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URECHOLINE IN MYASTHENIA GRAVIS

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ALTHOUGH THE ETIOLOGY of myasthenia gravis is still unknown, there has accumulated a certain amount of evidence[1, 2] to suggest that in myasthenia the precipitating factor centres around some disturbance of acetylcholine mechanism with a resulting failure in muscular contraction. This may be due to the lack of precursor substances for acetylcholine synthesis, lack of potentiator substances, or an excess of inactivator or competitor substances.

On the assumption that in myasthenia a relative quantitative deficiency of acetylcholine exists, the beneficial effects of prostigmine (neostigmine) were conveniently explained by the known propensity of this drug to inhibit cholinesterase, and to allow for larger amounts of acetylcholine at the motor end plate. That such an assumption is not quite correct has been demonstrated by numerous experimental and clinical observations,[3, 4] and the fact that certain prostigmine analogues rapidly relieve the weakness of myasthenia gravis, although they possess little or no anticholinesterase activity. Thus it appears that the beneficial effects of prostigmine in myasthenia gravis can be only partly explained by its cholinesterase inhibition, suggesting the existence of some other mechanism to account for its mode of action. Concerning the latter, Stuppler[5] has demonstrated that prostigmine may directly stimulate the denervated muscle itself, while Zaimis[6] believes that the effect of prostigmine is probably independent of acetylcholine, and that in some way it interferes with permeability changes during nerve activity. While all these observations are by no means conclusive in their relationship to myasthenia, they suggest a new approach to the treatment of this disease, firstly by substances which possess an anticurare action, assuming that such a substance is present in myasthenia gravis, and secondly by a substance which may directly stimulate the motor end plate, and thus initiate the process of muscular contraction. Of the latter, acetylcholine itself has been tried experimentally in myasthenia gravis, but when introduced into the body it is too rapidly destroyed to allow of a therapeutic evaluation. However, some of the choline esters which are more stable and resemble acetylcholine in action were tried in 1937 by Fraser[7] and his associates in two patients with myasthenia gravis. They observed that following a subcutaneous injection of acetyl β-methylcholine or carbaminoylcholine, some recovery of muscle power was produced in their patients which was delayed and prolonged as compared with the effects of prostigmine. Choline had no remedial effect.

Of the choline esters tried by Fraser, acetyl β-methylcholine is rapidly destroyed by cholinesterase and some of the manifestations which follow its use—e.g. sweating, salivation, lacrimation and hypotension—are potentiated by prostigmine. The second choline ester, the carbaminoylcholine, is fairly resistant to cholinesterase, but it is cumulative and its effects, e.g., flushing, sweating and abdominal cramps, can be only partly relieved with atropine. The two choline esters used by Fraser were tried by us for a short time on several patients with myasthenia gravis, but were soon abandoned because of their undesirable manifestations. Consequently a search was made for a less toxic choline ester which could be tried on our myasthenia patients.

Eventually a choline ester was found (urethane β-methylcholine chloride: Urecholine, Merck) which was singularly free of the undesirable effects of acetyl β-methylcholine and carbaminoylcholine, and at the same time was found to increase the muscle strength and lower the prostigmine requirement in the majority of our patients with myasthenia gravis. Urethane β-methylcholine chloride is a stable compound, not destroyed by cholinesterase, and possessing a weak nicotine action when given in therapeutic doses; its parasympathomimetic manifestations when they occur can be promptly abolished by atropine. The effects of this choline ester were evaluated on 10 patients with myasthenia gravis intermittently over a three-year period, and also in two control patients with bulbar palsy for one month.

CASE HISTORIES

CASE 1

A.R.—This 25-year-oldism white woman with a family history of hyperthyroidism was in excellent health until 5 years ago, when she commenced to earn her own living. Patient began to notice intermittent episodes of double vision, general tiredness and sudden loss of voice after periods of conversation. Gradually her symptoms increased in severity so that she was unable to get up in the mornings even with ephedrine and 32 to

42 tablets of prostigmine (each of 15 mgm.) daily. At that time patient could not walk farther than one block at a time or make one flight of stairs.

She commenced with small doses of Urecholine and this was gradually increased until at the 6th and 7th days of the trial she was taking 1 gm. per day. Apart from warmth and sweating there were no toxic manifestations. The urinary output was normal and the blood pressure remained unchanged. On the 4th day while taking 400 mgm. of Urecholine, patient's prostigmine requirement became lower, and on the 5th and 6th days of the trial she was taking only 18 tablets of prostigmine and required no ephedrine.

