

# OBSERVATIONS ON THE NATURE OF MYASTHENIA GRAVIS. THE EFFECT OF THYMECTOMY ON NEURO- MUSCULAR TRANSMISSION<sup>1</sup>

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This communication reports a study of the state of neuromuscular transmission, and the effects upon it of prostigmine and acetylcholine injected into the brachial artery, in five patients with severe myasthenia gravis, five months after the total extirpation of the thymus gland. The partial block in neuromuscular transmission and the abnormal reactions to the intra-arterial injection of prostigmine which existed pre-operatively (1, 2) have been altered profoundly. The results of these experiments indicate that in myasthenia gravis the thymus influences greatly the function of the motor nerves and the striated muscles which they innervate. These findings furnish objective evidence of an action of the thymus gland, and an analysis of the results may assist in understanding the normal physiological function of this structure.

In addition to changes in the physiological and pharmacological patterns of neuromuscular function which followed thymectomy, there occurred in three of the patients an extraordinary clinical improvement which developed concomitantly with the reversion of neuromuscular function toward normal.

## METHODS

The methods employed in this study have been described in detail previously (3). Injections of prostigmine and acetylcholine were made into the brachial artery. The ulnar nerve was stimulated through the intact skin above the elbow, by square waves lasting about one millisecond and presented singly, in pairs, or in salvos by the delay circuits of Marshall and Talbot (4). These stimuli, transformer-coupled to the stimulating electrodes, had an amplitude greater than necessary to elicit maximum action potentials from the muscle electrodes placed on the skin over the *m. abductor digiti quinti*. These muscle action potentials were led to the input of a condenser-coupled amplifier and recorded by means of a cathode ray oscillograph.

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## MATERIAL

The clinical histories of these patients have been recorded before (5).

*Patient P. C.* (Unit #225775). A thirty-three-year-old colored farmer developed severe and progressive myasthenia gravis in July 1940. He required 240 mgm. of prostigmine a day before operation and even then was incapacitated. The thymus was removed July 26, 1941. By August 9, 1941, he no longer required prostigmine. Since then there has been a steady return of strength and by February 1942, he was able to perform light work.

*Patient R. L.* (Unit #255345). A twenty-eight-year-old graduate student developed myasthenia gravis in August, 1940. By July 1941, she was confined to bed because of weakness and required 240 to 270 mgm. of prostigmine a day. The thymus was removed on August 4, 1941. She required no further prostigmine after August 18, 1941. By February 1942, she was working eight hours a day in the statistical department and the only residual evidence of former myasthenia was weakness of the muscles of the pelvic girdle, which made it necessary for her to walk with a wide base.

*Patient L. K.* (Unit #127185). A twenty-two-year-old colored woman who developed severe myasthenia gravis in 1935. In August 1941, her activities were greatly limited by weakness, despite the oral administration of 120 mgm. of prostigmine a day. The thymus was removed August 18, 1941. When discharged from the hospital in October 1941, she was walking and eating easily without any medication. In February 1942, she showed evidences of continued gain in strength. She felt that she required 7.5 mgm. of prostigmine in the morning on arising, and occasionally if she went out in the evening, she would take 15 mgm. of prostigmine. Her activity was not limited by weakness.

## RESULTS

### *The response to a single maximal nerve stimulus*

The characteristic electromyogram of the *m. abductor digiti quinti*, elicited by a maximal stimulus to the ulnar nerve, in normal subjects is marked by its uniformity. In any one individual, the voltage of the response never varies more than 15 per cent from day to day; in most instances, the variation is less than 5 per cent (6). This

constancy has been interpreted to indicate that under the conditions of the examination in the normal subject, all excitable muscle fibers respond to a single maximal motor nerve stimulus.

In contrast to the normal subject, the patient with severe myasthenia gravis exhibits an electromyogram which indicates that some of the available muscle fibers do not respond to a maximal nerve stimulus. This is suggested by the small amplitude of the action potential and by the effect of prostigmine which improves the muscle strength and increases the voltage of the responses. The reduction in amplitude of the action potential in the untreated myasthenic state is proportional to the number of muscle fibers which fail to respond to a maximal nerve stimulus (1).

