

THESIS

for the degree of M.D.
in the University of Edinburgh

A Contribution to
the Study of Myasthenia Gravis

by

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INTRODUCTION

Introduction.

In 1877 Sir Samuel Wilks of Guy's Hospital described a case of bulbar paralysis without anatomical changes. A girl had been "lethargic for want of will apparently" for a month. Within three days she developed great dysarthria and dysphagia and died from respiratory failure. No abnormality was found on post-mortem examination.

Erb in 1878 described a case of bulbar paralysis, which he considered to be a chronic progressive and fatal neurosis because the most careful microscopical examination of the nervous system gave a negative result, similar cases were described by his assistants and others.

Goldflein in 1893, showed that Erb's case belonged to this group. He reviewed twenty cases, and showed that remissions occur and relapses after apparent recovery.

In 1895 Jolly described the myasthenic reaction.

Campbell and Bramwell in 1900 described nine cases and reviewed the diseases as a whole. They thought that the cause was probably a toxin of microbic origin which attacked the nerve endings or axis cylinders.

Buzzard published a careful study of the lymphorrhages in 1905.

The causation of the disease is still unknown, theories of endocrine and metabolic disturbances have been promulgated. Marinesco thinks

that there is a disorder of the vegetative system, and that fatigue products cannot be removed.

Until 1929, when Harriet Edgeworth discovered the effect of ephedrine in her own case, no undoubted improvement in the original treatment had been made. Since then it has been found that several drugs, veratrine, physostigmine and its analogues, and potassium chloride temporarily relieve the symptoms.

My contribution to the treatment has been to show that physostigmine has this effect, that Prostigmin in large doses with atropine to counteract the parasympathetic "stimulation" will restore normal strength for several hours in severe cases of the disease, that this effect can be repeated without diminution several times a day, and that long continued administration of the drug produces no ill effects. A preliminary note on the action of physostigmine was published in a letter to the Lancet of 2nd June, 1934, and a case demonstrating the effect of a large dose of Prostigmin with atropine was shown at the Royal Society of Medicine on 8th February, 1935.

I consider that the hypothesis of the production of a curarising quaternary ammonium base by the action of a micro-organism on the intermediate products formed during muscular contraction within the muscle itself, best explains the course and symptoms of the disease.

Exactly how the symptoms are produced will not be explicable till the neuro-muscular mechanism and the chemistry of muscle are more fully understood.

It is not even possible to say whether the disease affects the nerve endings or the muscle till the controversy of Rushton and Lopicque has been settled.

*11.2. Kato's experiment
of Japanese incense*

It is conceivable that conduction between nerve and muscle fails when too high a degree of heterochronism is reached, and yet that the failure is due to interference with a chemical intermediary transmitter. Kato took the combustion of a stick of Japanese incense to represent the conduction of nerve impulse, a physico-chemical process when he showed that conduction is without decrement. If the kindling of a fire be taken to represent the excitation of muscle from nerve, the nerve being represented by a match or taper, the chemical intermediary by paper or firelighters, the muscle by coal, it will be seen that too high a degree of heterochronism can prevent conduction. Paper is readily inflammable, (excitable) but it will not ignite coal.

PHYSIOLOGY
OF
STRIATED MUSCLE.

THE PHYSIOLOGY OF STRIATED MUSCLE

The Neuromuscular Mechanism.

The Anatomical Structure of Muscle Fibre.

Voluntary muscle is composed of bundles of muscle fibres, about 0.05 mm diameter and of varying length up to 3 cm or a little more. Each fibre is enclosed in a structureless sheath, the sarcolemma, and consists of several myofibrils or sarcostyles which are made up of a series of contractile elements, the sarcomeres, placed end to end and enclosed in a granular material the sarcoplasm. When the muscle contracts the sarcomeres become shorter and thicker.

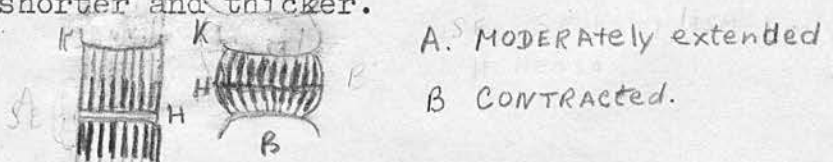


Diagram of Structure of Sarcomere. Sharpey Schafer

There are two kinds of fibres the red and the white. The red contract more slowly after a longer latency, the contraction lasting three times as long as it does in the white. In men most of the muscles contain both red and white fibres and also fibres of intermediate type. Fibres of similar speeds of contraction are arranged in groups. All the muscle fibres have a similar motor innervation, and they are all used for both posture and movement.

The motor unit consists of an anterior horn

cell, its axis cylinder, and from 150-200 muscle fibres. The axis cylinder divides into branches, each branch ending in a single muscle fibre. The neurilemma of the nerve fibre becomes continuous with the sarcolemma of the muscle fibre. The medullary sheath ends abruptly, and the axis cylinder branches in a mass of undifferentiated protoplasm, the motor end organ, which lies in contact with the sarcolemma immediately under the sarcolemma. The branches of the axis cylinder have varicosities upon them, and appear to end freely in the motor end organ, without being organically connected with it. Some of the nuclei in the end organ disappears when the axis cylinder degenerates.

When there is a sensory spindle in a muscle fibre, there are also two or more end plates from different anterior horn cells; when there is no sensory spindle there is only one motor end plate.

A. Medullated Nerve Fibre

B. Non-medullated Nerve Fibre

Diagram. End plate.



Skeletal muscles are also innervated by non-medullated fibres some of which have been proved to be post ganglionic sympathetic fibres. The same muscle fibres may be supplied by both somatic and sympathetic fibres. No effect is produced on resting muscle by stimulation of the sympathetic, but the contractions of fatigued muscle are raised

in height. The sympathetic innervation of skeletal muscle has been denied. Parasympathetic fibres have been said to reach the muscle by way of the sympathetic supply of the blood vessels.

Muscle tone depends on the somatic nervous system only. It has been shown by recording the action currents from small muscle groups that the tone is due to a slow (5-20 a second) and probably asynchronous discharge from the anterior horn cells, which causes groups of muscle fibres to contract in turn. When one group is contracting another is resting.

A single electrical shock to the motor nerve trunk causes a mechanical disturbance in the muscle, the "twitch". It consists of three main phases.

1. The latent period during which no apparent change takes place in the muscle.
2. A phase of shortening or contraction.
3. A phase of relaxation or return to the original length.

If the stimuli are repeated at short intervals a partial tetanus is produced by partial fusion of the twitches, or a complete tetanus, according to the rapidity of the stimulation. A rate of 60 stimuli per second usually results in a complete tetanus, no further mechanical response in the muscle can be produced by raising the rate.

Diagram. Twitch. Tetanus.

Action Currents

The single electrical shock to the motor nerve trunks also causes an electrical disturbance occurring half way between stimulation and the first sign of contraction. If the stimuli are repeated at short intervals the muscle action current shows separate electrical deflections corresponding to each stimulus.

The all or none hypothesis

Keith Lucas¹ using a very small muscle with only seven nerve fibres passing to it, found that only seven different strengths of contraction could be obtained no matter how the stimuli were arranged, or however the strength of contraction was increased. On this was founded the all or none hypothesis. It has recently been shown that the muscle twitch can be graded if the cut surface is stimulated. Microelectrodes of glass with a pore at the end can be introduced ~~inside~~ muscle fibres and part of the muscle fibres made to contract. These small contractions could be graded in size and had no accompanying electrical disturbance. It is the sarcolemma which gives the all or none quality to muscle. Like the nerve it receives it conducts excitation which throws the sarcomeres into mechanical disturbance. The sarcoplasm and

myofibrils conduct very slowly. The response of a single muscle fibre cannot be varied, by varying the stimulus only, the delicate gradation in power of voluntary contractions being due to the variable number of motor units and contractions, the maximal force being exerted when all the fibres contract. Pratt and Eisenberger² showed that as the strength of the stimulus is steadily increased, the response increases in a series of steps each of which corresponds to the occurrence of contraction in fresh fibres, which had been unaffected by the weaker stimuli. Each fibre which enters into contraction does so with maximal strength.

Chronaxie

Lapicque³ introduced the term chronaxie as a measure of the electric excitability of tissues. Hoorweg and later Weiss had shown that time plays a fundamental part in the excitation of nerves and muscles. Lapicque called the minimal intensity of current necessary to excite a tissue, the Rheobase, no lengthening of the time of stimulation will reduce the intensity of current necessary for excitation below this, but if the time of stimulation is progressively shortened, the intensity of current necessary to excite the tissue is proportionately increased. The time limit above which no variation in the minimal current necessary for stimulation occurs, varies in different tissues and was called by

Lapicque 'le temps utile'. It is difficult to measure this, so he chose as a measure of rapidity of excitation, the time required by a current of twice the intensity of the Rheobase to excite a tissue and called it the chronaxie. According to Lapicque if the chronaxie of the muscle becomes twice that of the nerve conduction fails.

Summation of Stimuli

If two stimuli, both subliminal, that is, insufficient to cause a contraction, are received within a short enough interval of each other they will be summated, and a contraction will occur. The time interval varies from tissue to tissue, and bears a relation to the chronaxie.

Refractory Period

For a very short time after stimulation a muscle is inexcitable to a second stimulus, in a frog's muscle the time is about 50, in mammalian muscle much shorter. It is greatly increased by reduction of temperature.

Muscle Chemistry.

Muscle contains about 75% of water and 20% of the proteins myosin and myogen. The proteins are in a state of weak gel. Other constituents of muscle are, the pigments, myoglobin and cytochrome, ~~B~~alanyl histidine, traces of fat, lecithin, cholesterol and various enzymes. The ash of muscle consists of potassium phosphate, with traces of calcium, sodium, magnesium and iron.

There are two main chemical processes accompanying muscular contraction, namely, the breakdown of creatine phosphoric acid and the production of lactic acid. In resting muscle about 40% of the total acid soluble phosphorus is found as creatine phosphoric acid and the same amount as adenosine triphosphoric acid. The soluble carbohydrate esters, including glycerophosphoric acid are present in small amount. On contraction, creatine phosphoric acid breaks down into creatine and phosphoric acid; adenosine triphosphoric acid also probably breaks down early into inosinic acid, ammonia and phosphoric acid. Glycogen by enzyme hydrolysis gives rise to hexose, which unites with the phosphoric acid which has been set free, and forms hexose monophosphate from which lactic acid is produced by a series of reactions. The creatine phosphoric acid and adenosine triphosphoric acid in the contracted muscle are diminished, and the soluble carbohydrate esters, and free orthophosphate are increased. These changes are

reversible, creatine phosphoric acid and adenosine phosphoric acid are resynthesized, most of the lactic acid is reconverted to glycogen, some of it being oxidised.

Pyruvic acid, methyl glyoxal, succinic acid, methyl guanidine and a number of other important intermediaries are present in muscle, and there are special enzyme systems to control them. It is known what place they take in the train of events which occur during muscle contraction.

The concentration of potassium in the muscles is 13 - 20 times as high as in the blood. Wojcieszak found that more potassium passed out from stimulated than from resting muscle.

Heat production can be separated into four distinct phases, correlated with corresponding phases of mechanical activity. It is not known how the chemical energy of contracting muscle is converted into mechanical energy. There are various theories, Hill⁴ thinks that it is a sudden and reversible gelation due possibly to an electrical discharge of charged colloidal surfaces followed by a dehydration.

The Chemical Transmission of Nerve Impulses.

It is now generally recognised that para-sympathetic effects are transmitted by the release of acetyl choline, and sympathetic effects by adrenalin, or a substance related to it, sympathin, at the periphery of the nerve fibres; and there is recent evidence⁵ to show that acetyl-choline acts as a transmitter at the synapses in autonomic ganglia, both para-sympathetic and sympathetic and from the end of the motor nerve to voluntary muscle. Both acetyl-choline and sympathin act on the effector cells (muscle, gland or autonomic ganglion cells) themselves, not on the nerve endings. Perfusion with these drugs after degeneration of the nerves, will cause the same effects on the effector cells as stimulating the nerves to them would have done before degeneration.

Before the chemical transmission of nerve impulses had been suspected, Langley and Anderson⁶ showed that the fibres later named cholinergic and adrenergic by Dale, could not replace each other, but that cholinergic could replace cholinergic, and that adrenergic could replace adrenergic nerve fibres. Anderson⁷ showed that even the post-ganglionic parasympathetic nerves from the ciliary ganglion could be partially functionally replaced by branches from the motor fibres to the ocular muscles in the eye of a kitten, though the end organs are different in these two nerves.

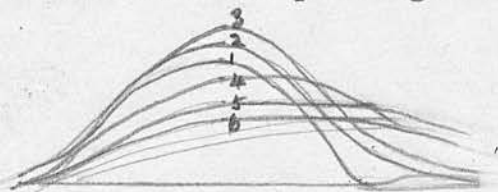
It is not yet known how the nerve impulse

causes the chemical transmitter of its action to appear, the view that it is not synthesized, but held loosely in some inactivating and protective complex is supported by the recent results of Vertiainen. Engelhart⁸ in one case was able to show that this complex disappears or is depleted when the nerve fibres degenerate. Its maintenance may be dependent on the arrival of nerve impulses at a normal rate. It may not be contained in any structure, but its permanent association with one type of neurone, cholinergic or adrenergic, suggest that it is actually in the nerve ending. It is not freely diffusible in the tissues, for it is instantly destroyed by the cholinesterase which is present in the blood and other tissues.

When Anderson removed the ciliary ganglion from the orbit of a kitten and allowed the fibres to degenerate, the sphincter of the pupil responded to pilocarpine, but not to physostigmine. He thought that this showed that physostigmine acted on a part of the nerve ending which degenerated with the fibres. Physostigmine inhibits the action of the esterase which destroys acetyl-choline, to this its constrictor effect on the pupil may be due. When the nerve fibres have degenerated, there may be no more acetyl-choline, and physostigmine no longer acts. Effector cells with a parasympathetic innervation and therefore accustomed to respond to acetyl-choline will also respond to pilocarpine and arecoline which are different from it in chemical structure and properties.

Fatigue.

If an isolated nerve muscle preparation be stimulated repeatedly, changes appear in the curve of contraction, the latent period and the length of contraction are prolonged and the height diminished.



Muscle curves, 4 5-6
Showing fatigue.

When the muscle no longer responds to stimulation of the motor nerve, it can be made to contract by direct stimulation. Nerve trunks have been shown to be almost indefatigable because they only conduct intermittently, it must therefore be the conduction from nerve to muscle which first become fatigued. In the intact animal similar fatigue curves can be produced, but the muscle still responds to direct stimulation, and stimulation through its motor nerve after fatigue has set in. The anterior horn cell or the chemico-physical central state close to it, must be the site of the fatigue.

The most readily fatigable parts of the motor unit, are the motor nerve cell, the conduction between nerve and muscle, the muscle, and the motor nerve trunk, in that order.

Fatigue depends on the accumulation of products of activity. It does not depend on the using up of substances available for the supply of energy for lactic acid formation stops long before all the glycogen has disappeared. In the presence of an excess of alkali it can proceed much further.

If the blood supply is lessened fatigue sets in more rapidly.

If left alone the isolated muscle will partially recover. The more fatigued it is, the longer must be the recovery period. Recovery is quicker if a stream of blood or salt solution is passed through the vessels, and in the presence of a free supply of oxygen. During recovery oxygen is used and CO_2 production is increased. A large amount of acid is known to be neutralised in severe fatigue. Hill suggests that there must be an effective buffer in muscle analogous to haemoglobin, possibly a sodium or potassium compound of protein.

Adrenaline has been shown to have a specific effect in removing fatigue,⁹ apart from its action in increasing the blood supply by dilating the arterioles of the muscles and raising the blood pressure. The height of contraction of fatigued muscle is raised.

¹⁰
Orbeli showed that stimulation of the sympathetic increased the height of contraction, after a latent period, of muscle fatigued by continuous stimulation through its motor nerve. The contraction of unfatigued muscle is not increased by stimulation of the sympathetic.

PHARMACOLOGY
OF
STRIATED MUSCLE.

THE ACTION OF DRUGS ON THE NEUROMUSCULAR
MECHANISM

Protoplasm is constantly undergoing chemical changes, both of breakdown and synthesis, in a definite order. An immense number of simple chemical reactions are produced, probably through the agency of ferments. Ferments act like catalysts, that is, they hasten chemical reactions without being themselves used up. In the living tissue they are co-ordinated, each ferment having a limited sphere of action. Certain drugs have a specific action on certain tissues, and it has been generally assumed that such a drug chemically combines in some way with some constituent of the cell. They may act by combining with any of the molecules undergoing chemical change or they may affect the ferments. A difficulty in the way of the supposition that they enter into chemical combination with constituents of the protoplasm is that the same action may be induced by a series of drugs which have no chemical reaction in common and cannot be supposed to enter into the same chemical combination with the cell protoplasm.

Some drugs may produce their effect by altering the surface tension of a cell in relation to the surrounding fluids. Adsorption compounds are formed with a change of electrical charge,

to this, the pharmacological action of these drugs may be due. Certain very powerful drugs act in this way, in many of them the amount required to produce a strong action is too small to form a monomolecular layer over the whole surface. The cell surface has therefore been pictured as not being uniform but having a "pattern".

