolarization block in the normal fibers in the same area. It would be expected that, if the ratio of abnormality is about equal to that of normality, the injection of the neostigmine would produce very little improvement in the total power of the muscle. The only reason that usual amounts of neostigmine (1.0 to 1.5 mg. intramuscularly in normal subjects) do not produce clinical signs of weakness in the large muscles of limbs is that the reserve of muscle power is sufficiently large so that the weakness would not be apparent from partial depolarized block. But in any stimulating nerve-to-muscle recording, in which only small units of muscle are examined or in the electronic ergogram, Fig. 6, which we use in our testing, it is clear that in the normal subject, even though not clinically detectable, there is always a decrement in the motor performance when anticholinesterase drugs are used. Therefore, it can be stated categorically that it would be extremely unusual, with a mixed response of this type to a drug, where there are abnormal and normal junctions, to obtain restoration to normal clinical values.

It is of interest to recall Lindsley's[26] early paper (1935) on the electromyogram in myasthenia and to note that he found irregularity of the unit discharge amplitude a prominent feature. This suggests that some units were normal with no amplitude depression of the action potential. Others were abnormal with marked loss of amplitude, dropping out in some places completely. This fits well with Coërs' findings since he insists on locating with electromyography areas of the muscle which show the myasthenic type of pattern for his special biopsy.

We can, from what we have said, define this disease as a disturbance in voluntary muscular function that involves both a rapid exhaustion as well as an exceedingly slow recovery. The muscles involved always show both of these phenomena. The abnormality may involve some muscles and not others, and indeed only parts of some muscles. In advanced and severe patients it is hard to find muscles that are not involved. (Group II and III of Osserman. See page 258 in this volume.)

We feel that the positive response to anticholinesterase drugs which is usually found in untreated myasthenic patients should not be in the clinical definition.

The most important difference between Myasthenia Gravis and ordinary normal tiredness or fatigue lies in the total failure of will power or emotional factors in overcoming the muscular exhaustion, or the pathologically slow recovery with rest. The normal person who is severely tired from a long day's work can, on receiving stimulating news such as inheriting a fortune, spend the evening in celebrating with his fatigue gone. In contrast, the myasthenic with only moderate dysphagia and ptosis receives no benefit at all in such situations; in fact may be made worse by excitement.

The diagnosis of Myasthenia if all of this is kept in mind, is usually made from

a good clinical history and the clinical observations of this type of pathological muscular exhaustion. It is then *confirmed* by the dramatic positive response to I. V. tensilon or intra muscular Neostigmine.

The treatment and management of these symptoms is fully covered in another communication.

SUMMARY

The origins of the modern treatment of myasthenia gravis go back to the fundamental work of Loewi and Dale, identifying a chemical transmission at the myoneural junction related to the enzyme cycles built around acetylcholine. The normal cycle is described involving cholinesterase and choline acetylase to restore the enzyme to its normal state. Abnormal cycles including competitive block due to curare-like substances as well as equally serious depolarizing block from too much anticholinesterase compound present, and similarities and differences between curare poisoning and myasthenia are discussed. Symptoms and diagnostic signs that are different from ordinary fatigue are described.

The chief feature of a pathologically rapid exhaustion of muscle power linked to an abnormal (10 times) slower speed in the recovery process defines myasthenia gravis as unlike any other neurological process.

The scattered and unevenly distributed microscopic abnormalities of the myoneural junction explain in part why so many patients are only partially helped by drug therapy.

RESUMEN

El origen del tratamiento moderno de la miastenia gravis tiene como punto de partida el trabajo fundamental de Loewi y Dale, por el cual se reconoció una transmisión química en la unión mioneural relacionada a ciclos enzimáticos construídos alrededor de la acetilcolina.

En el ciclo normal la colinesterasa y la colineacetilasa participan en la restauración de la enzima a su estado normal.

Se discutieron ciclos anormales que comprenden un bloqueo debido a sustancias del tipo curare, lo mismo que un bloqueo depolarizante igualmente serio por estar en exceso un compuesto anticolinesterasa. Se expuso también las diferencias y semejanzas entre el envenenamiento por curare y la miastenia.

La miastenia gravis por sus características especiales de dar lugar a un agotamiento patológicamente rápido de la potencia muscular, unido a una mayor lentitud (10 veces) en el proceso d e recuperación, se define como distinta a cualquier otro proceso neurológico.

La distribución desigual de las anormalidades microscópicas en la unión mioneural explican en parte porque tantos pacientes son auxiliados sólo parcialmente por la farmacoterapia.

RÉSUMÉ

L'origine du traitement moderne de la myasthénie grave a comme point de départ le travail fondamental de Loewi et Dale, dans lequel on a décrit une transmission chimique dans l'union myoneural relationnée à des cycles enzymatiques construits autour de l'acétylcholine.

Dans le cycle normal la cholinestérase et la cholinéacétylase participent dans la restauration de l'enzyme à sont état normal.

On a discuté des cycles anormaux comprenant un blocus dû à des substances du type curare, ainsi qu'un blocus dépolarisant également sérieux à cause d'exister un excès d'un facteur anticholinestérase. On a aussi décrit les différences et les ressemblances entre l'empoisonnement par le curare et la myasthénie.

La myasthénie grave, par ses caractéristi-

ques spéciales de donner lieu à un épuisement pathologiquement rapide de la potence musculaire, uni à une lentitude plus grande (10 fois) du procès de récupération, est completement différente de toute autre affection neurologique.

La distribution irrégulière des anormalités microscopiques dans l'union myoneural explique en part le fait pour lequel un grand nombre de malades ne sont améliorés que partiellement par la pharmacothérapie.

ZUSAMMENFASSUNG

Die Anfaenge der modernen Behandlung der Myasthenia gravis gehen auf die grundlegenden Arbeiten von Loewi und Dale zurueck, indem sie eine chemische Transmission an den myoneuralen Uebergangastellen feststellten die im Zusammenhang mit dem Enzym-Kreislauf um das Acetylcholin steht.

Der normale Zyklus eird beschrieben, der die Cholinesterase umfasst, um das Enzym in seinen normalen Zustand zurueckzubringen. Anormale Zyklen betreffen die competitive Blockierung durch Curareaehnliche Substanzen, sowohl als auch die ebenfalls ernste depolarisierende Blockierung hervorgerufen durch die Anwesenheit von einem Ueberfluss an der Anticholesterase-Verbindung, und es werden die Analogien und Unterschiede zwischen der Curarevergiftung und der Myasthenie diskutiert. Die Haupteigenschaften einer pathologisch schnellen Erschoepfung der Muskelkraft verbunden mit einer anormal geringeren (10 mal) Geschwindigkeit der Erholungsphase definiert die Myasthenia gravis als verschieden von jedweder anderen neurologischen Prozess.

Die hier und da auftretenden und ungleich verteilten mikroskopischen Anormalitaeten der myoneuralen Vervindungsstuecke erklaeren zum Teil warum sovielen Patienten nur teilweise durch die medikamentoese Therapie geholfen werden kann.

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Symptomatic Myasthenia

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Myasthenia usually is defined as a chronic disease with a progressive evolution which affects subjects from twenty to forty years old. It is characterized by an abnormal muscular fatigue principally in the cranial nerves and particularly in the motor eye nerves area which is also manifested at the faradic stimulation (myasthenic reaction).

This fatigue gradually goes away with rest and under the action of the cholynesterase's inhibitors drugs.

The nervous system does not present a significative pathological picture (Tronconi et al.); while the muscles may evidence a lipoidic infiltration and clusters of round cells known as "lymphorrhages".

The pathogenesis is still open to discussion, but the essential trouble seems to be an impairment of conduction at the myoneural junction.

The etiological factor is usually recognized, in the majority of cases, in a hyperplasia or neoplasm of the thymus (see references in Bassi, Montanari, Rouques, etc.). These changes in the thymus appear as typical of the myasthenic picture as it has been described above so that this etiological factor is considered one of the principal signs of the disease.

These are the fundamental characteristics of this disease, also called "asthenic bulbar paralysis", "myasthenia gravis pseudo-paralytic", "Erb-Goldflam disease", etc.

If myasthenia is an autonomous disease or if the myasthenic phenomenon is a result of different morbid conditions, has not yet been determined.

In writings on the subject, numerous cases are reported in which the symptomatological picture or the development is different.

Even the pathological changes in the nervous system, muscles and elsewhere are not always the same.

But especially the etiological factors involved present a wide variety. In our opinion it is justifiable to differentiate between Myasthenia, an autonomous disease and the other myasthenias, the so-called "symptomatic" ones.

The opinions on how these latter should be classified still are various and uncertain.

I think that all those myasthenias which are apparently in etiological relation with other diseases may be considered symptomatic. But it is necessary not to confuse myasthenia with the simple muscular asthenias which often occur in numerous morbid processes. Myasthenia can be described as a precocious muscular weariness approaching a semi-paralysis, subject to gradually disappear with rest and in any case to the prostigmine influence; topographical criterion and the presence of an electrical myasthenic reaction are not always necessary.

Symptomatic myasthenias should be taken into consideration in cases of: a) dysendocrinies except when the thymus is solely or principally involved; b) endogenous or exogenous toxicosis; c) infective diseases or inflammatory processes which do not directly affect the nervous system; d) inflammatory and degenerative diseases of the nervous and muscular system; e) other causes.

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In the thyroid gland diseases and especially in the hyperthyroidism the presence of myasthenic symptoms is not unusual (see

Cohen & King, Bassi, Bozzi, Montanari, Robbins & coll., Weickhardt & coll.).

According to Meadox and coll. indications of hyperthyroidism would be present in 6% of myasthenic patients.

In Flaiani-Basedow's disease still a simple adynamy is often present which is not to be confused with myasthenia as it is less accentuated and less fatigue results. It has less response to rest and little or none to prostigmine.

It is also necessary to distinguish thyreotoxic myopathies.

There has been criticism of a possible thyroidic etiology of myasthenia based on therapeutic results (Sauerbruch, van Bogaert) and considering the cases in which the evolution of the two diseases is antagonistic (Antognetti & coll.).

Nevertheless there are many documented therapeutic results obtained with a strumectomy and antithyroidic treatment (Petit-Dutaillis & coll., Kowallis & coll., De Falco & Balbi, Thorn & Tierney, Mc Eachern & Ross, Decourt & coll., Mazovec, etc.) besides the aggravations observed with the administration of thyroidic products (Kennedy & Wolff). These confirm the role of the thyroid gland in some cases of myasthenia. But this role should be carefully estimated in each case.

The opinions are discordant on the mechanism of the action of the thyroidic functional disorders in myasthenias. For some (Beretvas) it is a toxic action, for others (Mc Lean) it is an interference in the acetylcholine production. But it is more probable that the thymus may always be intervening, through its synergism with the thyroid (Sunder-Plassmann) and even in the myasthenic syndromes of the Flaiani-Basedow's disease.

Myasthenia due to parathyroid glands functional disorders is difficult to sustain. This hypothesis has been held by some authors but with disagreeing opinions and inconsistent records (Lundborg, Parhon, Claar & Colarusso, etc.). The removal of two histologically normal parathyroid glands carried out by Pennati brought about only a transitory and not much of a significative improvement. However, as Rouques affirms, myasthenia has never been observed in that typical hyperparathyroidic syndrome which is Recklinghausen's disease.

Myasthenia caused by suprarenal functional disorders is also debatable. The presence in myasthenia patients of signs of hyposurrenalism is not uncommon (Stern, Marinesco, Brem & Wechsler, Marie, Keschner & Strauss, Paulian & Aricesco, Taranto, Gougerot, Moehlig, etc.). Even in the case of hyperthyroidism it is difficult to diagnose myasthenia. In hyposurrenalism there is often an adynamy which is not a real myasthenia due to the difference in the intensity and location. In myasthenia there can be an hypotension which does not amount to a surrenal insufficiency.

Nevertheless, degenerative disorders (Brem & Wechsler) hypoplasy or atrophy (Marinesco, Marie, Bouttier & Bertrand, etc.) have been found in the suprarenal glands in myasthenic patients.

The most logical criterion sustaining a relationship between myasthenia and hyposurrenalism is the therapeutic one. The most remarkable improvement and even a cure have been obtained with treatments of surrenalic extracts (Dufour & Rouques De Foursac, Grocco, Murri, Marinesco, Marie, Sezary, van Bogaert, etc.) adrenaline (Birman & Agofonova), desoxycosticosterone (Maehlig, Mollaret & coll.) and at last even with ACTH (Soffer & coll., Faldi & Tesi). The antimyasthenic action of the latter, even though irregular (Tronconi), is interpreted by many as a surrenalic stimulation via hypophysis, but for others (Torda & Wolff), on the contrary, it should be interpreted as a direct action which increases the acetylcholine's synthesis stimulating the cholinacetilasic activity. The action increasing the thymus involution by ACTH would lead to another consideration of those endocrinous interrelations in which the thymus would always have its prevalent role.

A mention of the results obtained by the denervation of the carotid sinus is appropriate here. Already Antognetti had demonstrated in 1929 how this operation brought about a surrenal hyperfunctional hyperplastic reaction. According to this observation Leger and Thevenard began to

operate on myasthenic patients obtaining the first good results. The operation, useful even in Addison disease (see Perria and Sacchi) has been later extended to both the sinuses (Thevenard, Durupt, Pintus, Perria & Sacchi, Boudouresques & coll.) limited only to the denervation without removal of the glomus (Perria & Sacchi, Gopcevich & Solero, Della Beffa) or substituted with roentgentherapy (Delherm & Thevenard, Campailla & De Bellis) and even with infiltration of novocain (Strnad).

Therefore the exact nature of these relations still is not decided, although some relations between myasthenia and the hypofunction of the surrenal glands may be certain.

Myasthenias which often appear to be an effect of a modified activity of the sexual glands is a very delicate question.

The observations of myasthenias in the male hypogonadism (Curschmann, Fattovich) are probably due to chance.

On the contrary it is certain that the myasthenic symptomatology undergoes variations during the female sexual cycle and in relation to pregnancy.

Nevertheless it is very difficult to consider these myashenias as symptomatic because often they are only variations caused by the endocrinous factors mentioned above, that is modification of an etiologically well defined myasthenia gravis. The evaluation of these cases, as they have been commented on in literature, is particularly difficult; in fact the exclusive presence of the gonadal factors without the interference of other causes doesn't always appear evident.