In two of these patients we have had the oppor-

tunity of studying the state of neuromuscular transmission before and after thymectomy. In

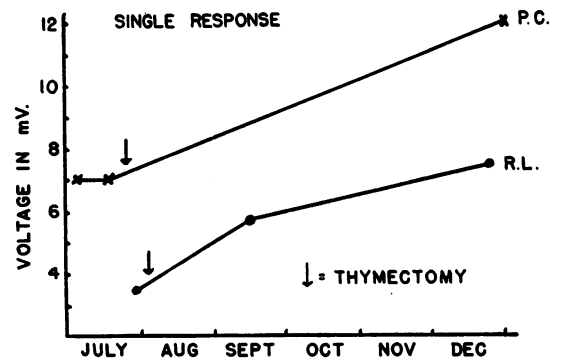


FIG. 1. THE VOLTAGE OF THE RESPONSE OF THE *M. Abductor Digiti Quinti* TO A SINGLE MAXIMAL STIMULUS TO THE ULNAR NERVE INCREASES AFTER THYMECTOMY Patients R. L. and P. C.

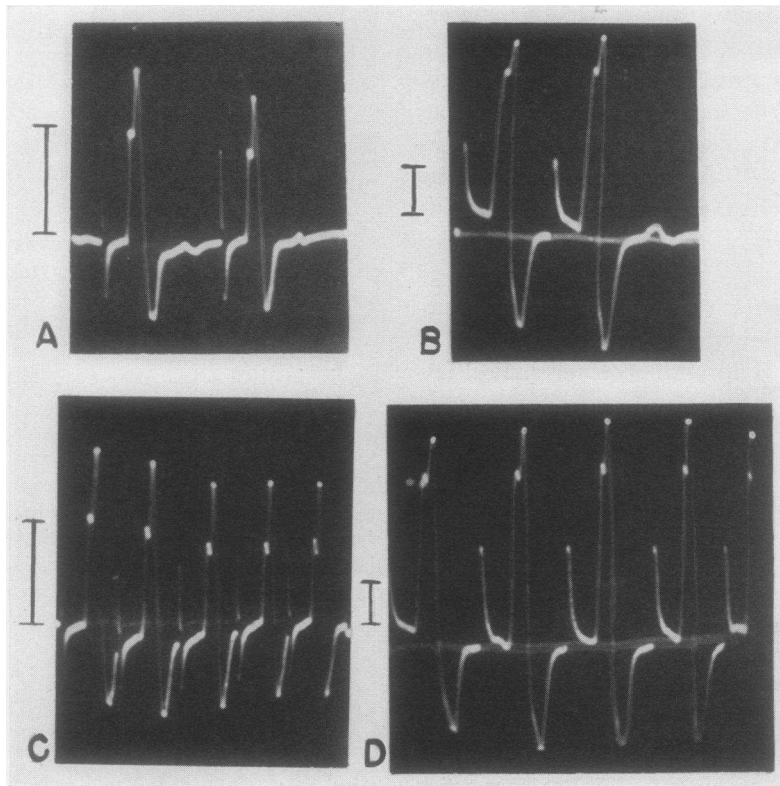


FIG. 2. PATIENT R. L.

A. Before thymectomy, the depression of the second response which follows at an interval of 32 msec. is 20 per cent. B. Five months after thymectomy, the second response at a 20 msec. interval shows slight facilitation. C. Before thymectomy, there is progressive depression of the responses to a train of maximal stimuli at 16 msec. intervals; the fifth response is but 74 per cent of the first. D. Five months after thymectomy, a train of maximal stimuli at 20 msec. intervals results in facilitation. Calibration = 2.0 mV.

both instances, without any adjuvant therapy, there has occurred a large increase in the voltage of the response to a single maximal stimulus. In R. L. the voltage rose from 3.5 to 7.4 mV., an increase of 110 per cent; in P. C. the voltage rose from 6.9 to 12 mV., an increase of 70 per cent (Figure 1). These rises in potential, indicating an improvement in neuromuscular transmission, were accurate reflections of the clinical improvement.

*Transmission of paired maximal stimuli;  
"the two-volley curve"*

In the normal subject, when two maximal stimuli, separated by a brief interval, are delivered to the motor nerve, the amplitudes of the corresponding muscle action potentials are equal (6). In these patients with severe myasthenia gravis, a depression of neuromuscular transmission, induced by the passage of the first volley across the junction, had resulted in a decline in the voltage of the second response of the pair (Figure 2A) (1, 7). Following thymectomy, the two-volley

response has been altered significantly. In the patient P. C., before operation, the voltage of the second response to a pair of stimuli delivered at an interval of 64 msec. had been only 40 per cent of the first. Five months after thymectomy, the voltage of the second response at the same two-volley interval was 82 per cent of the first (Figure 3). Thus the characteristic depression of neuromuscular conduction found during the myasthenic state had been greatly reduced.

