DISCUSSION

M. R. WESTERBERG (*University of Michigan Medical School, Ann Arbor, Mich.*): K. E. Osserman and G. Genkins have presented an extensive experience in the use of the Tensilon test. Certainly, the experience he reports today is vast.

In a classic case of myasthenia gravis where ptosis and dysarthria wax and wane as one takes the history and the patient shows typical weakness of the neck and girdle musculature, the diagnosis is easy to make whether one injects Prostigmine, Tensilon or just gives the patient a tablet of Prostigmine sublingually. At other times the diagnosis becomes very difficult, and the interpretation of tests carried out methodically and patiently requires considerable clinical accumen.

It has always been my impression from clinical observation that Tensilon as well as Prostigmine causes some objective increase in motor power in normal subjects and in those with pre-existing weakness, and, that, for this reason, care has to be exercised in the interpretation of the Tensilon test. When I received Osserman and Genkins paper and observed their statement that normal subjects do not increase in strength with Tensilon, I again tested student nurses and medical students with Tensilon and normal saline controls and again found demonstrable improvement in strength as measured by dynamometer testing for grip strength in these normal subjects with the Tensilon and not with the saline. In one healthy nurse, grip strength increased on the right from 140 to 210 and on the left from 100 to 180. Increase occurred immediately and was measured at the time the patient began to be aware of the eyelid twitching. Strength then rapidly declined, so that if it had not been tested immediately, one would have been unaware of the change. Nevertheless, this type of "normal" response can cause confusion at times both in patients with organic nervous system deficit and in patients without organic disease. We have seen patients with aneurysms and meningiomas in whom ocular palsies were altered by the injection. Even patients with muscular dystrophy and other myopathies may show a transitory improvement in performance after the injection of Tensilon. Apparently, any muscle, healthy or diseased, may respond.

Prostigmine has a similar stimulating affect, and, indeed, it has been used therapeutically in the past for this reason in patients with bulbar palsies and even in patients with poliomyelitis. This type of "normal" response is quite apart from that of hysterical patients in which great improvement may occur with the injection of any type of medication, and in which case double-blind injection series must be carried out before a proper evaluation can be made. Both the "normal" response and the hysterical response may lead to an improper diagnosis of myasthenia gravis. On the one hand other organic pathology may be overlooked or neglected, and on the other hand an hys-

tericál patient who does not have myasthenia becomes wedded to the diagnosis and its treatment. The use of oral quinine as a provocative test is helpful in some of these patients as is, of course, electromyography where the involvement is peripheral.

False-negative tests are few, if any, in our experience also, and although I have heard L. E. Eaton say that a Tensilon injection could make an untreated myasthenic worse, I do not believe I have ever seen this happen.

I agree with Osserman and Genkins that Tensilon testing can be difficult at times to interpret in patients already taking oral medications. I have seen ptosis and dysarthria worsen while motor power in the extremities improved following Tensilon in a patient who subsequently proved to be undermedicated.

The duration of the Tensilon affect in a severely ill patient who has been made worse by Tensilon testing is also difficult for me, at least, to judge. If the patient has had a cholinergic type of response to Tensilon with blockade, this lasts, I think, much longer in patients who are already on optimum medication than in untreated patients. As a result, one is left wondering whether the patient is worsening an hour later because he needs more medication or because the Tensilon is still effective. Fortunately, these very brittle patients are relatively rare, but I suppose the duration of the ill effect varies with the individual patient, and there are no rules for how long to wait to try the same procedure all over again.

We have had one interesting experience with overdosage of Tensilon itself. Five to six cc. (60 mg.) were given intravenously to a man with moderately severe myasthenia with bulbar involvement who then promptly developed respiratory distress. The patient was transferred to our intensive care unit with the endothracheal tube, but he never required tracheotomy; he was able to handle his secretions again in three hours and was back to preinjection strength again in about five hours.

I should like to ask Osserman and Genkins whether they have never seen an increase in strength in a control patient given Tensilon and also whether they have seen Tensilon deplete strength in a patient who was not on medication for myasthenia.

K. E. OSSERMAN: Thank you, Dr. Westerberg, for your discussion. The problem you raise of temporary improvement in strength following Tensilon, especially in nurses used as controls, is due to the type of measuring device used, i.e., a dynamometer. This measures only a single point of grip strength. Despite the use of a double-blind technique, there is no effect with a placebo, but there is an effect that the patient is aware of with Tensilon, i.e., eyelid twitching. It is for this reason that ergograms, which require 105 hand-grip squeezing of a bulb, clearly differentiate the difference in response between normal subjects and the myasthenic patient. Even with the ergogram, the first few squeezes can be higher in the normal control given Tensilon, but the entire pattern of the curve will be different. In the myasthenic patient

the curve after Tensilon, as compared to the control or placebo curve will show definite improvement. Whereas, the Tensilon curve in normal controls or non-myasthenic subjects will not show this kind of improvement.