Wolff and Milhorat, Nevin, Montanari and Romerio have reported cases of aggravations of the myasthenia during the menstrual period. According to Meyer a myasthenia can appear coinciding with the menopause.

Numerous cases of myasthenia appearing or worsening during the pregnancy have been described (Kohn, Tilney, Grosse, Steves, Mortara, Goñi, Wilson and Barr, Curschmann, Gianaroli, Fekete, Viets, Hansen, Gunn and Sanderson, Burr and Mac Carthy, Hum, Blumer and Streeter, Schaposnik and Eiras. etc.). Laurent in one case, observed during six of seven pregnancies, myasthenic manifestations which gradually went away after birth. Wilson and Barr have established that in myasthenic women the dose of prostigmine should be increased at every pregnancy. According to Viets and coll. the aggravations of myasthenia are more frequent in the first three months of pregnancy while an improvement in the next six months is not unusual. On the contrary improvements have been observed during the pregnancy by Goldflam, Wolff, Laurent, Reuter, Cecil, Blalock, Viets and coll., Fearnsides, Richter, Amelung and Lorenz, Montanari and Romerio. In other cases the myasthenia appeared after the birth (Nielsen & Roth, Goñi, Cohn, Bassi & Bassi, Della Beffa, Montanari) or at advanced nursing (Faldi & Tesi, Schaposnik & Eiras).

This variability also stressed by Schaposnik and Eiras makes an explanation very difficult of the role of the sexual glands in myasthenia. But some attempts have been made. For some (Rouques) myasthenias in pregnancy may only be a latent condition accentuated by the particular fatigue caused by this condition; for others, on the contrary, it would be a question of surrenal insufficiency (Elert); for others, according also to "ex-juvantibus" standards, the major cause should be attributed to the relationship between estrogenic hormones and progesterone.

It is appropriate here to mention those authors who basing their opinions on anatomical observations (Marinesco, Accornero, Tilney, Roussy & Rossi, Bruce & coll.) or therapeutical results (Mamou, Paillas & coll., Meredith, Simon, La Cava) indicate the hypophysis as the gland mostly responsible for some forms of myasthenia. The scarcity of observations and the complex function of the gland dissuade from a present discussion of such a possiblity.

As it has been noted almost all the endocrinous glands have been mentioned in the etiology of myasthenia. Not all the observations reported in the literature are available. It is also our opinion that in many cases not one but more endocrinous glands can be mentioned. Therefore the

question is posed if and when symptomatic myasthenias of a determined endocrinous disease except the thymus can be discussed. This, according to our opinion, can be affirmed especially for the thyroid and surrenal glands, but only when the myasthenic symptomatology is sufficiently typical and when the endocrinous functional disorders are clearly differentiated. On the contrary they are frequently muscular asthenias different from myasthenias or even with the characteristics of myasthenic disturbances but whose relationships are yet unknown even though at the hypothetical stage.

Among the various explanations of the modified biochemical transmission of the nervous impulses which is the basis of the myasthenic phenomenon, that of toxic origin is also considered.

This brings to consideration that group of myasthenias which can be considered as symptomatic of endogenous and exogenous poisonings.

A suggestive case is one of Perry's a typical myasthenic symptomatology, well responsive to prostigmine which came about in the same way as a diabetes mellitus.

In a botulynic poisoning, also complicated by other neurological symptomatology, Levi remarked on the myasthenic characteristics of motor disturbances. One case of myasthenia, very susceptible to prostigmine and apparently sustained by simil-alkaloid toxines due to intestinal parasites has been described by Vitello; myasthenia, in this case, was definitely cured in a short time after the elimination of the parasites.

Myasthenic symptomatologies have been also observed in petroleum (Gowers) and war gas (Guillain & Barre) poisoning and in alcoholism (Panara). The observation of Coulonjou and coll. is very interesting. They noticed within a period of a few years the appearance of an authentic myasthenia in many subjects from the same region which disappeared when they stopped chewing a brand of tobacco which had been defectively cured.

While a few of these cases remind one of the principal characteristics of the real myasthenia gravis, other cases result less typical due to the concomitant presence, for instance, of polyneuritic signs.

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The cases of myasthenia which are considered symptomatical of infective diseases or of inflammatory processes which do not directly affect the nervous system are rather numerous and take in various morbid fields.

Cases of myasthenia coming about during malaria have been observed by Mitra, Taranto and Méndez & Chávez; in Taranto's case however a hyposurrenalism was present.

Abricossof, Coriat, Focosi and Levi have shown where myasthenias appeared after influenza.

Myasthenic characteristics have also been observed during affection of the respiratory apparatus; by Accornero in a chronic bronchitis, by Long and Wiki in pneumonia, by Widal and Marinesco, Toussaint and the same Accornero in a pulmonary tuberculosis. Prostigmine gave good results in the cases in which it was administered.

In a case of Levi's the myasthenia came about after a tonsilitis with abcesses. In a case of Montanari's it came about after an extensive and grave furunculosis with a typical symptomatological picture and with the usual response to the test of prostigmine and curare. In a case of Thevenard's and coll., a typical myasthenia followed an antitetanic serumtherapy which caused grave allergic reactions.

Therefore these cases confirm the possibility that forms of myasthenia may be symptomatic of diseases which habitually don't have neurological complications and even of inflammatory processes which often cause divergent reactions.

Among the diseases which with major or minor frequency bring about neurological complications and can cause myasthenic disturbances, it is appropriate to mention typhoid fever (Prandi, Pineles, Jahrbuch), leprosy (Emery & Levy), diphtheria (Eulemburg, Ground, Capuzzo, De Luna & coll.), dengue (Trabaud), etc.

The chapter on symptomatic myasthenias of syphilis is interesting. In 1906 Charpen-

tier described a myasthenia of the limbs and the cranial nerves in a tabetic patient. In another tabetic Negro observed the next year a myasthenia involving the ocular muscles. Another connection between myasthenia and neurolues has been described by Nielsen and Roth in 1928. Recently (1954) Montanari described, based on pathological findings, a relationship between neurolues and myasthenia; this latter was a typical case, and except for the syphilis, there were no other apparent causes. The pathological table was characterized by: an absence of thymic tissue, demyelinisation of the posterior tract of the spinal cord and chronic type injuries of some cells of the brain stem.

The possibility of myasthenia by congenital lues is formulated by the same Montanari in an observed case.

Not all these cases have been completely documented from a clinical viewpoint and in the earlier cases use of prostigmine is absent; but in all the cases the myasthenic characteristics were well evident. In most of the cases we have to consider that it may be a real myasthenia and these do not have any other justifiable causes except those mentioned.

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It has been seen that some cases of myasthenia due to toxic factors presented polyneuritic signs. Besides such diseases as typhoid fever, leprosy, diphtheria and syphilis often produce neurological complications especially in the peripheral nervous system (cranial and spinal nerves), as has happened in some of the above reported cases.

This brings about a discussion of the relationship between myasthenia and the organic diseases of the nervous system. It is very interesting to relate the cases regarding the symptomatic myasthenias of inflammatory diseases of the nervous system.

Previously Claude affirmed that permanent paralysis is the final condition of the myasthenic muscular fatigue. Raymond distinguished three phases in the development of myasthenia: weariness, asthenia, paresis. Such is also the opinion of Brissaud.

Myasthenia cases with signs of damage to the peripheric nervous system are not uncommon. Negro has described a true myasthenia of peripheric origin.

Neurogenous muscular atrophies have been observed even by Erb and Goldflam and later by Brissaud, Grocco, Murri, Campbell & coll., Curschmann, Levi, Mattirolo, Myers, Raymond, Borgherini, Delbeke and van Bogaert, Sterling, Boudouresques and coll., Paillas and coll., Descamps; according to Markeloff muscular atrophies would be present in 10 % and more of myasthenia cases. Other authors (Remak, Stiefel, Walker) have observed fasciculations sometimes associated to atrophy (Sicard & Forestier).

During a poliomyelitis epidemic Zuccola observed a typical case of myasthenia; a similar case has been described by Trabaud.

Myasthenic symptomatologies occurring during epidemic polioencephalitis, von Economo type, have been described by Grosmann, Paulian, Sarbo, Higier, Hall, Guillain and coll., Wimmer and Vedmand, Feiling, Groenberg and coll., Olkon, Gut, Kouretas, Morelli and Salvi, Panara, Beining, Hallervorden, Calligaris, etc.

In some of these cases where polioencephalomyelitis was reported the following have been observed: muscular atrophies, fasciculations, abolition of the tendon reflexes and degenerative type electrical reactions that appear after some time and sometimes, as in a case of Wimmer's and Vedamand's subjected to variations of intensity paralleling the fluctuations of the myasthenic symptomatology. In a case described by Montanari and Romerio a symptomatology which evolved later as amyotrophic lateral sclerosis, began with the characteristics of a myasthenia; similar cases also recently described by Mulder, Lambert and Eaton.

These cases according to my opinion bear out the hypothesis, previously advanced, that there may be a relationship between the myasthenia and "organic" morbid processes of the central but above all the peripheric nervous system.

According to the aforementioned opinion of Claude, Raymond and Brissaud and others, it would therefore seem that, at least in some cases, myasthenia may be considered as a precocious and eminently

functional disturbance of the motor system which can later assume the characteristics of an organic injury.

This hypothesis which I advanced in a preceding work, still needs further confirmations.

The relationship between myasthenia and muscular diseases has already been discussed in the above mentioned alterations observed in the myasthenia so much that these changes suggested also a myogenous theory of the mentioned disease.

The possibility of considering some myasthenias as symptomatic of myopathies has been validated by more recent observations and with the critical revision of old, heterogeneous cases which seemed to be completely isolated (cases of myasthenic erytroedema, myasthenic erythematosous lupus).

Observations as those of Banduelle and coll., Störtebecker and others suggest, for instance, the possibility of considering a symptomatic myasthenia or polymyositis.

An interesting observation of Alajouanine, Lemaire and Bourguignon brings to mind similar forms in muscular distrophies, as previously observed by Stcherbak in 1904; other cases of this association have been recently described by Laruelle, and coll., Hosotte, Chor and Kesert, Rowland and Eskenazi, Walton, Geschwind and Simpson.

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Under the title of "Symptomatic myasthenias from Other Causes" I have gathered together very different observations; especially in respect to these it is difficult to express a judgment on the meaning of the observed myasthenic symptomatology.

In this chapter are included myasthenias coming about in the following ways: lymphogranuloma (Rossi & Caino), sarcoidosis (Javitt & Daniels) and bronchial and pulmonary neoplasy (Anderson & coll., Rooke & coll., Zbinden), which appeared after occipito-cervical traumas (Panara) and in a case even with the dislocation of the atlas (Apert & coll.) in cases of a diffused cranial hyperostosis with arterial hypertension (Mach & Jeanneret), after intense perphrigerations (D'Amato) and even along with psychic traumas (Levi, Nielsen & Roth).

It is, as it appears, an heterogeneous case group which could become even more conspicuous if other cases in the literature were reviewed. According to my opinion these other cases would present more uncertain characteristics.

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This review of symptomatic myasthenias does not pretend to be complete nor undebatable.

The concept of symptomatic myasthenia did not always have the possiblity to be profoundly and completely investigated.

Nevertheless all these forms of myasthenia which independently of thymic alterations appear concomitantly with the above mentioned morbid forms may be considered really symptomatic.

Elsewhere in this chapter about symptomatic myasthenias all the etiopathogenesis of the myasthenia, which is still not wholly explained except in its final manifestations, that is in the modified biochemism of the nervous transmission at the myoneural level, is emphasized and discussed.

Undoubtedly every contribution in world neurological literature on this subject will be useful for a better knowledge of the problem of myasthenia.

SUMMARY

The characteristics of myasthenia gravis are described and also how they are commonly recognized. The issue if myasthenia exists as an autonomous disease or not is then discussed briefly. The criteria to define the so-called symptomatic myasthenias are specified.

On the basis of an extensive review of the world literature symptomatic myasthenias are reviewed in the following order: a) dysendocrinies except when the thymus is solely and principally involved; b) endogenous or exogenous toxicosis; c) infective diseases or inflammatory processes

which do not directly affect the nervous system; d) degenerative and inflammatory diseases of the nervous system and of the muscular system; e) other causes.

The reported cases are not all recent and in part clinical and laboratory elements to judge the individual cases with certainty are absent but however they are adequate enough to provide a panoramic knowledge of that broad group of myasthenias which, apart from the typical picture of myasthenia gravis, appear to be etiologically related to the most varied morbid factors.

The necessary conciseness of this review excludes a detailed pathogenetic discussion of the different symptomatic myasthenias.

RESUMEN

Al señalar las características habitualmente atribuidas a la miastenia gravis, se discute brevemente si existe o no una miastenia como enfermedad autónoma y se precisan los detalles para definir las denominadas miastenias sintomáticas.

Después de una extensa revisión de la literatura mundial se recuerdan las miastenias sintomáticas de: a) Disendocrineas, exceptuando las tímicas; b) las toxicosis endógenas o exógenas; c) las enfermedades infecciosas o los procesos inflamatorios que no afectan directamente al sistema nervioso; d) las enfermedades inflamatorias y degenerativas del sistema nervioso y del sistema muscular; e) otras causas.

La casuística citada no es en su totalidad muy reciente y para parte de ella no hay elementos clínicos y de laboratorio suficientes para hacer un juicio seguro de cada caso; pero sin embargo es bastante sugestiva para un conocimiento panorámico del gran grupo de las miastenias que se apartan por alguna razón del cuadro típico de la miastenia gravis y que parecen tener relaciones etiológicas con los más distintos factores mórbidos.

La brevedad necesaria de esta revisión impide una discusión patogénica minuciosa de estas miastenias sintomáticas.

RÉSUMÉ

En soulignant les caractéristiques de la myasthenia gravis à celle ci communément attribuées, on discute brièvement la question sur l'existence ou moins d'une myasthénie comme une maladie autonome et on précise les détails pour définir les ainsi nommées myasthénies symptomatiques.