In the patient R. L., the alterations in the two-volley curve which were noted five months after thymectomy were even more striking. Prior to operation, the depression of the second response to a pair of maximal stimuli, separated by a 33 msec. interval, had been 20 per cent. In contrast, after thymectomy the second response was actually greater in voltage than the first (Figure 2). This phenomenon of facilitation, which appeared in this patient during the postoperative period of improvement, may be compared with a similar process which we have recorded in another patient (1) during a spontaneous remission when myasthenia was minimal.

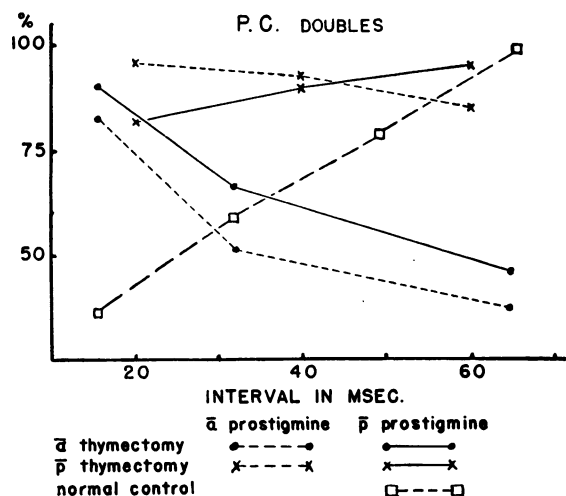


FIG. 3. TRANSMISSION CURVES OF PATIENT P. C.

The potential of the second response, expressed as percentage of the first, is plotted against the interval of the two stimuli, expressed in msec. *Before thymectomy:* ●- - - - ● = marked depression and ●- - - - ● the slight improvement after prostigmine. *After thymectomy:* x- - - - x indicates the depression of the second response which is minimal, and x- - - - x shows that after prostigmine there is a different slope to the recovery curve, approaching that seen in the normal subject: □- - - - □.

*Transmission of a train of maximal stimuli*

A salvo of maximal stimuli delivered to the ulnar nerve in a normal subject at 16 to 20 msec. intervals evokes a train of responses which are equal in voltage. In every myasthenic patient whom we have examined, this train of responses has been characterized by a progressive fall in the amplitude of the action potentials. The depression of the consecutive potentials has been roughly proportional to the severity of the myasthenia in the muscle examined; and the extent to which the defect in neuromuscular transmission has been repaired by prostigmine has also reflected the degree of clinical weakness.

Following thymectomy, the responses to the train of stimuli underwent a significant change in the direction of the normal response. In the patient P. C. before thymectomy, the fourth response to a train was depressed almost to extinction; and even after the intra-arterial injection of a large amount of prostigmine (1.5 mgm.), the fourth response was still only 41 per cent of the first. Five months after thymectomy, there had occurred a marked improvement in neuromuscular conduc-

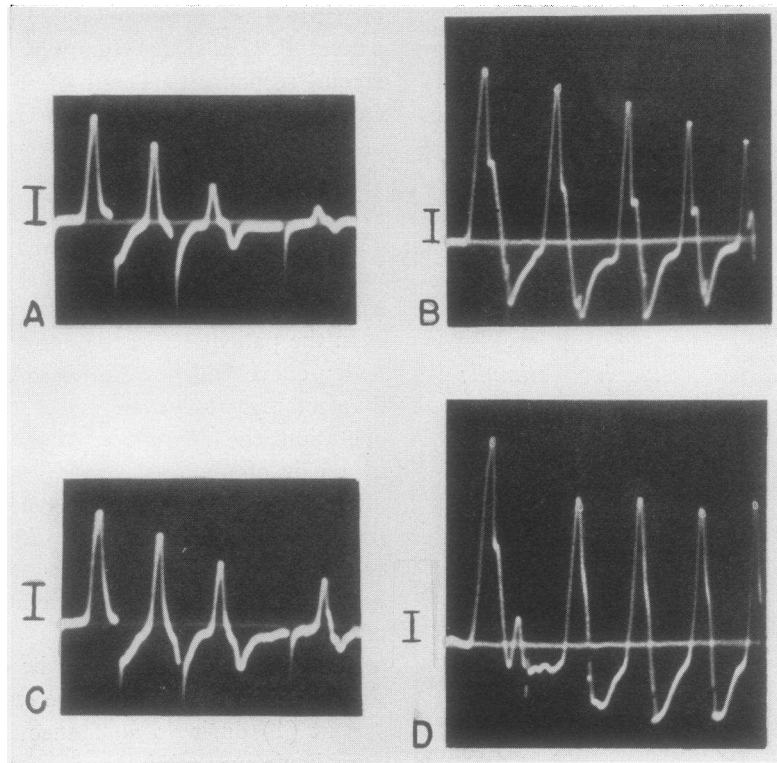


FIG. 4. PATIENT P. C.