In answer to the second question of whether Tensilon could deplete strength in a myasthenic patient who is not on specific medications, this can occur. This is seen in about one and one-half per cent of patients who are hypersensitive to Tensilon and manifest cholinergic reaction. For these patients, extremely small dosages of Tensilon, 0.1 to 0.2 mgm., combined with atropine sulphate are used as a testing dose to elicit a typical myasthenic response.

T. R. JOHNS (*University of Virginia, Charlottesville, Va.*): I hope that Dr. Osserman will permit me to be the devil's advocate.

In regard to the use of edrophonium as a *diagnostic* test: we have been impressed with the considerable number of false-negative tests or with results difficult of interpretation. That, along with our feeling that true "double-blind" pharmacologic tests should be done, and that all patients with disease of the motor unit should be in the hospital for an initial thorough examination have led us to de-emphasize the usefulness of edrophonium as a diagnostic test, and to favor the use of neostigmine or, if indicated, decamethonium or curare.

In regard to the use of edrophonium to evaluate drug therapy: We believe it is of great value and great fun to use. However, the very patient in whom one wishes to evaluate effectiveness of therapy per specific dose and to consider the question of myasthenic versus cholinergic crisis is one who will usually exhibit a tremendous variability in response of various muscle groups at a given time which leads to difficult interpretation. The evaluation of such tests requires considerable sophistication, and conclusions arising from them regarding therapy require even more.

K. E. OSSERMAN: For most patients, applicability of the edrophonium test is diagnostic in a clinic or office setting. When difficulties of interpretation, inconsistent results and variants on serial tests are met, we would certainly agree that hospitalization with complete neurologic study and the use of curare and/or decamethonium is indicated. We would disagree with any superiority of neostigmine over edrophonium as a diagnostic agent with the exception of its use in small infants or highly selected cases.

The second point raised regarding the management with edrophonium is in complete accord with the statements of our paper.

J. A. SIMPSON (*University of Glasgow, Glasgow, Scotland*): It would be a pity if criticism of the Tensilon test leads to its eclipse. In my experience this has been the most valuable advance in the clinical management of the patient with myasthenia gravis, but I agree with Dr. Osserman that it is essential to give a proper dose at the correct time. I would further emphasize points I have made previously: (1) only objectively determined improvement should be accepted as evidence of underdosage, never a subjective statement from the

patient; (2) neostigmine has a differential effect on muscles according to their degree of involvement by the myasthenic process. Respiratory muscles may be overdosed while others remain underdosed. It is, therefore, important to observe the bulbar and respiratory muscles in making a Tensilon test.

I believe that more patients die from overdosage than underdosage with neostigmine, due to failure to recognize that full power may not mark the transition from myasthenic to cholinergic weakness. The phenomenon of "resistance" may be due to desensitization in Thesleff's sense, but this should not be assumed without further evidence. I have been collaborating with Dr. A. Wilson of Liverpool in a study of the urinary excretion of neostigmine and pyridostigmine. Significant amounts are still being excreted more than 48 hours after withdrawal of treatment, so slow recovery may simply be due to drug persistence. I have treated one patient in "cholinergic crisis" with *d*-tubocurarine. The rationale was not end plate resting, as suggested by Churchill-Davidson, but direct drug antagonism in an attempt to displace acetylcholine for end-plate receptors. In 30 minutes the patient was considerably stronger. This observation could argue against the presence of a desensitization.

L. P. ROWLAND (*Columbia University, New York, N. Y.*): May I raise a question about the frequency of cholinergic crisis? At the Neurological Institute of New York, it has been the practice to withdraw medication from patients in crisis, a practice initiated by Dr. Clark Randt and the late Dr. Saul Korey when they were residents 15 years ago. During this interval, numerous patients have been seen in crisis. If some of them had been poisoned by drugs, there should be a period of improvement when drug treatment is stopped. But this is not seen. If there is any *clinical* change when the drug is stopped, the patient usually becomes weaker. Cholinergic weakness is a theoretical possibility, but it is difficult to prove how often it occurs in patients taking pyridostigmine or neostigmine by mouth.

K. E. OSSERMAN: Cholinergic crises must be divided into muscarinic side effects and true nicotinic ganglionic blockade resulting in weakness. The former obviously improve with drug withdrawal and administration of atropine. The latter may remain fixed as long as 48 to 72 hours. Elective tracheotomy and withdrawal of medication will already have been unitized by the time the patient begins to improve. Thus, it is difficult to discern the period of improvement referred to by Dr. Rowland. Such instances occur beyond question.

One must also eliminate from consideration the "brittle," drug-resistant patient who may mimic cholinergic crisis.