According to the theory of the chemical transmission of nerve impulses, when an impulse from a motor nerve arrives at a muscle fibre it produces acetylcholine, probably either by releasing it from a loose chemical combination or by re-synthesizing it. Acetylcholine causes the muscle to contract. Denervating a muscle makes it more sensitive to the action of acetylcholine. It would seem that there are two sets of chemical reactions, at least, (1) those subserving muscular contraction, the glycogen and phosphogen breakdown and resynthesis which appear to be stable even when the function of a muscle is severely affected, and, (2) the release of acetylcholine from the chemical combination in which it is loosely held, and which, it would seem, is influenced by many drugs whose site of action is at the motor nerve ending.

The conduction of the impulse in the nerve may also be affected by drugs, but only those in the lipoid material of the medullary sheath can come in contact with the axis cylinder. The

complicated structures at the nerve endings are much more susceptible to poisoning.

QUATERNARY AMMONIUM BASES

The organic derivatives of ammonia have an affinity for motor nerve endings on which most of them have a paralytic effect, which varies in degree in ways difficult to explain by their constitution.

Curare contains as active principle the quaternary base curarine, which is bound very quickly either chemically or by adsorption to the cell substrate on which it acts. The reaction is a reversible one, but the drug is long held fast to the substrate. Its first effect is to produce a condition like that due to fatigue, in the muscle. The short muscles of the extremities and eyes are first affected, then those of the trunk, head and neck, and, lastly, the respiratory muscles. The effect of the drug increases proportionately with the dose, till at last the muscle does not respond to stimulation through the nerve, though it can be stimulated directly and the nerve will still conduct. The classical experiment of Claude Bernard¹¹ in 1857 showed that the site of action of curare was at the nerve endings. Kühne¹² came to the conclusion that it did not act on the nerve endings, because he found that in the frog's sartorius, the irritability of the muscle

X
 X *Just*

varied with the number of the nerve endings, and that a paralysing dose of curare did not change the distribution of irritability.

Curare is ~~seventy~~ times less toxic by mouth than subcutaneously, largely because it is eliminated more rapidly than it can be absorbed. Curarine is found almost quantitatively in the urine. This is a general characteristic of the quaternary ammonium bases.

Lapicque's¹³ theory of curarisation put forward in 1906 was that isochronism is a necessary condition for the propagation of impulses from one tissue to another. Of the chronaxie of the two tissues diverges by more than a ratio of 2 : 1, then conduction between the two becomes impossible. He finds that curarisation raises the chronaxie of muscle.

Rushton¹⁴ has severely criticised this theory which is the "expression of experimental observation, and has not been developed deductively from the physics of the conduction of impulses". He raises objections to the experiments adduced to support the theory; and he finds that no satisfactory evidence has been produced that the excitation time of muscle and nerve are normally identical. He and other observers have not found that curare lessens the excitability of muscle. Strychnine shortens the excitation time of nerve, and

veratrine has been thought to shorten that of muscle, both producing curarisation. Lapicque claimed that after curarisation by veratrine, indirect excitation was restored by strychnine and vice versa. Rushton found that they did not antagonise each other, conduction was never restored, no matter which drug was applied first.

Curare and Fatigue

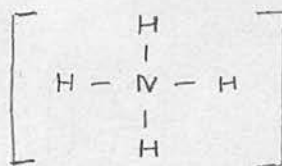
Fatigue raises the threshold of curarised muscle, and muscle deprived of its nerve supply by degeneration, while curare only affects the threshold of muscle with normal nerve endings. Adrenaline lowers the threshold of curarised muscle; it might be supposed that curare and fatigue had the same effect, and that adrenaline had the single action of opposing that effect, but as fatigue raises the threshold of curarised muscle, the action of adrenaline on it, might be explained by its antagonism to fatigue.

A characteristic of the curare action is that it accompanies the formation of a particular structure "with a fidelity unparalleled in any of the other relations between chemical constitution and physiological action"¹⁵. This structure is not primarily of a purely chemical nature, but due either to the influence of space arrangement, or to some fundamental property of the molecule which renders certain spatial relations of its component

groups possible.

Ammonium iodide is the simplest compound which shows the curare action, but the action becomes much stronger as the hydrogen atoms become substituted by the alkyl group. Tetramethylammonium hydroxide; the completely methylated substance is almost as toxic as curarine.

The compounds producing a curare effect have all a three dimensional space arrangement of their constituent group, and are all readily ionised.



It is the ions which seem to be responsible for the curare action, though not because of their ionic charge. "Some form of ionisation involving loss of electrons from the external shell favour the activity of the compound losing the ion. When tetramethyl ammonium chloride is ionised, the chlorine splits off, with its outer shell completed by an electron from the outer shell of the rest of the molecule, thus acquiring its ionic charge. The removal of such an electron from the constitution of the cation half of the molecule not only gives it a positive charge, but must also induce some rearrangement in the electronic constitution - setting up in all probability a strain which results in the development of the

ability to produce curare action.¹⁶"

Bases analogous to the quaternary ammonium bases, in which the nitrogen is replaced by arsenic, antimony, phosphorus, iodine and sulphur all have a curare-like action. Numerous alkaloids, strychnine, morphine and quinine, when transformed into quaternary bases. Methylstrychnine, methyldmorphine and methylquinine have a curare action.

Some non-quaternary bases, chenolin, pyridine piperidine have a curare-like action, as do various animal poisons of unknown chemical constitution such as those of the Cobra and Spectacled snake.

Most of these drugs have a strong pharmacological action, apart from the curare action.

Many of the compounds known as the metal amines especially those of cobalt, chromium and platinum have a curare action. The nature of the metal forming the base seems unimportant, but the ionic character of the complex is essential to the curare action.

Magnesium salts have a curare action.

PHYSOSTIGMINE

Physostigmine gives rise to fascicular twitchings of striped muscles, beginning in the hind limbs and spreading to all the muscles. These twitchings still occur, though weakened, after nerve section, and so must be of peripheral origin, but they do not occur after nerve degeneration, or after the

motor nerve endings have been paralysed completely with curare. There is conflicting evidence as to whether or no the twitchings are arrested by atropine. Henderson¹⁴ suggests that the fact that they are arrested by atropine is strong presumptive evidence that endings of a parasympathetic type are involved. They are believed to reach the muscles with the sympathetic nerves to the muscles, and possibly to serve for the regulation of heat.

The cholinergic nerves to plain muscle and to glands are stimulated by physostigmine, the heart is slowed, and its contractions weakened both by action of the drug on the vagus and on the muscle itself. The sphincter pupillae is contracted. Stimulation of motor nerve previously below threshold value takes effect under the influence of physostigmine. The muscles themselves are also rendered more irritable.

After a poisonous dose of physostigmine, the striped muscles are "curarised" and the animal dies of respiratory failure. The bowel is quiet but can be stimulated by pilocarpine. Physostigmine is less rapidly absorbed when taken by the mouth and nothing certain is known of its fate in the body.

There is a large difference in the lethal dose when given intravenously and orally, showing either that it is only slowly absorbed or that it is rapidly eliminated either unchanged or after

decomposition or combination with another substance in the body.

Stedman¹⁸ showed that physostigmine inhibits the action of the specific esterase, which brings about the destruction of acetylcholine and other cholines. The action of physostigmine in inhibiting cholinesterase is slow, it may take more than fifteen minutes, when the concentration of physostigmine is low. It is reversible, the enzyme regarding its activity when physostigmine which is a stable ester acts by combining with the enzyme in the same way and by the same mechanism. as the choline esters, thus 'blocking' the enzyme.

The action of physostigmine in stimulating the cholinergic nerves is believed by Dale¹⁹ to be due to the inhibition of this esterase, which destroys acetylcholine. The function of acetylcholine in the body seems to be partly connected with its rapid decomposition.²⁰

Cholinesterase is also inhibited by nicotine and other urethanes.

THE SYNTHETIC ANALOGUES OF PHYSOSTIGMINE

Stedman and Stedman²¹ in order to elucidate the relationships between the pharmacological properties of physostigmine and its chemical composition, synthesized compounds in which certain features of physostigmine molecule were produced. They found

that any substance which could be classified as a substituted phenyl of a substituted carbamic ester, or of carbamic acid itself, and which also possessed a basic group, would in general have physiological prospects like those of physostigmine. The pharmacological action of physostigmine depends on the presence in the molecule of the methyl carbamic ester group $\text{CH}_3 \text{NHCOO}$.

Aeschlimann and Reinert²² systematically investigated a series of alkyl, aryl dialkyl and aryl alkyl carbonic esters of phenols containing a basic substituent directly or indirectly attached to the phenyl radicle, for their physostigmine action. They found it to be strong in methyl, dimethyl, allyl, benzyl, and methyl phenyl carbamic esters of phenol bases, weak in ethyl- and phenyl- and absent in diethyl and diallyl-carbamic esters of the series.

The quaternary salts of the aromatic bases were more active than the hydrochlorides of the corresponding tertiary bases. When the basic radicle was in the side chain, the difference was less marked or reversed. Several related compounds which do not contain both a carbamic ester group and a basic constituent, they found to show no activity. They examined the variation in pharmacological properties on modifying the carbonic groups and the phenolic residue, and tabulated the degree of toxicity, the miotic activity, the

peristaltic action on the intestine, and the action on the frog's heart. The various properties were not always present in the same degree. A relatively slight modification of the carbamic ester group causes the miotic activity to be weakened or to disappear. The action on peristalsis is less specific than the miotic action; several simple quaternary ammonium compounds which do not contain a carbamic ester group cause as strong or stronger contractions of the living intestine as those with the groups.

The salts of weak tertiary aromatic bases are in general less toxic than the salts of strong tertiary bases and quaternary salts. In all the substances the ratio of the oral to the intravenous lethal dose is high.

Miotine, substance 28, the only synthetic salt of a tertiary base approximating physostigmine in activity was fully investigated by Stedman.²³ It can be resolved into optically active forms, of which the *laevo* is the more active miotic.

The substances 32 and 36 of the series were investigated more fully than the others by Aeschlimann and Reinert,²⁴ and substance 32 was introduced under the name of "Prostigmin" for its action on the bowel.

Toxic symptoms^{are} produced by substances 32 and 36 in rabbits, rats and mice; the first symptoms of poisoning is often a masticatory motion of the jaws

due to increased salivation. There is often a short initial period of excitement. Twitchings of the skin soon begin and the toes are spread out. Copious salivation and some defaecation occur. The respiratory rate rises and the pulse becomes slower. Respiration becomes laboured and convulsions set in. Death occurs from respiratory failure, while the heart is still beating. If death has come on slowly, oedema of the lungs is often found on post-mortem examination. In cats the same symptoms are produced with the addition of vomiting. In cats and mice the usual lethal effect of Prost²⁵igmin .5 mgn kg. injected intra-peritoneally can be counteracted by a previous injection of atropine 0.1 - 0.4 mgn Kg. If atropine is given just after the toxic effect has set in, mgn 10-20 per kg. intravenously is necessary to counteract the effect of Prostigmin mgn 0.5 - 1 per Kg body weight. In man 8 mgm of Prostignum have been given without ill effects, but in other cases alarming respiratory cases, diarrhoea and syncope have been produced by that dose.

ANTAGONISM TO CURARE

Physostigmine, Prostigmin and Miotine are all antagonists to curare while Peristaltikum, substance 36 is not.²⁶

It is of interest that prostigmin, a quaternary salt exerts an antagonistic action to curare (the

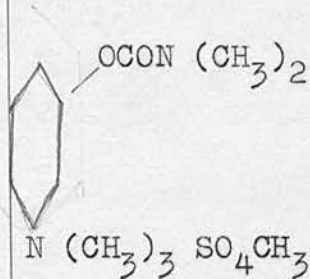
active principle of which is the quaternary base curarine) in the same way as physostigmine does. Aeschlimann²⁷ suggests that as it seems clear that quaternary compounds have an affinity for the motor nerves, Prostigmin may be selectively attached to the motor nerves, and that the carbamic ester then exerts an anti curare effect.

Stedman, Stedman, and Easson²⁸ have shown that the analogues of physostigmine prevent the hydrolysis of acetyl choline by cholinesterase.

Prostigmin

No.32

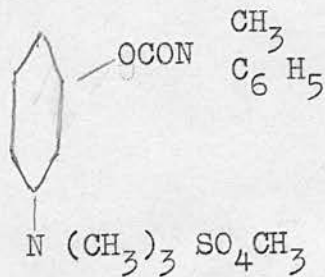
Dimethyl carbamic
ester of 3 oxy-
phenyl ammonium-
ethyl sulphate



Peristaltikum

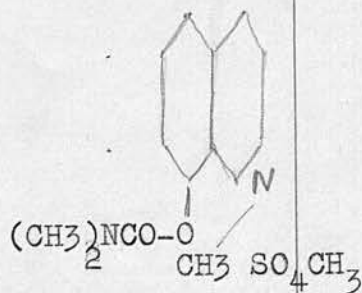
No.36

Methyl carbamic
ester of 3 oxy-
phenyl trimethyl
ammonium ethyl
sulphate



No.38

Dimethyl carbam-
ic ester of 8
oxymethyl quin-
olinium methyl
sulphate



Lethal dose
in mouse

Mgm per Kgm

Kgm per Kgm

Mgm per Kgm

Intravenous-
ly

0.5

3.5

0.5.

Orally

12.16

75

200

Miotic Action
in cat

0.5%
strong
after 30
min.

1.2%
slight
miosis

0.25 - 05%
definite
miosis
for sever-
al hours.

Isolated
rabbit
intestine

$1-2 \times 10^{-5}$
definite
increase
in tone

0.4×10^{-6}
strong
action

0.2×10^{-6}
definite
con-
traction

Isolated
frog heart

0.1%
slight
decrease
in tone

0.1% no
definite
action

Miotine

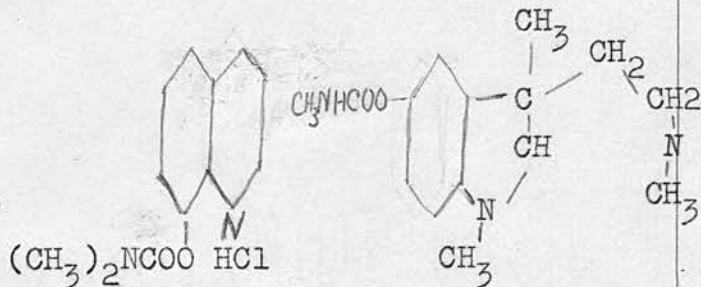
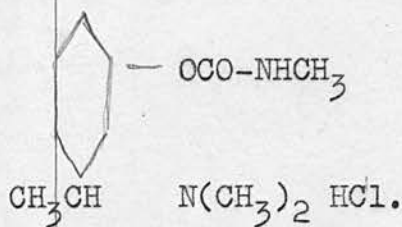
No.28

Methyl carbamic ester of a 3 hydroxyphenyl ethyl-dimethylamine hydrochloride

No.37

Dimethyl carbamic ester of 8 oxyquinoline hydrochloride

Physostigmine



Lethal dose for mouse	Mgm per Kgm	Mgm per Kgm	Mgm per Kgm
Intravenously	1.0	150	0.5
Orally	2.0	400	3
Miotic action in cat	0.1-0.5% several hours	0.5-1% definite	0.1-0.5% definite for several hours
	1-2% 24 hrs.		1-2% for 24 hours.
Isolated rabbit intestine	$0.2-0.25 \times 10^{-6}$ definite action	1×10^{-5} no definite action	$0.25-0.5 \times 10^{-6}$ contraction
Isolated frog heart	0.1% slight decrease of tone. 0.5% large decrease of tone.	-	0.1% strong decrease of tone as cessation of heats.

Caffeine in small amounts increases the height of contraction of unfatigued muscle, in large amounts it results in the liberation of too much lactic acid for the muscle to deal with by oxidation, the lactic acid coagulates the myosinogen. The caffeine does not seem to partake directly in the chemical reaction, it appears to release slowly and continuously the chemical events which normally occur only rapidly and discontinuously on stimulation. The whole curve of heat liberation in muscle after caffeine can be reproduced by applying a shock every few seconds, and so maintaining a continual release of energy.²⁹ The muscle contracture develops in an hour or two even when the muscle has only been soaked for five minutes in a caffeine solution and then removed to air.

Veratrine acts in an analogous way to caffeine but is faster and less persistent.³⁰ It liberates continuously the chain of processes normally released discontinuously by a shock or a series of shocks. The muscle contraction is greatly prolonged, the curve after a single stimulus resembling a tetanus. It was formerly believed that relaxation was prolonged, but the long contraction is now believed to be a tetanus because the ratio of heat production seems parallel to the tension and has the same value as obtains during the contraction of a tetanus.

If a normal medullated nerve laid in a solution of veratrine no effect is produced, but if it is left in nitrogen and a solution of veratrine the nerve impulse is altered, it is made to persist.

The after potential of the electrical phenomenon accompanying nerve activity is augmented and prolonged.³¹ This may have a bearing on the action of veratrine on muscle. Electromyograms of veratrinised muscle shows the usual spike belonging to the twitch followed by a potential lasting throughout the contracture. The contractile behaviour of the muscle may be secondary to an alteration of its excitatory mechanism analogous to that found in nerve. Protoveratrine and aconitine produce a prolonged after potential, much lower than that caused by veratrine. Caffeine does not prolong the after potential. Each successive stimulus to the muscle is followed by a quicker relaxation.

Paralysing alkaloids such as atropine and ergometrine produce their effects by acting on the effector cell, the muscle.³²

PATHOLOGY.

Morbid Anatomy.

