17213. Effects of Adrenocorticotrophic Hormone on Neuro-Muscular Function in Patients with Myasthenia Gravis.*

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The adrenocorticotrophic hormone of the pituitary gland has been administered to patients with myasthenia gravis mainly on the basis of the following observations and inferences: 1) the immediate cause of the symptoms of myasthenia gravis is a decrease of acetylcholine synthesis;[1-3] 2) administration of the adrenocorticotrophic hormone increases acetylcholine synthesis *in vivo*;[4] 3) increase of the lymphatic tissue (round-cell infiltration of various organs, mainly striated muscle[5] and "hyperfunctioning" thymus[6] have been found in patients with myasthenia gravis. Tissue fractionation studies[7,8] have shown that one of the sources of the substances that inhibit acetylcholine synthesis is the thymus. Administration of the adrenocorticotrophic hormone induces reduction in the mass of the thymus and the lymphatic tissue;[9,10] 4) removal of the pituitary gland in rats induces changes in the electromyogram[11] that closely resemble the abnormalities noted in patients with myasthenia gravis;[12,13] 5) the pituitary gland of several patients who died of myasthenia gravis showed accumulation of an eosinophilic colloid material suggesting altered function of the gland.[14-18]

This report aims to illuminate the nature of myasthenia gravis by a further analysis of its phenomenology. Therapeutic implications are outside its scope.

Material. Five patients with myasthenia gravis were women aged 24 (H.L.), 29 (J.R.), 31 (M.Y.), 37 (A.S.), and 45 (R.G.) years who had had myasthenia gravis for 4, 17, 10, 13, and 9 years, respectively. During the 3 years before this special study begun the patients experienced minor transient fluctuations but no long lasting or significant changes in their clinical states. They received a total of 300, 45, 180, 112, and 150 mg of neostigmine bromide a day, distributed over the waking hours, taken in from 3 to 6 hourly intervals. H.L. received also 75 mg of ephedrine sulfate, 3 g of potassium chloride, and 0.39 g of guanidine hydrochloride a day; R.G. also received 25 mg of ephedrine sulfate and 3 g of potassium chloride a day. The patients had had, in different degree of severity anorexia, general weakness, ptosis of the eyelids, weakness and easy fatiguability of the muscles of the palate, tongue, face, deglutition, arms, and legs.

Method. Various tests were performed

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with the patients with myasthenia gravis for one week. Thereafter, the patients were administered intramuscularly adrenocorticotrophic hormone in amounts of 20 mg every 6 hours for 5 days. Tests were performed during the administration of the hormone, for 4 days thereafter, and at biweekly intervals for another 12 weeks. The following tests were performed.

Electromyography. Muscle action potential records were taken during repetitive indirect percutaneous stimulation of the ulnar nerve by 10 and 30 pulses per second for 30 seconds, with a stimulus of supramaximal intensity and of one millisecond duration. The method was described by Harvey and Masland[13] and Torda and Wolff.[12] The records were taken daily at the same time of the day, 3 hours after administration of neostigmine bromide during the control period and the period of administration of the hormone, and from 6 to 15 hours after administration of neostigmine bromide thereafter.

Myography. Muscle function was also tested by an ergograph immediately after completion of the electromyograms. The ergograph consisted of a heavy spring attached to an isotonic lever writing on a kymograph. The spring was stretched 2.5 cm once a second by the index and middle finger of the right hand exerting a tension of 15 kg.

Acetylcholine synthesis. Acetylcholine synthesis in the presence of the blood serum was studied following the method described by Torda and Wolff.[2] The method consists of incubation of a tissue containing choline acetylase with blood serum and determination of the amount of acetylcholine formed during the period of incubation. The amount of acetylcholine synthesized in the presence of serum from healthy controls averaged 2.08 $\mu g \pm 7\%$ per 100 mg tissue containing the enzyme.