An attempt to maintain this patient on 1 gm. of Urecholine daily without prostigmine was unsuccessful. Subsequently, the patient was maintained on 250 mgm. of Urecholine daily, and in addition to the much reduced prostigmine requirements (Table I) she felt much better, and engaged in all sorts of activities which she was unable to perform before, such as walking up and down the stairs, curling her hair, or brushing teeth with one hand. After 1 month Urecholine was discontinued and a placebo substituted. For the first 10 days there were no changes in her condition and she continued to take 18 to 26 prostigmine tablets daily. After 14 days the prostigmine requirement went up to 32 tablets and her general condition deteriorated.

After 1 month Urecholine was started again with 250 mgm. daily (25 mgm. x 10) and continued for 5 months. During that time she was feeling much better and required less prostigmine (average 26) and no ephedrine. Shortage of Urecholine necessitated another period of placebo for 3 months during which period she relapsed and was unable to walk farther than one block at a time. Eventually, thymectomy was considered, and 6 months after Urecholine was discontinued the operation was performed. There was no improvement in the patient's condition six months after the operation; if anything, her condition deteriorated further. She required 38 to 45 tablets of prostigmine, plus ephedrine, and for most of the time she was confined to the armchair. Urecholine given to this thymectomized patient in a dose of 250 mgm. daily, after 1 week reduced her prostigmine intake from 45 to 30-32 tablets, and improved her muscular strength; she was able to engage in some household activities, mow the lawn, and walk better, and there was no need for ephedrine. That this improvement was due to the Urecholine and not to the thymectomy was subsequently shown when the drug was discontinued and the patient relapsed once more. Presently she is taking 200-250 mgm. of Urecholine daily, and improvement is maintained.

CASE 2

H.B.—This white woman, age 26, subjected to a lot of friction and tension at home, developed a bulbar and peripheral type of myasthenia 6 years ago. Patient's mother suffers from hyperthyroidism and exophthalmos. At the time of the trial the patient's prostigmine intake fluctuated from 12-22 tablets daily, her eyes were troubling her a good deal and there was some weakness of arms and legs. Patient was started on Urecholine under very close supervision and the drug was gradually increased until on the 7th and 8th days of the trial she was taking as much as 1 gm. of the drug daily in addition to prostigmine. Apart from some sweating, there were no undesirable effects; blood pressure and urinary function were normal.

On the 7th day of the trial, patient felt very much improved. Her eye weakness was almost gone and she was strong and full of vigour. In fact that day she picked up a piece of embroidery which she commenced before the onset of her disease, and completed it in one day, a feat which she had been unable to perform in the last three years.

At the same time her prostigmine requirement diminished and she was taking only 8-10 tablets a day. Patient continued with 250 mgm. of Urecholine daily for the next three months, and during that time she was maintaining her improved state taking only 6-9 tablets of prostigmine and engaging in heavy domestic duties. She observed that the usual deterioration of myasthenia which preceded and immediately followed her menstrual flow was absent while on Urecholine. After three months Urecholine was discontinued and after 10 days her weakness and prostigmine requirement increased. Afterwards Urecholine was tested on this patient on several occasions and each time there was some amelioration of her myasthenic phenomena and reduction in prostigmine dosage. Conversely, when on placebo her weakness increased and she required more prostigmine.

After 2 years, Urecholine was discontinued and the patient was observed for 6 months. During that time there was a gradual deterioration in her condition and at times she required as many as 35 tablets of prostigmine daily.

At the end of the 6 months, thymectomy was performed and this was followed by the disappearance of the bulbar myasthenia, generalized increase in muscle strength and a lowering in prostigmine requirement to only 1-6 tablets a day. Six months after the operation,

TABLE I.