D'après une ample revue de la littérature mondiale sont rappelées les myasthénies symptomatiques de: a) disendocrinies excepté les thymiques; b) les toxicoses endogènes ou exogènes; c) les maladies infectieuses ou les procès inflammatoires qui ne touchent pas directement le système nerveux; d) les maladies inflammatoires et dégénératives du système nerveux et du système musculaire; e) d'autre causes.

La casuistique reportée n'est tout pas très récente et pour part de celle-ci il n'y a pas d'éléments cliniques et de laboratoire pour juger avec sûreté dans chaque cas, mais toute-fois elle est assez suggestive pour la panoramique connaissance du grand groupe de myasthénies que s'écartent, pour quelque motif, du tableau typique de la myasthenia gravis et qui semblent avoir étiologiquement des rapports avec les plus différents facteurs morbides.

La nécessaire brièveté de cette revue empêche une discussion pathogénique detaillée de ces différents myasthénies symptomatiques.

ZUSAMMENFASSUNG

Die der Myasthenia Gravis gewöhnlich zugeschriebenen Kennzeichen werden untergeschtreicht und mit kurzen Worten wird die Frage gestellt, ob es eine Myasthenia als selbständige Krankheit gibt; ausserdem werden die Kriterium genau angegeben, um die sogennanten symptomatichen Myastheniae zu definieren.

Mit einer weiter Rundschau über die Weltliteratur, werden die symptomatischen Krankheiten besichtigt, welche verursacht werden von: a) Disendokrinie, die der Thymusdrüse ausgenommen; b) endogene oder exogene toxikose; c) Infektionskrankheiten oder Entzündungsvorgänge, welche zum Nervensystem nicht direkt gehören; d) Entzündungs— und Entartungskrankheiten des Nervensystems und des Muskelsystems; e) anderen Ursachen.

Nicht diese ganze Kasuistik ist neu und ein Teil von ihr ist ohne Klinik— und Laboratoriums - Daten, um jedes Kasum mit Sicherheit zu katalogisieren. Es ist aber ziemlich interessant, um jene grosse Gruppe von Myastheniae zu kennen, welche von sehr verschiedenartiger Ursachenforschung abhängen, weil sie das typische Symptomenbild der Myasthenia Gravis nicht vorstellen.

Die nötige Kürze dieser Rundschau erlaubt nicht eine ausführliche pathogenetische Verhandlung über diese verschiedenen symptomatischen Myastheniae.

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Aspects Electrophysiologiques de la Myasthénie

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Ce sont les travaux de Jolly (1895) qui ont inauguré l'étude électrophysiologique de la myasthénie, en montrant dans cette affection la diminution progressive d'amplitude d'une contraction musculaire obtenue par des trains tétanisants successifs de stimulus faradiques. Le même auteur montra que cette diminution apparaît aussi bien dans les cas où la stimulation est appliquée au point moteur du muscle, que dans ceux où elle porte sur le nerf. On sait aujourd'hui que dans les deux cas l'excitation intéresse des fibres nerveuses motrices, du moins dans les conditions habituelles de stimulation (G. Bourguignon, 1923).

L'application à l'étude de la myasthénie des notions classiques concernant l'excitabilité en fonction du temps et en particulier de la chronaxie a été effectuée par G. Bourguignon (1940). Des modifications assez importantes des indices d'excitabilité ont été mises en évidence dans la fatigue myasthénique (A. Bourguignon, 1950).

Le premier travail électromyographique (EMG) consacré à la myasthénie semble avoir été celui de Dittler et Günther (1914), qui observèrent après un exercice dynamométrique une diminution d'amplitude des potentiels dérivés par électrodes de surface sans modification de la fréquence du rythme de Piper. Herzog (1917), pratiquant la méthode de stimulation-détection (stimulation du nerf — enregistrement de la réponse électrique du muscle), mit en évidence la diminution d'amplitude de cette réponse au cours de la fatigue myasthénique. Schaeffer et Brieger (1922) confirmèrent ces données initiales. Depuis ces premiers travaux EMG, la mise au point de l'aiguille coaxiale piquée dans le muscle, l'utilisation de l'oscillographe cathodique, accessoirement celle d'inscripteurs électromagnétiques à plumes et plus récemment celle de techniques d'addition permettant de dégager très nettement la réponse électrique du nerf (Calvet et Scherrer, 1955) ont permis d'étendre notre connaissance de l'électrophysiologie de la myasthénie.

Dans ce qui suit, on envisagera successivement:

I — L'analyse électrophysiologique du trouble myasthénique par l'étude:
— de la contraction volontaire,
— de la contraction provoquée par stimulation électrique
— et de la réponse électrique du nerf obtenue par stimulation.

II — L'interprétation électrophysiologique du trouble myasthénique

III — Les conclusions pratiques.

I — Analyse électrophysiologique du trouble myasthénique

A — Activité électrique du muscle au cours de la contraction volontaire dans la myasthénie

Les investigations portant sur l'activité électrique du muscle myasthénique au cours de contractions volontaires répétées aboutissant à la fatigue ont tenté de préciser soit le comportement d'une seule unité motrice (UM), soit celui de l'ensemble du muscle.

Il est très malaisé de suivre avec certitude, même avec une électrode coaxiale fine, l'activité d'une seule UM lors d'une contraction musculaire suffisamment intense et

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prolongée pour aboutir à la fatigue. Les résultats d'une telle investigation ont été publiés par Lindsley (1935): il a observé chez le myasthénique, sous l'effet d'une fatigue provoquée par une contraction prolongée, que la fréquence des potentiels d'UM reste constante, que leur amplitude fluctue, mais tend à diminuer, et que souvent après un certain délai, des "manques" apparaissent dans l'activité pulsatoire des UM. L'interprétation de ces résultats est rendue difficile par notre connaissance insuffisante du comportement chez le sujet normal du potentiel d'UM dans une contraction relativement intense et prolongée.

L'étude de l'activité électrique d'un grand nombre d'UM peut être réalisée soit par électrodes externes, soit par électrodes piquées dans le muscle. Dans la fatigue myasthénique, précisant les recherches anciennes citées ci-dessus, Brazier (1944) a observé

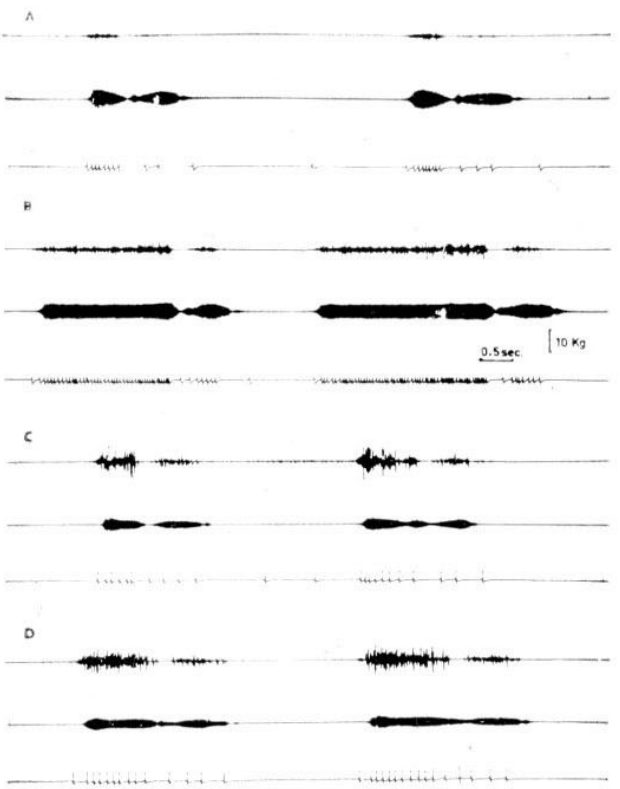

Fig. 1. — Augmentation de l'activité électrique du muscle sous l'effet d'un travail dynamique intense (Triceps brachial). A et B: sujet normal; C et D, myasthénique; A et C: au début du travail; B et D: à la fin du travail. Première dérivation: EMG dérivé par électrodes externes; deuxième dérivation: dynamogramme; troisième dérivation: EMG intégré. Sujet normal: 2028 kgm. en 75 mn, charge 6 kg. Myasthénique: 66 kgm. en 2,2 mn, charge 5 kg.

une diminution de l'activité électrique globale. Thiebaut, Isch et Isch-Treussard (1953) lors d'une contraction maximale constatent également que le tracé devient rapidement moins ample et moins riche, ce que supprime l'injection préalable de néostigmine. Il n'y a pas, d'après ces derniers auteurs, de parallélisme entre les perturbations électriques et les symptômes cliniques.

En réalité, les modifications de l'activité électrique globale du muscle myasthénique ne peuvent être appréciées que si on tient compte du comportement électrique du muscle normal au cours de la fatigue. Il a été démontré (Scherrer, Lefebvre et Bourguignon, 1957; Scherrer et Monod, 1961) que lors d'une contraction non maximale maintenue pendant un certain temps ou répétée un certain nombre de fois, on observait chez le sujet normal un accroissement de l'activité électrique pour une performance mécanique constante. Cette augmentation a été mesurée grâce à une technique d'intégration de l'EMG, qui montre que l'activité électrique d'un muscle normal peut doubler ou tripler au cours de la fatigue, pour développer une même force. C'est cette augmentation de l'activité électrique pour une performance mécanique constante, qui est atténuée ou manque dans la myasthénie (Scherrer et Bourguignon, 1959) comme le montre la figure 1. On constate parfois que l'augmentation de l'activité électrique est remplacée par sa diminution, pour une même performance mécanique, ce qui peut amener la quasi disparition de l'EMG lorsque la force de contraction a elle-même chuté (fig. 2). En règle générale, la néostigmine atténue, voire supprime, les anomalies électriques qui viennent d'être décrites (fig. 2).

B — Réponses électriques du muscle à la stimulation du nerf chez le myasthénique

La stimulation supra-maximale du nerf moteur, associée à l'enregistrement du potentiel d'action du muscle, représente la technique la plus largement utilisée depuis Harvey et Masland (1941). Le stimulus peut être un choc unique, un double-choc ou une série de chocs itératifs appliqués à une fréquence susceptible de provoquer la tétanisation.

Fig. 2. — Effets du travail dynamique intense et de la néostigmine sur l'EMG global du muscle myasthénique. Muscle triceps brachial. Première dérivation: EMG dérivé par électrodes externes. Deuxième dérivation: dynamogramme. A et D: Travail dynamique avec épuisement, durée: 13,55 sec, charge de 2,5 kg. Mouvements exécutés au début (A) et à la fin (B) du travail. C et D: contractions isométriques maximales avant (C) et aussitôt après (D), le travail. E et F: contractions isométriques maximales avant (E) et 50 mn après l'injection intra-musculaire de 0,5 mg de néostigmine (F). Soulignons l'étonnante diminution de l'activité à la fin du travail (B et D).

La technique du *choc unique* n'avait tout d'abord révélé à Harvey et Masland (1941), à Botelho, Deaterly, Austin et Comroe (1952) aucune différence d'amplitude entre la réponse électrique du muscle des sujets normaux et des sujets myasthéniques. Plus récemment, Johns, Grob et Harvey (1955) ont montré, par une étude statistique de l'amplitude de cette réponse, qu'elle est significativement plus grande chez le sujet sain que chez le myasthénique. Pour l'abducteur du 5º doigt, chez 20 sujets normaux ils ont trouvé une amplitude moyenne de 7,5 mv et chez 26 sujets myasthéniques, 5,4 mv. Cette différence est supprimée par la néostigmine.

La technique du *double-choc* a permis de mettre en évidence au cours de la myasthénie deux phénomènes intriqués et de sens contraire: le phénomène de facilitation et le phénomène de dépression tardive. Plusieurs auteurs ont, depuis Harvey, Lilienthal et Talbot (1941), étudié le phénomène et insisté sur l'importance de ces deux variations antagonistes du bloc neuromusculaire dans la myasthénie (Desmedt, 1961).

La facilitation apparaît surtout pour des doubles-chocs espacés de 10 à 100 ms: l'augmentation d'amplitude de la réponse électrique au deuxième stimulus par rapport à la première réponse est de l'ordre de 10 à 30 p.100. Quand l'intervalle entre les deux chocs augmente, on observe une diminution d'amplitude de la réponse au deuxième choc par rapport a la première reponse. Cette diminution qui, pour Johns, Grob et Harvey (1955), peut avoir son maximum après une seconde, dure parfois plus de dix secondes. La dépression tardive peut disparaître sous l'action de certains agents pharmacodynamiques et également du potassium, comme l'a montré Desmedt (1955).

La technique de *tétanisation,* même à des fréquences relativement basses, met en évidence des phénomènes de même type. La stimulation itérative provoque une diminution de l'amplitude des réponses électriques du muscle. Cette diminution est d'autant plus importante que la fréquence de tétanisation est plus grande comme on peut le voir sur la figure 3. L'amplitude de la réponse se maintient à un niveau constant quand la tétanisation est poursuivie un certain temps, comme on le voit sur la même figure et sur la suivante. Du fait de la coexistence du phénomène de facilitation, la diminution d'amplitude des potentiels est irrégulière à la phase initiale de la tétanisation. Ce phénomène de facilitation peut éventuellement masquer la diminution d'

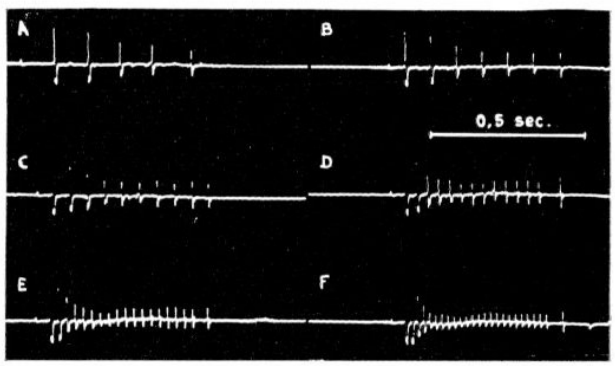

Fig. 3. — Stimulation maximale du nerf cubital par trains. Enregistrement de l'éminence hypothénar chez un sujet myasthénique. Fréquence de stimulation croissante. A: 10/sec; B: 12/sec; C: 20/sec; D: 30/sec; E: 40/sec; F: 50/sec.

amplitude à la phase initiale de la tétanisation.