B. SHERMAN (*Cook County Hospital, Chicago, Ill.*): What is your choice between Mestinon and Prostigmine?

K. E. OSSERMAN: In general, for most patients Mestinon has a smoother and more dependable therapeutic effect. Occasional patients may miss the

peak strength obtainable with Prostigmine but usually come to prefer the smoother Mestinon effect.

L. R. ZELDOWICZ (*University of British Columbia, Vancouver, B. C., Canada*): Neostigmine and edrophonium chloride are important diagnostic tests, but they have significant limitations, namely: (1) The response must be dramatic to be diagnostic for myasthenia gravis. (2) The edrophonium test is particularly suitable in ocular and bulbar forms where its effect can be judged without much of the patient cooperation. This is important because subjective improvement may occur in a fatigue state of neurasthenia which can be misinterpreted for myasthenia not only by the patient but also by the physician. (3) Edrophonium or neostigmine may produce a moderate false positive result in neurological diseases with pseudomyasthenic exhaustion, i.e., progressive spinal amyotrophy, bulbar palsy, polymyositis and others.

Decamethonium-edrophonium test devised by Churchill-Davidson and Richardson[1] has several advantages: it does not depend to a significant degree on patient cooperation; and it gives objective values of the evoked muscle action potential depicting the state of neuromuscular transmission. In mild and focal forms of myasthenia, the test shows increased resistance of muscle membrane to depolarization requiring larger doses of decamethonium (3 mg. or over) to produce paralysis and only slight or no drop of the evoked muscle action potential (see FIGURE 1). In generalized and more advanced myasthenia, the decamethonium-edrophonium test usually shows competitive (nondepolarizing) block. This is evident by early paralysis and a drop of muscle action potential. Both the weakness and the drop of the evoked muscle action potential recover following administration of 10 mg. of edrophonium and, therefore, prove that the decamethonium induced block was of a competitive kind (see FIGURE 2). An opposite effect occurs in a normal person; namely, administration of edrophonium produces more weakness and further drop in the evoked muscle action potential (see FIGURE 3), and this is because of a depolarizing block.

Resistance to depolarization and competitive (nondepolarizing) block may coexist in different muscles of the same individual and even in different fibers of a single muscle (dual block). This may account for "brittleness" of some patients in whom higher dosage of cholinesterase inhibitors are required to improve strength in some muscles, while deepening paralysis may occur in other muscles with increased medication. The decamethonium-edrophonium test is positive for myasthenia also in muscles clinically unaffected, and this is in contrast to neostigmine or edrophonium test which show effect only in the weak muscle. The decamethonium-edrophonium test proves, therefore, that in myasthenia gravis, no matter how mild and localized, the neuromuscular junction defect is generalized throughout the skeletal musculature. The decamethonium-edrophonium test remains positive in clinical remissions whether spontaneous or following thymectomy. This is of considerable

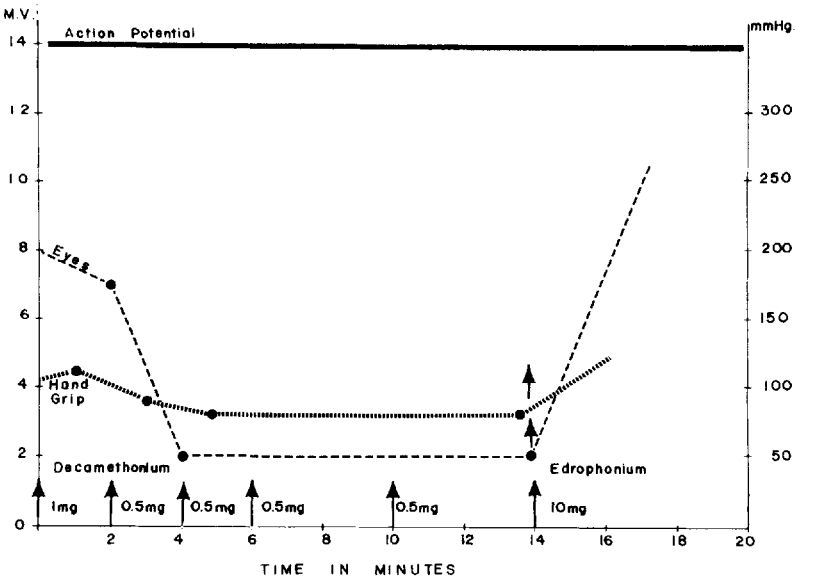

FIGURE 1. Evoked muscle action potential remains unchanged showing resistance to depolarizing by decamethonium iodide.