The presence of lymphorrhages has been regarded as typical of myasthenia gravis. They have been found in the skeletal muscle on biopsy, and on post mortem examination at different intervals before and after the onset of rigor mortis. Their distribution in the muscle is unequal, in one part they may be numerous, in another absent. Prolonged and careful search is necessary; as many as eighty sections of muscle have been examined before a lymphorrhage has been found. This may be the reason why they have not been found in all cases of the disease. It also raises the question whether lymphorrhages might not be found in normal muscles if looked for equally carefully. Similar appearances have been described in exophthalmic goitre, and Buzzard found them in the muscles in a case of amyotrophic lateral sclerosis.

The lymphorrhages are collections of round cells with large round or slightly oval nuclei, of the same size as lymphocytes and indistinguishable from them. Sometimes a few polymorphs, plasma cells, and mast cells have been found among the lymphocytes. Often a capillary can be seen transversing the lymphorrhage or in close proximity to it. Serous exudate may be present. There are no obvious changes as a rule around the foci of cells which infiltrate the tissues in the same way as do red blood corpuscles in capillary haemorrhages, hence the

name which was given to them by Buzzard.³³ They may be invisible to the naked eye or a few m.m. across.

The fact that the lymphorrhages are not more numerous in longstanding than in recent cases of myasthenia gravis has been thought to show that they are transitory.

Buzzard describes what he considers may be a condition preceding the formation of a lymphorrhage. In the cardiac muscle of one of his cases of myasthenia gravis, he found a capillary crowded with white blood corpuscles, chiefly lymphocytes, but with no red corpuscles in it. Some of the lymphocytes had escaped into the neighbouring tissue.

The lymphorrhages have been oftenest found in the skeletal muscles perhaps because they have been most frequently looked for there, but they have also been found in the heart muscle and in many other organs. In the muscles they are found between the fibres, and in the muscular sheath, occasionally they invade the muscle fibre. They are seen better in transverse than in longitudinal sections. Neither the number nor the size of the lymphorrhages found in a muscle bears any relation to the degree to which function has been altered in that muscle. They have even been found in cases of myasthenia gravis in the muscles not affected by the disease.

Changes in the muscle fibres and sarcoplasm have been described by numerous authors, but they are much less often found than the lymphorrhages.

Buzzard found alterations in the muscle fibres

in all five of his cases. The changes were more marked in the fibres nearest to the lymphorrhages as a rule. Transverse sections showed that some of the fibres were rounded and non-angular, seeming to be swollen, larger than normal, and "paler and more yellow in hue". He recognised that such fibres could be found in normal muscles, but thought that they were more numerous in his cases. He also found fibres with altered refractile property, and occasional pericentral vacuolation or central nucleation and vacuolation.

In all his cases a few muscle fibres were abnormal, not identically, but all like those associated with an early stage of muscular atrophy, suggesting that they "would have resulted in a grave muscular degeneration if the morbid process had been continued". He thought it not surprising that a true muscular atrophy occurred in some cases.

Disappearance of transverse striation and exaggeration of longitudinal striation of the muscular fibres, variability in staining, and fatty degeneration of the sarcoplasm varying in degree from the slightest to the grossest, proliferation of the nuclei of the sarcolamme, numerous abnormally pale fibres and increase in the interstitial connective tissue have been described many times, as has simple atrophy of individual muscle fibres and bundles. The changes are always discrete and scattered irregularly through the muscle.

Bourgeois³⁴ found that some muscle fibres

contained fine granules of pigment, not massed together, and in the septa between the bundles of muscle fibres "pseudocysts" of pigmentary origin, which he thought were pigmentary products of muscle degeneration.

Glycogen granules³⁵ have been found to be increased in number and diminished. In many cases no inflammatory, degenerative or atrophic changes could be found in the muscles.

Athenasius and Marinesco³⁶ found numerous mast cells around the vessels in the muscles.

Marinesco³⁷ found dilatation and engorgement of the capillaries in the muscle, with alterations in the endothelium. He also found an unduly large number of capillaries, with numerous branches.

The Central Nervous System.

In nearly all cases no abnormality of the central nervous system can be detected.

Lymphorrhages have occasionally been described. Buzzard³⁸ found one in a posterior root ganglion, and Mandelbaum and Celler³⁹ found one in the medulla.

Chromatolysis in the anterior horn cells or intramedullary root fibres has been detected by numerous observers. Small haemorrhages have been found but can be accounted for by the terminal asphyxia which is common.

No neuroglial reaction has been described except by D. McAlpine⁴⁰ in one case.

Ependymitis has been found in several cases.

Dejerine and Thomas⁴¹ have described a slight alteration in the cortex in one case, with degeneration of the pyramidal fibres. Raymond and Alquier⁴² described numerous microscopic areas of softening chiefly in the basal ganglia in another case.

Mott and Barrada⁴³ in one case found a general diminution of the basophilic substance throughout the central nervous system, with vacuolisation and chromatolysis of nerve cells, and lipoid granules in the perivascular spaces.

These and other findings are too exceptional in cases of myasthenia gravis to have any bearing on the pathogenesis.

No abnormality in the cerebro-spinal fluid has been reported. Murri⁴⁴ found alteration in the termination of the motor nerve endings, Bourgeois⁴⁵ was unable to find any.

The Thymus.

Weigert⁴⁶ found a malignant tumour of the thymus in a case of myasthenia gravis in 1901. In the same case he found numerous foci of small lymphoid cells with a few epithelioid cells in the muscles between the fibres, and scattered over the external and internal perimysium. These he considered to be metastases. Attention was thus drawn to the thymus and abnormalities of the thymus have since often been found in myasthenia gravis, some authorities say in fifty per cent on cases. As lymphorrhages are much more often present than abnormalities of the thymus it is not likely that they are metastases.

Persistence of the thymus is common in normal persons and may be commoner than is usually believed for a close search of the mediastinum is necessary to exclude the presence of remnants.

Three kinds of thymic abnormality have been found in myasthenia gravis.

1, Simple hypertrophy, in which the histology is normal. Eosinophils may or may not be present. Normally they are present in childhood but do not persist into adult life. Hassall's corpuscles may or may not be degenerated.

2. Hypertrophy with degeneration and formation of multilocular cysts.

3. New growths, usually lymphosarcomata, occasionally rarer malignant tumours.

Alter and Osnato⁴⁷ described a case of myasthenia gravis associated with status lymphaticus. The thymus was enlarged and there were multiple thymic nodules elsewhere, the site of extreme inflammatory changes. The thyroid was also enlarged and the left lobe contained a large parathyroid. There was enlargement of the lymphatic glands generally, and extensive lymphoid infiltration and atrophy of the striated muscle fibres. The heart and aorta were hypoplastic.

The Thyroid.

Abnormalities of the thyroid are less commonly found than those of the thymus in cases of myasthenia gravis. Lymphorrhages are often present. Interstitial fibrosis and colloid degeneration with

proliferation of epithelium and formation of new vesicles were first described by Buzzard. ⁴⁸ Hypertrophy of the thyroid has been described many times, and sometimes there has been evidence of hyperecturity.

The Supra-renal Glands.

Lymphorrhages have been found, in one case causing mechanical destruction of neighbouring cells. Other abnormalities are rare.

The Pituitary.

In one case a large pituitary adenoma was found.

The Liver.

Buzzard found lymphorrhages sometimes in the portal space, sometimes in the middle of the lobule. In one case he found small areas of necrosis of the liver cells, and dilated spaces containing cells in the capsule of Glisson.

The Kidney.

Lymphorrhages have been found. Buzzard describes the lymphocytes in one case as being spread out between the tubules.

The Pancreas.

Lymphorrhages have been found here.

The lungs may show signs of bronchopneumonia. Small haemorrhages may be found on the pleura when the patient has died of asphyxia.

METABOLISM.

THE METABOLISM

Until recently most of the work on the metabolism in myasthenia gravis consisted of analyses of the blood and urine.

Creatinine plays an important part in muscle metabolism and its excretion has been much studied. Spriggs⁴⁹ found that less creatinine both absolutely and relatively to the total nitrogen was excreted. Pemberton⁵⁰ found that the excretion of creatinine might be as low as it is in cases of true muscle wasting, and that there was increased loss of calcium.

Diller and Rosenbloom⁵¹ found uric-acid and creatinine both below normal, an increased loss of calcium, and that neutral sulphur was below normal in relation to total nitrogen.

Bookman and Epstein⁵² studied the excretion of nitrogen, phosphorus, sulphur, calcium, magnesium, ammonia and creatinine in a case of myasthenia gravis at rest, during exercise, and during the administration of epinephrine, thymus, calcium, ovarian and testicular extract. They found no abnormality except that the excretion of creatinine was below normal, and that creatine was sometimes excreted.

The various substances administered by mouth made no difference.

Williams and Dyke⁵³ found creatine in the urine

of four cases of myasthenia gravis while on a creatine-creatinine free diet. They found on biopsy that the creatine in a muscle was below normal.

Bourgeois⁵⁴ found creatinine excretion above normal in three of his cases and below normal in one.

In the case of Harriet Edgeworth⁵⁵ the only positive observation as regards metabolism, was a lowered creatinine excretion, and a daily creatine Mildred Adams⁵⁶ found nitrogenous and inorganic substances to be normal in all cases before treatment. A small amount of creatine was excreted in all cases; the creatinine was perhaps slightly lower than normal.

Claude and Blanchetière⁵⁷ have found that in serious cases there is a notable diminution in the excretion of uric acid, during the remission the opposite is the case.

The Blood Calcium.

There is an extreme variability in the results got by various analytic procedures.

Markeloff, Spiller⁵⁸, Marinescô⁵⁹ and Parhon⁶⁰ found an excess of calcium in the blood, while Bookman and Epstein⁶¹, and Bourgeois⁶² found it to be normal, and Pemberton⁶³ found slight hypocalcaemia.

Lactic Acid.

Kauffmann⁶⁴ in a case of myasthenia gravis in which

the liver was diseased found a tendency to acid intoxication which he thought was due to an excess of lactic acid.

⁶⁵Boldt, and ⁶⁶Mohr have studied lactic acid in normal individuals, and find that it is increased on working days.

⁶⁷Spriggs, Bookman and ⁶⁸Epstein, and Diller and ⁶⁹Rosenbloom found no increase in lactic acid in three myasthenic cases.

Acidity and Alkali Reserve.

Bourgeois and ⁷⁰Mollaret obtained the following result:

	PH.	Alkali Reserve Total CO ₂	Alkali Reserve CO ₂ as bicarbonate.
Before fatigue	7.41	66	62.8
After fatigue	7.46	68	65

These figures are normal.

Blood glucose

Bally and Opperman found an increase, and ⁷¹Patrzek a decrease in the blood sugar.

The Blood Metabolism.

The variations found have been within the normal limits, ⁷²Keschner's figures vary from + 17% to - 11% from + 15% to - 3%.

The Chemistry of Muscle in Myasthenia Gravis.

⁷³ Nevin considers that the importance of the change in the phosphorus holding compounds during muscle contraction, especially the breakdown of creatine phosphoric acid is such that a study of their changes would give some definite indication as to the presence or not of any abnormality in the intrinsic chemical mechanism in pathological muscles. The results he obtained in a piece of rectus femoris obtained at biopsy from a case of myasthenia gravis were of the same order as in normal muscle.

	<u>Resting.</u>		<u>Contracted.</u>		<u>Recovered.</u>	
	Mg.	% Total	Mg.	% Total	Mg.	% Total
Total acid soluble phosphorus per gramme of muscle.	1.395	-	1.218	-	1.090	-
Free orthophosphate	0.150	10.7	0.443	36.3	0.135	12.4
Creatine Phosphoric acid.	0.566	40.6	0.163	13.4	0.445	40.8
Adenosine triphosphoric acid.	0.538	38.6	0.369	30.3	0.349	32.0
Soluble esters.	0.141	10.1	0.243	19.9	0.161	14.8
Insoluble esters.	0	-	0	-	0	-

He concluded that the chemical processes which accompany activity and recovery in the myasthenic muscle differ in no significant way from those which are characteristic of healthy muscle, though muscle function is grossly disturbed.

ETIOLOGY

and

PATHOGENESIS

ETIOLOGY

Myasthenia gravis is not hereditary or familial, only occasionally has the disease occurred in two members of the same family. It is commoner in women than in men, and the age of onset is usually between puberty and fifty years of age. A few cases under the age of ten have been reported. Goldflam⁷⁴ had a patient aged four years and nine months, and Kolliter one of five years. The diagnosis in the case of the child of two and a half reported by Mailhouse is doubtful. The onset has occurred at the other extreme of life, Boothby⁷⁵ had a patient of over eighty, the onset in the case of Briggles⁷⁶ was at seventy-three and Keschner⁷⁶ had a case beginning at the age of sixty-nine.

The disease is rare but not extremely rare. Cases have been reported in most of the white races.

It has been alleged that there is a congenital predisposition to the disease, and those who develop it are usually delicate and anaemic subjects but this is by no means always the case. Anomalies of development, infantilism, hypoplasia of the arteries, deformity of a cervical vertebra, facial hemiatrophy and polydactyly have been reported in association with myasthenia gravis.⁷⁷

Diseases which have been found in association

with myasthenia gravis are encephelitis lethargica⁷⁸, progressive muscular atrophy, Friedreich's ataxia, muscular dystrophy⁷⁹, sclerodermia and exophthalmic goitre.⁸⁰ Of these associations exophthalmic goitre is the most frequent; the others could be explained by coincidence.

In a considerable number of cases the symptoms have first been noticed shortly after some infectious disease⁸¹ such as influenza (Edgeworth)⁸² scarlet fever (Campbell)⁸³ typhoid fever (Sinkler)⁸⁴ diphtheria (Grund,⁸⁵ Kramer,⁸⁶ Gerson⁸⁷).

It is possible that the symptoms have merely been made worse by these infections, and so have been made manifest to the patient. Intercurrent infections such as nasal catarrh are known to make the symptoms worse. Bourgeois⁸⁸ suggests that infections may predispose to the disease by causing a lowered resistance.

Unexplained rises of temperature occur during the course of the disease in some cases. It is possible that the onset of the disease is pyrexial in some cases.

Myasthenic syndromes have been described as occurring after encephelitis lethargica by but as Mc Alpine⁸⁹ points out, most of the reported cases are either definitely encephelitis lethargica, or myasthenia gravis.

Cases having their onset during pregnancy have

been reported by Goldflam⁹⁰, Tilney⁹¹, Burr and MacCarthy⁹²,
 and Hun, Blumer and Streeter⁹³. The frequency with
 which this occurs is not greater than can be explain-
 ed by coincidence. Remissions during pregnancy
 with relapses after confinement have been described
 by Goldflam⁹⁴.

Pathogenesis

Various endocrine disturbances have been regard-
 ed as the cause of myasthenia gravis. In most cases,
 however, there is no evidence of endocrine disturb-
 ance, and when there is such evidence, different
 endocrines are involved in different cases. The
 endocrine functions of the thymus, which is most fre-
 quently enlarged are doubtful. The fact that abnor-
 mality of some endocrine is fairly often found in
 myasthenia gravis has led to the opinion that the
 endocrine system in general is affected. The good
 results obtained by the injection of suprarenal
 extract, has led to the theory that adrenal deficiency
 is the cause of the disease, though lesions of the
 suprarenals are extremely rarely found. Marinnesco
 thinks that disturbances of the sympathetic are the
 primary cause of myasthenia gravis, and that the
 endocrines, especially the suprarenal are deranged by
 this disturbance of the vegetative system.

⁹⁵
 Bourgeois thinks that as the endocrines neutralise
 the products of fatigue normally, this function must
 be over exerted in myasthenia, which may account for

the frequency of endocrine abnormalities in the disease. He also thinks that alteration in the endocrines may be a predisposing factor to the disease.

Metabolic Disorders

There is no evidence of metabolic disorder in most cases, the creatinuria frequently present is merely evidence of decreased muscular activity.

It would be difficult to account for a disorder which is asymmetrical, and which may be narrowly localised to a particular muscle for many months or even years, by a metabolic disturbance, or the formation of an endogenous poison.

Exogenous Toxaemia

Asymmetry and narrow localisation are frequently found in lesions due to infections or exogenous toxins. The relapses and remissions characteristic of the disease are also characteristic of infections, especially virus infections. The frequent onset after an infectious disease, and occasional rise of temperature during the course, are rather in favour of an infective origin of the disease.

The only constant lesions found in the muscles are the lymphorrhages, and they are not proportionate in size and number to the degree of myasthenia, and are found in muscles both at biopsy and necropsy which were clinically not myasthenic.

If they are really characteristic of myasthenia

and not to be found in normal muscles after as careful a search as is necessary to find them in myasthenic muscles, they should be of some pathogenic significance. The question arises as to whether the lymphorrhages could be regarded as inflammatory, and therefore evidence of an infection. The general opinion is that they are not inflammatory. As a rule there is no inflammatory reaction of the tissues around the lymphorrhages, serous exudation has been described however, sometimes the muscle fibres near the lymphorrhages are more degenerated than in the rest of the muscle, and sometimes a few polymorphs, mast cells, and plasma cells are present among the lymphocytes.

As the motor nerves to the voluntary muscles are cholinergic and physostigmine and its analogues inhibit the action of the esterase which destroys acetyl choline, it might be thought that in myasthenia gravis this esterase was too active, but E.A.B.Pritchard found that it was normal in amount and activity.

Substance 38, which has a more powerful inhibiting action on cholinesterase than Prostigmin, has a decidedly weaker effect on the symptoms of myasthenia gravis.