Aussitôt après l'arrêt de la tétanisation, le phénomène de facilitation réapparaît (fig. 4); on peut l'appeler dans ces conditions potentiation post-tétanique (Botelho, 1955; Alajouanine, Lefebvre, Scherrer et Gremy, 1957).

L'enregistrement simultané de la réponse électrique et de la réponse mécanique du muscle myasthénique lors d'une tétanisation électrique du nerf a été réalisée par Botelho (1955) et reprise tout récemment par Desmedt (1961). Pour Botelho, la diminution d'amplitude de la réponse mécanique est plus importante et plus constante que celle de la réponse électrique. Inversement, la potentiation post-tétanique apparaît plus précocement pour le phénomène mécanique que pour le phénomène électrique accompagnant la contraction musculaire. Desmedt aboutit à des conclusions différentes. Pour cet auteur, les deux types de réponses sont strictement parallèles et varient toujours dans la même proportion, comme le montre la figure 5 qui lui est empruntée.

C — Le potentiel de nerf dans la myasthénie

Il ne peut être question d'enregistrer chez l'Homme l'activité du nerf lors d'une contraction volontaire. Seule la volée synchrone déterminée par une stimulation électrique du nerf lui-même est décelable. On peut avoir recours à une technique d'addition de la réponse pour dégager celle-ci du bruit de fond (Calve et Scherrer, 1955); une simple superposition des réponses sur oscil-

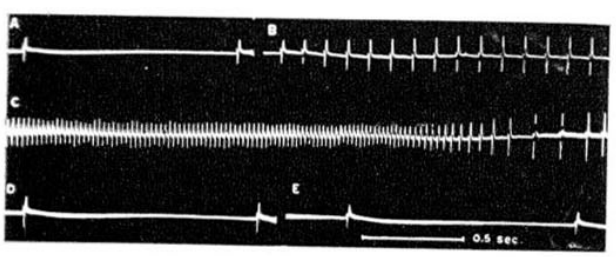

Fig. 4. — Effets d'une tétanisation. Stimulation du nerf cubital, enregistrement à l'éminence hypothénar. A: avant tétanisation, B: début de la tétanisation, C: tétanisation à 50/sec et potentiation post-tétanique, *D: 30 sec après tétanisation, E: 60 sec après tétanisation. Base de temps: 0.5 sec.*

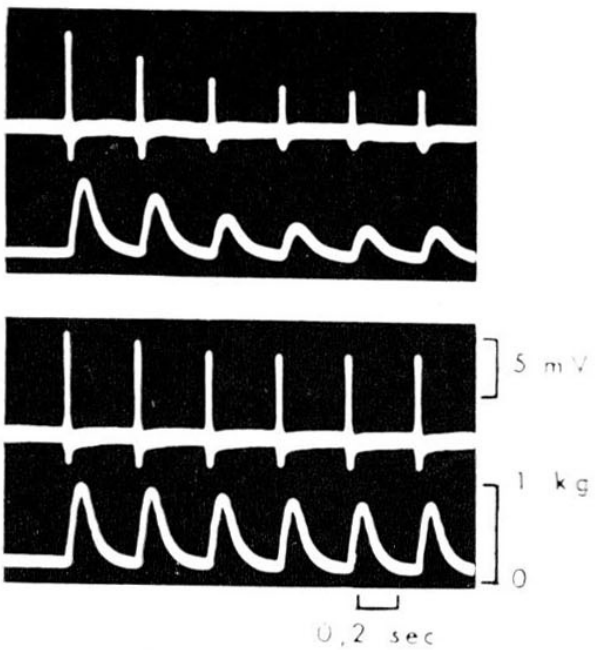

Fig. 5. — Réponses électriques (tracé du haut) et réponses mécaniques (tracé du bas) de l'adducteur du pouce; stimulation supramaximale du nerf cubital au poignet à 3/sec. En haut: sans traitment; en bas: après administration de pyridostigmine. Remarquer le parallélisme de la variation des réponses électriques et mécaniques. (D'après DESMEDT, *1961).*

lographe cathodique donne souvent des résultats suffisamment nets. L'enregistrement de la réponse électrique du muscle peut être faite conjointement à celle du nerf. C'est en effectuant un tel enregistrement simultané qu'Alajouanine, Scherrer et Bourguignon (1959) ont pu montrer que lors d'une tétanisation on assiste à une chute de la réponse électrique du muscle, cependant que celle du nerf reste constante.

L'étude de ces auteurs a porté sur le nerf cubital et les muscles de l'éminence hypothénar. Le nerf était soumis pendant 1,5 mn à des chocs supramaximaux de fréquence tétanisante (30/sec); le potentiel de nerf était recueilli par des électrodes de surface et la réponse électrique du muscle par une aiguille coaxiale piquée dans l'éminence hypothénar. La figure 6 montre que, dans ces conditions, le potentiel de nerf reste inchangé sous l'effet de la tétanisation, tandis que la réponse électrique du muscle décroît du début à la fin de celle-ci, pour reprendre son amplitude initiale 2 mn après l'arrêt de la tétanisation. La figure 7, où l'enregistre-

ment du potentiel de nerf a été réalisé selon la méthode d'addition précédemment citée, confirme l'immuabilité de la réponse électrique du nerf, pendant la tétanisation.

La non participation du nerf au processus myasthénique ressort également de l'étude de la vitesse de conduction du nerf qui reste inchangée au cours de la fatigue myasthénique (Desmedt, 1961). Cette vitesse de conduction peut être mesurée en comparant les latences des réponses électriques du muscle à des chocs appliqués en deux points différents du nerf, au coude et au poignet par exemple pour le nerf cubital. La figure 8 empruntée à Desmedt montre que la différence entre les latences des réponses musculaires, autrement dit la vitesse de conduction, reste constante quel que soit le degré de la fatigue myasthénique, traduite ici par la diminution d'amplitude du potentiel musculaire.

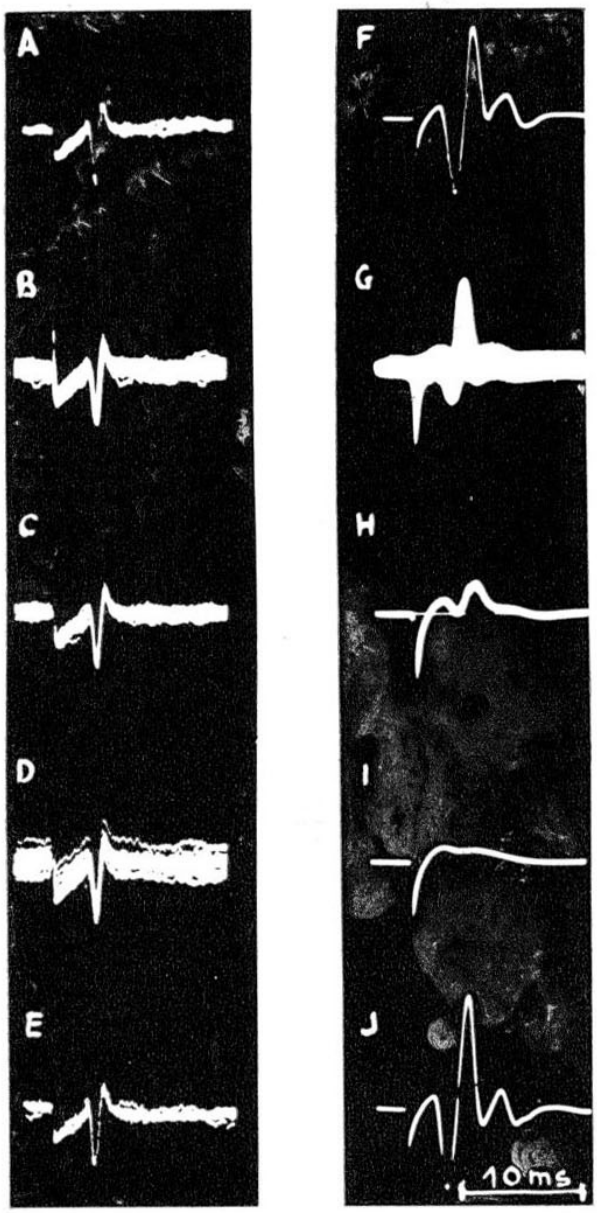

Fig. 6. — Enregistrement simultané de la réponse électrique du nerf (à gauche) et du muscle (à droite), avant, pendant et après une tétanisation de 90 sec. Tétanisation du nerf cubital, supra-maximale pour la réponse musculaire, à 30/sec. A et F: avant tétanisation; B et G: après 30/sec de tétanisation; C et H: après 60 sec de tétanisation; D et I: en fin de tétanisation; E et J: 2 mn après tétanisation.

II — L'interprétation électrophysiologique du trouble myasthénique

Les données analytiques obtenues par l'électrophysiologie viennent d'être exposées. Elles autorisent certaines discussions et conclusions concernant le trouble myasthénique lui-même. Nous discuterons successivement de la participation éventuelle dans le trouble myasthénique:

— de la fibre nerveuse,
— de la jonction neuromusculaire
— et de la fibre musculaire elle-même

Dans un dernier paragraphe, on verra comment on peut comparer la fatigue myasthénique et la fatigue musculaire normale en se basant sur les données de l'EMG

A — *La fibre nerveuse* — Il a été démontré que les fibres nerveuses répondent pendant plusieurs minutes à une stimulation itérative ayant une fréquence de 30/s. Ce fait témoigne d'une capacité fonctionnelle satisfaisante des fibres nerveuses, bien qu'il puisse être intéressant de préciser par des recherches complémentaires la limite de leurs possibilités en les soumettant à des fréquences de stimulation plus élevées.

Si, dans la myasthénie, l'intégrité fonctionnelle des fibres nerveuses elles-mêmes paraît probable, à la lumière des données électrophysiologiques, on ne peut l'affirmer pour les ramifications terminales de ces fibres. Un certain nombre d'arguments histologiques et physiologiques (Desmedt, 1961) tendent même à faire admettre que c'est au niveau de ces ramifications que pourrait siéger le trouble fondamental de la myasthénie. Il faut d'ailleurs considérer que les ramifications nerveuses terminales font partie intégrante de la jonction neuromusculaire.

B — *La jonction neuromusculaire* — Que

la myasthénie soit due à une atteinte de la jonction neuromusculaire est une notion actuellement admise, à la fois sur la base des données pharmacologiques et électrophysiologiques. Parmi ces dernières, qui seules nous intéressent ici, se trouve l'analogie frappante qu'il y a, d'une part entre la chute rapide de la réponse électrique musculaire et les phénomènes de facilitation et de dépression observés dans la myasthénie et d'autre part les processus déterminées chez l'animal par les substances curarisantes dont l'action élective porte sur la plaque motrice. On a d'ailleurs pu montrer la présence d'une excitabilité persistante du muscle stimulé directement après épuisement des possibilités de transmission de la jonction neuromusculaire (Struppler et Struppler, 1961). Cette dernière constatation jointe à celle de la persistance d'une réponse électrique du nerf dans l'épuisement myasthénique localise nécessairement à la jonction neuromusculaire le trouble myasthénique.

Au niveau de cette jonction, la discussion reste ouverte quant au rôle possible des terminaisons nerveuses ou des substances réceptrices de la plaque motrice elle-même (Grob et Johns, 1961). Des enregistrements du potentiel de plaque motrice, dont la réalisation chez l'Homme se heurte cependant

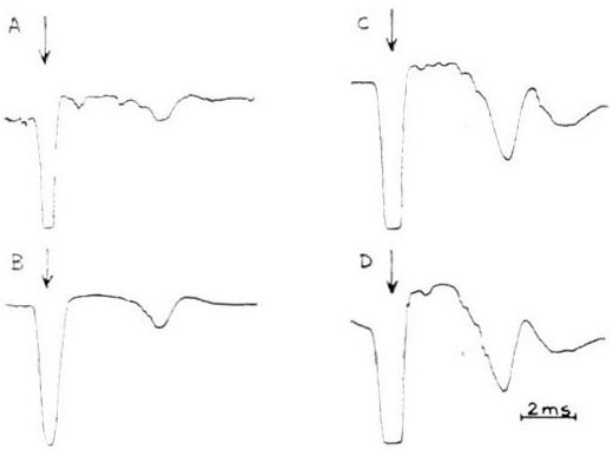

Fig. 7. — Enregistrement du potentiel de nerf, avant, pendant et après une tétanisation. Première tétanisation: A avant; B après tétanisation de 90 sec. Deuxième tétanisation: C après 30 sec, D après 60 sec de tétanisation. Le potentiel du muscle, non reproduit avait chuté dans les deux tétanisations entre 30 et 60 sec. Les flèches indiquent le choc artefact.

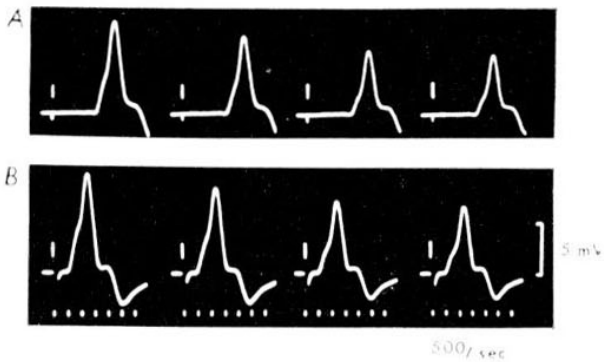

Fig. 8. — Réponse électrique des muscles hypothénariens à une stimulation supramaximale du nerf cubital au coude (A) et au poignet (B). La différence de latence entre les réponses est constante, quelle que soit l'amplitude de celles-ci. (D'après DESMEDT, *1961).*

à de très grandes difficultés, aideraient à trancher ce problème.

C — *La fibre musculaire* — En tenant pour acquis que le trouble myasthénique siège au niveau de la plaque motrice, on peut cependant se demander si la fibre musculaire elle-même est absolument indemne dans la myasthénie. On a vu que Botelho avait cru pouvoir conclure à un trouble de la contractilité musculaire, indépendant du bloc de la jonction, trouble que Desmedt n'a pu cependant confirmer. Il semble que l'utilisation de techniques de stimulation directe du muscle myasthénique épuisé devrait permettre de préciser l'état fonctionnel de la fibre musculaire.