CHANGES IN PROSTIGMINE AND EPHEDRINE INTAKE IN 10 PATIENTS WITH MYASTHENIA GRAVIS WHILE ON URECHOLINE

	Pre-trial		*Urecholine 200 - 1,000 mgm. daily*		*Response to thymectomy (Nos. 1 -5)*		*Urecholine in thymectomized patients 150-250 mgm. (Nos. 1-4)*	
	Prostigmine 15 mgm.	*Ephedrine gr. ¼*	*Prostigmine 15 mgm.*	*Ephedrine gr. ¼*	*Prostigmine 15 mgm.*	*Ephedrine gr. ¼*	*Prostigmine 15 mgm.*	*Ephedrine gr. ¼*
No. 1 A.R.	38 - 42	2	18 - 26	–	38 - 45	2	30 -	-
No. 2 H.B.	18 - 22	–	8 - 10	–	1 - 6	-	intolerance	
No. 3 H.N.	26 - 32	2	16 - 22	–	20 -	-	16 -	-
No. 4 R.W.	36 -	–	not on Urecholine		21 - 22	2	17 - 18	-
No. 5 C.M.	32 - 36	2	32 - 36	2	0 - 1	-		
No. 6 G.G.	6 - 7	2	4 -	–				
No. 7 P.P.	3 - 5	–	2 - 3	–				
No. 8 C.O.	35 - 45	2	32 - 34	–				
No. 9 B.S.	12 - 14	2	6 - 7	–				
No. 10 W.S.	7 - 8	2	6 - 7	–				

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Urecholine in 100 and 150 mgm. doses was tried again on this patient. On the third day of the trial she complained of a jittery feeling, weakness, sweating and fainting on several occasions. An attempt was made twice to administer Urecholine to this patient but she was no longer able to tolerate this drug.

CASE 3

H.N.—This white woman, age 22, developed myasthenia suddenly while in her 7th month of pregnancy. Preceding the onset of muscle weakness she suffered a severe influenzal episode and this was followed by a prolonged shock and anxiety when she learned that her husband had pulmonary tuberculosis. Patient gave birth to a normal child and for the first few months after delivery her condition was stationary and she controlled most of her symptoms with 12 tablets of prostigmine and ephedrine gr. ¼, twice daily. After 6 months her general condition deteriorated with weakness of arms and legs, difficulty in swallowing, regurgitation of fluids through the nose, and slurred speech, and she developed an exophthalmos which responded to injections of prostigmine.[8] At the time of the trial, the patient was taking 28-30 tablets of prostigmine plus ephedrine, and on this regimen she obtained only incomplete relief from symptoms.

There was no beneficial response when Urecholine was given to the patient in 50, 75 and 100 mgm. doses for a period of 3 weeks. However, when Urecholine was increased to 200 mgm. daily for 1 month, after 3 days the patient felt much stronger and the troublesome bulbar manifestations—as regards speech and swallowing in particular which before responded only partly to prostigmine—were much improved. She required less prostigmine, 16-18 tablets daily, and had no need for ephedrine.

Improvement was maintained for 1 month while on Urecholine. After 1 month placebo was substituted and in 7 days she reverted to her original condition, taking 26-30 tablets of prostigmine and ephedrine, and was very much troubled by her bulbar manifestations. Subsequently, Urecholine was tried on this patient for periods ranging from 1-3 months, and on each occasion there was a generalized increase in muscle strength, a feeling of well-being, reduction of prostigmine requirement, and no need for ephedrine. The sharp decline in muscle strength which in her case occurs regularly for 2-3 days before the menstrual flow was absent when on Urecholine.

When off Urecholine for 4 months her general condition greatly deteriorated and severe bulbar and ominous respiratory manifestations developed. Patient was admitted for thymectomy. However, even after 4 weeks of complete bed rest, her bulbar muscles were resistant to prostigmine and respiratory excursions left much to be desired. Urecholine was administered to the patient in 175 mgm. daily doses, and her bulbar manifestations, particularly as regards swallowing and speech, were partly relieved. The respiratory excursions increased by ⅛ to ¼ inch and prostigmine requirement diminished by 10 tablets daily. A successful thymectomy was performed. After a stormy postoperative period, patient made an uneventful recovery and three months after the operation she can look after her home and children. The exophthalmos is no longer noticeable and the patient is taking less prostigmine (Table I).

Urecholine administered to this patient in 175 mgm. daily doses has still further reduced her prostigmine intake and increased her muscle strength; only residual difficulty in speech remains. That this was not entirely due to the thymectomy operation was demonstrated when after three weeks Urecholine was discontinued; she returned to her pre-Urecholine state in a matter of five days and some difficulty with speech recurred.