It does not seem likely that physostigmine and its allies produce their effects in myasthenia gravis simply by inhibiting cholinesterase.

The rapid spread of fatigue to the muscles generally when one group of muscles is fatigued in a case of myasthenia gravis points to the humoral spread of something generated in that group of muscles to the

others. The muscle seems to produce something during its contraction which "curarises" itself, and is transmitted by the blood stream to the other muscles. It is characteristic of curare action that it accompanies the formation of a particular structure "with a fidelity unparalleled in any of the relations between chemical constitution and physiological action." It seems probable that the myasthenic muscle forms during its contraction some readily conisable compound with a three dimensional space arrangement of its constituent groups. Most quaternary ammonium bases are of this nature, and have a curarising action. A minute amount would be enough to interfere with the physico-chemical reactions of the synthesis in which acetyl choline is held.

It is known that neurine, a quaternary ammonium base, trimethyl-irnyl ammonium hydroxide can be formed from choline in the muscles by the action of bacteria. The action of neurine is to "curarise" the striped muscles and slow the heart.

It seems possible that in myasthenia gravis a micro-organism, perhaps a virus, acts on some substance formed temporarily during muscle contraction to form a curarising quaternary ammonium base, substance x, which acts on the muscle in which it is formed, and is carried by the blood stream to the rest of the muscles. Even while the body is at rest some muscle fibres are contracting to maintain tone, so that some substance x would always be formed, but as the symptoms improve with rest, the destructive powers of the body must be supposed then to remove the

accumulation of substance x formed during exertion.

It is of interest that while physostigmine and Prostigmin antagonise curarine, and Peristaltikum does not, all three relieve the symptoms of myasthenia gravis.

It is also of interest that atropine does not affect the action of physostigmine and its analogues on the striated muscles in myasthenia gravis, but antagonises their action on smooth muscle; though both the motor nerves to striated muscle and the parasympathetic post-ganglionic fibres are cholinergic.

SIGNS AND SYMPTOMS

AND

DIAGNOSIS



Signs and Symptoms.

The disease is characterised by a variable weakness and undue fatigability of the striated muscles. No other symptoms are constantly present in myasthenia gravis.

The weakness may be slight or so great that a muscle cannot be moved voluntarily and will not react to Faradism. The response to Galvanism is never lost. The rapidity with which fatigue can be induced varies from undue fatigue after considerable prolonged exertion, such as a walk of several miles, to inability to repeat a movement once or twice. The degree of weakness and undue fatigability are clinically proportionate to each other. Both are increased by exertion and emotion, and lessened or removed for a time by rest. If one group of muscles is fatigued by exertion, the other muscles become fatigued also.

Any striped muscle in the body may be affected, but the incidence of the disease is greatest on the muscles which are innervated from the brain stem, they rarely, if ever, escape throughout the course of the disease. Weakness and undue fatigability are often first noticed in those muscles which are most used.

As a rule, the corresponding muscles on each side of the body are affected, but to a degree differing on the two sides. Ptosis is often unilateral. The incidence may be said to be

unequally symmetrical.

Permanent paralysis is said to occur in some of the chronic cases, and to affect chiefly the ocular and facial muscles, but even when a muscle cannot be moved voluntarily, does not react to Faradism and does not improve after rest, complete recovery has occurred. Severe ptosis which has been constantly present for many years has been completely removed for a time by an injection of Prostigmin. It seems questionable whether permanent paralysis ever does occur, though it may be long impossible for the patient to be able to move a particular muscle.

The Onset.

Usually the patient can remember the hour when the first symptom became apparent. Most often ptosis or diplopia is noticed, or some action becomes impossible, something may be dropped from the hands, for instance, or the leg may give way and the patient fall. Occasionally there is general undue fatigability at the onset. Not uncommonly the disease shows itself soon after a pyrexial illness such as influenza.

One region only may be involved for months, and, in a few cases, for many years. Other muscles may become affected rapidly or slowly, usually in a series of exacerbations rather than a steady increase.

The Course.

Remissions are characteristic of the disease. They may be complete or slight, and may last for some

weeks or for several years. The incidence of the disorder on various regions varies somewhat from time to time. The intensity of the symptoms varies from day to day and week to week. It is increased by intercurrent infections such as nasal catarrh. Over exertion one day, will make the symptoms worse the next. Extremities of heat and cold are injurious. In some cases the symptoms are always worse during the menstrual periods, in others no difference is appreciable. During pregnancy there is sometimes an amelioration. The duration of the disease varies from two weeks to over twenty years.

Death results from cardiac or respiratory failure. Cardiac failure may come on suddenly without previous distress, the patient dying in a minute or two, apparently from syncope, or death may occur during an attack of tachycardia.

Spontaneous respiratory crises are a common cause of death, which may be also brought about by exhaustion of the respiratory muscles from over exertion, sometimes due to an emotional outburst.

Respiratory infections are commonly fatal owing to failure of the respiratory muscles. Aspiration pneumonia is frequent. Death also occurs during the choking fits caused by difficulty in swallowing.

Individual Symptoms.

The Skeletal Muscles.

In a few recorded cases ocular symptoms

only have occurred, and it is extremely rare for them to be absent.

Ptosis, the most constant symptom in myasthenia gravis is almost invariably present, it is often the first symptom to appear, and it may remain the only symptom for months. It is never equal on both sides, and it may be entirely unilateral. The left eyelid is affected earlier and more severely than the right in the great majority of cases. There is a tendency for the same eyelid to be affected, when myasthenic symptoms return after a complete remission.

The degree of severity varies from slight drooping of the eyelid towards the end of the day, or after repeated upward movements of the eyelid, to complete closure of the eye even on waking in the morning. Use of other muscles or emotion, increases ptosis, or produces it when it is not constantly present. The severity of the ptosis is not necessarily proportionate to the severity of the other symptoms.

A characteristic attitude of myasthenics, holding the head backwards, is adopted to enable the patient to see in front of him when the ptosis prevents this. In some case he has to hold the eyelid open.

Rarely there is retraction of the upper eyelids, which may lag behind the eyeballs when the patient looks down.

The external ocular muscles are affected in

the majority of cases of myasthenia gravis, they are affected asymmetrically and the resulting diplopia is sometimes the first symptom of the disease. The weakness and fatigability may be slight so that the patient only has diplopia at the end of the day, or there may be complete external ophthalmoplegia. The degree to which each muscle is affected varies from time to time during the day probably according to the amount of exercise it has had. The weakest muscles in the morning may not be the weakest in the evening.

The internal ocular muscles are only exceptionally affected the pupils may react more and more sluggishly on repeated excitation, but the reflex is never abolished.

The muscles of the face are almost always affected. Often all the facial muscles are toneless, so that the whole face seems to droop and the naso - labial folds are exaggerated, giving a typical expression, the myasthenic mask. This is accentuated towards the end of the day and after exertion and emotion. It can be well seen in photographs. Various muscles are more severely affected in different cases. The orbicularis palpebrarum is very frequently weak, the eye cannot be closed against resistance.

Weakness of the orbicularis oris interferes with blowing and whistling, and speech. When the weakness is extreme the patient may have to hold the lower lip up in order to speak. The typical nasal or snarling smile of the myasthenic is due to the

weakness of the zygomatics preventing the corners of the mouth being drawn back. The furrow of the smile is above the upper lip.

The muscles of the lower jaw, masseters, pteryzoids, and buccinators are frequently affected so that chewing is made difficult or impossible. The weakness is often so great that the myasthenic has to keep the mouth shut by propping up the chin with his hand.

The ptosis is compensated for by contracting the occipito-frontalis and so wrinkling the brow, unless that muscle is too weak for that to be possible as is frequently the case. The eyebrows are elevated also by the action of the levator palpebrae superioris unless these muscles are also too weak.

The tongue is frequently so weak that it cannot be protruded or thrust into the cheek normally. Movements are sometimes so weak that even a grape cannot be crushed against the hard palate. These movements of the tongue are not equally severely affected.

Difficulty in swallowing results from weakness of the soft palate, which allows liquids to regurgitate through the nose; and from weakness of the muscles of the tongue, the glossopalatine and the constrictors of the pharynx. Food seems to stick in the throat, so that meals have to be eaten slowly. If the muscles closing the entrance to the larynx are weak, food may pass through it, and aspiration pneumonia result. Difficulty in swallowing is always

worse towards the end of a meal and towards the end of the day. Malnutrition is apt to result when the difficulty is great.

The voice is given a nasal tone when the soft palate is weak, and when the laryngeal muscles are involved it is soft, and aphonia may develop, especially after talking for a time. After a rest the voice improves. Weakness and fatigability of the muscles has been observed on laryngoscopic examination.

The muscles of the back of the neck are very frequently involved, the head tending to fall forwards so that the patient has to support it with the hand.

The shoulder girdle muscles are very commonly affected, so that when the arms are held out on a level with the shoulders they slowly sink. It is often impossible for the patient to raise her arms above her head.

The muscles of the arms and hands are often involved. The flexors of the fingers may be so weak that it is impossible to hold anything in the hands, and the fingers may be kept habitually flexed owing to weakness of the extensors.

The muscles of the trunk and those of the pelvic girdle are often affected, though less commonly than those of the shoulder girdle, and they tend to be affected later in the course of the illness. When the patient walks she sways from side to side, either at once or after a little distance according to the severity of the affection. Standing is harder than walking because it is more difficult to

balance. It may be difficult or impossible for the patient to raise herself up or to turn over in bed, when the paraspinal and abdominal muscles are affected.

The leg muscles are usually involved still later in the course of the illness, they may give way so that the patient falls, or it may be found impossible to lift the legs enough to ascend stairs or to get on to a 'bus.

In some cases there is a general weakness of the skeletal muscles, without those innervated from the bulb being picked out. "Slipping" of joints owing to weakness of the muscles supporting them has been described, it does not occur during a remission.⁹⁶

The respiratory muscles are affected less frequently than the other skeletal muscles, and only in severe cases of the disease. They may be affected soon after the onset or not for years. Remissions may occur.

Rapid, shallow breathing due to weakness of these muscles makes respiratory infections more dangerous, and bronchopneumonia is a common cause of death in myasthenia gravis.

Paroxysms of dyspnoea, respiratory crises, occur, coming on suddenly at first after exertion or excitement, later spontaneously. Suddenly the patient feels a constriction of the thorax, the respiration becomes rapid and shallow, and too weak to draw enough air into the lungs. The tongue may fall back occluding the air passages. Cyanosis may occur. Tenaceous mucus is secreted and may have to

be removed by hand.

These attacks may last for a few minutes and recur frequently or they may last for several hours. They are a common cause of death.

The Tendon Reflexes.

Usually the tendon reflexes are present and they can be diminished or abolished by repeated percussion, returning after a rest. They may be sluggish, and sometimes they cannot be elicited, but it is rare for them to be constantly absent.

Muscular Tonus.

Tonus is often diminished in the muscles of the face, giving the typical expression, the myasthenic mask. In the muscles of the trunk and limbs it is not often noticeably diminished except in very severe cases.

Trophic Changes.

In cases with great difficulty in swallowing the muscles share in the general malnutrition, and when a muscle has been disused for a long time it atrophies to some extent. In the great majority of cases of myasthenia gravis, wasting other than this does not occur, but occasionally localised atrophy of particular muscles has been noted.

The Temperature.

Pyrexia sometimes occurs during exacerbations of the disease especially if there are respiratory crises. The temperature may rise to 104°F . Temperatures of 99°F . are of common occurrence apart

from exacerbations.

The Cardiovascular System.

The pulse is often slightly more rapid than normal. In a few cases it has been slower but this may be coincidence merely. Paroxysms of tachycardia occur in some cases, usually after other severe symptoms have been present for some time, but occasionally, as in the case of Dr. Harriet Edgeworth⁹⁷ at the onset of the disease. Death often occurs during one of these paroxysms. Sometimes it occurs apparently from syncope without previous symptoms referable to the heart. Probably the cardiac muscle is involved in the disease.

The Digestive System.

Constipation is common in severe cases of myasthenia gravis. It has been ascribed to the involvement of the plain muscle of the bowel but this is uncertain.

When chewing and swallowing are affected, the intake is small, and consists chiefly of food which leaves little residue to be evacuated. In some cases weakness and undue fatigability of the skeletal muscles cause dyschezia. Incontinence due to weakness of the sphincter ani does not appear to occur.

Urinary Symptoms.

Micturition is nearly always normal in myasthenia gravis. A few cases with urinary incontinence have been described, and this has been attributed to involvement of the striated muscles of the vesical sphincter.

Sensory Symptoms.

A heavy feeling in the affected muscles is usual, varying with the degree of weakness, and occasionally the muscles feel stiff. Slight aching pains are not uncommon. In some cases severe pains have been described, but this is exceptional, and it is not certain that they are due to the disease.

Diminution in cutaneous sensibility has been described in a few cases, but has not been generally recognised as a symptom of myasthenia gravis.

Psychic Symptoms.

The mind remains clear throughout the illness. Depression especially in severe cases is the natural result of the patient's condition on his mind, there is no evidence that it is directly due to the disease.

In some cases apathy and torpor have been described, and attributed to the inclusion of the mind in the general asthenia. Apathy as a result of despair might well be the reaction of certain temperaments to the symptoms of myasthenia gravis at its worst.

In mentally unstable subjects ideas of persecution may arise, the symptoms of the disease being the exciting cause.

Diagnosis.

The rarity of the disease and the disappearance of the symptoms after a rest makes it one which is frequently not recognised for a long time after the onset, though the clinical picture is so distinctive that the diagnosis is easy in most cases.

⁹⁸ Boothby gives figures showing the interval between the onset and the correct diagnosis in twenty-two cases of myasthenia gravis.

Number of cases. Interval between Onset and Diagnosis.

1	2 weeks.
3	4 weeks.
1	4 months.
1	6 months.
1	1 year.
4	2 years.
3	3 years.
3	4 years.
2	5 years.
1	6 years.
1	8 years.
1	15 years.

⁹⁹ Karl Briegleb is of the opinion that the diagnosis is frequently missed in Germany, and that the disease is not very rare.

Hysteria or malingering may be suspected because the weakness and undue fatigability are temporarily so much ameliorated by a short rest, that they may not be apparent when the patient is being

examined. This happened in a case described by Clifford Allbutt. A young girl complained of weakness and difficulty in moving, but on examination he could find no abnormality and told the mother so. Soon after he had left the house, he was called back to find the girl dead. An outburst of passionate weeping after a scolding from her mother had so exhausted the respiratory muscles that they failed. In the case of Harriet Edgeworth¹⁰⁰ the diagnosis was delayed by the fact that on two occasions the symptoms disappeared because she rested for an hour or so before examination.

When the weakness occurs first in the muscles innervated from the cord, the diagnosis is particularly difficult, especially as this weakness may follow an infectious disease, such as influenza, and be attributed to it. If myasthenia gravis is thought of, however, the diagnosis can be made by eliciting the undue fatigability by exercising the muscle complained of.

Some cases of myasthenia gravis are seen first by an ophthalmologist because of the diplopia. Abrahams¹⁰¹ on testing for heterophoria found that in myasthenia gravis the external ocular muscles behaved as they do in no other condition. They did not appear to be weak but relaxation after contraction was unduly slow. He thinks that this, as well as the extreme variability of the diplopia is of diagnostic value and comes to the conclusion that the muscles in myasthenia gravis are not truly weak. Fatigued

muscle relaxes more slowly than unfatigued muscle however, and Abrahams' findings can be explained by the behaviour of myasthenic muscle like fatigued muscle. The slowness of relaxation would be more readily appreciable by his methods than the weakness.

A history of ptosis or diplopia, absent in the mornings and coming on during the day is diagnostic of myasthenia gravis, distinguishing it from encephalitis, in which a typical ocular paralyses like those found in myasthenia gravis, are particularly apt to occur, syphilis, progressive nuclear ophthalmoplegia, congenital ptosis, and disseminated sclerosis, in which diplopia may be the first symptom.

Polyneuritis in mild cases may be mistaken for myasthenia gravis. Negro¹⁰² has described such cases of polyneuritis as a particular kind of myasthenia gravis.

Landry's paralyses with attacks of suffocation may suggest the respiratory crises of myasthenia gravis.

Botulism can be distinguished by finding the cause.

None of these diseases show the variability of the symptoms and improvement after rest of myasthenia gravis.

In Addison's disease the fatigability and asthenia are constant but Claude¹⁰³ thinks that there are transition stages between adrenal insufficiency and myasthenia gravis.

Garlier's disease is found in Switzerland. The usual troubles are like those in myasthenia but

the muscles of the face are rarely affected, and the flexors are more affected than the extensors. The symptoms last a few minutes and come on ten or twenty times a day.

Kubisagori is a disease occurring in Japan among workers in rice fields who have to bend towards the ground. It is characterised by paralysis lasting 10 - 15 minutes, disappearing on resting and reappearing when the original position is resumed. There is hyperaemia of the optic disc and indistinctness of objects seen which do not occur in myasthenia gravis.

In atypical cases of myasthenia gravis, such as the one described by Nevin,¹⁰⁴ in which there were, for years, attacks of paralysis lasting for a few days, with intervals of complete recovery, before the course of the disease became more usual, the diagnosis is difficult.

It may also be difficult where there is some other disease as well as myasthenia gravis.

Exophthalmic goitre not infrequently, encephalitis lethargica, progressive muscular atrophy and muscular dystrophy occasionally coexist with myasthenia gravis.