D — Fatigue myasthénique et fatigue normale

L'EMG de la contraction volontaire montre une augmentation de l'activité électrique globale du muscle dans la fatigue du sujet normal: cette augmentation fait défaut dans la myasthénie. Une telle différence peut s'interpréter assez aisément si on admet que sur le muscle normal la défaillance due à la fatigue intéresse le mécanisme contractile, cependant que c'est la jonction qui est en cause chez le myasthénique. Dans le premier cas, la dépolarisation de la fibre a lieu, cependant que la contraction manque, ce qui détermine un accroissement des phénomènes électriques pour une même performance mécanique: dans le cas de la myasthénie, le blocage au niveau de la jonction supprime simultanément les

phénomènes électriques propagés et les phénomènes mécaniques au niveau de la fibre musculaire.

III — Conclusions pratiques

Le clinicien n'attend pas seulement de l'électrophysiologie des précisions sur le substratum fonctionnel du trouble myasthénique. Il lui demande également de contribuer au diagnostic de la maladie et d'en suivre le traitment, c'est à dire d'en mesurer l'intensité.

C'est l'étude de la réponse électrique du muscle à la stimulation nerveuse qui constitue à l'heure actuelle le test électrophysiologique le plus intéressant de la myasthénie. On peut éventuellement apprécier simultanément la diminution de la réponse mécanique. Dans les myasthénies sévères, la chute d'amplitude de la réponse électrique et mécanique du muscle est rapide et aucun doute n'est permis quant à la nature pathologique de cette diminution. Il n'en va cependant pas de même pour les myasthénies frustres ou prédominant sur des muscles dont on ne peut stimuler le nerf. Dans ces cas, la diminution de la réponse ne survient que pour des tétanisations plus durables ou effectuées à des fréquences plus élevées. Or on sait que ce type de tétanisation risque d'entraîner la chute de la réponse d'un muscle normal. Nous ignorons en effet les limites dans lesquelles le muscle continue à répondre normalement à une tétanisation, chez le sujet sain.

Il est d'ailleurs possible que, dans ces cas de myasthénie frustre, il soit intéressant d'étudier non la réponse électrique ou mécanique détérminée par stimulation du nerf, mais les possibilités ergométriques de la contraction volontaire (Scherrer et Bourguignon, 1961).

RESUME

Après un bref historique et un rappel des méthodes électrophysiologiques utilisées dans la myasthénie, les auteurs précisent les résultats de l'analyse électrophysiologique du trouble myasthénique par l'étude de la contraction volontaire, de la contraction provoquée par stimulation électrique et de la réponse électrique du nerf obtenue par stimulation. Il apparaît que lors de l'épuisement myasthénique la réponse électrique et mécanique du muscle diminue cependant que l'électroneurogramme reste constant.

Les données électrophysiologiques localisent le trouble myasthénique à la jonction neuromusculaire. La discussion est ouverte pour connaître le rôle respectif au niveau de cette jonction, de la ramification nerveuse terminale et de la plaque motrice elle-même.

Dans un dernier chapitre, les auteurs envisagent très brièvement l'utilisation de l'électrophysiologie pour le diagnostic de la myasthénie.

RESUMEN

Después de una breve historia y una revisión acerca de los métodos electrofisiológicos utilizados en la miastenia, los autores precisan los resultados del análisis electrofisiológico del trastorno miasténico por el estudio de la contracción voluntaria, de la contracción provocada por la estimulación eléctrica y de la respuesta eléctrica del nervio obtenida por estimulación. Parece que cuando ocurre el agotamiento miasténico la respuesta eléctrica y mecánica del músculo disminuye mientras que el electroneurograma queda constante.

Los datos electrofisiológicos localizan el trastorno miasténico en la unión neuromuscular. La discusión queda abierta para conocer el papel respectivo al nivel de esa unión, de la ramificación nerviosa terminal y de la placa motora misma.

En un último capítulo, los autores encaran muy brevemente la utilización de la electrofisiología para el diagnóstico de la miastenia.

SUMMARY

After briefly summarising the historical background and the electrophysiological methods presently used in myasthenia gravis, the authors specify the results of the electrophysiological analysis of the myasthenical disturbance by the study of the voluntary contraction, the contraction evoked by electrical stimulation and the electrical response of the nerve obtained by stimulation.

During the myasthenical exhaustion, it appears that the electrical and mechanical responses of muscle diminish and that the electroneurogram remains constant.

The electrophysiological datum localises the myasthenical disturbance at the neuromuscular jonction. The discussion is open for further understanding of the respective role of the terminal nerve ramifications and of the motor-end plate itself.

In the last chapter, the authors cite very briefly the use of electrophysiology for the diagnosis of myasthenia gravis.

ZUSAMMENFASSUNG

Im Anschluss an eine kurze geschichtliche Darstellung und die Anführung der Methoden, die in der Myasthenie angewandt werden, präzisieren die Autoren die Resultate der elektrophysiologischen Analyse der myasthenischen Störung. Untersucht wurden: die freiwillige kontraktion, die durch den elektrischen Reiz hervorgerufene Kontraktion und die elektrische Antwort des Nervs, der gereizt wurde.

Es hat sich herausgestellt, dass die elektrische und mechanische Antwort des Muskels bei einer myastenischen Erschöpfung schwächer wird, während das Elektroneurogramm sich nicht verändert.

Gemäss der elektrophysiologischen Angaben tritt die myasthenische Störung an der neuromuskulären Junktion auf. Das Ziel der eröffneten Diskussion ist, die wechselseitige Rolle der Nervenendverzweigung un die der motorischen Endplatte an der Stelle der Junktion zu erforschen.

Im letzten Kapitel befassen sich die Autoren kurz mit dem Gebrauch der Elektrophysiologie für die myasthenische Diagnose.

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Studies in Myasthenia Gravis: Treatment

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Approximately 90% of all patients diagnosed as having myasthenia gravis, were dead within two years of onset prior to the discovery of drug therapy in 1934[1]. At present this mortality rate has decreased to 15-20%. Until the cause and cure of myasthenia gravis is discovered, our major goals are to decrease these rates even further and to return these patients to as near normal a way of life as possible. Thus, we resort to drug therapy using newer analogues of physostigmine and recent anticholinesterases in an effort to better the rehabilitation of the myasthenic. To further aid in reducing the mortality rates and possibly induce remission, recourse to thymectomy, radiotherapy to the thymus or treatment with glandular extracts are administered in selected cases.

Application of the following clinical classification[2] will permit through its prognostic evaluation, the necessity for employing the more drastic modalities for possible induction of remission.

Clinical Classification

Transient Neonatal: Baby born of a myasthenic mother, develops symptoms at birth or within first few days of life; with complete remission by sixth week of life and no history of recurrence. Therapy may be necessary and actually life-saving in the early days. Prognosis is excellent.

Juvenile: Children born of *non*-myasthenic mothers. Their myasthenia remains permanent. May occur at birth or any time to puberty. Ophthalmoplegia, complete or partial, with severe bilateral ptosis, relatively unrelieved by drug therapy, is characteristic. Siblings and cousins have been reported. Prognosis is good.

Adult Group:

I: Localized, non-progressive myasthenia, with perhaps one eye affected. Prognosis is good.

II: Generalized myasthenia, with gradual onset involving more than one set of striated muscle, both bulbar and skeletal. Spontaneous remissions and exacerbations may occur early or late.
This group is amenable to drug treatment. Prognosis is fairly good.

III: Acute fulminating onset of generalized myasthenia with severe bulbar manifestations with frequent crises. Do not respond well to drug therapy. Prognosis is poor.

IV: Late, severe myasthenia which develops at least two years after onset of Group I or II symptoms. Prognosis is poor.

V: Myasthenic in whom muscular atrophy is a distinct and prominent feature. Prognosis is fair.

In a group of 500 patients at The Mount Sinai Hospital, the following Table describes the distribution according to the above classification.

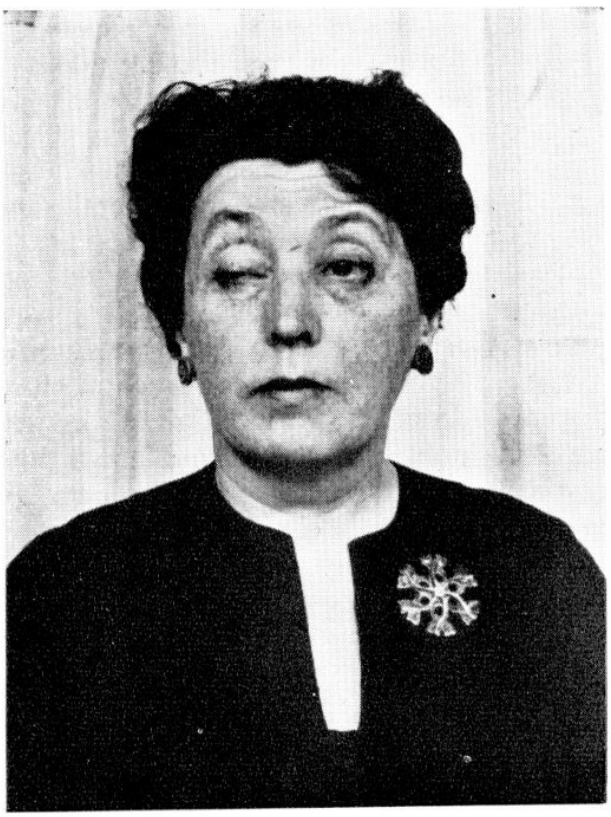
TABLE I

	Nº of Patients	*Percentage*
TRANSIENT NEONATAL	8	1.6%
JUVENILE	37	7.4
GROUP I	127	25.4
II	194	38.8
III	57	11.4
IV	49	9.8
V	28	5.6
TOTAL	500	100.0%

It will be noted from the Clinical Classification and Table of Distribution that approximately 75% of all myasthenics will usually do well with drug therapy, individually adjusted to fit the patient.

(Figures I and II.)

IMPROVEMENT WITH DRUG THERAPY INDIVIDUALLY ADJUSTED TO FIT PATIENT



Before Anticholisnesterase Therapy

After Anticholinesterase Therapy

Drug Therapy

Three important factors in the management of drug administration are: 1) choice of drug; 2) optimal dosage of drug; 3) frequency of administration.

Choice of Drug

Pharmacologic therapy depends upon a group of relatively short acting potent anticholinesterases.

Neostigmine (Prostigmin) bromide has been effectively used for a quarter of a century. It is not habit forming as requirement for the drug diminishes if the patient goes into remission. Its disadvantages are its short duration of action (approximately two hours); its side-effects (epigastric distress, sweating, salivation, lacrimation, nausea, abdominal cramps, diarrhea and muscle fasciculations) are pronounced and at times difficult to control despite the use of atropine. Atropine sulfate should not be used routinely, as it masks the early warning signs of approaching overdosage. Prostigmin bromide is available as a 15 mg. scored tablet which is usually prescribed for use every two to three hours. Dosage will vary from patient to patient and indeed will vary within the same patient depending upon the amount of activity and the appearance of stressful conditions such as menses, infection or emotional trauma. Thus, no specific dose requirement can be recommended, although the usual starting dose in a new patient is one tablet t.i.d. When the patient cannot swallow, Prostigmin is available as a methylsulfate for parenteral use. An intravenous dose of 0.5 mg. is equivalent to 1.5 mg. intramuscularly or 15 mg. orally. Ampules of 1:4000 yielding 0.25 mg. per cc., ampules of 1:2000 yielding 0.5 mg. per cc. and 10 cc. vials of 1:1000 yielding 1 mg. per cc. are obtainable.

Pyridostigmine (Mestinon) bromide, an analogue of Prostigmin is more effective than Prostigmin in the relief of myasthenic symptoms affecting the small muscles innervated by cranial nerves, particularly the muscles involved in ptosis, diplopia and dysarthria. Its diurnal duration of action is perhaps one-half hour longer than that of Prostigmin. The nocturnal relief with Mestinon is one of its most important advantages since no dosage is required during the night; and even the patient with dysphagia arises in the morning able to swallow the first dose of the day. A striking advantage of Mestinon over Prostigmin is the low incidence of muscarinic side-effects so that the need for routine atropine is markedly reduced, as the range of therapeutic and toxic levels of Mestinon is much greater than that of Prostigmin. Nevertheless, the usual side-reactions will occur as soon as overdosage is reached with Mestinon. Most patients on Mestinon therapy are satisfied with the sustained feeling of well-being throughout the day. Mestinon bromide is available as a 1/4 scored 60 mg. tablet which is generally replaceable tablet for tablet with Prostigmin and prescribed every three to four hours in most cases. A prolonged action Mestinon bromide is available as a scored "Timespan" tablet containing 180 mg. which has the immediate effect of a regular 60 mg. tablet. This form is slowly released so that its duration of action lasts approximately 2 to 2½ times than that of the regular Mestinon tablet. Its greatest advantage is in its use for nocturnal relief and is frequently prescribed as the last dose of the day, regardless of which drug may be used during the day.

Ambenonium (Mytelase) chloride is a bis molecule and is entirely different in structure from Prostigmin or Mestinon. It has an excellent effect on the peripheral muscles affected by myasthenia and gives a more sustained increase in strength. Its value for bulbar myasthenia is midway between that of Mestinon and Prostigmin. Mytelase is definitely longer in action than Prostigmin and possibly slightly longer than Mestinon in the daytime hours but has the same nocturnal effect as regular Mestinon. It has less toxic side-effects than Prostigmin but more than Mestinon. The side-effects differ from those of Mestinon. Central nervous system side-effects are more evident such as headache. Other early signs of overdosage are muscle fasciculations and weakness. Gastrointestinal side-reactions are not as common as with the other two drugs but do occur late when overdosage is approached. Mytelase has a distinct advantage for the patient in crisis who is in the respirator. It causes less bronchial secretions than the other anticholinesterase drugs. Mytelase chloride is available as a scored 5, 10 and 25 mg. tablet. Approxi-

mately 6 mg. of Mytelase chloride is equivalent to 15 mg. of Prostigmin bromide or 60 mg. of Mestinon bromide. Mytelase should be started cautiously with a 5 mg. dose and gradually increase to therapeutic levels. It is usually given every four hours. A syrup containing 15 mg. to 5. cc. can be obtained for respirator patients fed through a nasogastric tube.