CASE 4

R.W.—This is a highly strung and active young boy of 15, who one year ago started complaining of tiredness while at a boarding school. Very sensitive, he tried to cover it up from his superiors, but after several months his weakness increased and he started with difficulty in swallowing, developed nasal speech and eventually, when a diagnosis of myasthenia was made, had to take 36 tablets and also injections of prostigmine because of respiratory difficulties.

Nine months after its onset the disease progressed so rapidly that little hope was given for his survival. Thymectomy was performed at the Mayo Clinic and a large thymus mass removed at operation. After a stormy postoperative period, the patient improved noticeably, his prostigmine requirement diminished slightly, and he regained power in his arms and legs to a considerable extent, and had no more respiratory difficulties. However, his speech was slurred and indistinct, and he could not chew or swallow solid food. Urecholine began with 100 mgm. daily and after two days this was increased to 200 mgm. After six days only, patient's strength was markedly increased. He is feeling strong and well, finds that he can talk for most of the day, and is able to chew solid food and swallow it with no difficulty. At the same time his prostigmine requirement has further decreased and he is not taking any ephedrine.

CASE 5

C.M.—This young woman of 22 observed a generalized weakness at the age of 16; 1½ years following this, difficulty in swallowing and trouble with speech occurred. Six months later nasal regurgitation of liquids and diplopia with ptosis started. Four years after the onset the patient became pregnant; in her last six months of pregnancy she required no medication and was symptom-free. She gave birth to a normally developed male child. However, he was limp, had ptosis and could not swallow, and for three months required large doses of prostigmine. After pregnancy the patient's condition swiftly deteriorated and she could not walk, even on large doses of prostigmine. An attempt to treat this patient with ACTH and cortisone made her condition much worse and dangerous bulbar and respiratory manifestations developed. After four days of hormonal therapy this was stopped and patient started on Urecholine, 200 mgm. daily for four days, followed by 300 mgm. daily for four days, and 400 mgm. daily for two days. There was no improvement in her condition while taking this amount of Urecholine. Eventually she underwent thymectomy with an excellent clinical response.

CASE 6

G.G.—This young woman, age 22, while visiting her brother's farm several years ago accidentally injured a calf. The day after the incident she had a fit of remorse and depression, and the following morning she woke up with a numb and expressionless face, nasal speech, and difficulty in swallowing. In the succeeding months her general condition deteriorated and the weakness, particularly of the bulbar musculature, increased. When first seen the patient was not on prostigmine and her response to ephedrine, gr. ¼, twice daily, was evaluated for a period of several months. Afterwards Urecholine, 200 mgm. daily, was substituted for one month. Comparing the data obtained it would appear that in her case Urecholine was superior to ephedrine in maintaining the general muscular strength. The latter, however, was more effective in relieving some of her bulbar weakness. After this trial she was stabilized with 6-7 tablets prostigmine, and ephedrine gr. ¼, twice daily, and on this dosage, although vastly improved, some of her bulbar manifestations persisted. Urecholine, 200 mgm. daily, has reduced her prostigmine intake to four. She is symptom-free and does not require any ephedrine.

CASE 7

P.P.—This white woman, age 24, started with myasthenia six years ago. The onset was insidious and the disease is mainly peripheral in character. This patient can control her weakness, which is never very great, with 3-5 tablets of prostigmine daily.

Urecholine, 250 mgm. daily, given to this patient for one month produced some subjective improvement and some reduction in prostigmine dosage (2-3 tablets a day). After one month a placebo was substituted and although her general condition did not change very much she required more prostigmine (3-5 tablets). Subsequently, Urecholine in 200 to 250 mgm. daily doses was tried on this patient on numerous occasions, and the results obtained were essentially similar to those obtained in our first trial. The patient observed that the usual deterioration of her myasthenic condition during the menstrual flow did not occur while on Urecholine.

CASE 8

C.O.—This white male, age 36, a very hard-working medical practitioner, developed myasthenia three years ago very shortly after a severe domestic conflict.

A few weeks after its initial onset the weakness rapidly increased, involving the bulbar and peripheral musculature, and only incomplete relief from symptoms was obtained with 35 to 45 tablets of prostigmine and ephedrine gr. ¼, twice a day.