Jolly's myasthenic reaction may give some help in diagnosis but it cannot always be elicited in myasthenia gravis and sometimes is given in other conditions.

The use of ephedrine in diagnosis was suggested by Harriet Edgeworth; its effect is much less than that of Prostigmin and more difficult to estimate.

Prostigmin has a stimulating effect on the motor "nerve endings" generally; cases of Bell's palsy and

traumatic neuritis which are recovering, in particular, are improved for a short time by an injection, but a dramatic amelioration is only produced in myasthenia gravis. This specific effect could quite well be used for diagnostic purposes.

ELECTRICAL REACTIONS

OF

MUSCLES.

THE ELECTRICAL REACTIONS OF MUSCLES IN
MYASTHENIA GRAVIS

In 1895 Jolly¹⁰⁵ described what he called the Myasthenic reaction, which, he believed, occurred only in myasthenia gravis. He found that during stimulation of the nerves or muscles by tetanising faradic currents, repeated at intervals of seconds, the muscular contractions became weaker with each stimulation and eventually failed, but that after a short rest the muscle regained its normal excitability. He also found that if the current was applied continuously from a quarter to a whole minute, the contraction uniformly diminished and sooner or later, according to the strength of the stimulation, disappeared. After a minutes rest the same procedure could be repeated.

The myasthenic reaction can be obtained by using any kind of electric stimulation, tetanic faradising currents condenser discharges, or even the galvanic current, provided the intervals between the contractions are short enough. If the intervals are not short enough, the reaction may not be obtained when the myasthenia is slight. There is disagreement about the possibility of obtaining the myasthenic reaction with the galvanic current. Jolly thought it could not be obtained, but others have been able to elicit it. In severe myasthenia, the muscle may not have time to recover between the

the stimuli. When the alternating galvanic current is used, there is always time for recovery between the stimuli, so that the myasthenic reaction does not appear.

In some cases of myasthenia gravis the myasthenic reaction has not been elicited. Bourgeois¹⁰⁶ thinks that it can almost always be elicited in myasthenia gravis if the tetanising faradic current is used in sufficient intensity for a sufficiently long time, and the electrode is not allowed to move. Failures to elicit it he attributes to errors in technique as a rule.

In a case of myasthenia he found that after a few minutes stimulation with the continuous tetanising faradic current, the muscle becomes progressively weaker and even completely relaxed. With the interrupted current the height of the contraction became progressively less, and eventually, instead of a tetanus, a simple twitch only occurred. The twitch progressively diminished in height till the muscle no longer responded at all. If a rest of about a second was allowed, a tetanus was obtained again, and on repeating the procedure a similar succession of events occurred. When the height of the contraction was diminishing the initial height could be required by augmenting the intensity of the stimulus. He regards the myasthenic reaction as a fatigue reaction. In a normal subject he

found that no change in the contraction was produced by stimulating a muscle or its motor nerve with the tetanising faradic current, whether continuous or interrupted for an hour, when the muscle was not doing external mechanical work. When mechanical work is done the classical curves of fatigue can be shown, the contraction becoming progressively slower and diminished in height, and the excitability less.

More of the fibres of a muscle are contracted when external mechanical work is done, they have, therefore, less time to recover from fatigue.

In various pathological states fatigue is more readily produced than in normal conditions. Before Jolly discovered the reaction in myasthenia gravis, which he, believing it to be specific, named the myasthenic reaction, Brenner, Benedict and Erb had occasionally found it in various maladies such as poliomyelitis, hemiplegia and Parkinsonism. It has been elicited in many different conditions since. Markeloff¹⁰⁷ found it in a case of familial periodic paralysis. Salmon¹⁰⁸ elicited it in hysteria, traumatic neurosis, exophthalmic goitre and angioneurotic oedema. Kortner found it in carbon disulphide poisoning, and Mayer Gottlieb in veratrine poisoning. Bohm¹⁰⁹ elicited it in muscles poisoned by protoveratrine. Marinesco¹¹⁰ obtained it in muscles when the venous return was obstructed

and also when the arterial flow was obstructed. Keschner doubts whether the reaction obtained in many of these conditions is the true myasthenic reaction, in others he thinks the conditions mentioned were complications of true myasthenia gravis. Bourgeois¹¹² thinks that the myasthenic reaction can be obtained in many other conditions, but that it is much more frequently found in myasthenia gravis than in any other condition.

The myasthenic reaction is not always most marked on those muscles which are most affected by myasthenia gravis. Bourguignon¹¹³ explains this by saying that, as a rule only some of the fibres of a muscle are involved, and if the great majority of the muscle fibres are severely affected, they cease to contract so soon after stimulation is begun, that the loss is not noticed and the reaction is considered to be normal. If the rapid diminution in the height of the tetanus is noticed, the myasthenic reaction may be considered to be slight, because the diminution does not recur, owing to the non-recovery of severely affected fibres. The reaction may be considered well marked if the fibres are slightly affected, so that the fatigability is longer in appearing, and therefore more noticeable.

Pritchard¹¹⁴ using condenser discharges varying from 5-900 per second stimulated the ulnar nerve in a normal and in a myasthenic patient, and recorded

the resulting movements of the fifth finger at the metacarpophalangeal joint.

He found that in the normal person a single condenser discharge gave a single isometric twitch, while a series of discharges at frequencies up to 500 per second gave a tetanic contraction in which the steeply rising curve of tension increase was followed by a horizontal plateau of maintained tension at the same height.

In the myasthenic patient he obtained the following results.

1. The simple twitch following a simple stimulus was like that obtained in a normal person, but repeated twitches fell off rapidly in the way characteristic of myasthenia.

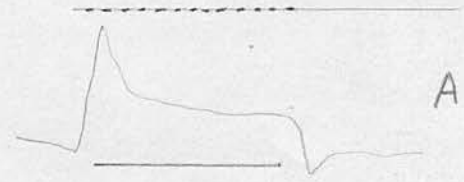
2. With brief (1-5 records) periods of repetitive stimulation the curves of tetanic contraction show a change in general form as the frequency of repetition is increased.

With low rates (40 per second) the curve is like that obtained from a normal person, when the frequency is increased to 80 per second, after the initial steep rise, the curve falls slightly before becoming horizontal. As the frequency is progressively increased the maximal height initially obtained remains unaltered, but the drop to the plateau becomes progressively greater, till at a frequency of

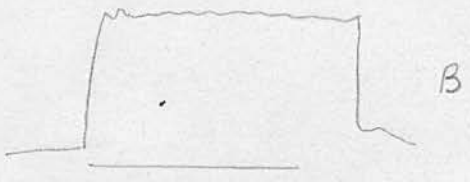
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500 per second, in some cases it is only just above the base line, and less than $\frac{1}{8}$ of the height of the original contraction.

A. Curve obtained from myasthenic muscle



B. Curve obtained from normal muscle



After an injection of Prostigmin the myasthenic muscle gives a normal curve

Time marker $\frac{1}{10}$ record
Frequency 900 per second

Curves with a form like this have been obtained in no other condition than myasthenia gravis.

Fritchard considers that the form shows that the site of the disturbance is at the "myoneural junction."

ACTION CURRENTS

The action currents in normal and myasthenic muscles have been studied.

¹¹⁵Piper using normal muscle found that in fatigue there was a diminution in the number of the diphasic oscillations in the string of the galvanometer, produced by action currents in the muscle. In a healthy non-fatigued muscle the number of oscillations is 50 a second, in fatigue it falls to 30 or even 20 oscillations a second. "It seems as

if all the impulses transmitted by the nerve do not reach the muscle." Athanasii and Harrison had reported that the action currents in myasthenia gravis were smaller than normal, and this has been confirmed by many observers.

Herzog¹¹⁵ found no other alteration than this in the electromyogram in myasthenia, the number of oscillations were not diminished. Comparing his results with those of Piper in normal muscle, he concluded that fatigue in myasthenia gravis was essentially different from fatigue in a normal person. He considered that fatigue in myasthenia began in the muscle, whereas in the normal subject it began in the nervous system. Woolf, Kleitman and Cobb¹¹⁷ found that in the electromyogram of myasthenia gravis the only change was of amplitude which was small in the beginning increased during work at first and then diminished. When a healthy muscle was fatigued the frequency became less and the amplitude greater; these changes have been shown to result from a greater degree of synchronism of the muscle units and a greater degree of volleying of the innervation impulses, and are attributed to a central nervous mechanism, rather than the peripheral neuro-muscular or muscular apparatus. Bourgeois¹¹⁸ found that the myograms produced by using Marey's tambour on the biceps muscle were more regular in myasthenics than in normal subjects. He

found that the electromyograms of fatigued myasthenic muscles are superimposable on those of fatigued healthy muscle. He did not find that in fatigue, either of a healthy or myasthenic muscle that the rhythm was less than about 50 a second, in both, the amplitude was diminished. He thinks that this leads to the conclusion that fatigue in a myasthenia is of the same nature as physiological fatigue.

The difference, when it exists, between the electromyogram of fatigued myasthenic, and fatigued healthy muscle could be explained by fatigue occurring at the "myoneural junction" and at the anterior horn cell, respectively.

CHRONAXIE IN MYASTHENIA GRAVIS

The drawback to the use of chronaxie in clinical work is the difficulty of measuring it exactly. G. Bourguignon¹¹⁹ derived a way of measuring the chronaxie of muscle in men which he thought was as accurate as the measurement on muscle nerve preparations. He found that fatigue produced an augmentation of the chronaxie of the motor point in the muscle to two or three times the normal. On resting, the normal muscle regained its normal chronaxie. The chronaxie of nerve did not vary. With Bourgeois he measured the chronaxies in series in the muscles in cases of myasthenia gravis. The initial chronaxie depended on the

general state of the patient as regards fatigue, often it was normal. They passed a tetanising faradic current and then stimulated the motor point of the muscle at intervals of two seconds, estimating the chronaxie each time for about half an hour. The chronaxie rose rapidly at first, then fell to normal and rose again. He interprets this observation by concluding that the tetanising current fatigued many fibres, so that their chronaxie increased till they became inexcitable, and the chronaxie appeared to be normal because other fibres which had not been stimulated were responding. In their turn these fibres were fatigued by the stimuli at intervals of two seconds and the chronaxie rose again. When they omitted the tetanising faradic current, but used stimuli at intervals of two seconds, they found that the chronaxie rose more slowly, then fell below the initial level, before returning to it. The fibres were less fatigued and remained excitable longer; when normal chronaxie returned they thought it was because other fibres previously at rest were stimulated.

When five minutes rest was allowed between the stimuli the chronaxie did not rise.

CASES

Mrs. M.-Aged 56.

History.

Fourteen years ago the left eyelid drooped and there was some weakness of the arms, worse after exertion and towards the end of the day. This lasted for six months and was evidently a mild attack of myasthenia gravis. She was at work the whole time and had no medical attention.

Four years ago she had a gastric ulcer which was treated medically. Two years ago she had neuritis in the left arm, and seven months ago she had non-specific infective arthritis.

Present Attack.

Towards the end of February 1934, she found she was unable to hold her shopping bag, and that when she knelt to do the hearth her head fell forwards. There was pain as well as weakness. After 18th March 1934, she had to remain in bed, and had difficulty in sitting up, a few days later her jaw began to drop so that she had to hold it up with her hand, and her left eyelid began to droop at the same time. Speech became indistinct after a few words, swallowing was slow and fluid sometimes regurgitated through her nose. On 27th March she was unable to lift her arms above her head, and a few days later, the middle and ring fingers of both hands became very weak. All the symptoms became much worse when she was excited. They were worse towards the end of the day, and

improved after a rest. Constipation was troublesome. She was depressed, and later said she did not remember much about this period of her illness.

On 9th April there was left ptosis, extreme weakness of the orbicularis oculi and some difficulty in convergence. There was marked weakness of the masseters and the temporals, some weakness of the sternomastoid, and the muscles of the shoulder girdle, and of the flexors of the middle and ring fingers of both sides. Speech was indistinct, swallowing slow, with regurgitation through the nose towards the end of the meal. The tendon jerks were all present. There was no wasting, no sensory disturbances, and no other physical signs in the nervous system. The tonsils were unhealthy. The "myasthenic" reaction was obtained in the left deltoid, the masseters did not respond at all.

Radiograms taken on 18th April, 1934, showed no evidence of enlargement of the thymus. There were opacities in the upper zones of both lungs, showing the presence of chronic tuberculous lesions, probably inactive.

At 11 a.m. on 11th April, 1934 a hypodermic injection of physostigmine salicylate gr.1/80 was given. In about forty-five minutes the left eyelid "went up", the jaw dropped rather less, but was still very weak, the arms could be raised above the head several times, speech became distinct, swallowing was less slow, and there was no regurgitation through the nose. The patient said she felt less heavy.

This effect lasted for two to four hours and wore off gradually. There was no nausea, vomiting, colic or faintness. Next day and on the three following days the injection was repeated with the same effect. The masseters responded enough to Faradism after an injection to raise the jaw slightly. The blood pressure and pulse rate were the same before and after an injection. No miosis was produced. On 14th April and 20th April cinema films were made showing the patient before and after an injection.

Given by the mouth physostigmine salicylate gr.1/60 produced no obvious effect, but gr.1/50 produced a slight effect in an hour. Daily injections of physostigmine gr.1/60 or 1/50 were continued. The effect of gr.1/50 was slightly greater than that of gr.1/60 and it lasted from two to five hours.

The effects were not quite uniform. On visiting days when the symptoms were always worse the injections made little or no difference to them, and occasionally on other days the effect was slight or delayed for no apparent reason. One injection of gr. 1/45, given on a visiting day made the patient feel faint and trembly, her "inside seemed all on the work" and she "felt as if something was going to happen". The effect of this injection was greater than usual and lasted for six to seven hours.

While the symptoms were severe the injections were given an hour before the principal meal, when improvement had begun they were given in the afternoon so that she could dress herself. On three

occasions she had two injections a day.

On 16th June an injection of l.c.c.(0.5mgm.) of "Prostigmin" (Hoffmann-Le Roche) was given. This is a synthetic analogue to physostigmine and has similar actions but depresses the heart muscle less. It was introduced for the treatment of paralytic ileus. The effect on the myasthenic symptoms was like that of physostigmine gr.1/60, coming on and lasting about the same time.

With the exception of thirteen days the patient had daily injections of physostigmine gr.1/60 or 1/50, or Prostigmin lcc, from 11th April to 24th July. She had fifty-seven injections of physostigmine gr.1/60, nineteen of gr.1/50, two of gr.1/45 and eighteen of Prostigmin.

Atropine gr.1/100 was given with the injection of "Prostigmin" on two occasions. It made no difference to the effect on the myasthenic symptoms.

<u>Date.</u>	<u>Injections.</u>	<u>Results.</u>
16.4.34	Distilled Water lcc.	None.
17.4.34	Pilocarpine Nitrate gr.1/20	Sweating and salivation.
21.4.34	Strychnine gr.1/30	Tight feeling in muscles.
1.5.34	Adrenalin m. \bar{v}	Palpitation.
11.5.34	Acetyl Choline .05gm.	None.
12.5.34	Ephedrine gr.1/2	None.
27.5.34	Acetyl Choline 0.1gm.	None.
16.8.34	Femergin Tab. I.	Headache.

On 15.10.34 Tr. Veratrine m.30 by mouth was given at 11.50 a.m. At 12.50 p.m. the patient was able to

raise her arms slightly better than before.

No injections were given on:-

27.4.34

23.5.34

24.5.34

26.5.34

19.6.34

Towards the end of May the patient complained of a feeling of nausea, and loss of appetite, and the injections were stopped for four days. These symptoms did not improve till after the injections had been recommenced. It is doubtful whether they were due to the repeated injections of physostigmine.

In the beginning of June definite improvement in the myasthenic symptoms was noted. For the first time the patient felt as if "elastic were at the back of them, drawing them up." The tongue felt "short" and the frenulum seemed to drag. The symptoms continued steadily to improve and by 24th July they were so slight that regular injections were stopped.

On 18th August the patient was discharged. The Ptosis and dropping of jaw had gone, there was no difficulty in speech or swallowing. She sometimes needed help in dressing herself and was unable to make her own bed, otherwise she could do everything she wanted to do. She had gained one stone in weight.

Since her discharge the patient has reported every two months. There has been no return of the symptoms, and there is now only a slight weakness of the back.

Miss C. Aged 40.

History Apart from scarlet fever and diphtheria at the age of six the patient had always been well until the onset of the present illness. In February 1928 the arms became weak and easily tired. She was unable to raise them above her head. This weakness and fatigability of the arms increased till one day she dropped something which she was carrying in her right hand because she could no longer hold it. Diplopia began about three months later, and soon after that the upper left lid used to droop at night. She continued her work as a parlourmaid though she could only do a little at a time. Speech became rather indistinct if she talked much. In July 1929 she was admitted to the Middlesex Hospital, while there, the symptoms improved a little and she was sent to a Convalescent Home till September when she went back to her work. She remained at work, though she could only do a little, such as dusting and answering the door, till January 1930 when the symptoms became rather worse and she was readmitted to the Middlesex Hospital where she had deep x'ray therapy over the thymus. Again she improved a little and was sent to a Convalescent Home in May. On her return, her legs gave way while she was at the railway station, and she was readmitted to the Middlesex Hospital. Within a month she had improved

appreciably and she was discharged to a Hostel. In September 1930 she went back to work as a parlourmaid. The arms were weak, the legs had improved, but she could only walk short distances. Diplopia continued. She only did very light work. In January 1931 she was readmitted to the Middlesex Hospital. In April swallowing became difficult and fluids sometimes regurgitated through the nose at the evening meal. While in the Hospital she was treated with ephedrine gr. $\frac{1}{2}$ three times a day with benefit. Whenever the ephedrine was stopped the symptoms became worse. She improved so much that she was able to go back to light work. Diplopia continued, she was still unable to raise her arms above her head, and she could only walk for short distances. Swallowing was only difficult when she was tired. She remained at light work for two years taking ephedrine gr. i three times a day all the time.