Combinations:

Some patients who are not well controlled with a single drug may be treated more satisfactorily with combinations of Prostigmin, Mestinon or Mytelase. Mestinon and Mytelase are used for patients with predominant bulbar involvement. Prostigmin and Mytelase are best for patients with predominant peripheral muscular weakness. One should reserve the use of combined drug therapy to those patients whose myasthenia is relatively stable and whose intelligence in handling their own drug dosages has been proven.

Experimental Drugs:

While theoretically desirable, long acting, semi-permanent anticholinesterases have not met with success in myasthenic because they have created problems of cholinergic toxicity[3] except in a small percentage of stable patients. Drugs falling into this classification are the alkylphosphates such as diisopropyl fluorophosphate (DFP), tetraethylprophosphate (TEPP), hexaethyltetraphosphate (HETP) and octomethylprophosphoramide (OMPA); the BC drugs such as bis-Prostigmin (BC-40), bis-Mestinon (BC-51 "Ubetrid")[4] and an alkyl phosphothiocholine (2-diethoxyphosphinylthioethyltrimethylammonium iodide) Phospholine Iodide.

Shorter acting anticholinesterases currently under investigation but still clinically unestablished include galanthamine[6] and other newer synthesized compounds based on extracts derived from plants. These lycoramine derivatives are potent. Under investigation also is 8-dimethylcarbamyloxy-1-1,2,3,4-tetrahydroquinolinium methylsulfate (Mer-31).

Adjuvant Drugs:

In isolated cases, use of ephedrine sulfate and potassium salts still meets with some enthusiasm and occasional results. Ephedrine sulfate, 25 mg. t.i.d. gives an increase in strength in some patients not completely controlled with anticholinesterase therapy alone. The potassium salts, 5-10 grains t.i.d. may also be helpful. These two drugs may be used separately or together in addition to the basic treatment medication. If no improvement is evident, adjuvant drug therapy should be discontinued. Quanidine and urecholine have been advocated but not found to be of any particular value. Atropine sulfate hypo-tablets, 0.4 mg. (1/150 grain) should be prescribed at the first visit. The patient is told not to take them unless side-reactions develop, in which case one or two tablets are swallowed or placed under the tongue.

Drugs Contraindicated:

Curarizing compounds, d-tubocurarine and certain other drugs such as quinine, quinidine and magnesium sulfate should *never* be prescribed. The myasthenic patient is hypersensitive to these compounds. Respiratory depressants including morphine should be avoided. Demerol may be used preoperatively. All sedatives should be used in small doses. No enemas should be given post-operatively to the myasthenic patient. The best anesthetics are nitrous oxide and cyclopropane. Ether is contraindicated.

It is difficult to determine which drug will be the best for the individual patient. Experience would seem to indicate that Mestinon is the drug of choice since it provides the best control with minimal side-reactions for approximately one-half of the patients. In the remaining group, Prostigmin or Mytelase alone or in various combinations may be most satisfactory. Surprisely, patients with Group I symptoms, usually involving only eyes, are sometimes resistant to anticholinesterase medication; will require large amounts of drugs from as much as 2-5 tablets per dose to relieve ptosis and diplopia. Even at this level of drug therapy there may be incomplete relief of their symptoms. In such cases it

may be advisable to withdraw all anticholinesterase therapy and resort to mechanical aids such as lid-crutch and eye patch. Of course, specific drug administration must be given if other symptoms develop.

Optimal Dosage

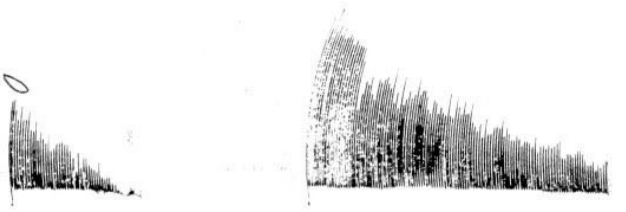
Correct dosage may be determined by one of three methods: 1) clinical evaluation; 2) edrophonium (Tensilon) chloride testing[7]; 3) intravenous Mestinon bromide titration[1], which is a fairly accurate but *dangerous* procedure.

Clinical Evaluation: The patient is given an arbitrary dose of treatment drug, usually one tablet three times a day. The patient is asked to observe the degree of relief of symptoms he obtains on this dose and to note the appearance of muscarinic side-reactions. If the side-reactions are prominent, the dosage is too high and he is asked to reduce the amount of drug. If there is no relief or insufficient relief of myasthenic symptoms from one tablet, the dose is increased by one-half tablet. This continues until maximal effect is obtained. Since the symptomatology varies during the day and with the amount of activity of the patient, it may be necessary to vary the dosages within the day.

Tensilon Chloride Testing: In addition to the diagnosis of myasthenia gravis being made with Tensilon[1], the administration of 2 mg. of Tensilon intravenously approximately one hour after ingestion of oral treatment drug, is used for the evaluation and the management of drug dosage. If the patient is adequately medicated no change occurs and drug dosage remains the same. If the patient is under-medicated, an increase in muscle strength occurs and drug dosage needs increasing. If the patient is over-medicated, further increase in muscle weakness occurs with marked muscarinic side-reactions indicating the need for a decrease of drug dosage. As Tensilon is evanescent in action, little danger is incurred by its use. The effects of Tensilon are noted within 30-60 seconds after administration. In children and in adults with inaccesible veins, 5-10 mg. of Tensilon may be injected subcutaneously and its effect noted within 2-5 minutes. Effects are illustrated by ergographs herein.

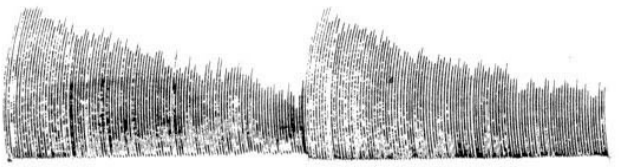
(Fig. III, IV, V.)

ERGOGRAMS ILLUSTRATING TENSILON RESPONSE IN MANAGEMENT OF DOSAGE



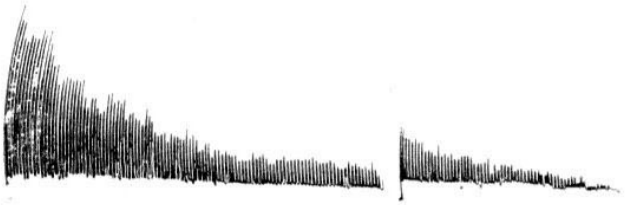
Control *Tensilon*

Ergogram showing myasthenic reaction.



Control *Tensilon*

Ergogram showing optimal or adequate response.



Control *Tensilon*

Ergogram showing cholinergic reaction.

Intravenous Mestinon Bromide Titration: In an attempt to obtain proper amount of dosage at the first visit or at subsequent visits when the patient is seen in a basal state, a method of intravenous titration with Mestinon bromide has been developed which requires certain precautions as this procedure may be hazardous. A major hazard is the development of severe cholinergic reaction if anticholinesterase drugs are given rapidly or in large amounts. If the patient complains of stomach cramps or abdominal queasiness, the *titration must be discontinued immediately.* A syringe

containing 1 mg. of atropine sulfate must always be prepared and available before titration is started. If ever in doubt, inject atropine intravenously. It cannot possibly hurt the patient and may prevent a good deal of trouble. The titration method was evolved using the conversion table noted herein.

TABLE II

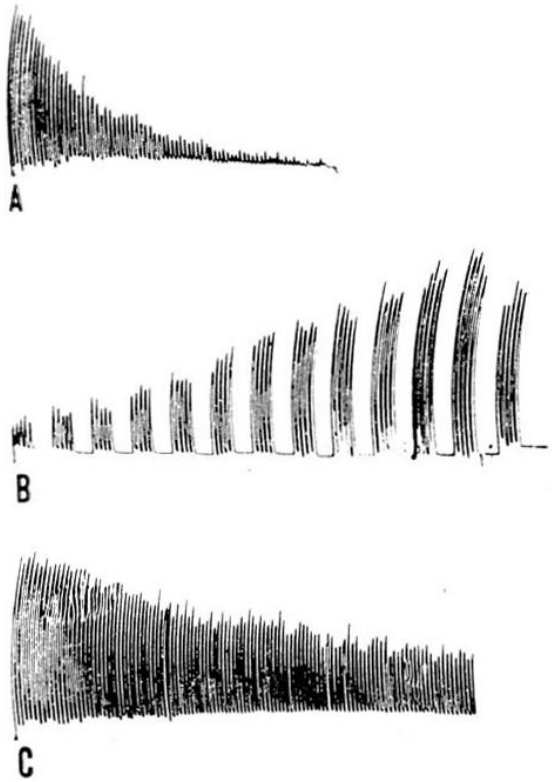
EQUIVALENT DOSAGES

	Oral Route		*Intravenous Injection*		*Intramuscular Injection*
PROSTIGMIN	15 mg.	=	0.5 mg.	=	1.5 mg.
MESTINON	60 mg.	=	2.0 mg.	=	2.0 mg.
MESTINON TIMESPAN	180 mg.	=	2.0 mg.	=	2.0 mg.
Mytelase	6 mg.		———		———

The patient is evaluated and certain outstanding myasthenic symptoms are used as a criteria for improvement. The titration must be stopped when maximum improvement in any *one* sign is achieved. If the drug is pushed to relieve all symptoms, cholinergic reactions may develop and even collapse may ensue.

(Figure VI.)

MESTINON TITRATION



Ergogram. "A", before medication. "B", with increments of 0.25 cc. Mestinon bromide each minute, showing best effort at 2.75 cc. and a fall-off at 3 cc. (6 mg.). "C", ergogram five minutes after titration.

Method of Titration: A syringe is filled containing 2 mg. Mestinon bromide per cc. One-quarter cc. increments are injected every two minutes (using a stop watch for timing) until maximal relief is obtaied in the *one* myasthenic symptom being used as the criterion for improvement. Table II illustrates equivalents to oral dosage for any of the four drugs, therefore, dosage can be estimated by the total amount of Mestinon bromide injected intravenously.

Frequency of Administration: Clinically, the frequency of dosage can best be determined by observing when the effects of medication begin to wear off or experimentally by performing hourly Tensilon tests to observe patient when a myasthenic reactions occurs. If clinically, anoptimal response cannot be achieved the treatment drug should be changed.

Resistance to Anticholinesterase Medication

Patients may become resistant to Prostigmin requiring ever increasing amounts, especially when intervening infection or psychic trauma occurs. When this does happen the patient is usually equally resistant to the other anticholinesterase drugs. Constantly increasing the dosage may lead to cholinergic toxicity and

eventually to cholinergic. crisis. Recognition of cholinergic toxicity now is a generally accepted finding in the management of myasthenia gravis. Thus, the effectiveness of drug therapy is variable in the myasthenic patient. Most patients obtain sufficient relief with drug therapy to maintain a fairly normal life, however, the response to therapy in some patients leaves much to be desired. When this happens, the patient may have to be maintained on clinically sub-optimal levels and recourse to mechanical aids such as a lid-crutch to overcome ptosis and an eye-patch to permit the patient single vision, a homogenizer to prepare foods so that the patient may swallow with minimum effort. If dysphagia is a persistant problem causing a marked loss of weight, recourse to gavage feedings through a nasogastric tube or even gastrostomy[8] may be resorted to. Mechanical suctioning may be of great help to clear saliva and mucus from the nasopharynx. In extreme cases of resistance to anticholinesterase medication, particularly with respiratory embarrassment, it may be advisable to admit the patient to the hospital and resort to respiratory assistance. All anticholinesterase medication is withdrawn from three to seven days, at the end of this time, resistance to anticholinesterase drugs should be broken.

Crisis

Sudden unexplained death is still not rare in myasthenia gravis. Two forms of crisis may occur: 1) *myasthenic crisis* in which the patient is resistant to anticholinesterase drugs; 2) *cholinergic crisis* due to marked overtreatment with these drugs[9]. In the former the history is usually one of intervening infection, emotional trauma, perhaps a relation to the menstrual cycle or cessation of medication. The usual dose of treatment drug becomes ineffective but there is no history of increased weakness or side-reactions after the taking of medication. In cholinergic crisis the history may start in much the same manner. As the patient keeps increasing the amount and frequency of medication the therapeutic effect is decreased and side-reactions such as pallor, sweating, myosis of the pupil and severe gastrointestinal upset occur. It is important to distinguish these two forms of crisis. Tensilon may be very helpful in differentiating crisis; 2 mg. injected intravenously will temporarily improve the patient in myasthenic crisis. When administered to the resistant patient[10] no effect is noted from Tensilon. If Tensilon is injected and the patient is temporarily made worse, then the crisis is cholinergic in nature. If further anticholinesterase medication is given in cholinergic crisis, death may ensue. The use of one mg. of atropine sulfate controls muscarinic side-reactions. Specific antidotes (oximes) are now available in the form of pralidoxime iodide (Protopam "PAM")[11]; 1-1½ grams are used to counteract over-depolarization reactions. Oxime drugs are most effective in treating cholinergic crisis precipitated by double bond phosphorus anticholinesterases. When cholinergic crisis is due to quaternary ammonium substances, oximes are only partially effective[1]. If respiration becomes weakened or fails, it is most important that the patient be kept alive by artifical respiration. An open airway must be maintained and frequent suctioning may be necessary to remove excessive secretions. Bronchoscopy or even tracheostomy may be necessary. Once the patient is given mechanical respiratory assistance, it is important to keep the tracheobronchial tree free of secretions and to maintain proper respiratory exchange. One should not assume that because mechanical assistance is resorted to, the patient is getting sufficient oxygen. The patient must be closely observed for the development of cyanosis, the chest examined to detect a good exchange of air in the lungs and the tracheostomy observed to make sure that the tracheobronchial tree is not blocked by secretions which must be mechanically removed by suctioning directly or through a bronchoscope. Oxygen is administered with nebulized moisture and Alevaire can be added to assist in the removal of secretions. It is best not to give any anticholinesterase medication to the patient while in the respirator. If the patient is in cholinergic crisis, this permits the over-

dosage effects of the drug to wear off. If the patient is in myasthenic crisis, the respirator permits him to survive during this period without medication and usually lowers resistance to the therapeutic agents when they are reinstituted. It is best to withhold cholinergic medication for at least the first seventy-two hours and sometimes for as long as seven days. After seventy-two hours, attempts to wean the patient from the respirator are begun. It is not advisable to give atropine to dry the secretions as this may cause thickening of mucus and blockage of air passages. Despite antibiotic therapy, an elevated temperature will usually persist until the patient is out of the respirator and able to cough vigorously thereby removing secretions in the alveoli. The patient is fed intravenously or through a plastic nasogastric tube. Proper intake and output and electrolyte balance must be maintained. Mechanical respiratory assistance may be undertaken by either positive or negative pressure devices. Currently the positive pressure apparatus permits easier nursing care of the patient.