The patient started Urecholine, 50 mgm. daily for one week, and as no improvement was obtained this was increased to 100 mgm. for two weeks. There was no response to Urecholine at this dose level and the results were interpreted as a failure. Three months later, with more information available, he commenced Urecholine 200 mgm. daily for four weeks, and during that time he felt much better. There was some lowering of prostigmine to 30-32 tablets a day, and he felt strong enough to go fishing, drive his car for long distances, and engage more actively in his practice. Because of shortage of the drug, some uncertainty as to the proper maintenance level, and his fear to take what appeared to be a large amount of the drug, the dose was reduced to 100 mgm. daily for the next four months. During these four months he felt generally better, but his prostigmine requirement diminished but little.

Because of shortage of the drug he was off Urecholine for three months and during that time his condition gradually deteriorated and he became increasingly resistant to prostigmine. He died suddenly in a myasthenic crisis, following a chest cold.

CASE 9

B.S.—This 38-year-old white man started with myasthenia five years ago. The onset was insidious in character and the symptoms were mostly confined to the bulbar musculature. Prior to the trial, the patient was taking 12 to 14 tablets of prostigmine daily and ephedrine, gr. ¼, b.i.d. On this regimen he managed to do some fairly heavy farm work, but at times had to rest for a few hours daily because of generalized weakness and occasionally required injections of prostigmine because of sudden attacks of generalized paralysis and collapse. Urecholine started with 100 mgm. daily for the first week; 200 mgm. daily in the 2nd week, and 300 mgm. daily in the 3rd and 4th weeks. With these amounts of medicine there were no abnormal intestinal, bladder or vasomotor phenomena. At the end of the first week of treatment this patient's intake of prostigmine diminished from 12 tablets to 6 or 7 tablets daily, he required no ephedrine and he noticed that the smaller doses of prostigmine with Urecholine were "more effective" than the larger doses of prostigmine, plus ephedrine, which he had been taking previously.

His strength has increased and the ocular weakness and dysphagia are much improved.

While on Urecholine he had no more abdominal cramps which he used to get with 12 tablets of prostigmine. After one month Urecholine was discontinued for four weeks and a placebo substituted. The patient did not notice any change in the first week but during his 2nd week on placebo a definite deterioration set in. The ocular manifestations of myasthenia increased, abdominal cramps returned and his prostigmine requirement went up to 12 to 14 tablets per day. When Urecholine, 300 mgm. daily, was given once more to this patient a most striking improvement occurred. On the 3rd day his ocular myasthenia was improved so markedly that for the first time in 12 months he was able to drive his car alone. He required only 6-7 prostigmine tablets a day, and stopped taking ephedrine. He continued on Urecholine for two months, feeling very well and taking about half of the pre-Urecholine dose of prostigmine. However, the shortage of Urecholine necessitated withdrawal of this drug for another month. Once again after a few days his general condition deteriorated and he required more prostigmine. After one month the drug was given to him in a divided dose of 325 mgm. daily. After a few days the patient's eye symptoms improved, he felt strong and prostigmine intake decreased to 5-8 tablets daily. He continued with this amount of Urecholine for the next three months, and apart from some minor fluctuation improvement was maintained and prostigmine dosage reduced. There were no ill effects on 325 mgm. of Urecholine daily for three months, and no abnormal manifestations were noted.

After the drug was discontinued he reverted to 12-14 tablets of prostigmine and his myasthenia became exacerbated. Subsequently, Urecholine was tested on this patient on numerous occasions, with a satisfactory improvement in symptoms and reduction in prostigmine dosage.

CASE 10

W.S.—This highly intelligent and active white woman has been suffering from myasthenia for the last 25 years. In her case, there is a family history of hypothyroidism. The patient is also hypothyroid with a B.M.R. of −25, and she requires 2¼-2½ gr. of thyroid daily. A study of her past history reveals a seesaw relationship between the thyroid state and her myasthenic condition. The larger doses of thyroid appear to exacerbate her symptoms. The latter are mostly confined to the bulbar musculature, but at times there is a fair amount of generalized muscular weakness as well. Prior to Urecholine, the patient obtained only incomplete relief from symptoms with 8 tablets of prostigmine and ephedrine gr. ¼, twice daily. After many years of setbacks and disillusionment, her attitude towards this trial was critical in the extreme.