A. Train of maximal stimuli at 16 msec. intervals before thymectomy. B. Same test five months after thymectomy at 20 msec. intervals showing rise in action potential and increased efficiency of neuromuscular transmission. C. Before thymectomy, showing the moderate improvement in transmission after injection of 2.0 mgm. prostigmine into the brachial artery. D. Same as B. but after 1.0 mgm. of prostigmine intra-arterially. Calibration = 2.0 mV.

tion, even though no prostigmine had been administered (Figure 4). The patient R. L. showed before thymectomy a characteristic progressive decrease in the voltages of the consecutive responses to a train of maximal stimuli. Five months after operation there was a complete reversal of the depressed response and a significant facilitation of the successive responses appeared (Figure 2). The occurrence of a similar phenomenon in another patient (B. W.) has been described before (1). The presence or development of facilitation may be a valuable criterion of the state of the myasthenic process, for in these two instances it has appeared during the development of a remission, the one spontaneous and the other apparently induced by extirpation of the thymus. A process of facilitation of this degree has never been seen in normal subjects, in whom the variations do not exceed 5 per cent.

#### *The action of prostigmine*

The effect on neuromuscular function of prostigmine injected into the brachial artery of normal subjects may be summarized briefly:

- (a) Profound paresis of the muscles in the injected extremity.
- (b) Fascicular twitching of the muscles in the injected extremity.
- (c) Repetitive action potential in response to a single nerve stimulus.
- (d) Depression of neuromuscular transmission, produced by the passage of one volley across the junction. This depression is greatest immediately after the first volley and disappears, in most instances, within 100 msec. (3) and therefore is of a different nature from the depression after activity in patients with myasthenia gravis.

The effect of prostigmine in the myasthenic patient is quite different and produces:

- (a) Partial or complete return of motor power.
- (b) No fasciculations.
- (c) No repetitive response despite enormous doses (2 to 3 mgm.).
- (d) Repair of the existing defect in neuromuscular transmission to or toward a normal response (1, 2).

These four differences in the effect of prostigmine on normal and myasthenic subjects were employed to estimate objectively the change in neuromuscular function which had occurred in the myasthenic patients following removal of the thymus.

*Motor power.* Before operation, five of the patients showed an increase in strength, locally and then generally, after the intra-arterial injection of prostigmine. The degree of improvement was roughly proportional to the initial weakness. In two patients, R. L. and L. K., who had regained almost normal strength after thymectomy, the intra-arterial injection of prostigmine in moderate doses (0.75 and 1.0 mgm.) produced weakness. In a third patient, P. C., who had had the severest myasthenia of the entire group and had experienced enormous clinical improvement after thymectomy, the injection of prostigmine into the brachial artery five months after the operation produced an increase in strength significantly greater than the same amount of drug (1.0 mgm.) had effected before operation. The remaining two patients, R. S. and M. W., whose myasthenia had been least severe and who had made virtually no clinical recovery, showed little or no change in this reaction to prostigmine, when tested two months after operation.

*Fasciculation.* None of these five patients had developed local or general fasciculations in response to the intra-arterial injection of prostigmine before thymectomy. All of these patients developed local fasciculations postoperatively. The extent and frequency of the fascicular twitches were less than occurs in the normal subject. However, fasciculations could be induced with an amount of prostigmine (1.0 mgm.) which before thymectomy failed to produce fasciculations in any instance. This observation itself

constitutes objective evidence that, in each patient from whom the thymus was removed, neuromuscular function was altered, for the evidence available indicates that prostigmine fasciculations originate at or near the nerve endings (8).

*Action potential.* The partial block in neuromuscular transmission which had existed pre-operatively in the patients tested had been decreased by prostigmine, so that the amplitude of the action potential evoked by a single stimulus increased after the administration of prostigmine. This was in direct contrast to the response of a normal subject in whom the amplitude of potential in response to a *single* stimulus was not affected by prostigmine. Post-operatively, in the two patients in whom tests for comparison were available, the change in potential after prostigmine became minimal or insignificant. The patient R. L.