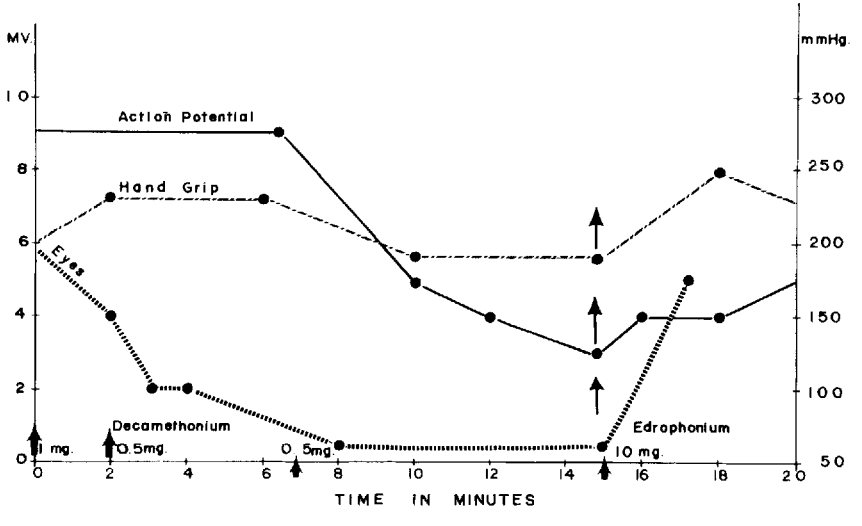

FIGURE 2. Reversal of the drop of the evoked muscle action potential by edrophonium showing nondepolarizing (competitive) block.

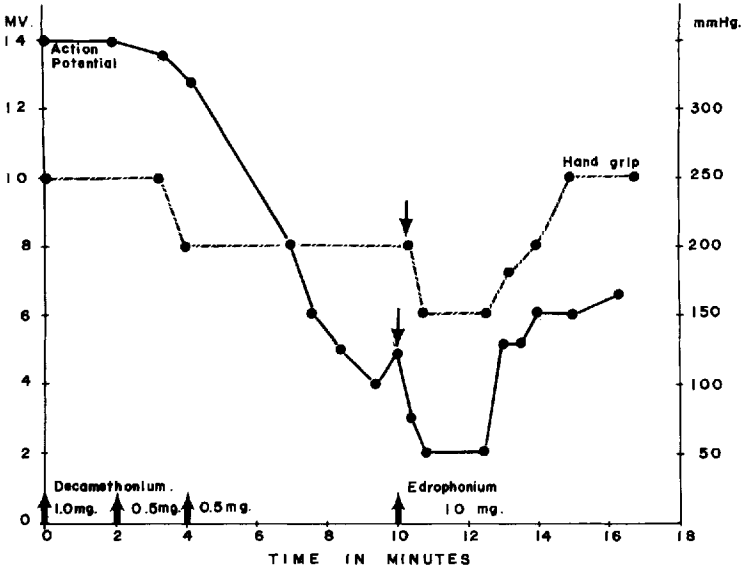

FIGURE 3. Normal muscle. Early drop of evoked muscle action potential by decamethonium, increased by edrophonium, representing depolarizing block.

practical significance for the anesthetist and also for prognosis. If the result of the test is negative, it can retrospectively dispel a diagnosis of myasthenia as in the case of recurring states of fatigue in psychoneurosis.

In our experience[2,3] with 42 cases, the decamethonium-edrophonium test was free of false-positive results either in normals (14 cases) or in neurasthenia or in neurological diseases with pseudomyasthenic symptoms. Out of 28 patients referred to the diagnostic clinic as myasthenia gravis patients, only 18 proved to have myasthenia. In a case of botulinum intoxication and in a case of extraocular palsies from brain stem encephalitis, the edrophonium test gave a false-positive result, while the decamethonium-edrophonium test was negative for myasthenia and helped to solve a conflicting diagnostic problem.

References

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K. E. OSSERMAN: Myasthenic muscle is hypersensitive to *d*-tubocurarine and is resistant to decamethonium (C-10). Churchill-Davidson and Richardson have pointed out that in some myasthenic muscles a dual block may ensue after an initial depolarizing block. The decamethonium-edrophonium test is based on the presence of such dual blockade, which may not always occur.

In our experience, decamethonium-edrophonium testing has been necessary in only a very few patients. The test is fraught with hazards:

(*1*) The term "clinically uninvolved" muscle is ambiguous as it implies clinically uninvolved but "latently myasthenic" muscle. "Latently myasthenic" muscle is difficult to determine. During testing there may be serious complications as truly uninvolved muscles may become totally paretic. If these muscles are respiratory ones, apnea results.

(*2*) There is no good, rapid antidote to C-10 toxicity of normal muscle. The test is, thus, of necessity, an inpatient procedure.

Since anticholinesterase drugs are good antidotes to *d*-tubocurarine, this is a much safer test than the decamethonium-edrophonium test. The *d*-tubocurarine-edrophonium test is reserved for the approximately five per cent of patients whose diagnosis cannot be resolved by edrophonium alone. As previously stated, we have resorted to the decamethonium test only on a rare occasion.