Results. During the 5 days of administration of ACTH all patients experienced a gradually increasing disability lasting until the second day after the completion of the injections. Thereafter, the patients exhibited increased well being, they began to reduce the daily intake of neostigmine bromide spontaneously (H.L. from 300 mg to 45 mg; M.Y. from 150 mg to 15 mg; A.S. from 112 mg to 15 mg; R.G. from 180 mg to 90 mg; and J.R. from 45 mg to 15 mg) and omitted the other medications. A partial remission of the symptoms occurred in all instances manifesting itself in marked decrease of muscle weakness, the easy fatiguability, and the anorexia. The ptosis of the eyelids, the weakness and easy fatiguability of the muscles of palate, tongue, face, deglutition, arms, and legs became less evident. However, the remission was incomplete, the muscle groups most severely involved in each patient showed only a partial recovery, as is to be expected after a muscle dysfunction of several years duration. Though not clearly definable, it is probable that there is some dwindling of the improvement in muscle function with the lapse of time. This incomplete remission persisted from the completion of administration of the hormone to the writing of this report (approximately 3 months).

Electromyography. Healthy subjects maintained the muscle action potential unaltered during repetitive indirect stimulation with 10 pulses per second for 30 seconds (Fig. 1A) and nearly unaltered (average decrease of 12%) during stimulation with 30 pulses per second for 30 seconds.[12,13] Before administration of the hormone patients H.L., M.Y., A.S., and R.G. exhibited the known decline of the amplitude of muscle action potential during repetitive indirect stimulation. The decline of the amplitude exceeded in all instances 35% on stimulation with 10 pulses per second for 30 seconds and 55% on stimulation with 10 pulses per second for 30 seconds (Fig. 1B-1E). During the period of administration of the hormone the abnormalities noted in the electromyograms of the patients gradually decreased. After completion of administration of the hormone and while on reduced medication the patients were so altered as to maintain the amplitude of action potential during repetitive indirect stimulation in a manner resembling that of healthy subjects. Patient J.R. had before and after administration of the hormone a normal electromyogram (Fig. 1F) as commonly occurs in patients mildly to moderately ill with myasthenia gravis. The electromyograms re-

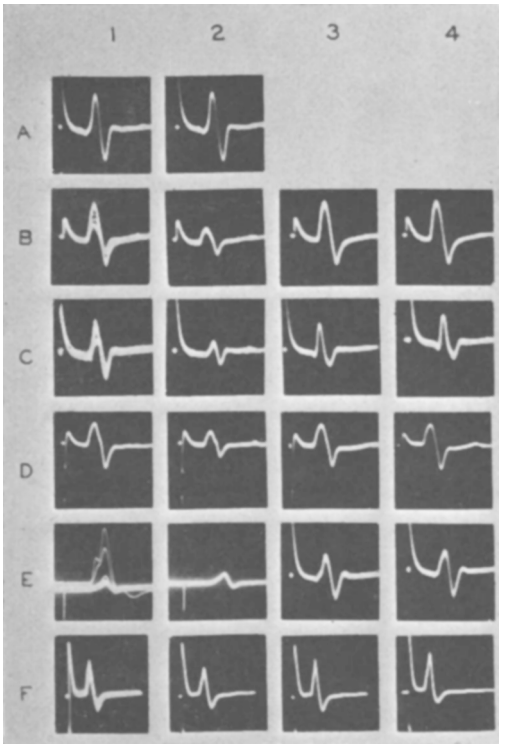

FIG. 1.

Effect of adrenocorticotrophic hormone on muscle action potential during repetitive indirect percutaneous stimulation of the ulnar nerve with 10 pulses per second.

Column 1 represents action potential records taken during the first few pulses of a 30 second stimulation period. Column 2 represents records taken at the end of the 30 second stimulation period. Column 3 represents action potential records taken during the first few pulses of a 30 second stimulation period the third day after completion of the series of administrations of the hormone. Column 4 represents records taken at the end of the 30 second stimulation period. Records in column 1 are comparable with records in column 2 of the same line and records in column 3 are comparable with those of column 4 of the same line since the position of the electrodes remained unchanged during the 30 second stimulation period. Records in column 3 are not comparable with those in column 1 of the same line since the recording electrodes could not be placed in exactly the same position on successive days. In all records the sweep circuit of the oscilloscope was synchronized with the stimulator so that successive stimuli and muscle action potentials were superimposed on the screen of the cathode ray tube. Group A contains records taken from a healthy control; group B records from patient H.L., group C records from M.Y., group D records from A.S., group E records from R.G., and group F records fom J.R.

mained normal up to the writing of the present report (approximately 3 months).