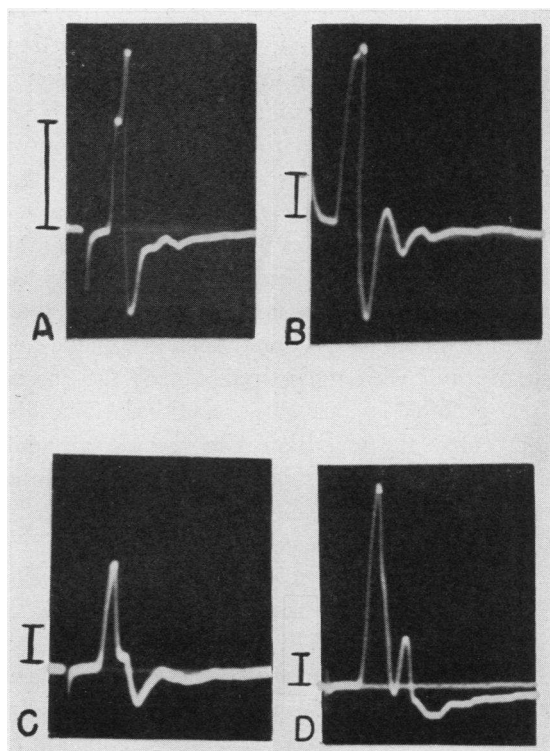


FIG. 5. REPETITIVE RESPONSE TO SINGLE STIMULI AFTER INTRA-ARTERIAL PROSTIGMINE

Patient R. L.: A. Before thymectomy; no repetition. B. After thymectomy a repetitive response appeared.

Patient P. C.: C. Before thymectomy there was no repetitive response. D. Repetitive response developed after thymectomy.

Calibration = 2.0 mV.

had shown a rise in voltage of 34 per cent pre-operatively, and five months after thymectomy the rise was less than 2 per cent, which was within the normal variation. The patient P. C. had shown a rise of 19 per cent before thymectomy and 8 per cent after.

*Repetitive response.* In the normal subject, the response to a single motor nerve stimulus is a single diphasic wave; the intra-arterial injection of prostigmine converts this single wave into a repetitive response, consisting of a series of three or four spikes which fall off rapidly in voltage and duration and which are separated by approximately equal time intervals (3). If the ulnar nerve is stimulated by two maximal stimuli separated by a short interval, the repetitiveness of the second response is greatly diminished until the stimuli have been separated by 48 msec. or more.

In these myasthenic patients before thymectomy we had not been able to detect a repetitive response to single stimuli, although observations had been made after the intra-arterial injection of large doses of prostigmine (2.0 mgm.). However, in three of these patients whose electromyograms were studied, there appeared following thymectomy a repetitive response to single motor nerve stimuli after moderate doses of prostigmine (0.75–1.5 mgm.) (Figure 5). The return of repetitive activity was not complete, for there were only one or two additional spikes in the first response and with the paired stimuli the second response failed to become repetitive. The development of the repetitive response was an additional alteration in neuromuscular function toward a normal pattern.

*Neuromuscular transmission.* A study of the "two-volley curve" revealed much less depression of neuromuscular transmission after single or multiple responses. The changes observed before the administration of prostigmine have been described above. Before thymectomy, prostigmine always had reduced the neuromuscular junctional depression created by the passage of a single volley; in some instances, normal neuromuscular transmission had been completely restored. After thymectomy, when little or no neuromuscular junctional depression existed in two of the patients (*v. s.*), the intra-arterial injection of prostigmine produced a slight but definite depression

of conduction after the passage of one volley across the junction. In the patient R. L., for example, five minutes after the intra-arterial injection of prostigmine, when moderate weakness had developed, a train of maximal nerve stimuli evoked responses which fell in amplitude until the fifth response was only 74 per cent of the first (Figures 6 and 7). This progressive depression of the responses after prostigmine is similar to that seen in the normal subject.