Urecholine started with 75 mgm. daily, and as no improvement was obtained after 10 days, this was increased to 150 mgm. and after a few days to 200 mgm. daily. At the latter dose level, a striking relief from symptoms was obtained. Her prostigmine requirement diminished and she discontinued ephedrine, which she has been taking for many years. The patient took her car on a long trip, a feat she had been unable to perform for a long time, and she felt full of vigour and well-being. She states: "Having decreased prostigmine from 8 to 6 tablets daily, I increased Urecholine to 200 mgm. daily. In the 16 days that I have been on this increased dosage I have enjoyed a better state of health than at any time since my relapse of a year and a half ago. I have risen in the morning free of that indescribable fatigue and weakness which characterize the myasthenic's day, and have carried that feeling of well-being with me throughout the day, displaying endurance which has been quite remarkable for its constancy. The facial and eyelid muscles have been most responsive, both of which have shown more stubborn resistance to treatment at all times than any of the other symptoms. In the spontaneity of my smile I have lost the cause of an embarrassment which I have carried through the years. The weak, stiff sensation about the lips and

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mouth seem to have given way to a freer, easier movement both morning and night, times when normally these muscles show greatest weakness. This I have been able to achieve on the reduced amount of prostigmine.

"Summing up I may say that the combined use of 6 prostigmine tablets and 200 mgm. Urecholine daily produces far more beneficial results than the greater amounts of prostigmine taken alone."

Patient maintained her improved state while on Urecholine. However, when this was discontinued after 10 days she suffered a gradual exacerbation and required more prostigmine and at that time she describes her condition as follows: "My 25 days without it have convinced me of its worth, and enabled me to evaluate it properly. My condition during that period compared unfavourably with the 16-day period preceding, in which time I took 200 mgm. Urecholine daily. Brief daily recordings, though they do not tell the whole story, reveal a decline in strength, with emphasis on the facial and neck muscles. Within two weeks I relapsed to my pre-Urecholine fluctuating status where I was 'up' one day and 'down' the next, and unable to enjoy the same measure of good health.

". . . . I am quite convinced that Urecholine is very beneficial to me . . . and my feeling has been confirmed since resuming the drug six days ago. Yesterday and today (the sixth day) I have been very conscious of an increase in muscle tone of the neck and face. At this moment of writing, I can smile more naturally than at any time since I was stricken 25 years ago. Urecholine, as a booster to prostigmine, has been more successful in treating my facial muscles than any previous drug employed."

The beneficial effects of Urecholine on this patient were confirmed on numerous occasions. She has become increasingly dependent on this drug.

COMMENT

It is difficult to assess a new form of therapy on a small number of patients, particularly when they are suffering from a fluctuating form of disease like myasthenia gravis. However, the results of this investigation, which was extended over a three-year period, repeatedly indicate that the urethane choline ester, "Urecholine," is beneficial in myasthenia gravis, and at times some very striking improvements were obtained in the majority of patients under trial.

No such beneficial changes were observed in these patients when a placebo was substituted for Urecholine for periods varying from one to three months. In the two bulbar palsy patients, apart from symptoms of overdosage when more than 200 mgm. was given, Urecholine produced no beneficial effects.

On a daily dose of 200 to 250 mgm. of Urecholine, there was usually a latent period of five to 14 days before a definite increase in muscle strength could be observed. This improvement was most noticeable in the small muscles innervated by the cranial outflow, the intercostals and peripheral musculature in that order, and was not diminished by prostigmine resistance. In some of our patients a striking increase in muscle strength has been repeatedly obtained with Urecholine, e.g., relief of myasthenic facies (W.S.), improved swallowing and speech (H.N., R.W., and G.G.), ability to perform intricate work (H.B.), increased strength of arms and legs (B.S., G.G. and A.R.); later when Urecholine was discontinued or a placebo substituted a relapse occurred, thus leaving no doubt as to its efficacy in this disease. After Urecholine is discontinued there is usually a latent period of 7-14 days before the deterioration in muscle strength sets in. Coincidental with the clinical improvement in the 9 patients, their need for prostigmine lessened and they required no ephedrine. (Table I. Patient A.R. required 45%; H.B., 55; H.N., 34½; R.W., 18; G.G. 30; P.P., 37½; C.O., 17½; B.S., 50; and W.S. 13% less prostigmine.) This improvement in muscle strength while on Urecholine and less prostigmine was greater and better sustained than that observed on larger doses of prostigmine alone, or prostigmine with ephedrine.