In September 1933 she had to do some extra work which tired her so much that she felt she could not carry on, and she was readmitted to the Middlesex Hospital. She was treated with glycine without improvement, and then with glycine and ephedrine, which helped her a little, but she did not improve as much as before. She was transferred to St. Giles' Hospital and thence to St. Benedicts. Ephedrine was discontinued but the symptoms remained about the same till September 1934 when she became much worse. The back muscles now became weak, and she could only walk

for a few steps unsteadily. Swallowing became more difficult, and fluids regurgitated through the nose. Speech became slow and indistinct after a few sentences. She was depressed, and did not care whether she was alive or dead. On 24th October she was transferred to St. Alfege's Hospital.

Condition on admission 24.10.34

The patient was somewhat undernourished. There was unequal ptosis, the left eyelid drooping more than the right, and bilateral external ophthalmoplegia. The muscles of the upper extremities especially those of the shoulder girdle, and the flexors of the fingers were very weak, more so on the left than on the right side. There was weakness of the muscles of the lower part of the back and of the lower extremities. The tendon jerks could not be elicited in the arms or the legs.

The thyroid was enlarged but there were no symptoms of hyperthyroidism. There were no other physical signs. A radiogram showed no evidence of enlargement of the thymus.

The patient complained of constant diplopia even on waking in the morning, and of difficulty in swallowing, after a few mouthfuls fluid regurgitated through the nose. She was unable to feed herself throughout a meal because of the fatigability of her arms. Raising herself up in bed and standing were difficult. She could only walk for a few steps slowly and unsteadily.

All the symptoms became worse as the day

wore on, and after exertion. When she tried to walk both eyelids drooped and her speech became slower. Most of the time she would lie limply in bed, not taking much notice of anything. Constipation was troublesome.

Treatment.

On 24.10.34 at 12.10 p.m. a hypodermic injection of Prostigmin 2 c.c. (1.0mgm.) and Atropine gr.1/100 was given. At 1 p.m. the grip was found to be decidedly stronger and the patient was able to eat her food more quickly than usual and without regurgitation. She felt less heavy.

Daily injections of Prostigmin 0.1mgm. and Atropine gr.1/100 given half an hour before the principal meal were continued. After the first few days, when she became more confident, the patient found she could walk quite well for a short distance without support for from two to four hours after the injection. There was no colic, vomiting or other ill effect, and the patient felt much better than before the injections were begun. No dryness of the mouth was caused by the atropine.

On 10.11.34 and successive days the atropine was reduced to gr.1/120, gr.1/150, gr.1/180, gr.1/200, gr.1/250, gr.1/300, gr.1/400 and gr.1/500 respectively. There was still no colic or vomiting after the hypodermic injections of 0.1mgm. of prostigmin, so atropine was discontinued.

On two occasions Prostigmin 1.5mgm. was given by the mouth. On the first the patient felt

very sick though she did not vomit and the effect on the muscles was very slight. On the second the sickness was less, and the effect on the muscles better, though still much less than that of the hypodermic injection of 0.1mgm.

From 24.11.34 to 6.12.34 two injections a day of Prostigmin without atropine were given, 0.5mgm. at 10 a.m., which enable her to swallow her principal meal easily, and without regurgitating, and 0.7mgm. at 1 p.m., after which she could get up and walk about a little during the afternoon.

On 6.12.34 an injection of Prostigmin 1.5mgm. without atropine was given at 10 a.m. This was followed in about half an hour by colic which lasted for a few minutes. The next day atropine gr.1/200 was given with Prostigmin 1.5mgm. and no colic resulted.

On 8.12.34 Prostigmin 2.0mgm. with atropine gr.1/200 was given without causing colic. Daily injections of this amount were continued till 18.12.34, when Prostigmin 2.5mgm. with atropine gr.1/200 was given. Slight colic resulted in half an hour, so the atropine was increased to gr.1/150. This was ~~quite~~ not quite enough, so with succeeding injections of Prostigmin 2.5mgm., atropine gr.1/100 was given. This prevented colic and did not cause dryness of the mouth.

The increase of muscular power was proportionately greater with the increase in the doses of Prostigmin. It also came on earlier and lasted longer.

<u>Amount of Prostigmin.</u>	<u>Onset of effect.</u>	<u>Duration of effect.</u>
Mgm.	Minutes.	Hours.
0-5	30-45	2-3
1.0	20	4-5
1.5	10	4-5
2.0	8	5-6
2.5	5	6-8
3.0	4	6-8

From four to five minutes after an injection of 2.5mgm. of Prostigmin the ptosis disappears and the range of movements of the eyeballs becomes full. The tendon jerks, which before the injection are usually absent, return. A few minutes later the patient can raise her arms above her head and her grip becomes strong. In a few more minutes she can sit up easily in bed and in about fifteen minutes she can walk steadily for several hundred yards, and polish the ward floor with a heavy floor polisher. The effect increases a little more for about an hour, remains maximal for about four hours and wears off gradually.

On 12.4.35 a hypodermic injection of Prostigmin 0.3mgm. with atropine gr.1/100 was given at 9 a.m. The effect came on rather more rapidly than that of 2.5mgm., seemed to the patient to be greater and lasted about an hour longer. There was no colic. Daily injections of 0.3mgm. were continued.

On 22.4.35 an injection of 3.5mgm. of Prostigmin was given at 8 a.m. with atropine gr.1/100.

The effect came on a little quicker than that of 0.3mgm. and the patient felt stronger. It wore off in about the same time. Colic came on in ten minutes, was severe for half an hour, gradually lessened and ceased in an hour after the injection. There were no other ill effects.

No further injections of 3.5mgm. and no larger injections have been given.

When the effect of an injection of Prostigmin is beginning to wear off, another injection will renew it. The effect of the second injection depends on the dose and how far the effect of the first injection has worn off. With an injection of 3.0mgm. at 8 a.m. and 1.0 or 1.5mgm. at 2 p.m. the patient could get about for ten hours or so, but she felt less strong in the afternoon than in the morning. When three injections were given, 3.0mgm. at 8 a.m., 1.0mgm. at 2 p.m. and 1.0mgm. at 5 p.m., she could get about for twelve hours, but was less strong in the afternoon. With two injections 3.0mgm. at 8 a.m. and 2.5mgm. at 2 p.m., the patient can get about for twelve hours and she feels as strong in the afternoon as she does in the morning. The largest amount of Prostigmin which has been given in one day is 6.5mgm. given in three doses, 3.0mgm. at 8 a.m., 2.0mgm. at 2 p.m. and 1.5mgm. at 5 p.m.

The more the patient exerts herself after an injection the more quickly the effect wears off and the weaker she is when it has worn off. Usually she feels more tired and her muscular power is less

after the effect has worn off than before she had the injection. If she has been about all day she is sometimes unable to turn over in bed during the night. When she exerts herself more than usual, there is a subjective sensation of stiffness in the muscles towards the end of the day. Occasionally she still feels stiff in the morning; after she has had the injection this feeling wears off.

When the patient had had daily injections of large amounts of Prostigmin for some time, and had been doing a little light work every day, she became more helpless during the night and in the morning before the injection, than before the treatment with Prostigmin was begun. The effect of the injections did not lessen. If she had exerted herself very much the day before, the duration of the effect of an injection would be less.

On 28.5.35 injections of Prostigmin were omitted for two days. The next morning she was a little stronger than usual, and on 30.5.35 she was just as she had been before the treatment with Prostigmin was begun. This showed that the myasthenic symptoms were not being made worse, apart from a temporary increase in severity, when the effect of an injection had worn off, attributable to the increased amount of muscular work done while the patient was under the influence of the injections.

The pulse rate and blood pressure before and after an injection of Prostigmin 2.5mgm. with atropine gr.1/100 were 80 and 80, and 120/80 and

125/80 respectively.

One hour after the injection the eyes were examined and accommodation found to be normal.

Electrocardiograms were made before and after an injection of Prostigmin 2.5mgm. and atropine. Another electrocardiogram was taken at 2.30 p.m. half an hour after an injection of Prostigmin 2.5mgm. with atropine gr.1/120 and a second a half hour after after one of Prostigmin 3.0mgm. and atropine gr.1/100.

On 24.2.35 at 11 a.m. a hypodermic injection of 0.1mgm. of Peristaltikum with atropine gr.1/200 was given. An effect came on in half an hour similar to that of 0.1mgm. of Prostigmin. At 12 noon another injection of Peristaltikum 1.5mgm. with atropine gr.1/200 was given. The combined effect seemed equal to that of Prostigmin 2.5mgm. but it lasted much longer. It wore off very gradually and did not quite disappear till about 6 a.m. the next morning according to the patient who was awake most of the night watching the effect of the injections.

Next day Peristaltikum 0.1mgm. was given at 11.35 a.m. with atropine gr.1/100, and at 12 noon another 1.5mgm. of Peristaltikum were injected. The results were the same as before.

Injections of Prostigmin 2.5mgm. and atropine gr.1/100 were then resumed. On 26.2.35 the patient felt very stiff and tired, and the injections of Prostigmin did not have as good effect as usual. This can be attributed to her having kept about much

longer on the day when she had Peristaltikum, and to loss of sleep.

On 4.4.35 at 9 a.m. Peristaltikum 2.5mgm. was given with atropine gr.1/100. The effect came on in about twenty minutes, but became maximal more slowly than that of Prostigmin. She was not able to walk for forty-five minutes. She did not feel as strong as after a similar amount of Prostigmin, but the effect lasted much longer. It began to wear off at 9 p.m. The same dose of Peristaltikum was given the next day with a similar result. Injections of Prostigmin were then resumed.

On 8.4.35 at 9 p.m. an injection of Peristaltikum 0.1mgm. and atropine gr.1/100 were given to find out whether the effect would last long enough to enable the patient to give herself an injection the next morning. At 8 a.m. the next day she could use her hands well enough to be able to give herself an injection. The effect did not quite wear off till 9.30 a.m.

On the whole the patient preferred the injections of Prostigmin to those of Peristaltikum, because the effect came on more quickly and she felt stronger. She liked to have an injection of Peristaltikum at 5 p.m. because the effect lasted through the night, and she could move about in bed more easily. If she were obliged to give herself an injection of Prostigmin in the morning, Peristaltikum 0.1mgm. given about 9 p.m. would enable her to do so.

On 17.12.34 a hypodermic injection of physostigmine salicylate gr.1/50 was given without atropine. In twenty-five minutes the ptosis became much less, and in an hour the patient could sit up. The effect on the muscles was rather less than that of 1 c.c. of Prostigmin. She felt sick and disinclined to eat and in two hours she vomited. There was no colic. Later in the day Prostigmin 3c.c. with atropine gr.1/100 was given with the usual effect.

On 20.12.34 an injection of physostigmine salicylate was given at 11 a.m. with atropine gr.1/100 to prevent sickness. In spite of the atropine the patient felt sick so another injection of atropine gr.1/100 was given at 12 noon. She still felt sick though she did not actually vomit. She also felt a little faint and disinclined to move but she thought the muscles were stronger than before the injection was given.

On 17.1.35 at 4.30 p.m. when the effect of an injection of Prostigmin 5 c.c. and atropine, which had been given at 10 a.m., was wearing off, an injection of physostigmine salicylate gr.1/50 was given. At 5 p.m. the patient became pale and complained of nausea, atropine gr.1/100 was then injected. By 5.30 p.m. the ptosis had gone and the patient thought she would be strong enough to walk but she was afraid to do so because of the nausea and the feeling of faintness which still continued. There was no actual vomiting and no colic.

No further trials were made of Physostigmine.

Control injections were given none of which had any effect on the myasthenic symptoms.

Date	Injections	Results
3.12.34	Ephedrine 2 gr.	A "frightened feeling"
13.12.34	Geneserine 1 cc.	None apparent
31.12.34	Lobeline 1 cc.	" "
27.1.35	Water 5 cc.	" "
2.2.35	Water 5 cc.	" "
23.5.35	Cortin 5 cc.	" "
21.8.35	Cortin 10 cc.	" "

The effect of Peristaltikum 4 mgm. is less intense than that of Prostigmin 3 mgm.

On 24.6.35, when the effect of an injection of Prostigmin 5 cc. with atropine gr. 1/100 had worn off, potassium chloride grammes 12 in water was given. Improvement on the myasthenic symptoms followed in about twenty minutes and lasted for two hours. It was approximately as great an improvement as that usually caused by 1 cc. of Prostigmin. There was some nausea and a feeling of heat.

On 25.6.35 sodium chloride grammes 4 in water was given when the effect of Prostigmin had worn off. It had no effect on the myasthenic symptoms.

From 27.6.35 to 17.7.35 potassium chloride grammes 3 in water was given daily at 1 p.m., 5 p.m., and 8 p.m. The patient liked it, and said she felt better after it. Injections of Prostigmin 2.5 mgm. with atropine gr. 1/100 at 8 a.m. and 2 p.m. were continued.

On 17.7.35 potassium chloride was omitted and Tr.Veratrine m.15 given by mouth at 1 p.m., 5 p.m. and 8 p.m.; this relieved the symptoms as much as potassium chloride, and the patient preferred it because it tasted better. This dosage of tincture of Veratrine was continued till 25.7.35.

On 19.7.35 Aconite m.5 was given by the mouth; it made the patient feel sick and did not relieve the myasthenic symptoms.

On 25.7.35 ephedrine gr.½ was given at 1 p.m., 5 p.m. and 8 p.m. The myasthenic symptoms were not lessened as they were soon after taking Tr. Veratrine or Potassium, but they became no worse or little worse towards the end of the day. Ephedrine seemed to prevent the patient from "running down", the effect of the Prostigmin seemed to remain much longer when ephedrine was taken as well. She was able to be up and about all day with one dose of Prostigmin at 8 a.m. and ephedrine at 1 p.m., 5 p.m. and 8 p.m., though she was decidedly weaker in the morning than in the afternoon, and she could sit up in the morning and eat her breakfast before the injection of Prostigmin. She preferred one injection of Prostigmin with ephedrine to two injections of Prostigmin without ephedrine, because the effect lasted much longer.

From 5.8.35 to 10.8.35 caffeine citrate grs.5 was given at 1 p.m., 5 p.m. and 8 p.m. instead of ephedrine, but the patient became weaker on the whole

and she complained that it made her sweat.

Since 17.8.35 with the exception of a few days, she has had an injection of Prostigmin 3 mgm at 8 a.m., with Atropine gr. 1/100, another of Prostigmin 2.5 mgm at 2 p.m. with atropine gr.1/120, and ephedrine gr.½ by mouth at 1 p.m., 5 p.m. and 8 p.m. With this dosage she is able to be up all day and do light work. In the morning she would be able to give herself an injection if necessary. Two other substances of Aeschl mann's series were tried, No.37 which was prepared for administration by mouth, and No.38, which on biological assay seemed to prevent the destruction of acetylcholine by cholinesterase, more powerfully than Prostigmin.

On 27.8.35, 10 mgm. of No.37 was given by the mouth and on 23.9.35, 20 mgm. were given, injections of Prostigmin and ephedrine by the mouth being omitted both times. On neither occasion was any improvement in the myasthenic symptoms detected.

On 27.8.35 three injections of 1 mg. of No.38 of the series were given at half hourly intervals.

Dynamometer reading of the grip	R ¹	L ¹
Before	0	4
After	12	16
Four hours after the first dose	0	0

On 15.9.35, 3 mgm of No.38 were given.

Dynamometer reading	R ¹	L ¹
Before	0	0
After	12	9

The effect wore off in three or four hours, and the patient did not feel nearly as strong as after Prostigmin.

The dynamometer readings after Prostigmin 3 mg. varies from R^l 18 - 21 L^l 15 - 18

The total amounts of Prostigmin and Peristaltikum in milligrammes which have been given each month are

	Prostigmin	Peristaltikum
	mgr	mgr
1934 October 24-31	8	
November	32	
December	59	
1935 January	77.5	
February	65	5
March	77.5	
April	152	7.5
May	149	12
June	165	
July	165	4
August	168	
September	165	

From the beginning of January 1935, till the end of May, daily injections of atropine gr. 1/100 have been given. Since the beginning of June, atropine gr. 1/100 has been given every morning and gr. 1/120 every afternoon. No dryness of the mouth or other ill effect has been observed.

The nutrition of the patient has improved, by February 1935 she had gained one stone in weight. There has been only slight improvement in the myasthenic symptoms; the grip is stronger, and since February there has been no deplopia. Ephedrine is the best of the adjuvants to Prostigmin, it lessens the fatigue at night when the effect of Prostigmin has worn off. The symptoms are only relieved temporarily by the treatment, but to such an extent that the patient is able to be up and about all day, and do moderately light work, instead of having to be washed, dressed, and either remain in bed or be pushed about in a wheeled chair.

Miss W. - aged 35.

History.

At the age of four she had Potts' disease with a psoas abscess. She had to lie flat on her back for two years and wore a plaster jacket for three more. She completely recovered and remained well till the age of seventeen when the present illness began.