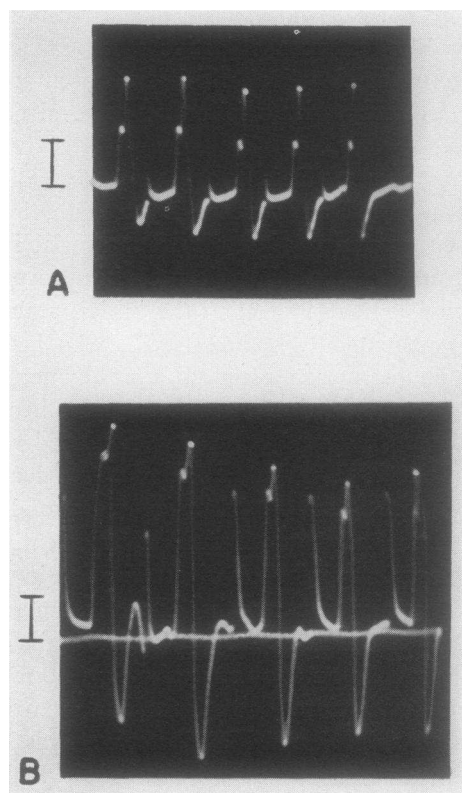


FIG. 6. PROSTIGMINE DEPRESSED NEUROMUSCULAR TRANSMISSION AFTER THYMECTOMY

Patient R. L. A. Train of maximal stimuli at 16 msec. intervals before thymectomy; 1.0 mgm. of prostigmine has been given and the responses are equal. B. Same test after thymectomy, at 20 msec. intervals; there is a depression of the successive responses characteristic of the normal. Calibration = 2.0 mV.

#### *The action of acetylcholine*

In the normal subject, the intra-arterial injection of 20 to 40 mgm. of acetylcholine produces, among other effects, a transient weakness of the extremity. By contrast, in the myasthenic patient, there

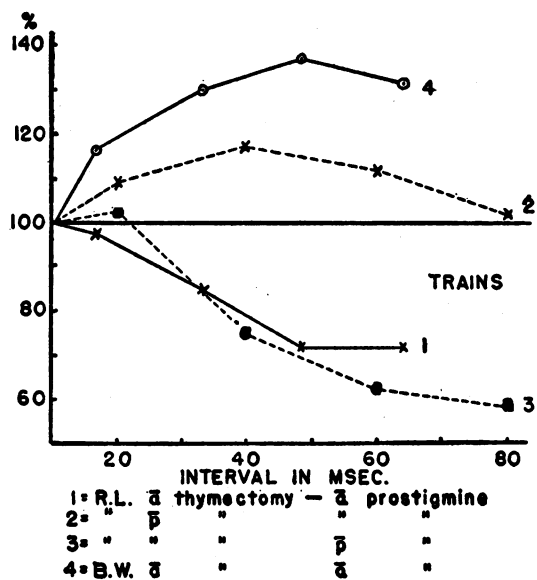


FIG. 7. TRANSMISSION CURVES OF RESPONSES TO TRAINS OF MAXIMAL STIMULI OF THE PATIENT R. L.

Potentials expressed as in Figure 3. 1. Before thymectomy there is a progressive depression; no prostigmine. 2. After operation the responses are facilitated; no prostigmine. 3. After thymectomy prostigmine produces a depression similar to that observed in the normal subject. 4. Patient B. W. (1) showing facilitation during a spontaneous remission.

is a sudden involuntary contraction of the injected muscles. In the patient P. C., the only one in whom we have had the opportunity to restudy the effect of intra-arterial acetylcholine postoperatively, the injection of 20 mgm. of acetylcholine produced a definite brief contraction of the muscles of the injected extremity, but the violence of the contraction was strikingly less than before thymectomy. In addition, as soon as the contraction had relaxed, it was found that the power of the grip was markedly decreased. This transient effect lasted about thirty seconds. It is important to note that this weakness which is characteristic of the normal subject never had been found in this patient before operation.

#### DISCUSSION

In a previous communication (2) it was suggested that the defect in neuromuscular function which characterizes myasthenia gravis results from a reduction in the amount of transmitter substance, acetylcholine, released at the nerve endings in response to a motor nerve volley. This interpreta-

tion followed a consideration of the evidence summarized below.

(a) Prostigmine repaired the neuromuscular defect occurring in myasthenia gravis and has been shown to protect acetylcholine released at the nerve endings from hydrolysis by cholinesterase.

(b) In the normal subject, prostigmine in high concentration (injected intra-arterially) produced a profound local paresis; in the myasthenic, however, prostigmine increased motor power. Since acetylcholine in sufficiently high concentration depresses neuromuscular function, it was thought likely that the paresis produced in the normal subject results from an accumulation of acetylcholine to a depressant concentration, owing to the anticholinesterase action of prostigmine. The failure of prostigmine to produce weakness in the myasthenic muscle suggests that insufficient acetylcholine is available to accumulate to a depressant concentration (Figure 8).