An attempt to maintain two of our patients (A.R. and H.B.) on very large doses (1 gm. daily) of Urecholine alone without prostigmine was unsuccessful. Although much stronger they still required some prostigmine. It is remarkable that apart from sweating no toxic phenomena were observed in the two myasthenia patients receiving this huge amount of drug.

At a later date, patients A.R. and H.B. had their thymus gland removed and six months later they were tried again with Urecholine. In A.R. thymectomy has produced no improvement; if anything, her weakness increased and she required more prostigmine. Urecholine, given to this patient in a 200 mgm. daily dose, has once more increased her muscle strength and reduced the prostigmine intake (Table I).

Patient H.B. six months after thymectomy could be classified as belonging to the Group B of Keynes: "virtually well, minimal prostigmine dosage" (Table I). When tried with 150 mgm. of Urecholine she complained of a "jittery feeling, weakness, sweating and fainting." An attempt to administer Urecholine to this patient on two different occasions was unsuccessful. In H.N. Urecholine in 175 mgm. doses daily was used for 14 days prior to the thymectomy. In her case some of the bulbar manifestations of myasthenia, as regards speech, swallowing and breathing, which were responding poorly to prostigmine, improved while on Urecholine and she required less prostigmine. While she was on

this combined prostigmine-Urecholine therapy, a successful thymectomy was performed. Three months after the operation there was a noticeable improvement in this patient's strength, and she required less prostigmine (Table I). Urecholine in a 200 mgm. dose reduced her prostigmine intake further, and produced an additional increase in muscle strength.

In R.W., who was never on Urecholine before, six weeks after the thymectomy operation this drug given in a 200 mgm. dose improved swallowing and speech, and he required less prostigmine.

In four women (H.B., H.N., P.P. and G.G.) the usual deterioration in muscle strength, which slightly preceded and immediately followed the onset of menstrual flow, was absent when on Urecholine.

In three patients (B.S., H.B. and H.N.), who had been experiencing some abdominal cramps after prostigmine, administration of the drug and the subsequent reduction in prostigmine have abolished this effect.

The observation that a choline ester, which behaves like acetylcholine when introduced into the body, can produce an improvement in the muscle strength of myasthenia patients may be a valuable clue to the understanding of this disease. However, it would be difficult to assume that this was due to the overstimulation and an overflow of acetylcholine from the parasympathetic nerve endings and accumulation of acetylcholine in the body.

There was but little evidence of parasympathetic stimulation in our patients receiving very large amounts of this drug. For a time, the urethane (ethylcarbamate) component of Urecholine was suspected as the responsible agent, firstly, on account of some slight structural similarity to prostigmine (dimethyl carbamic ester of 3 hydroxyphenyl trimethyl ammonium methylsulphate), and secondly because of the possibility of its having induced a general thymus-lymphoid hypoplasia, assuming that these structures are incriminated in the etiology of myasthenia gravis.

With this in mind a trial of urethane alone, in 325 mgm. daily doses, was undertaken for two months on five patients with myasthenia gravis. Apart from minor fluctuations the data obtained showed it to be ineffective in reducing the prostigmine intake, or increasing muscle strength, although its sedative effect proved to be of some limited value. Furthermore, in one of our patients (H.N.) there was no histological evidence of thymus or lymphoid hypoplasia after being treated with Urecholine prior to thymectomy. Thus, with the amount of evidence at the moment available, our data tend to support Fraser's original suggestion that in myasthenia, choline esters are utilized in the elaboration of a precursor, from which acetylcholine is set free at the neuromuscular junction, and also that some defect of acetylcholine function is probably present in this disease. The mechanism of this phenomenon is not clear.

SUMMARY

1. In nine out of 10 myasthenia patients observed intermittently over the last three years, a urethane choline ester, "Urecholine," when given in comparatively large doses has increased their muscle strength, and significantly lessened the need for prostigmine.

2. This increase in muscle strength while on Urecholine plus less prostigmine was greater and better sustained than that observed on larger doses of prostigmine alone, or prostigmine with ephedrine.

3. Urecholine, while in no way replacing the value of prostigmine in myasthenia gravis, appears to be a useful adjunct in the treatment of this disease.

4. The patients suffering with myasthenia gravis possess a remarkable tolerance for very large doses of this drug.

ADDENDUM

Since the completion of this report it has been found that cyanocobalamin (vitamin B_{12}) in a one mgm. intramuscular daily dose, potentiates the action of Urecholine in myasthenia gravis.

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