Myography. The 10 control women stretched the spring on the average 150 times before occurrence of fatigue. Before administration of the hormone the patients with myasthenia gravis the average number of contractions (10 exper.) before occurrence of fatigue were 31 (R.G.); 44 (A.S.); 47 (M.Y.); 75 (H.L.), and 110 (J.R.). During the period of administration of the hormone the number of contractions slightly and gradually increased. After completion of administration of the hormone the work performance continued to increase and reached the fifth day the maximum. This was 105 (R.G.); 120 (A.S.); 180 (M.Y.); 250 (H.L.); and 175 (J.R.). Although this test involves motivation, such sudden and dramatic increase in performance suggests an improvement of the function of the neuromuscular system *per se*. The improved work performance persisted for the past 3 months.

Acetylcholine synthesis. In the presence of serum of the patients with myasthenia gravis the synthesis of acetylcholine as compared to healthy control subjects decreased by 55 (R.G.); 50 (H.L.); 42 (M.Y.); 40 (A.S.), and 25 (J.R.) %. In the presence of blood serum taken the third day after completion of administration of the hormone and biweekly thereafter during the past three months the ability of serum to support acetylcholine synthesis approximated normal values. Decreased acetylcholine synthesis in the presence of serum is specific for myasthenia gravis. The more severe the myasthenia gravis the less well the serum supports the activity of choline acetylase.

Comment. Administration of adrenocorticotrophic hormone to patients with myasthenia gravis was first begun by Torda and Wolff.[4,19] Beginnings of remission were observed in the 2 patients treated in the New York Hospital. Because satisfactory objective procedures testing neuromuscular function *per se* had not been elaborated in this laboratory at the time inferences concerning the effect of the hormone on patients with myasthenia gravis were deferred. A remis-

[19] Torda, C., and Wolff, H. G., unpublished data, also Records of New York Hospital.

sion of the symptoms of myasthenia gravis in a moderately ill woman after administration of the hormone was reported by Soffer and collaborators[20] without application of objective testing procedures. The transitory impairment observed during the period of administration of the hormone was also observed by Hellman.[21] The increased general disability during the administration of the hormone may be due to changes in electrolyte distribution,[25] and in various metabolic processes (increase of secretion of some steroid hormone,[22-26] adverse effect on carbohydrate metabolism[25] and decrease of glutathione content of blood.[22]) These processes apparently offset the gradually improving function of the neuromuscular apparatus *per se*.[19]

The above investigations indicate that administration of the adrenocorticotrophic hormone induces changes suggesting the beginnings of an incomplete remission in patients with myasthenia gravis. If the view suggested by this laboratory[1-3] be valid, *i.e.*, that the immediate cause of the symptoms of patients with myasthenia gravis is a decrease in the synthesis of acetylcholine, then the observation that administration of the hormone increases the synthesis of acetylcholine[4] becomes extremely pertinent to an understanding of the apparent remission of symptoms observed in patients with myasthenia gravis after administration of the adrenocorticotrophic hormone. Because of its long lasting effects, it is inferred that the adrenocorticotrophic hormone acts upon some basic regulatory mechanism.

Summary. 1. Five patients moderately to severely ill with myasthenia gravis received 400 mg adrenocorticotrophic hormone given in amounts of 20 mg every 6 hours.

2. Changes that may indicate the beginnings of an incomplete remission occurred after completion of the injections. These changes consisted of decrease of the symptoms and outward manifestations of muscle dysfunction, disappearance of the abnormalities noted in the electromyogram, increased work performance on the ergograph, and increase to normal of the ability of serum to support acetylcholine synthesis. The incomplete remission is long lasting.

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17214. Alkaline and Acid Phosphatase Activity of the Embryonic Chick Retina.

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Evidence has been accumulating which indicates that the phosphomonoesterases may be associated in some way with the differentiation of embryonic tissue. Moog[1] has demonstrated that the common alkaline and acid phosphomonoesterase activity increases

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