(c) If the amount of transmitter substance available for release were reduced, it should, in effect, produce functionally a partial "denervation." And this "denervation" might be expected to lower the effector's threshold to the transmitter substance (9). Such sensitization to the transmitter substance, acetylcholine, does occur in the myasthenic muscle; and thus the hypothesis that the transmitter agent has been reduced in quantity gains further support.

This concept of the fundamental defect at the neuromuscular junction emphasizes the relation of the amount of transmitter released to the threshold of muscle excitation by the transmitter. Any factor which increases the amount of transmitter released will improve neuromuscular function in the myasthenic. A secondary effect might be expected to be a corresponding increase in the threshold of the muscle to acetylcholine as the neuromuscular junction approaches normal: a "functional regeneration."

Certain striking similarities between partial curarization and myasthenia gravis suggested that the neuromuscular defect in myasthenia gravis might result from the action of some circulating substance. In the light of known pathological changes occurring in myasthenia gravis, the thymus might be a likely source of this hypothetical agent. This hypothesis has been submitted to experimental

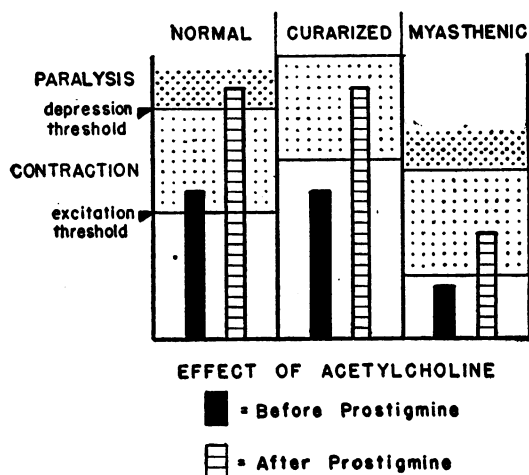


FIG. 8. EFFECT OF ACETYLCHOLINE

The quantum of acetylcholine released by a single stimulus is represented by the solid columns. The effect of this quantum is increased by prostigmine and this is represented by the barred columns. In *normal* muscle, the quantum of acetylcholine released exceeds the excitation threshold and maximal contraction results. When the effect of this quantum is increased by prostigmine until it exceeds the depression threshold, then paralysis results. This depends upon the fact that acetylcholine depresses neuromuscular transmission in higher concentrations. In *curarized* muscle, the quantum of acetylcholine is not altered but the elevation of the excitation threshold renders the normal amount of acetylcholine less effective. Prostigmine increases the effect of this quantum and the contraction range is reached once again. This is the "decurarizing" effect of prostigmine. In *myasthenic* muscle, the excitation threshold is lowered ("functional" partial denervation) but the quantum of acetylcholine is reduced to an even greater degree ("inadequate" acetylcholine release); submaximal response results. Prostigmine enhances the effect of this "inadequate" quantum and, as it exceeds the lowered excitation threshold, improved transmission results.

proof (5), and the results which have been described here, indicate that the thymus plays an important but as yet unidentified role in the pathogenesis of myasthenia gravis. An analysis of this role is being undertaken.

The study of neuromuscular function has indicated that after thymectomy profound alterations toward a normal pattern occurred in the three patients who exhibited such extraordinary clinical improvement. There has been recorded the development of local fasciculations following the intra-arterial injection of prostigmine; the muscle action potential, in response to a maximal motor nerve stimulus, increased enormously, indicating

that more muscle fibers were excited; the characteristic depression of neuromuscular function following activity at the junction had been eliminated or greatly diminished; the response to a single stimulus after the injection of prostigmine became repetitive as in the normal subject; in two subjects, a normal depression of neuromuscular function developed after the intra-arterial injection of prostigmine; and in one subject, the muscle threshold to acetylcholine injected into the brachial artery rose.

The phenomenon of facilitation which developed in patient R. L. after thymectomy is similar to that observed in another myasthenic patient B. W. (1) during a spontaneous remission. It has not been observed in any other subject, either normal or myasthenic. There are few experimental data which might furnish a clear explanation for the appearance of this change in neuromuscular function, but a consideration of the facts available, suggests a possible explanation which is consistent with the concept of myasthenia gravis proposed before (2).

Brown (10) confirmed the original observations of Bremer and Homès (11) on neuromuscular function in partially curarized preparations, and showed again that the second response to a rapid train of maximal motor nerve stimuli gained in amplitude (facilitation), and then the subsequent responses lost amplitude rapidly until they became constant at a greatly reduced level. Brown suggested that this long depression is due to insufficiently rapid replacement of acetylcholine, to which curare has raised the threshold of the muscle fibers. He postulated that the augmentation of the first responses occurring during the first 50 msec. of the train resulted from a separate process of facilitation. These observations may be interpreted to indicate that the amount of acetylcholine released by each successive volley in a train of nerve stimuli decreased until the rate of its synthesis is equal to the rate of release.