At a Christmas party in 1916 the guests remarked that the patient could not smile properly, and that she looked "peculiar, as if she were crying". She did not feel any weakness or undue fatigability and danced as much as usual.

Her work was to make protectors for the eyes for soldiers. Lead was used, but none of the workers had any symptoms of lead poisoning. She continued this work and felt no different from usual till one day in February 1917, while on her way to business, a parcel containing her overall which she was carrying under her right arm slid down to the ground, and she could not pick it up. She "went against a wall" to pick up the parcel, and then found she could only walk on with difficulty because of the weakness of the legs and swaying from the waist. Her left eyelid began to droop soon after and she found that she could not eat anything hard because of the weakness of the jaws.

She continued to go to work, but the symptoms steadily got worse. At first she went by 'bus, but after a time found she could not lift her

legs on to the step. Then she went by Underground but at times she could not stand and had to hold on to the railings of the lift. Once she fell outside the station. The weakness increased towards the end of the day.

On 7th April, 1917 she was admitted to the Royal Waterloo Hospital, while there symptoms continued to increase. In July 1917 she went to Charing Cross Hospital, she remained there for seven weeks and then was sent to a Convalescent Home in Brighton, and from there to the Isle of Wight. Her symptoms remained about the same till February 1918 when she was still in the Isle of Wight. Swallowing became difficult, food "caught in her throat" and fluids regurgitated through her nose. She could only eat slowly. Speech was slow, when she was tired she had to hold her lower lip up to enable her to talk. She began to fall about frequently, once, after going up a flight of stairs she fell backwards down them; and once, while she was on the cliffs, and sudden heavy rain came on, she could not get up from her seat, but fell on the ground, and had to lie there while someone brought a mackintosh and an umbrella.

In June 1918, she returned home. Breathing now became difficult at times, even when she was resting, but it was always worse when she exerted herself. Swallowing was very difficult, and she had to be washed, dressed and carried about.

On her 19th birthday in October 1918, she was admitted to the Westminster Hospital, where her

disease was diagnosed for the first time as myasthenia gravis. While there her speech became worse and her other symptoms did not improve. In seven weeks she was discharged to her own home, where she remained till she was admitted to St. Alfege's Hospital in April 1935. There was no improvement in her symptoms, which indeed, became rather worse till 1927. She sat up out of bed for a few hours each day but never went outside. The left eyelid drooped so much that the eye was completely closed, and the right eyelid began to droop. When she read she had to hold her right eyelid up with her finger.

In 1927 someone suggested that she should go out in a bath-chair. She did this and seemed to improve a little. She could sit up a little longer, and could walk for about eight yards with ease, then she had to stop and rest. She could wash herself, but it took half an hour to do it. Swallowing remained difficult but she did not have the attacks of difficult breathing. Diplopia came on suddenly and has continued on and off ever since. Now for the first time she found that she had three days of intense weakness before the menstrual flow began.

In 1933 she became weaker and had to be helped more. The left eyelid drooped so that the eye was completely closed. Breathing became difficult at times again. For eight days together she could hardly breathe night or day. Sometimes when she went to church with two people helping her she could not breathe when she got there, and her

head began to tremble. Often she could not even go out in the bath-chair. There were two weeks of increased weakness before the monthly periods. When the flow began the weakness lessened. She became very depressed, and often felt as if she "could not go on another week". She did not show this to other people, and was generally considered to be of a cheerful and contented disposition. Throughout the whole of her illness she has been constipated. On 2nd April, 1935 she was admitted to St. Alfege's Hospital.

Condition on admission.

There was bilateral unequal ptosis, the left eyelid drooping so much that the eye was closed, bilateral limitation of the movements of the eyes. The upper extremities were weak, especially the muscles of the shoulder girdles and the extensors of the fingers. She could not raise her arms above her head, or straighten her fingers which were always slightly flexed. Her grip was feeble. There was weakness also of the back and legs, she could only walk a few yards at a time, unsteadily, swaying from the waist. The knee jerks were present but sluggish. There were no other physical signs. Radiograms showed no evidence of enlargement of the thymus.

Treatment.

On 2.4.35 at 11.55 a.m. a hypodermic injection of Prostigmin 2.5mgm. was given with atropine gr.1/100. In about five minutes, the ptosis

of the left upper eye-lid had almost, and that of the right had quite gone. The lateral movements of the eyeballs became full. She felt less heavy. In another minute or so her grip became stronger, and she could raise her arms above her head. By 12.8 p.m. she could walk well and steadily up and down the ward. She had never before been able to do this since the onset of the illness eighteen years ago. Half an hour after the injection the ptosis of the left upper eyelid had gone, but this eyelid drooped readily, though comparatively slightly, whenever she exerted herself or felt excited. It was drooping constantly after 3 p.m., but she did not begin to weaken till 5.30 p.m., and at 6.30 p.m. she was still able to walk steadily down the ward. There was no colic or other ill effect, except slight dryness of the mouth.

The next morning she felt rather stronger than on admission. Peristaltikum 2.5mgm. with atropine gr.1/100 was given hypodermically at 10 a.m. The ptosis improved as much as on the day before, in twenty minutes, and in thirty minutes she could walk well. The left eyelid began to droop constantly after 3 p.m., but the patient did not feel weak all day and was able to walk steadily at 9 p.m. She thinks she could still have walked at midnight. The increase in muscular power was decidedly less than after the same dose of Prostigmin, but it lasted much longer.

On 4.4.35 Prostigmin 2.5mgm. with Atropine gr.1/100 was given with the same effect as before.

On 5.4.35 Peristaltikum 2.5mgm. with atropine gr.1/100 was given. This time the effect did not come on for half an hour and was not maximal for an hour and a half, but it lasted as long as before.

Injections of Prostigmin 2.5mgm. with atropine gr.1/100 were continued. On 11.4.35 Prostigmin 3mgm. with atropine gr.1/100 was injected at 10 a.m. The effect was maximal till 4 p.m. and gradually wore off. The patient felt stronger than after 2.5mgm. and the effect came on a little more quickly.

On 17.4.35 Peristaltikum 2.5mgm. was given at 8 a.m. without atropine. No colic resulted, and the effect on the myasthenic symptoms was the same as usual and lasted as long.

On 22.4.35 Prostigmin 3.5mgm. with atropine gr.1/100 was given at 8 a.m. The effect came on a little earlier than after 3mgm. Colic began in ten, and lasted for fifteen minutes. The left eyelid was not better raised than with 3mgm. By 4 p.m. the effect had almost worn off.

Daily injections were continued. Prostigmin 2.5mgm. with atropine gr.1/100 were given at 8 a.m. and 1mgm. without atropine at 1 p.m. and 5 p.m. on most days. Sometimes Peristaltikum 1.5mgm. was given at 5 p.m. instead of Prostigmin 1mgm. The effect was slightly less strong, but lasted throughout the night.

On 3.6.35 daily injections of Prostigmin 3mgm. with atropine gr.1/100, at 8a.m. and Prostigmin

2.5mgm. with atropine gr.1/120 at 2 p.m. were begun. With this dosage the patient felt stronger in the afternoon, but could not remain up and about as long as when she had 1mgm. of Prostigmin at 2 p.m. and 5p.m. One dose of Peristaltikum 4mgm. with atropine gr.1/100 was given at 8 a.m. The effect came on in fifteen minutes, and was as strong as that of Prostigmin 3mgm.

About two weeks after the beginning of the treatment, the patient found that in the morning before an injection she was not able to move as well as she could before admission. Usually she could not raise herself up in bed, and often during the night, she could not turn over.

For three days from May 16th no Prostigmin was given. On the second morning the patient could move better than on the first, and on the third she could move as well as she could before the treatment was begun. Injections of Prostigmin were resumed, and in about two weeks she again found that she was weaker before the morning injection.

On 24.6.35 Potassium chloride grammes 12 in water by mouth was given. An effect almost equalling that of Prostigmin 0.5mgm. came on in about twenty minutes and lasted for about two hours. There was no nausea or other ill effect. Diuresis occurred.

On daily doses of potassium chloride grammes 3 in water at 1 p.m., 5 p.m. and 8 p.m., as well as Prostigmin 3mgm. at 8 a.m. and 2.5mgm. at 2 p.m., the patient felt less heavy and said she could turn better in bed

Sodium Chloride grammes 4 in water by mouth on 25.6.35 had no effect whatsoever.

On 16.7.35 Physostigmine gr.1/50 and atropine gr.1/100 were injected at 2 p.m. instead of the second injection of Prostigmin. The effect came on in about thirty minutes, and was almost equal to that of Prostigmin 1mgm., but the patient was nauseated and felt giddy and disinclined to move. She vomited once. There was no colic.

On 17.7.35 at 11.5 a.m. Tr. Veratrine m6 in distilled water 10cc. was given intravenously. At 11.7 a.m. the eyelids felt less heavy and the left eyelid did not droop so much. The fingers could be straightened a little at 11.9 a.m. She felt less heavy generally, but could not raise herself up in bed. No increase in this effect occurred, and at 11.28 a.m. the left eyelid began to feel heavy again, and by 11.30 a.m. she felt as she did before she had the injection.

This effect is less than that of Potassium chloride grammes 3 by mouth. When this is given after the effect of an injection of Prostigmin has worn off, she is able to sit up in about half an hour.

On 13.8.35 ephedrine gr.½ was given by the mouth at 1 p.m., 5 p.m. and 9 p.m., the injections of Prostigmin 3 mgm. and atropine gr.1/100 at 8 a.m. and Prostigmin 2.5 mgm and Atropine gr.1/120 at 2 p.m. being continued. Subjectively the patient feels a little stronger after ephedrine. No increase in strength can be demonstrated but the weakness does not come on so quickly. The heavy feeling after the effect of Prostigmin has worn off, does not come on, and she can move about in bed easily during the night and get out of bed and walk a few steps before the injection of Prostigmin when she is having ephedrine. Ephedrine seems to hinder the onset of fatigue, rather than remove it when it comes on.

On 7.8.35 caffeine citrate gr.5 by the mouth was given at 1, 5 and 9 instead of ephedrine. The patient thought it helped her as much, but it prevented sleep and was discontinued on 13.8.35. Injections of Cortin in doses of grammes 5 and grammes 10 produced no appreciable change in the myasthenic symptoms.

Peristaltikum mgm.4 has almost as intense an effect as Prostigmin mgm.3. No.37 of Aeschlemann's series in doses of 10 and 20 mgm. by the mouth made no change in the myasthenic symptoms.

No.38 of the series, 3 mgm. was given by injection. The effect was less intense than that of the same amount of Prostigmin and passed off more quickly.

Dynamometer readings	R ¹	L ¹
Before No.38	9	4
After "	11	11
Before Prostigmin	4	3
After "	21	21

The total amounts of Prostigmin and Peristaltikum which have been given each month are

	Prostigmin	Peristaltikum
	mgm.	
1935 April	104.5	4
May	141	6
June	154	
July	88	4
August	165	
September	165	

The largest single dose of Prostigmin ever given was 3.5 mgm. and the largest amount in one day was 6.5 mgm., distributed as follows, 3 mgm. at 8 a.m., 2.5 mgm. at 2 p.m. and 1 mgm. at 6 p.m. The largest single dose of Peristaltikum was 4 mgm.

Daily injections of atropine gr.1/100 were given from 2.4.35 to 24.5.35.

Since 24.5.35 atropine gr.1/100 has been given every morning and gr.1/120 every afternoon. Slight dryness of the mouth is produced for a short time.

The long continued administration of Prostigmin has had no ill effects. Ephedrine prevents the increase in fatigue at night which is the one

drawback of large injections of Prostigmin.

The left eyelid now remains up much better than it did at the beginning of the treatment.

The nutrition of the patient has improved. She is able to be up and about all day, and do light work. One of the trials she used to have was that people used to 'look at her' when she went out; they no longer do so. She says that she is now able to 'live' for the first time since the onset of the illness eighteen years ago.

No remission has occurred.

No remission has occurred

TREATMENT

and

PROGNOSIS

Treatment.

Since the disease was first recognised it has been known that over exertion, excitement and extremes of temperature make the symptoms of myasthenia gravis worse, and avoidance of these has always been recommended.

Electrical treatment was early found to increase the symptoms.

The remissions characteristic of the disease make it difficult to appraise the value of remedies. Strychnine, in doses up to 1 - 3 gr. daily, lemons with sugar, liver extracts, endocrines such as thyroid, pituitrin, insulin, adrenaline and whole supra-renal glands have been extensively tried, in some cases with apparent success, in others without. Whole supra-renal gland seemed to be the most successful of the endocrines.

Operative treatment has even been tried, thymectomy was reported to have improved one case. Ptosis has been relieved by operation.¹²⁰ Radio-therapy of the thymus has been tried.

The first advance was made when Harriet¹²¹ Edgeworth discovered the effect of ephedrine in 1929. Boothby¹²² introduced glycine therapy soon after, in the Mayo Clinic. Ed. Forster¹²³ in 1930, found that veratrine lessened the symptoms for a few hours, each time it was given.

In 1934 physostigmine was found by me to relieve the symptoms for a few hours, and Prostigmin in large doses with atropine to counteract the

parasympathetic effects, to restore normal muscular power for several hours to severe cases of the disease. This effect has been confirmed by E.A.B. Pritchard¹²⁴ and L.P.E. Laurent¹²⁵ and many other observers. One severe case of myasthenia gravis was said not to respond to doses of 1.5mgm. of Prostigmin, but this is a comparatively small dose.

L.P.E. Laurent¹²⁶ in 1935 found that potassium chloride also lessened the weakness and fatigability for a short time.

Supra-renal Extracts.

Adrenaline has not been found to be of benefit in myasthenia gravis, but Marie and Bouttier¹²⁷ and several observers have reported good results from supra-renal extracts. Bourgeois¹²⁸ found that one case improved very much on hypodermic injections of extracts of the whole gland. He used doses varying from 10cg. to 40cg. in twenty-four hours.

Roche, Demole and Duchosal¹²⁹ report immediate improvement in a case treated by intravenous injections of Cortigène, when the injections were stopped he relapsed. More lasting improvement followed fifteen intramuscular injections, and the improvement continued after two more courses of ten intramuscular injections. Before treatment the muscle responded to stimulation for three minutes, six months later it responded for six minutes.

Other cases have not responded to supra-renal extracts, and some have become weaker and died while being treated.

Harriet Edgeworth¹³⁰ found that adrenaline had an adverse effect in her case. She tried five differently prepared supra-renal substances with the following results:-

1. A common commercial preparation of supra-renal substance - No effect.
2. Supra-renal extract prepared by the Wilson Laboratory - Adverse effect.
3. Extract prepared by Alfred Koehler from half supra-renal gland - Adverse effect.

4. Extract prepared by C.C.Wang from the inter-renal body of the dogfish. - Slight improvement on minute amounts.
5. Frozen fresh beef supra-renal extract prepared by Kendal, Szant and Gyorgi - No improvement in the muscles, but decrease in nervous tension and insomnia.

Insulin.

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Merinasco G. and Vasilescu N. report good results from injections of insulin in two cases of myasthenia gravis. They gave fifteen units twice daily with 7 - 15 pieces of sugar. After the first hundred units improvement occurred. They advise giving courses of injections for ten to fifteen days, the total amount of insulin for a course not to be more than 500 - 600 units. After an interval of twenty to thirty days the treatment is resumed. They consider that the metabolism of carbohydrate is redressed, and the state of acidosis which is present modified.

Veratrine.

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Ed. Forster treated twelve cases of myasthenia gravis for three years with veratrine. He found that improvement occurred in each case lasting for some hours. A quick effect was produced by intravenous injections of Tinct. Veratrine m6 in distilled water 10c.c., which helped at once in respiratory crises. A more prolonged though less extreme effect lasting for some hours was produced by giving Tinct. Veratrine m 15 thrice daily by the mouth. The symptoms returned when the effect of the drug wore off.

The optimum dose varied with the individual, usually it was 8 minims thrice daily, in some cases, 3 - 4 minims. Toxic symptoms were faintness, vomiting, salivation and diarrhoea.

Measurements of the chronaxie were made before and after the administration of veratrine. It was increased immediately after, then decreased for thirty minutes, forty-five minutes after it had returned to the original value.

Ephedrine prolonged the duration of the effect of Veratrine.

EPHEDRINE

The effect of ephedrine on myasthenia gravis was discovered accidentally by Dr Harriet Edgeworth¹³³ during the summer of 1929. She had suffered from myasthenia gravis for ten years and while taking tablets of ephedrine gr.1/8 for another purpose, found that her muscular power was improving more than it had for many months. When she stopped taking the ephedrine, the weakness returned, and when she resumed it her strength increased again. The improvement seemed to reach its maximum in two weeks, and when ephedrine was stopped the gain in strength was lost in 48 hours. It was discontinued without her knowledge for several weeks during which she became bedridden and had difficulty in speaking and chewing. In a few days after taking ephedrine 6/8 gr. a day, she was able to walk the distance of the room, and her other symptoms improved. She discontinued ephedrine seven times abruptly; four times while taking 2/8 gr. daily, each time the gain in strength was lost in 48 hours, and three times while taking 6/8 gr. daily, when the gain in strength was lost more slowly, beginning on the second day and continuing for two weeks.

The possibility of the improvement being due to any psychic effect was excluded by the giving and omitting of the drug sometimes without her knowledge.