Thymectomy

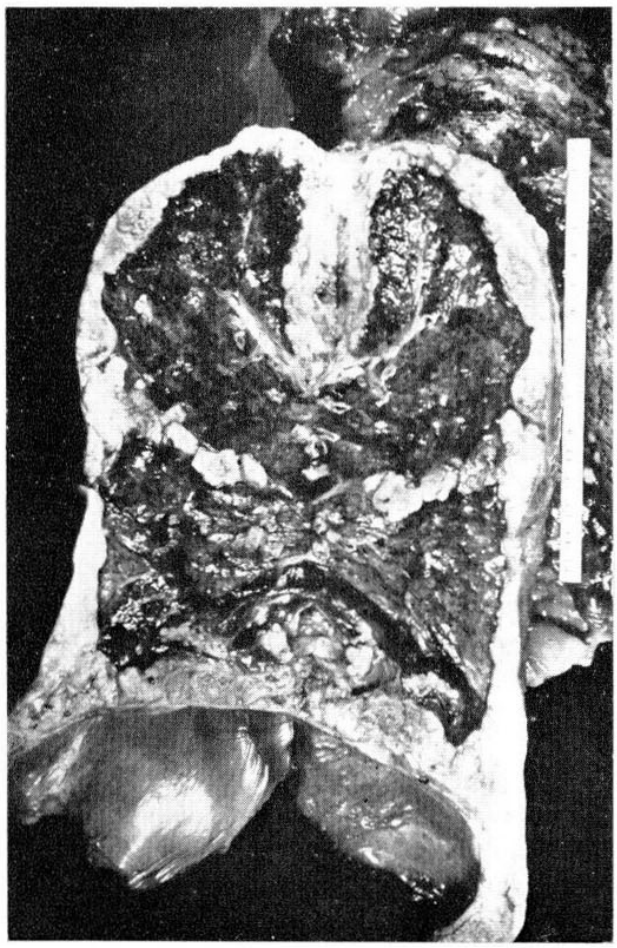
At present, sex is not the major factor in the selection of patients for thymectomy in an attempt to induce remission; but age, duration and severity of the myasthenic syndrome are[12, 13]. Patients of both sexes who are relatively young and have had severe myasthenia for less than two to five years are the ones who apparently derive the best results from this procedure. Thymoma has been found in 15% of patients with myasthenia gravis. Patients with thymoma have an aggravated form of myasthenia with the greatest percentage occurring in Group III and IV. Despite their myasthenia, these patients require thymectomy because of the possible malignancy of the tumor[15]. The post-operative care of the patient for thymectomy can be eased greatly if one resorts to routine tracheostomy at time of surgery with no administration of anticholinesterase medication in the immediate post-operative period. The reinstitution of such anticholinesterase therapy awaits a demand schedule based on clinical symptoms shown by the patient. The application of these newer techniques of management has rendered thymectomy a procedure with acceptable risk during which there should be no significant hazard to the patient[14].

Indications for Thymectomy:

1. To possibly improve remission rate: Myasthenic patients under 40 (without thymoma); severe, rapidly progressive; unresponsive to drugs; duration of their myasthenia under 5 years; no sex differentiation.
2. For prevention of tumor complications:

(Figure VII.)

MALIGNANT THYMOMA



Complete encasement of the visceral pleura of the lung by malignant thymoma with superficial invasion of the subpleural lung parenchyma. Note also the infiltration of tumor along the lung fissure. This patient also had myasthenia gravis.

Myasthenic patients with thymomas-because of high potential incidence of malignancy (75-80%).

Recommended Techniques:

1. No respiratory infection. Patients prepared psychiatrically, familiarized with staff and equipment.
2. Endotracheal anesthesia — light: minimal use of atropine and muscle relaxants, ether contraindicated.
3. Median sternotomy — transpleural underwater mediastinal drainage.
4. Obligatory tracheostomy (cuffed tracheostomy tube).
5. No anticholinesterase drug therapy administered during surgery. Following immediate post-operative period (18-72 hours), parenteral "demand" schedule for respiratory adequacy only.
6. Continuous observation in complete care unit:
   (1) Exacting tracheobronchial toilet; (2) Free use of bronchoscopy; (3) No enemas.
7. Respiratory assistance when necessary. The use of a positive pressure unit is recommended as an aid in nursing care.

Radiotherapy

Radiotherapy including cobalt teletherapy to the anterior mediastinum has been used in myasthenia gravis in an attempt to induce remission or to improve the course of myasthenia in patients without thymoma, as well as in the treatment of thymic tumours associated with myasthenia gravis. This form of therapy is not to be undertaken lightly as patients have developed a disturbing feature in that the requirement for anticholinesterase medication decreased, at times sharply, but the patient's clinical response to the new dosage levels was less predictable and less efficient than at previous higher dosages. If attemps to increase medication were started at the lower levels, patients developed clinical cholinergic reactions. Complete resistance to specific drug therapy occurred and three patients died while receiving mechanical respiratory assistance.

Dosages have varied from 600-6000 roentgen units, the usual amount being 2000r to the anterior mediastinum in an effort to ameliorate the course of the myasthenia. Dosages aer started at very low units and gradually increased depending upon the tolerance of the patient. Results are difficult to evaluate accurately since the effects of radiotherapy are usually delayed, during which time spontaneous improvement or remission, which is characteristic of the myasthenic syndrome, may have taken place. Nevertheless, radiotherapy offers some hope of halting the downward path of the patient who is not eligible for thymectomy.

Supervoltage radiotherapy in the amount of 6000-8000r is advocated in the treatment of thymoma. As yet, too few cases have been so treated to assess this procedure properly. Wherever possible, primary thymectomy is the procedure of choice.

Glandular Therapy

The use of adrenocorticotropic hormone (ACTH) and corticosteriods has been advocated for the induction of remission in myasthenia gravis[16]. Results have varied from enthusiastic to derogatory. Improvement, when it occurs follows an initial period of marked exacerbation of symptomatology. One must caution that deaths have been reported with the use of ACTH[1]. This work is still experimental in nature and needs further confirmation. At present, it cannot be stated that either ACTH or corticosteriods have a specific place in the treatment of myasthenia gravis. When used, the best dosage schedule is to administer 25 mg. of the aqueous ACTH intramuscularly, q 6 h for four days. Improvement will occur as a rebound phenomenon after the cessation of injections.

Parotin, a crude parotid extract[17], has been advocated as being beneficial in the selected case with severe myasthenia gravis requiring large doses of medication. Partially confirmed[18] are the earlier reports from Japan, that with the use of the parotid extract, patients could be better controlled with a reduction in amounts of dosage of specific treatment drug. The method of action of this extract is unknown and

further investigation is needed as no further confirmation of these results are as yet available.

The use of the sex hormones in appropriately selected male and female patients is still under investigation[19].

Comment

Treatment for myasthenia gravis in the future will probably not be in the field of anticholinesterase drugs, which are palliative at best. Research is now concentrating on the possibility of an auto-immune mechanism which may lead to a more specific therapeutic approach.

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SUMMARY

Before the discovery of drug therapy for myasthenia gravis, approximately 90% of these patients died within two years of onset. At present this mortality has decreased to 15-20% through the use of newer analogues of physostigmine, which are a group of short acting potent anticholinesterases. Of the compounds in use the three which have the widest therapeutic range and easiest clinical applicability are neostigmine (Prostigmin), pyridostigmine (Mestinon) and ambenonium (Mytelase). Mestinon has a prolonged-action form in the nature of a "Timespan" tablet. All these drugs are interchangeable and have a basic equivalent action so that 180 mg. of Timespan Mestinon is equivalent to 60 mg. regular Mestinon, 15 mg. of Prostigmin and 6 mg. of Mytelase. Adjuvants used are ephedrine and potassium. It is difficult to determine which of these drugs will be best suited for the individual patient, although it would seem that majority of patients prefer Mestinon. Mestinon is the drug of choice with which to start the fresh myasthenic. Management of drug therapy depends upon clinical judgement, pyridostigmine titration and the use of edrophonium (Tensilon) to judge the adequacy of oral drug dosage. Two mg. of Tensilon is given intravenously approximately one hour after ingestion of the oral treatment drug; 1) if the patient is adequately medicated, no change occurs; 2) if the patient is undermedicated, there is an increase in strength and drug dosage needs increasing; 3) if the patient is overmedicated, further increase in weakness occurs with marked muscarinic side-reactions indicating need for decrease of drug dosage. While theoretically desirable, long acting, semi-permanent anticholinesterases have not met with success in myasthenia gravis. A number of shorter acting anticholinesterases are currently under investigation, but are still clinically unestablished.

To further aid in reducing the mortality rates and to possibly induce remision thymectomy, radiotherapy to the thymus or treatment with glandular extracts are employed in selected cases.

Treatment for myasthenia gravis in the future will probably not be in the field of anticholinesterase drugs, which are palliative at best. Research is now concentrating on the possibility of an autoimmune mechanism which may lead to a more specific therapeutic approach.

RESUMEN

Antes del descubrimiento de la terapia medicamentosa para la miastenia gravis, aproximadamente el 90% de los pacientes morían sin que transcurrieran 2 años después del comienzo de los síntomas. Actualmente esa mortalidad ha descendido al 15-20% por el uso de los medicamentos recientes del tipo de la fisostigmina, los cuales constituyen un grupo de potentes anticolinesterasas de acción breve. De los compuestos en uso, los 3 que tienen la más amplia acción terapéutica y más fácil apli-

cación clínica son la neostigmina (Prostigmin), la piridostigmina (Mestinón) y la ambenonium (Mitelasa). El Mestinón tiene una acción prolongada bajo la forma de una tableta de Timespán. Todas estas drogas son intercambiables y tienen una acción equivalente básica, de tal modo que 180 mmg. de Timespán Mestinón, equivalen a 60 mmg. de Mestinón común, a 15 mmg. de Prostigmina y a 6 mmg. de Mitelasa. Los coadyuvantes usados son la efedrina y el potasio. Es difícil determinar cuál de estas drogas se adaptará mejor a cada paciente aunque parecería que la mayoría de los pacientes prefieren el Mestinón. Mestinón es la droga de elección con la cual comenzar en el miasténico recién tomado. El cuidado de la terapéutica medicamentosa depende del juicio clínico, de la titulación de la piridostigmina y el uso del edrofonion (Tensilón) para juzgar lo adecuado de la dosis medicamentosa oral. 2 mmg. de Tensilón son dados por vía intravenosa, aproximadamente 1 hora después de la ingestión de la droga usada por vía oral; 1) si el paciente está adecuadamente medicado ningún cambio ocurre; 2) si el paciente está submedicado hay un aumento de las fuerzas y la dosis de la droga necesita ser aumentada; 3) si el paciente está sobremedicado hay un ulterior aumento en la debilidad con marcadas reacciones colaterales de tipo muscarínico que indican la necesidad de disminuir la dosis de la droga. Aunque teóricamente deseables, las anticolinesterasas de acción prolongada, semipermanente, aún no han tenido éxito en la miastenia gravis.

Un número de anticolinesterasas de acción más breve son investigadas actualmente; pero no están todavía clínicamente bien definidas.

La radioterapia del timo o el tratamiento por extractos hormonales son medios empleados en ciertos casos precisos y pueden inducir a una remisión.

El tratamiento futuro de la miastenia gravis, no estará probablemente en el campo de las drogas de acción anticolinesterásica, las cuales son a lo sumo paliativas. Las investigaciones se concentran actualmente en la posibilidad de un mecanismo de autoinmunización que pueda conducir a una terapéutica más específica.

RESUME

Avant la découverte d'une thérapeutique par drogues contre la "myasthénie grave", à peu près 90 % des malades mouraient dans les deux ans qui suivaient son apparition. Actuellement, la mortalité est 15 à 20 %, grâce à l'introduction d'analogues plus récents de la physostigmine, qui forment un groupe d'anticholinesterases à action rapide et éfficace. Parmi les produits de synthèse utilisés, les trois composés avec action thérapeutique la plus étendue et les plus susceptibles d'application clinique, sont la neostigmine (Prostigmin), la pyrodostigmine (Mestinon) et l'ambenomine (Mytelase). Le Mestinon se présente aussi comme un médicament à effect prolongé, sous forme d'une tablète "Timespan". Toutes ces drogues sont interchangeables et ont une action mesurable en unités équivalentes, si bien que 180 mg. de Mestinon à effect prolangé équivalent à 60 mg. de Mestinon ordinaire, et 15 mg. de Prostigmin à 6 mg. de Mytelase. Les adjuvants employés sont l'éphédrine et la potasse. Il est difficile de déterminer laquelle de ces drogues conviendra le mieux à chaque patient, bien que la plupart des malades semblent préférer le Mestinon. Ce dernier est indiqué dans le traitement des myasthéniques récents. L'utilisation de ces drogues est commandée par l'observation clinique, par le titrage avec la pyridostigmine et par les indications de l'edrophonium (Tensilon), qui permet de constater si la la dose de médicament, pris par voie bucale, est adéquate. On donne 2 mg. de Tensilon, par voie intravénale, une heure environ après l'ingestion de la drogue: 1) lorsque la dose est adéquate, aucun changement se manifeste; 2) quand la dose est insuffisante, on constate un accroissement de force musculaire, ce qui appelle une augmentation de la dose; 3) quand la dose est excessive, l'affrè lissement musculaire est encore plus prononcé, accompagné de réactions muscariniques secon-

daires qui appellent une réduction de la dose.

L'alilation du thymus, la radiothérapie du thymus ou le traitement par extraits hormoneux sont des moyens employés dans certains cás précis et peuvent induire une rémission. Dans l'avenir, le traitement de la maladie ne consistera probablement plus dans l'application d'anticholinesterases specifiques, qui sont des palliatifs.