This theory is applied to myasthenia graphically in Figure 9. The decline in acetylcholine released toward a constant output is represented by the solid lines. The brief superimposed facilitation process is indicated by the broken lines. In the normal state, all of the innervated muscle fibers respond even when the amount of acetylcholine



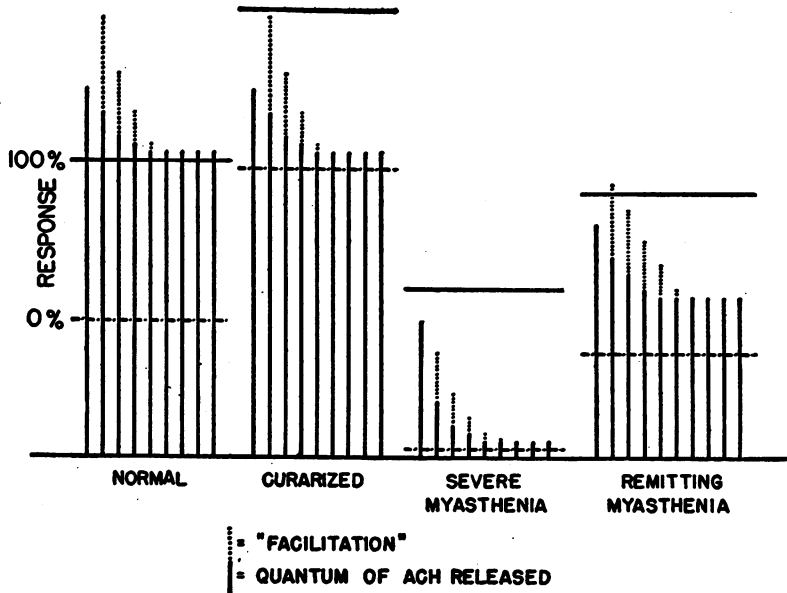


FIG. 9. THEORETICAL DIAGRAM RELATING THE QUANTA OF TRANSMITTER SUBSTANCE RELEASED TO THE APPEARANCE OF FACILITATION

For description see text.

released has reached its minimum, because this minimum still exceeds the threshold for response of the least excitable fibers. Thus any change in amount of transmitter occurring above this threshold will not be detected. When the muscle has been partially curarized, however, the threshold at which every fiber responds is higher. Consequently the variations in amount of transmitter released, and in the facilitation process, will appear as variations in the submaximal response of the muscle as a whole. In the state of severe myasthenia, the hypothetical fall in acetylcholine output is represented by the shorter solid lines which diminish very sharply. The concomitant lowering of muscle threshold to acetylcholine is represented by the lower threshold for total fiber response. The facilitation process may operate here as well as in the normal or curarized muscle, but the abrupt decline in the amount of acetylcholine released obscures the facilitation, so that the responses still decline rapidly. During a remission, whether spontaneous or induced, the threshold for total fiber response rises toward normal and the amount of available transmitter is assumed to increase. This would constitute a transition stage between severe myasthenia and normal function; in this stage, the relation of muscle threshold to the amount of transmitter re-

leased would be similar to that occurring in the partially curarized muscle. Under these circumstances, the previously obscured process of facilitation would become apparent.

SUMMARY

1. Five patients with severe myasthenia gravis have been restudied up to five months after total extirpation of the thymus. Three have shown a great degree of clinical improvement.
2. Electromyographic studies demonstrated that (a) a larger number of muscle fibers responded to a maximal motor nerve stimulus, and (b) there was greater efficiency in the transmission of pairs and trains of maximal motor nerve stimuli across the neuromuscular junction.
3. The intra-arterial injection of prostigmine, in contrast to its effect before thymectomy, now produced (a) local fascicular twitching, (b) repetitive response to a single stimulus, (c) normal local paresis and a depression of neuromuscular transmission in two of the patients, and (d) greater effect of prostigmine in the third.
4. In one patient, the intra-arterial injection of acetylcholine produced less contraction than before thymectomy and the contraction was followed by transient weakness.

5. The evidence indicates that in certain individuals the thymus plays an important role in the pathogenesis of myasthenia gravis. The changes after thymectomy indicate an increase in the amount of transmitter substance available at the neuromuscular junction.

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