She continued to take ephedrine gr. 6/8 daily and in 1933 reported that the improvement had continued and had been apparently uniform. Larger doses of ephedrine temporarily increased her strength but were invariably followed in two or three weeks by such adverse symptoms that she always had to reduce the dose. She found that the dose which gave the greatest effect in the first few weeks would not produce continuous improvement over long periods. An added advantage in using a smaller dose was that she could take an extra dose in emergencies to counteract the effects of exposure to cold or heat, a menstrual period, a respiratory infection, or unusual exertion. She found the benefits due to ephedrine far outweighed the adverse effects.

The literature is full of disagreements with regard to the action of the drug, but clinical results have shown that it produces effects like those of adrenaline, lasting longer but less intense. It is more stable than adrenaline and can be taken by the mouth. Nothing is known of the fate of ephedrine in the body, except that it apparently passes through the liver unchanged.

Many cases of myasthenia gravis have been treated with ephedrine since its introduction. No immediate increase in muscular power can be demonstrated after the administration of ephedrine, but patients like it, and say they feel better on it.

The remissions and relapses characteristic of the disease make it difficult to estimate the effect of the remedy, but there is a consensus of opinion that many cases improve while taking the drug, and relapse when it is discontinued. The improvement is moderate in degree.

Mc Alpine¹³⁴ reported the effects of ephedrine in six cases of myasthenia gravis, all of whom improved. Three were having natural remissions but in the other cases the improvement appeared to be due to the drug. One case was given 3 gr. daily for over two years; with smaller doses the symptoms became worse and the larger dose had to be resumed. The only untoward result was a rise in blood pressure. He advises that doses larger than gr. 1½ daily should seldom be given. Larger doses do not cause a correspondingly greater improvement. Susceptibility to ephedrine varies but doses larger than 3-4 gr. a day are seldom tolerated.

Cases of myasthenia gravis have become worse and have died while taking ephedrine; this may mean that the beneficial effects of ephedrine have not been sufficiently powerful to counteract the cause of the symptoms, rather than that ephedrine has no beneficial effect in some cases of the disease.

GLYCINE

The beneficial effects of the administration of glycine in cases of muscular dystrophy (in which creatinine is present) reported by Thomas, Milhorat and Technor,¹³⁵ and Milhorat, Technor and Thomas¹³⁶ led W. Boothby¹³⁷ of the Mayo Clinic to think that it would, presumably from building up the phosphocreatine content of the muscle, be unlikely to be beneficial in cases of myasthenia gravis. He has reported considerable success in cases of myasthenia gravis treated with glycine. In all but one case, in which it was not well tolerated, causing nervousness and insomnia, ephedrine was given as well as glycine. Out of twelve patients, four were much improved, six improved and two did not respond. In a later report Boothby stated that out of forty six cases of myasthenia gravis treated with glycine and usually also with ephedrine, all but two who died while being treated responded favourably. Thirteen were able to do full work, and eight light work. One died before the treatment could be begun, one improved on the treatment but gave it up, grew weaker and died, one committed suicide, and one died of pneumonia.

The best dosage for glycine he finds is between 10 and 30 gm. daily, divided into five or six doses; and for ephedrine gr 1/16 or 1/8 three to five times daily. He has evidence suggesting that when ephedrine is

given about fifteen minutes after glycine, the effect of both is increased. Patients who are intolerant of ephedrine do best on glycine alone. After the administration of glycine an increased creatinuria may occur, which later falls, and the clinical improvement is coincident with this fall.

¹³⁸ Schmitt and ¹³⁹ Remen also found that glycine therapy produced improvement in myasthenia gravis. Remen concluded that in myasthenia gravis there is a disturbance of creatine creatinuria metabolism which can be corrected by glycine and that this disturbance may be a failure of the muscle to build up creatine phosphoric acid. If glycine is of benefit in myasthenia gravis it is unlikely that it is because of the alteration which it produces in the creatine metabolism for the results of Nevin who investigated the phosphorus holding compounds in myasthenia gravis, showed that they were normal.

Glutamic acid has been given in myasthenia gravis and its beneficial results are stated to be as good as those of glycine.¹⁴⁰

Creatine is an amino-acid containing a highly basic substance guanidine, and phosphoric acid. It is probably formed in the body from specific amino acids, glycine and glutamic acid chiefly, and is stored or metabolised almost entirely in the skeletal muscles. In the resting state it is mostly found in

combination with phosphoric acid, as creatine phosphoric acid.

In adult males all the creatine formed in the tissues is metabolised in the muscle and none appears in the urine. In children some creatine is excreted in the urine. When it is produced in excess of the needs of the muscular system. All the creatine formed in the body cannot be stored or metabolised by the degenerated muscles in muscular dystrophy and some is excreted.

Glycine when given in large doses evidently leads to an increased production of creatine for the time being, and thus to increased excretion. This will occur in excessive wasting or disuse of the muscles from any cause.

In myasthenia gravis the creatinuria appears to be a secondary effect of the disease.

Very faint handwritten notes, possibly bleed-through from the reverse side of the page.

Potassium Chloride.

Feldberg and Vertiainen¹⁴¹ found that the addition of potassium chloride to the perfusing solution stimulated the ganglion cells, and in amounts not large enough to do this directly, raised the excitability of the ganglion cells by about 50% to preganglionic stimulation, that is to acetyl-choline which is liberated at the preganglionic nerve endings. Physostigmine in a weak solution $1 - 10^6$ strongly 'sensitized' the ganglion cells to injection of acetyl-choline, lowering the threshold 8 - 20 times, and also lowered the threshold by one third to one half for other substances including potassium ions.

On the grounds that any substance known to facilitate production or utilisation of acetyl-choline might be expected to have a favourable influence on myasthenic symptoms. L. P. G. Laurent¹⁴² gave potassium chloride 2 grammea five times a day in water to cases of myasthenia gravis. Half an hour after the draught there is subjective improvement which passes off in an hour, there is also slight increase in muscular power. Twelve grammes produced almost as intense effect as an injection of 0.5mg. of Prostigmin. He finds that doses of 4 - 6 grammea six times a day are a useful adjuvant to treatment with Prostigmin. No increase in the intensity of the effect of Prostigmin could be demonstrated when Potassium Chloride was given at the same time. Diuresis and mild diarrhoea are the only ill effects which have ever been produced. The blood potassium is appreciably raised.

Physostigmine.

The symptoms of myasthenia gravis are temporarily very much lessened whether it is given by the mouth or by injection. Doses of gr.1/60 hypodermically begin to take effect in about half an hour, the improvement continues for two to four hours, wearing off gradually; larger doses have a more intense and prolonged effect. On account of the slow absorption relatively much larger doses have to be given by the mouth. Atropine does not lessen the effect of physostigmine on the myasthenic symptoms, nor does it increase it, but it antagonises the stimulating effect on the parasympathetic, this antagonism is more powerful if atropine is given shortly before the physostigmine. The susceptibility of individuals to atropine varies and different amounts are required to antagonise the parasympathetic effects of physostigmine in different cases.

The tolerance of individuals to physostigmine varies greatly; the great majority of people are unable to tolerate even doses of gr.1/50 by injection. In the case of a healthy subject the symptoms after an injection of physostigmine gr.1/50 were as follows; in about half an hour an uneasy feeling, like that of sea-sickness, came on, which was relieved by recumbency, the subject felt that she wanted to lie still. Vomiting occurred an hour after the injection, and again three quarters of an hour later. There were loud intestinal rumblings at intervals, but no colic and no diarrhoea. The effect wore off in three

hours. The same subject again had an injection of physostigmine gr.1/50, this time with atropine gr. 1/100. No appreciable effect was produced, the subject would not have been aware from the symptoms alone that any injection had been given.

In the cases of Miss C. and Miss W., atropine gr.1/100 did not prevent faintness and nausea or vomiting, though there was no colic.

Denny Brown¹⁴³ reported a case in which physostigmine by the mouth preceded by belladonna had an effect comparable in intensity with that of Prostigmin 2mg., with atropine gr.1/100. Tincture of belladonna m 20 was given by mouth, followed in ten to fifteen minutes by physostigmine salicylate gr.1/6 in water. Improvement began in twenty minutes, was fully developed in one to two hours, and maximal for five hours. He advocated the administration by mouth of physostigmine gr.1/8 once a day for long periods.

Laurent¹⁴⁴ reported three cases in which physostigmine gr.1/10 - 1/8 preceded by Tr. belladonna m 15 - 20 had been given by mouth. In all of them gastric disturbances were produced, and in two cases, faintness. Where these ill effects were severe, there was no improvement in the myasthenic symptoms.

As atropine does not antagonise the depressing effect of physostigmine on the heart muscle, which may possibly be a contributory cause of the faintness, though animals poisoned by physostigmine die from respiratory paralysis with the heart still beating,

it seems advisable to test the tolerance of the patient by giving small doses of physostigmine, say gr.1/150 with atropine gr.1/100, increasing gradually, and if there is any sign of cardiac depression discontinuing the drug. The effects on the alimentary tract of parasympathetic stimulation could theoretically be prevented by giving sufficiently large amounts of atropine.

When mild cases of myasthenia gravis tolerate physostigmine well, it is to be preferred, because of the cheapness to Prostigmin and though physostigmine is too toxic to be given in the large doses required to relieve the symptoms sufficiently, in severe cases, it could be substituted for some of the doses of Prostigmin. Administration in amounts of gr.1/50 - 1/60 daily for four and a half months produced no ill effects in the case of Mrs. M., and there was no lessening in intensity or duration of the effect.

PERISTALTIKUM - substance 36 of Aeschlimann's series produces an effect like that of Prostigmin on the myasthenic symptoms, less intense but of longer duration, coming on in about twenty minutes, slowly increasing, lasting for twelve hours, and wearing off slowly and gradually, not completely disappearing for eighteen hours.

This longer duration would seem to be of great advantage, but both Miss C. and Miss W. preferred Prostigmin because they did not have to wait for the effect so long, and it was more intense. The largest dose of Peristaltikum given was 4mgm., the effect of which was decidedly less intense than that of 3mgm. of Prostigmin. Peristaltikum is slightly less toxic than Prostigmin and could therefore be given in larger doses. When it is not convenient to have two or more injections a day, Peristaltikum would be useful. At present it is not on the market.

Two other substances of Aeschlimann's series have been tried:-

No. 38 is given by injection, and has an effect like that of Prostigmin, but less intense and of shorter duration.

No 37, is given by the mouth, but doses of 10mgm. and 20mgm. produced no improvement in the myasthenic symptoms.

Prostigmin, No. 32 of Aeschlimann's series in sufficiently large doses temporarily removes the symptoms of myasthenia gravis. The effect begins to come on in four or five minutes, increases rapidly for fifteen minutes, and then slowly for an hour, remains maximal for several hours, the number depending on the amount of work done, and wearing off in about the same length of time as it took to come on. No lessening of the effect occurs after prolonged administration nor is there any ill effect on the general health.

The effects of parasympathetic stimulation, colic, and in a few cases, vomiting, can be counteracted by atropine, the depressing effect of Prostigmin on the cardiac muscle is extremely slight compared with that of physostigmine.

If the patients exert themselves while Prostigmin is having its effect, they are more fatigued when the effect has worn off, than they were before the injection was given. This gives one the impression that the muscles, while being used are forming something which poisons them, substance x, and that this is prevented from doing so by Prostigmin, but when Prostigmin no longer exerts its effect, presumably because it is destroyed in the body, substance x which is less rapidly destroyed seizes upon the muscle. As the symptoms of myasthenia gravis are relieved by rest, substance x, must also be destroyed in the body. When the body is at rest the destructive powers of the body gain ground on

substance x, though some is being formed by the contraction of the muscular fibres which maintain tonus.

When Prostigmin has been administered daily for two weeks or so, and the patients have been exerting themselves, their weakness is somewhat greater in the morning before the injection than it was before the course of injections was begun. Denny Brown¹⁴⁵ queried whether the last state of these patients might not be worse than the first, whether it might not be a case of "flogging a tired horse."

Prostigmin was stopped for a few days in two cases which had reached such a step, and the patients returned to their former state (of being somewhat less weak before the morning injection) in two days. The increase in weakness was therefore not permanent, the probable explanation of its occurrence is that during exertion much x substance was being formed, and though prevented from acting while Prostigmin was exerting its effect, accumulated so that the body took two days to "work off" the accumulation.

The benefits of treatment by Prostigmin enormously outweigh this disadvantage, which moreover can be prevented by giving ephedrine, as has been shown in the cases of Miss C. and Miss W. With ephedrine gr. $\frac{1}{2}$ at 1 p.m., 5 p.m. and 8 p.m. the increased fatigue after Prostigmin does not occur, the patients are a little stronger in the morning before the first injection of Prostigmin than they were before the treatment was begun.

In both these cases full strength returns for several hours; they can hold their own in a pillow fight with the nurses, and sometimes "terrorise" them by trying to lift them up, to show how strong they are. In the case of the lighter nurses they succeed.

It is probable that with sufficiently frequent doses of Prostigmin, supplemented by ephedrine, even a heavy days work could be done.

PROGNOSIS.

The prognosis has been entirely altered by the discovery that it is possible to ameliorate the symptoms of myasthenia gravis by the administration of drugs, of which Prostigmin is the most powerful.

Formerly the outlook was regarded as gloomy, because of the high percentage of deaths in the published cases, though long remissions occurred in many cases and a few patients had lived for many years, in most recorded cases death supervened within a few years of the onset.

It should now be possible to prevent the overwhelming of the patient by the disease, with Prostigmin and an adjuvant, ephedrine if it is tolerated, if not, Potassium chloride. Deaths from inanition, aspiration and respiratory failure should not now occur. It is not yet known what the cause of the heart failure is, or whether Prostigmin would prevent it, but the presumption is that it would.

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The outlook as regards enjoyment of life has been entirely changed, patients unable to work can now earn their own livings, bedridden and semi-bedridden patients can live a normal life at the cost of fifty pounds or so a year.

SUMMARY
and
CONCLUSIONS

Summary and Conclusions.

A brief account has been given of the neuromuscular mechanism, the muscle chemistry, and the chemical transmission of nerve impulses. Dale's view that acetyl choline is the substance acting as a transmitter from the motor nerve ending to a voluntary muscle has been accepted. The fact that a fatigued muscle remains contracted for a considerably longer time than a normal muscle, and the action of adrenaline on fatigued muscle have been mentioned.

In the section on the pharmacology of striated muscle the "curarising" action of most quaternary ammonium bases, and the fact that physostigmine acts by inhibiting the cholinesterase which destroys acetyl choline have been emphasized. The synthetic analogues of physostigmine described, and the formulae and biological array of those used in the treatment of myasthenia gravis have been given. The actions of caffeine and veratrine have been discussed. The lymphorrhages are the only lesions which are almost constantly found; endocrine abnormalities are not sufficiently constant to be of etiological significance. Apart from occasional creatinuria the metabolism in myasthenia gravis is normal, the muscle chemistry as estimated by the changes in the phosphorous holding compounds is normal in spite of gross disturbances of function.

The infective origin of the disease is regarded as likely, because of the absence of evidence of an endocrine or general metabolic

disturbance, and the difficulty of supposing that such disturbances could cause narrow localisation of the symptoms for long periods of time, as well as from the occasional unexplained rises of temperature, and the fairly frequent onset of the symptoms after a pyrexial illness.

The formation of a curarising quaternary ammonium base, in the myofibrils during their contraction, and its destruction by the body, would account for the symptoms. Such bases might conceivably be formed from choline in the muscle by bacterial action, the quaternary ammonium base neurine, which curarises the voluntary muscle and slows the heart is so formed. A minute amount would be sufficient to produce the symptoms.

There is no clear evidence of any muscle or organ other than the striated muscles and the heart being involved. One group of muscles only may be affected for years. The duration varies from two weeks to thirty-five years or more; death usually occurs from respiratory or cardiac failure.

The diagnosis is usually easy, but symptoms may disappear if the patient rests before the examination, they will be manifested if the suspected muscles are exercised. In a doubtful case the specific action of Prostigmin would decide. Abrahams' diagnostic eye sign is interesting in that it shows that the contraction of a myasthenic muscle is prolonged as it is in fatigue.

The electrical reactions of muscles are described, Bourgeois' view that they are not different

from those of fatigued muscles except in degree is mentioned. Pritchard's electromyograms show that the tetanus in myasthenia gravis is not maintained when the frequency is over 80 a second.

Three case of myasthenia gravis which have been treated with physostigmine or Prostigmin are recorded in detail. An account of the treatment has been given. Several drugs, physostigmine, Prostigmin and other analogues, veratrine, and potassium chloride temporarily lessen the symptoms of myasthenia gravis. Of these Prostigmin is the most powerful, and ephedrine in the two cases recorded, the most useful adjuvant.

Conclusions.

1. The course and symptoms of the disease can be best explained by the action of a curarising quaternary ammonium base, produced by microbic action on the intermediate products formed during muscular contraction within the muscles.
2. That the symptoms can be temporarily removed by the action of several drugs, of which Prostigmin is the most powerful.
3. Long continued daily administration of large doses does not cause a diminution in the effect of the drug, nor are untoward results produced.
4. Muscles weak from disease may regain strength.
5. Atropine in doses varying with the individual counteracts the undesirable effects of parasympathetic stimulation.
6. Adjuvants such as ephedrine, potassium chloride or veratrine are helpful.

"17.1000 This treatment is not curative, but it enable even a severe case of myasthenia gravis to lead a normal life. No case of myasthenia gravis should now die of the disease.

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