Les recherches les plus récentes portent sur la possibilité de'un mécanisme d'auto-immunité; ces recherches pourraient conduire à une thérapeutique plus specifique.

ZUSAMMENFASSUNG

Vor der Entdeckung der Arzneibehandlung für die Myasthenie Gravis starben ungefähr 90 Perzent der Patienten innerhalb zwei Jahren vom ersten Krankheitsanfall. Gegenwärtig ist die Sterblichkeitsziffer nur 15-20 % dank der Anwendung neuer Physostigminanalogen, einer Gruppe kurzfristiger aber hoch wirksamen Anticholinesterasepräparaten. Die drei Präparate sind Neostigmin (Prostigmine), Pyridostigmin (Mestinon) und Ambemonium (Mytelase). Ausser der gewöhnlichen Mestinon Tablette ist dieses Mittel auch in einem langfristigen Präparat erhältlich. Alle erwähnten Drogen sind in der folgenden Weise austauschbar: 180 mg. des langfristigen Mestinons gleicht 60 mg. des regulären Mestinons sowohl wie 15 mg. Prostigmin und 6 mg. Mytelase. Ephedrin und Kalium sind Aebenmittel die manchmal auch in Gebrauch gezogen werden. Es ist schwer festzustellen welches Präparat in Einzelfällen vorzüglich ist. Jedoch scheinen die meisten Patienten Mestinon vorzuziedhen. Mestinon ist auch die Auswahlsmedizin für die Anfangsbehandlung aller neuen Fälle der Myasthenie. Die Handhabung der Arzneibehandlung hängt von den folgenden Punkten ab: 1) der klinischen Beobachtung; 2) der Titrieranalyse mit Pyridostigmin, und 3) dem Gebrauch von Edrophonium (Tensilon) um die Gemässzeit der mündlich eingenommenen Arzneimenge zu schätzen. Ungefähr eine Stunde nach der Medizineinnahme werden 2 mg. Tensilon intravenös verordnet: 1) falls der Patient zureichende Medizin erhalten hat wird keine klinische Veränderung stattfingen; 2) falls die Arznei nicht zureichend ist wird man eine Verbesserung des Kraftzustandes bemerken und man muss die Arzneimenge erhöhen; 3) hat der Patient aber bereits zuviel Medizin erhalten dann wird einen allgemeinen Schwächezustand sowohl wie muskarinische Seitenreaktionen bemerken und die Medizindosis muss daher verringert worden. Wogegen es theoretisch wünschbar wäre langfristige oder halbdaverhafte Anticholinesterasepräparate für die Myasthenie Gravis zu benützen haben sich leider solche Präparate nicht bewährt. Eine Anzahl solcher kurzfristigen Mittel sind jetzt in der Untersuchung aber sind noch klinisch unerprüft.

Um die Sterblichkeitsziffer zu reduzieren und um mögliche Symptomnachlassung zu erwirken, werden in Einzelfällen auch chirurgische Entfernung oder Bestrahlung der Thymusdrüse oder Behanflung mit Nebennierenrindepräparaten versucht.

Die zukünftige Behandlung der Myasthenie Gravis liegt wahrscheinlich nicht im Bereich der Anticholinesterasepräparaten die sowieso nur lindernd wirken. Die Forschung konzentriert jetzt an der Möglichkeit einer auto-immunen Pathogenese in der Hoffnung einen mehr direkten therapeutischen Zugang zu finden.

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Personality

Prof. HEINRICH PETTE

Once upon a time in a happy Germany, the waltzes encircled the whirling couples, and the students sang while clashing their beer steins. Art, philosophy, literature, music were the topics of conversation. In that elating atmosphere Heinrich Pette spent his student years free from economic worries. To complete his medical education he attented the Universities of Marburg, Munich, Berlin, and Kiel.

His ancestors were peasants of West Germany, and two generations of professional people hasn't erased the healthy, and vigorous appearance of those that are in constant contact with nature.

The joy of getting his M. D. degree was dinned by the thunder of the canons. The First World War broke out and caught young Pette in its tentacles. First he went overseas, and afterwards he served as a doctor in Army hospitals.

The shadows of sorrows fell upon his spirit. The war was over, but the happy times were gone forever. The economic situation didn't allow him to fulfill his wishes of going abroad. Feeling very depressed about the destiny of his country, his only thought was to work, to work hard and to regain for his medical training the time lost during the war years.

He first interest tended toward General Medicine, to which he devoted most of his time during his student years. On several occasions in 1919, as a voluntary physician, he accompanied Prof. Nonne on his rounds at the Neurological Clinic at the Eppendorf Universitary Hospital. Nonne,

who was outwardly very authoritarian surprised Dr. Pette, by offering him a post as an assistant in his clinic. The relationship of master-pupil soon gave way to a very warm friendship which was, maintained for forty years until Dr. Nonne's death at the ripe age of 98 in 1959. Dr. Pette relates to us that a few weeks before his departure from this world, Dr. Nonne called him and made him promise that at the posthumous ceremony in this honor, he would be the sole speaker.

Rapidly he advanced in his career from first assitant in 1920 to Docent in Neurology in 1924. Those were hard years in Hamburg. Even though Eppendorf Hospital was an internationally recognized medical center the necessary equipment was lacking and the secretaries and technicians needed to carry on their work. The medical activities were considered primary but without disregarding laboratory research. In this place outstanding scientists like Kümmel, Fränkel, Schotmüller, Sudeck, Wilbrand, Nonne, Brauer had worked.

Dr. Pette's schedule was a very heavy one being a clinician. He was at that time unfamiliar with basic scientific investigation. He remembers with deep gratitude how Alfred Jakob in Hamburg and Walter Spielmeyer in Munich introduced him to the fascinating realms of Neuropathology. Dr. Pette's vacations during his first years as a assistant were spent in their laboratories at a time when both men were already famous for their contribution to science. As he probed deeper into clinical Neurology he realized that its domain was too vast to be included as a part of Internal Medicine or Psychiatry, but deserved to be regarded as an autonomous discipline.

Nonne was a very bright clinician and on top of that a remarkable teacher. He was famous for his investigations on diseases of syphilitic origin of the nervous system. At first Dr. Pette worked on the same subject but pretty soon he was attracted toward experimental Biology.

Neurological scientific circles of Europe were at that time still under the impact of the puzzling and multiphacetic epidemic encephalitis (Von Economo) that had as one of the four Apocaliptic plages, marauded every country.

He began by investigating the virus of herpes which according to the hypothesis of Dörr and Levaditi, was supposed to be the agent generating encephalitis.

However this theory was later discarded. But the herpetic encephalitis produced experimentally by Dr. Pette, was considered as a model to perform investigations concerning the problem of Neurological diseases of virus origin, especially Poliomyelitis.

He also carried on experimental studies on the so called encephalitis spontaneous of the rabbit, produced by "Encephalitozoon cuniculi", which several authors had claimed responsible for the encephalitis epidemic and also of the paralysis. Dr. Pette demonstrated that this spontaneous encephalitis of the rabbit had no connection with human pathology.

Nevertheless these studies lead him to formulate the so called hypothesis of activation, that is, the evolution of an infection due to the alteration of the inmunological properties of the organism, sets in motion a second infection by an agent that until then hadn't been regarded as pathogenic. These studies were rounded out by others concerning the so

called bipolar phenomena, and they gave Dr. Pette the basic to enunciate the hypothesis of neuroalergy.

These studies put him in personal contact with Dr. Dörr in his Institute of Hygiene in Basel and Dr. Levaditi in the Institute Pasteur, in Paris. By that time Levaditi had attracted several specialists to work with him on this problem like P. Lepine from Paris and Nicolau from Bucharest.

More and more neurologists were becoming interested in Dr. Pette's methods of investigation, and no doubt that brought about his being proposed by Dr. Guillain (Paris) for a conference at the First International Congress of Neurology (1931) with Bernard Sachs as President and Henry Alsop Riley as Secretary. On the third day of the Congress the subject "Acute Infection of the Nervous System of Not Purulent Origine" was treated; C. Marburg, G. Marinescu, J. C. Greenfield, A. Wimmer, H. Pette, Andre Thomas, and L. van Bogaert successively talked at that session.

This Congress where 40 nations were represented gave to Dr. Pette the chance to establish a bond of international scientific cooperation with other specialists and to met many neurologists whose names were familiar to him through medical literature, such as Purves Stewart, Ariens Kappers, R. Bing, Harvey Cushing, Foster Kennedy, Clovis Vincent, Percival Bayley, Egas Moniz, Sherrigton, Pavlov, Ken Kure, Kinnier Wilson, V. M. Buscaino, B. Brouwer, Del Rio Hortega and many others. That was for Dr. Pette an unforgetable experience.

He also recalled that in the last session of this first Congress it was discussed whether Neurology belonged to Internal Medicine and to what extent it must be considered linked to Psychiatry.

Foerster on that occasion stated "Neurology should be considered a specialty of Medicine and to be separated from other specialties not only in practice but also in teaching."

The following international congresses held every four years, the last one being in Rome (in 1961) have shown how much not only clinical investigation but those related to basic sciences have evolved.

Dr. Pette particularly enjoyed them not only because of the enlightment on diferent neurological problems provided the specialists, but also the warm friendship and the cooperation found amongst specialists from the different countries.

In the conference given by Dr. Pette at the Congress in Berne on "Comparative Considerations of the Acute Infectious Diseases with predominance in the Grey Matter of the Nervous System" he presented the results of experimental studies with the virus of poliomyelitis in monkeys.

In those days the problem of how a neurotropic virus reaches the central nervous system, was very much discussed. Jointly with Dr. H. Demme and St. Környey he tried to prove the theory of Neuroprobasia, which means the migration of the virus through the neuroaxis. This theory has been for many years accepted as evident by the most important authors in the United States like B. Rodian, A. Sabin and others for further experimental studies. In 1949 Dr. Pette shed more light on this concept in work performed along with Ch. R. Beherend, G. Doering and H. Kalm in the sense that the polio virus must be found in the blood before the

appearance of neurological damage. In the International Congress of Poliomyelitis held in Copenhagen (1951) Dr. Pette suggested to look for the virus in the blood during the prodromic phase. This was the basis of the theory still in force now a days that the Poliomyelitis like other enterovirus diseases has a general infectious character.

Diverse topics were studied by Dr. Pette in his numerous contributions to Neurological literature, amonst them and besides those related to neurobiological problems, were studies on clinical problems and investigations concerning the disturbances of the regulatory neurovegetative functions. He demostrated through his observations that the so called general symptoms of brain tumour are in reality local symptoms; besides he was fond of studying problems related to constitutional biology and also on the topic of circulation and the nervous system.

When Dr. Pette reached the Chair of Neurology after Dr. Nonne's retirement, in 1934, it was his ambition to tackle the whole problem of the therapeutic procedure in Neurological Diseases. Then and afterwards fighting againt the resistance offered by the neurosurgeons, he was able to create a Neurosurgical department in his service and he believed that this proved to be beneficial for surgeons and neurologists alike.

Then a teamwork began that was to be scientifically very fruitful.

Dr. Pette recalls with pleasure the time spent as assistant in Dr. Foerster's Clinic which was engaged in his important investigations on brain surgery.

He along with Cushing is considered by Dr. Pette as the founders of Neurosurgery with a Neurophysiological foundation.

At the time Dr. Pette left his service to Dr. R. Janzen in 1958, it had become an ideal center of Neurological investigation embracing Neuropathology, Neuroanatomy, Neurophysiology, Neurobiology, the diagnosis and therapy of the nervous system, in a service with the complete facilities of a modern Neurological center.

In a talk at a memorable event "50 years of the German Neurological Society" in 1951, he expressed that Neurology couldn't confine itself to the clinical diagnosis but should also be permeated with Neurophysiology, Neurobiology, Biochemistry and especially Neurochemistry which would impel Neurology to another great leap forward.

As President and organizer of the German Congress of Internal Medicine he tried once more to establish bonds between Neurology and the vast realm of Internal Medicine.

By happy circumstances Dr. Pette found through marriage his best collaborator Edith Graetz who had a neurological background. She proved to be not only a devoted wife and mother of four children but her fine spirit, keen intelligence and comprehension made her an ideal participant in the many fascinating problems in which Dr. Pette was engaged in, especially on the concept that demyelinating encephalomyelitis including multiples sclerosis are the expression of an inmuno pathological reaction of the organism. Thanks to the fabulous grant from a Hamburg merchant and to Mrs. Pette's organizing spirit it was posible for Dr. Pette to establish a laboratory for neurological investigations.

An efficient circle of collaborators are engaged there in the investiga-

tion of the problems concerning Neurobiological infections brought about by virus and encephalomyelitis by demyelination.

Dr. and Mrs. Pette are very active in their work and always in touch with other centers of investigation in Europe and exchanging ideas with known personalities in their field. They maintain with their collaborators not only scientific relations but a very warm human contact, and they feel very pleased that many of their scientific offspring are presently in very high positions and highly reputed in scientific circles.

In all his fruitful career Dr. Pette showed that his decision to become a doctor instead of a theologician as his Professor wanted was a very wise one. He said to us that as a consequence of the will of his teacher he devoted his time in high school learning Hebrew instead of English.

His professor was very much disappointed when young Pette turned his sights toward Medicine *but as Dr. Pette affirmed there is not much difference between these two disciplines, since both of them Theology and Medicine have the finality to guide and protect human life, to have an intimate knowledge of the inner world, and to help people in their sufferings and sorrows.* Dr. Pette achievements are even more significant if we consider all the difficulties that he had to surmont to attain a steady scientific activity. The years of the Second World War, were the hardest ones. But the energetic spirit remained unchanged among the disastrous effect of the war. In 1943 his Clinic was completely destroyed by the bombing. But as a counterpart his own little world, his home was a source of satisfaction. He said, still when every thing was the darkest, he enjoyed a great happiness within the family circle. Four children a daughter, a doctor in philosophy in Drama, a son dedicated to Virology, another to Biochemistry and a fourth one has chosen Law as a career.

Besides his family Dr. Pette finds enjoyment studing History both ancient and modern. His dynamic spirit, maintain this medico alert and productive. The passing years have not slowed his step in the least, but rather have enriched his person with knowledge, experience and a broad deeply penetrating out look on life.

VICTOR SORIANO.